Development of a New Rare Disease Registry

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Dedicated to all rare disease patients and their families around the world

Abstract

The notion of rare diseases was rarely heard of twenty years ago. As of the 21st century, there has been a notable interest in rare diseases and research and development of orphan medicines (Yazhou, Jinxiang, 2015). Rare disease registries are essential instruments in the field of rare diseases for research purposes. Research may be restricted due to the registries being heterogeneous.

Two questionnaires, one for healthcare professionals and one for the public including rare disease patients, were developed, validated, and disseminated. Rare disease patients were recruited via the National Alliance for Rare Diseases Support Malta (NARDSM). The experience and awareness of laymen with regards to rare diseases was analysed. The level of the professionals' awareness and experience about rare diseases and orphan medicines was analysed.

Two hundred and twenty-eight people completed the public questionnaire. Thirty-seven percent of the respondents knew or were related to someone with a rare disease. Thirteen percent of the respondents were rare diseases patients. Eighteen percent of the rare disease patients had encountered problems while trying to obtain an orphan drug.

Seventy-three HCPs completed the questionnaire for HCPs. Fifty-three percent of the respondents had diagnosed, encountered or examined a rare disease patient at a point in their career. Thirty-two percent of the respondents had dispensed or tried to dispense an orphan drug. Twenty-seven percent of the respondents had encountered various problems while trying to obtain an orphan drug for patients.

The questionnaire results showed that the healthcare professionals lacked more awareness and knowledge than the public. Consultations with members of the NARDSM were held

to discuss material to be included in the information leaflet. An information leaflet for healthcare professionals was developed.

Three rare disease registry templates from European organisations were analysed. Data elements for a rare disease registry were identified from the three templates based on applicability and relevance to the local register used by NARDSM.

Rare disease research is very patient-oriented and patient involvement is beneficial. Through the information booklet, healthcare professionals are empowering their patients and encourage registration to rare disease registries. Harmonisation of rare disease registries will encourage research and development on national and international levels.

Acknowledgments

I would like to thank my boyfriend, friends and family for their continuous support, my classmates for making these five years unforgettable, the volunteers and staff at the National Alliance for Rare Diseases Support Malta for assisting me, Professor Anthony Serracino-Inglott and Dr Maresca Attard Pizzuto for their help and guidance.

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List of Abbreviations

CFR	Code of Federal Regulation
CHMP	Committee for Medicinal Products for Human Use
CPGs	Clinical Practice Guidelines
CUPs	Compassionate Use Programmes
EAPs	Expanded Access Programmes
EMA	European Medicines Agency
EURORDIS	European Organisation for Rare Diseases
ERN	European Reference Network
EU	European Union
FDA	Food and Drug Administration
INSERM	French National Institute of Health and Medical Research
HAS	French National Authority for Health
HCPs	Healthcare Professionals
HTA	Health Technology Assessment
KFDA	Korean Food and Drug Administration
MARD	Malta Alliance for Rare Diseases
MMA	Malta Medicines Authority

NARDSM	National Alliance for Rare Diseases Support Malta
NIH	National Institute of Health
NHS	National Health Services
NPP	Named Patient Program
ODA	Orphan Drug Act
OD	Orphan Drugs
ORDI	Organisation for Rare Diseases India
POYC	Pharmacy of Your Choice
RDs	Rare Diseases
RDR	Rare Disease Registries
SUS	Sistema Único de Saúde
USA	United States of America
WHO	World Health Organisation

Chapter 1

Introduction

1.1 Background

The notion of rare disease was rarely heard of or spoken of twenty years ago. As of the beginning of the 21st century, there has been a significant rise in awareness about rare diseases (RDs) and an increase in research and development of new orphan drugs (OD). This chapter gives a brief overview of the progress that has been made so far with regards to RDs and orphan medications.

1.2 History of Rare Diseases and Orphan Drugs

There appears to be no clear indication of how RDs started to become a global interest. It was the Orphan Drug Act (ODA) of 1983 that introduced the category of RDs for development of new drugs. Before that, RDs were simply used as a term when physicians were dealing with a very delicate diagnosis. The definition of RDs was in fact needed to establish the definition for orphan drugs (Herder, 2017).

In the US, the Kefauver-Harris Amendments of 1962 to the Food, Drug and Cosmetic Act of 1938 led to the verification of the efficacy of medicinal products available since the 1938 in the US (Asbury, 1985). The term orphan drugs was an umbrella term for "drugs for single usage, drugs for chronic diseases, drugs with anticipated legal liability, drugs for use in diseases endemic to third world countries" which were all non-profitable (Huyard, 2008). It was in the 1970's with rising concern for rare disease patients that led to the 1983 ODA to come up with the contemporary definition for orphan drugs (Herder, 2017). In 1984, the ODA then redefined RDs as conditions "affecting fewer than 200,000 people in the United States." (Department of Health and Human Services USA, 2001).

1.2.1 Rare Diseases, Orphan Diseases or Neglected Diseases?

RDs are characterised by their low prevalence and their heterogeneity. Due to the rare disease patients being a minority, RDs lack public awareness. Little research is conducted on these diseases and therapy is generally not available or scarcely available. "Neglected diseases are common, communicable diseases that mainly affect patients living in developing countries." Little research is conducted on these diseases since they are not so common in industrialised countries. They are 'neglected' by the pharmaceutical industry since sales are unprofitable. Orphan diseases include both RDs and neglected diseases. They are 'orphan' of research initiative, market value and public health policies (EURORDIS, 2005).

1.3 Definition of Rare Diseases

The European Organisation for Rare Diseases (EURORDIS) is a non-governmental, non-profit association which represents over 700 organisations for rare disease patients from over 60 countries in Europe. EURORDIS (2005) defines rare disease as "a disease that occurs infrequently or rarely in the general population." The definition for a rare disease varies between legislation and policies and to this date no standard definition for RDs worldwide has been identified (Yazhou, Jinxiang, 2015). In the European Union (EU) a rare disease is defined as a condition affecting less than 5 in 10,000 people while in the United States of America (USA) it is defined as a condition affecting less 1 in 200,000 people. The Food and Drug Administration (FDA) considers a rare disease to be one that affects less than 200,000 patients in the USA, less than 250,000 in the EU and less than 50,000 patients in Japan at any given time (Yazhou, Jinxiang, 2015). These definitions only define the threshold for rarity of the clinical entity. RDs are chronically debilitating

or life threatening, and they all share common characteristics. RDs are most of the time disabling and are of psychological, social, emotional and financial burden to the patient and close relatives. Half of RDs occur in childhood and have almost no effective treatment or are incurable (EURORDIS, 2005; Dawkins et al, 2016).

Up till 2007, it has been estimated that there are 6000-8000 RDs recorded globally and 80% of them are thought to be genetic in origin (EURORDIS, 2017). It is still difficult to quantify the exact number of RDs since the area of RDs is still progressing in research and development. Information is also scarce in developing countries and regions such as Africa and South America (Gammie et al, 2015). It is estimated that 473 million individuals suffer from a rare disease worldwide. Rare diseases are individually rare, but collectively common (Ferreira, 2019).

The original ODA did not incorporate a definition for 'rare diseases' that was incidence-based. The ODA primarily described RDs as a condition that "occurs so infrequently in the Unites States that there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from the sales in the Unites States of such drug" (Herder, 2017) Amendments were made in the ODA, re-establishing the definition of a rare disease as one that: affects less than 200,000 persons in the United States, or affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will recovered from sales in the United States of such drug (Orphan Drug Act, 1983).

According to Yazhou and Jinxiang, (2015), the current existing definitions for rare diseases are prevalence-based. Rare diseases are now defined by their maximum

incidence rate, which is that of 5 in 10000 in Europe, 7.5 in 10000 in the USA and 4 in 10000 in Japan, respectively (Huyard, 2009).

In 2015, Richter et al carried out an analysis in which 269 definitions associated with RDs from 1109 organisations were identified. According to this analysis, the majority of the definitions included disease prevalence. Other descriptions and criteria were sometimes also mentioned. These descriptors included the disease's severity, whether it is life-threatening, if it is of genetic origin and if there are other treatment options. (Badyal, 2006, Simoens et al 2012). Both Desser (2010) and McCabe (2006) argue that the severity of a rare disease is not a determining characteristic as it also common for more prevailing diseases.

According to Richter et al (2015), a rare disease is "a health condition that affects a small number of people compared with other prevalent diseases in the general population." In the study, the definitions of RDs included prevalence thresholds that ranged from 5 to 76 cases/100,000 population. The average global prevalence threshold resulted to be 40 cases/100,000 people. Other terminology that was qualitative such as 'life-threatening' or 'debilitating' was used either implicitly or explicitly in 58% of the definitions. Findings from this study showed that at least one definition of rare disease in every jurisdiction participating in the study included a prevalence threshold. The use of prevalence rather than incidence is more appropriate since prevalence describes how widespread a disease is rather than its rate of occurrence. The use of a prevalence threshold allows international comparison of RDs. During this study it was noted that most EU governments adopted the EU definition for rare disease which shows the desire of harmonisation of a prevalence threshold for RDs on a political platform. The study concluded that including the term 'rare disease' paired with a prevalence threshold in the range of 40 to 50 cases /100,000, could provide a practical point of departure for a harmonised definition for rare diseases.

Table 1. 1: Average prevalence used in definitions per jurisdiction.

Adopted from: Richter, T., Nestler-Parr S, Babela R, M.Khan Z, Tesoro T, Molsen, E et al. Rare Disease Terminology and Definitions—A Systematic Global Review: Report of the ISPOR Rare Disease Special Interest Group. Value in Health 2015; (18);.906-914.

Jurisdiction	Cases per 100,000 people	Range	
		Min.	Max.
Korea	5	5	5
Australia	9	9	9
Taiwan	10	10	10
Denmark	13	1	20
Russia	19	7	50
Sweden	21	10	50
South Africa	25	25	25
Turkey	38	1	50
Canada	38	1	50
Wales	38	2	50
The Netherlands	39	1	50
Japan	39	39	39
European Union	40	2	50
United Kingdom	40	1	50
England	40	1	50
Scotland	40	2	50
Spain	43	2	50
Italy	43	<1	50
Poland	45	2	60
Germany	46	12	50
Czech Republic	50	50	50
Argentina	50	50	50
Colombia	50	50	50
Mexico	50	50	50
Slovakia	50	50	50
France	50	50	50
Chile	50	50	50
Ireland	50	50	50
India	51	2	100
Brazil	58	50	65
United States	64	64	64
China	76	<1	150
Global average	40		

The rarity of a disease might not be applicable to all countries and regions around the world. This issue was brought up by the 2004 WHO background paper on RDs. The report argued that a disease might be rare in one region but not in another such as in the example of Thalassaemia (de Vrueh, Baekelandt, 2013).

According to Richter et al (2015), another issue that is associated with the definition of RDs is the term used to define these diseases. Some countries may describe RDs as orphan diseases or genetic diseases. According to the WHO background paper on RDs (2013), the term ‘orphan diseases’ was used to describe diseases that due to their rarity, they were not worth investing in. The term “neglected disease” emerged in the 1990’s to describe

tropical infectious disease that existed in poor remote areas which also lacked investment. The definition of 'orphan diseases' relies on the concept of rarity, either in terms of number of individuals with the disease in the USA or as prevalence rates in Europe and other countries. The term 'orphan diseases' combines a number of diseases like genetic diseases, rare cancers, infectious diseases and autoimmune diseases. Nowadays the term 'rare diseases' is favoured and is used in legislations. The term also includes orphan diseases.

1.4 Rare Disease Definitions in Different Countries

A rare disease may only affect a very small number of people, but considering the vast number of RDs, these small numbers accumulate and have a significant influence on public health. Every country has its own definition and most of the definitions are prevalence-based. The ranges for prevalence range from 1 in 2000 to 1 in 500000. (Dharssi et al, 2017). The World Health Organization defines a rare disease as one that affects "0.65-1 out of every 1000 inhabitants" (Lavandeira, 2002).

European Union

The Regulation (EC) No 141/2000 of The European Parliament and of the Council of 16 December 1999 on Orphan Medicinal Products defines a rare disease in the EU as one that affects less than 1 in 2000 citizens in the EU.

United States of America

The 1983 ODA which was released by the FDA, describes a rare disease in the USA as one that: "affects less than 200,000 persons in the United States or affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or

condition will recovered from sales in the United States of such drug. Determinations under the preceding sentence with respect to any drug shall be made on the basis of the facts and circumstances as of the date the request for designation of the drug under this subsection is made" (Orphan Drug Act, 1983).

Japan

Originally in Japan, RDs were referred to as 'intractable diseases (Nambyo)'. In 1995, the Ministry of Health and Welfare revised the definition of RDs to "a disease of unknown aetiology with no effective treatment that presents a major financial and psychological burden and that is rare (fewer than 50,000 total patients)". Nowadays, RDs are termed "rare and intractable diseases" in Japan (Song et al, 2012).

Taiwan

Taiwan enacted the Rare Disease and Orphan Act in 2000 (Shafie et al, 2016). The Taiwan Ministry of Health and Welfare considers a disease or condition to be 'rare' if the prevalence rate is less than 0.01% of the population (1 in 10,000) (Pacific Bridge Medical, 2017).

South Korea

The Korean Food and Drug Administration (KFDA) issued an official notice in 2003 describing RDs as "diseases which affect small population (≤ 20,000) without appropriate treatment and substitutional treatment modalities" (Song et al, 2012).

China

A broadly used definition for RDs in China has been the WHO's definition of a rare disease, (a disease with an incidence of 0.65–1‰). However, the validity of the WHO's

definition has been debated on since definitions of rare disease from countries and organizations have been referred to consistently (Yazhou, Jinxiang, 2017). These definitions have a relatively broad scope and cannot be applied to China. One example is that RDs listed by Orphanet that have a low prevalence were not considered as RDs by most doctors in Shandong Province, China, according to a previous study by Heng and Yazhou in 2012. China lacks epidemiological data on RDs which makes it difficult to validate a definition for RDs since most rare disease definitions are prevalence-based (Yazhou, Jinxiang, 2017). In May 2010, a definition was agreed upon on consensus of experts reached by the Genetics Branch of the Chinese Medical Association. The definition considers a rare disease to be one that affects 1 in 500,000 people or a neonatal morbidity of less than 1 in 10,000 people (Han et al, 2012).

Australia

In Australia, 6-8% of the population suffers from a rare disease. Currently, there is no definition for RDs in Australia. Patient organisations recognize the EU definition for RDs (1 in 2000) as the standard definition for RDs in general.[1]

India

Like many other developing countries, India has no standard definition to date. The Organisation for Rare Diseases India (ORDI) suggests that a rare disease is one that affects 1 in 5,000 people or less. This definition is applied, considering the large population of India. [2]

[1] Rare Voices Australia. Rare Voices Australia Fact Sheet [Internet]. 2018. Available from: http://rva.blob.core.windows.net/assets/uploads/files/RVA%20Fact%20Sheet.pdf. Accessed [2018 Mar 8]
[2] Rare Disease Definition | ORD India [Internet]. Ordindia.org. 2018 [cited 2018 Mar 8]. Available from: http://ordindia.org/about-rd/rare-disease-definition/.

Brazil

With the creation of the National Health System (Sistema Único de Saúde – SUS) in 2010, Brazil incorporated universal health coverage in its legislation, acknowledging health as citizens' right and a responsibility of government. [3] Passos-Bueno et al in 2014, describe how the SUS introduced the "Policy for the Integral Attention to Subjects with Rare Diseases" in Brazil, which summarised guidelines for providing comprehensive care and treatment to rare disease patients in the public unified health system. The policy referred to the definition of the WHO for RDs, as those affecting less than 65 out of 100,000 individuals (Passos-Bueno et al, 2014, Giugliani et al, 2016).

[3] Lindelow M. The hallmark of the Brazilian National Health System (SUS). The World Bank [Internet]. 2018 [cited 2018 Mar 8];. Available from: http://www.worldbank.org/en/news/opinion/2013/12/20/brazil-sus-unified-public-healthcare-system-new-study

Table 1. 2: Orphan drug policies in different countries.

Adopted from: de Vrueh R, Baekelandt E, de Haan J. Background Paper 6.19 Rare Diseases. World Health Organisation; 2013.

	United States	Japan	Taiwan	Australia	EU
Program established	1983 – Orphan Drug Act modified the Federal Food, Drug and Cosmetic Act	1993 - Pharmaceutical Affairs Law amended	2000- Rare Disease and Orphan Drug Act.	1998 – developed in collaboration with USA	2000- Orphan Medicinal Products Regulation
Prevalence criterion for rare disease	Less than 200 000 patients in USA(<7.5:10 000)	Less than 50,000 patients in Japan (<4.1: 10 000)	Less than 1 persons in 10 000.	Less than 2 000 patients in Australia (<1.1:10 000)	Life-threatening or chronically debilitating disorder that affects less than 5:10 000 in EU
Requirements for designation	Rare disease or R&D costs cannot be recovered in seven years	Rare and serious disease; no other treatment available, must be a high health care priority	Drugs with major indications for the prevention, diagnosis and treatment of rare diseases	Rare disease or product is not commercially viable	Rare disease, or product unlikely to be developed without incentives or new product will be of significant benefit
Products eligible for orphan designation	Drugs and biologicals (including vaccines and in vivo diagnostics)	Drugs, biologicals and medical devices	Drugs and biological and special nutrient foods	Drugs, vaccines or in vivo diagnostic agents	Drugs and biologicals (including vaccines and in vivo diagnostics)
Market exclusivity	Seven years; prevents same product being approved for the same indication unless clinical superiority is shown	Re-examination period extended from four to 10 years	Ten years . During this period, no applications for registration and market approval of pharmaceuticals of the same kind will be approved	None; second product with the same active ingredient will not be designated unless clinical superiority is shown	Ten years; can be reduced to six if orphan criteria no longer met
Other benefits	Regulatory fee waivers, 50% tax credit on clinical research after designation; grants for clinical research (pharma and academia eligible); protocol assistance; faster review if indication warrants; research grants for medical devices and medical food.	Application fee reduced (?); grants for clinical and non-clinical studies (only pharma eligible) up to 50% of yearly R&D costs available up to three years; 6% tax reductions for (pre) clinical research; protocol assistance on request; faster review if indication warrants.	Patients ailments are now included in National Health Insurance coverage for major diseases and injuries and whose co-payment can be waived.	Regulatory fee waivers; no grants, no tax credits, protocol assistance on request; priority review	Regulatory fees can be reduced or waived, access to centralized procedure, protocol assistance. Individual Member States have to implement measures to stimulate the develop-ment of orphan medicinal products (Article 9 of Regulation

1.5 Orphan Drugs

EURORDIS defines orphan drugs as "medicinal products intended for diagnosis, prevention or treatment of life-threatening or very serious diseases or disorders that are rare."[4] Rarity in Europe and Japan is that of a disease affecting less than 250,000 people while in the USA it affects less than 200,000 people (Cui and Han, 2015).

Orphan Drug Legislations are used by various countries to boost, research, development, and marketing of orphan drugs. These legislations aid in overcoming financial hurdles of product development and restricted profitable income (Babar et al, 2015). Table 1.3 shows OD legislations along the years in different countries.

Table 1. 3: Timeline of Orphan Drug Legislations

Adapted from: Pamplin, College of Business Magazine, Virginia Tech, 2013. Available from: http://www.magazine.pamplin.vt.edu/spring13/orphandrugs.html and Shafie A, Chaiyakunapruk N, Supian A, Lim J, Zafra M, Hassali M. State of rare disease management in Southeast Asia. Orphanet Journal of Rare Diseases. 2016;11(107).

1983	USA develops Orphan Drug Act
1991	Singapore passes orphan drug legislation
1993	Japan passes orphan drug legislation
1997	Australia passes orphan drug legislation
2000	Taiwan and EU pass orphan drug legislation
2003	South Korea passes orphan drug legislation

[4] EURORDIS. What is an orphan drug? [Internet]. Eurordis.org. 2009 [cited 2018 Mar 19]. Available from: https://www.eurordis.org/content/what-orphan-drug

For a drug to undergo designation, it must comply with the criteria stated by Regulation (EC) No 141/2000. The molecule should be indicated for a "life-threatening or chronically debilitating condition affecting not more than 5 in 10000 persons" and no alternative, effective treatment for the same condition has been licensed. The applicant can apply for designation at any stage of development of the medicinal before this can be approved for marketing authorisation (Regulation EC No141/2000). Applications are then reviewed by the Committee for Medicinal Products for Human Use (CHMP) before getting their marketing authorisation. As of the year 2000, there have been 2200 medicines that received an orphan designation. Over 160 of the 2200 medicines with an orphan designation successfully obtained a marketing authorisation and an orphan status in the EU.[5] Pharmacotherapy is available for only 3% of RDs (Czech et al, 2020).

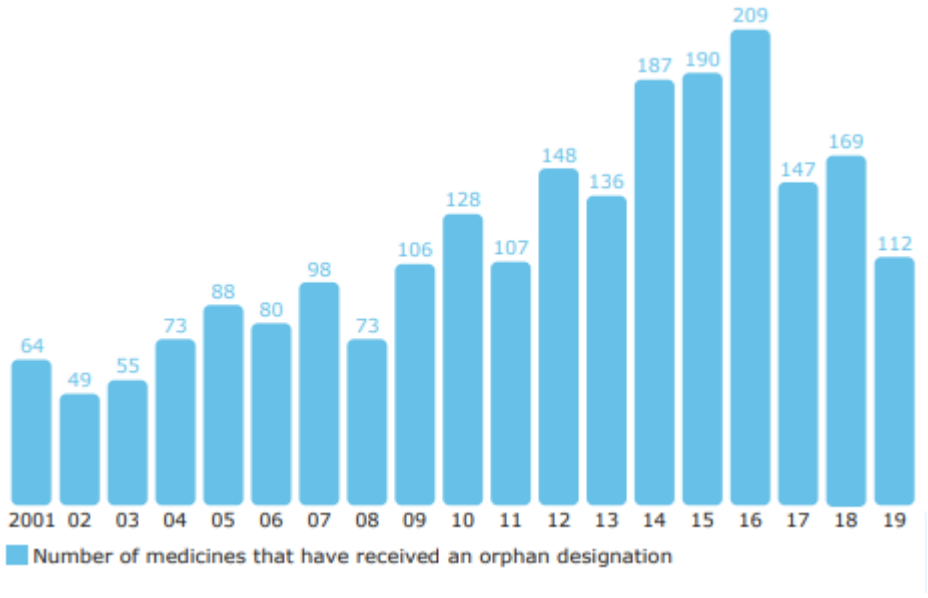


Figure 1. 1: Number of medicines that have received an orphan designation.

Adopted from: European Medicines Agency. Orphan Medicines in the EU [Internet]. 2020 [cited 25 June 2020]. Available from: https://www.ema.europa.eu/en/documents/leaflet/leaflet-orphan-medicines-eu_en.pdf

[5] European Medicines Agency. Orphan Medicines in the EU [Internet]. 2020 [cited 2020 Jun 25]. Available from: https://www.ema.europa.eu/en/documents/leaflet/leaflet-orphan-medicines-eu_en.pdf

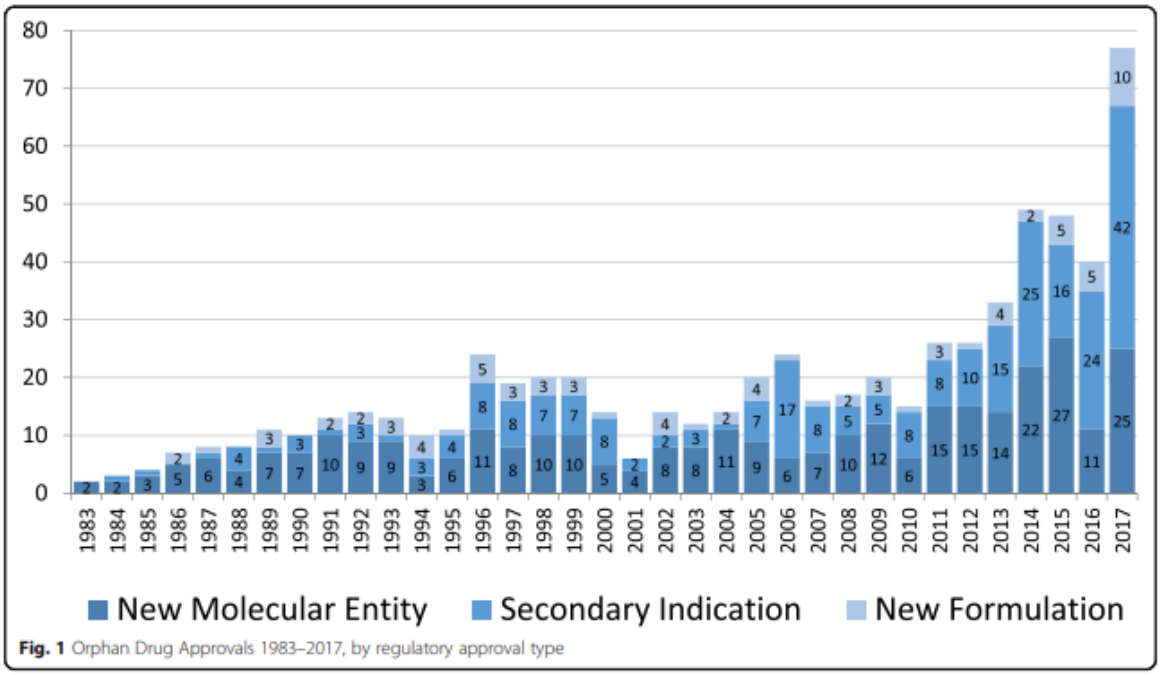


Figure 1. 2: Orphan Drug Approvals 1983-2017.

Adopted from: Miller K, Lanthier M. Investigating the landscape of US orphan product approvals. Orphanet Journal of Rare Diseases. 2018;13(1):3.

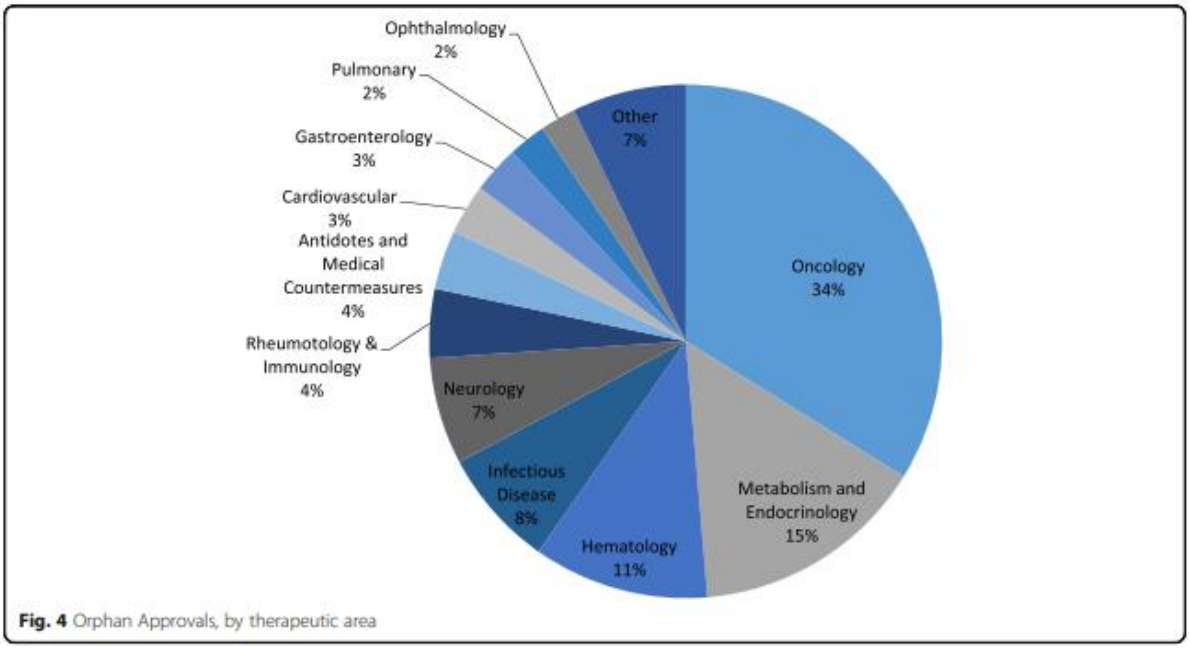


Figure 1. 3: Orphan Approvals by therapeutic area.

Adopted from: Miller K, Lanthier M. Investigating the landscape of US orphan product approvals. Orphanet Journal of Rare Diseases. 2018;13(1):3.

1.5.1 Definitions of Orphan Drugs

The definitions of Orphan Drugs vary according to legislations and policies in different countries.

European Union

"A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:

a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or
   that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment and
b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition (Regulation EC No141/2000)."

According to European regulation No141/2000, only drugs for human use can be designated as 'orphan drugs. Veterinary medicines, medical devices, nutritional supplements and dietary products cannot be considered as 'orphan drugs'. The European regulation n° 141/2000 defines orphan medicinal product' as "a medicinal product

designated as such under the terms and conditions" of the Regulation. The terms and conditions are that the drug "is intended for treating a life-threatening disease that meets the prevalence criterion and no satisfactory treatment is available" (Cheng, 2017).

United States of America

"Orphan drugs are used in diseases or circumstances which occur so infrequently in the USA, that there is no reasonable expectation that the cost of developing and making available in the USA a drug for such disease or condition will be recovered from sales in the USA for such drugs (Orphan Drug Act, 1983)." In 1985 and in 1990 the OD definition was broadened to include products other than medicines. This included biologics, medical devices and medical foods, particularly parenteral nutrition and nutraceuticals.[6]

Japan

On 1 October 1993, the Japanese government emended the pharmaceutical law by introducing special requirements related to research and development of OD. In particular, the Orphan Drug Development Program was launched by the Ministry of Health Labour and Welfare. The amendments stated that orphan drug status can be granted to a drug, provided it complies with the following criteria:

- "The disease for which use of the drug is claimed must be incurable. There must be no possible alternative treatment; or the efficacy and expected safety of the drug must be excellent in comparison with other available drugs.

[6] Orphanet: About orphan drugs [Internet]. Orpha.net. 2018 [cited 2018 Mar 9]. Available from: http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=EN&stapage=ST_EDUCATION_EDUCATION_ABOUTORPHANDRUGS_USA#policy

- The number of patients affected by this disease in Japan must be less than 50 000 on the Japanese territory, which corresponds to a maximal incidence of four per ten thousand."[7]

- There needs to be scientific rationale to justify the need for the drug (Cheng, 2017)

Singapore

The third orphan drug legislation published worldwide was Singapore's legislation. The Medicines Act was published in 1991 with Chapter 176 section 9 dedicated to OD (Franco, 2012). The Act described an orphan drug as a medicinal product which has been identified by any doctor or dentist as an appropriate cure for a rare disease which has no effective alternative for treatment (Cheng et al, 2017).

Taiwan

An Orphan Drug is defined as one that has "major indications for the prevention, diagnosis and treatment of designated rare diseases" (Cheng, 2017).

Australia

The Therapeutic Goods Administration in Australia offers regulations of the designations of orphan drugs. Designation for orphan drugs in Australia is intended for drugs which aim to treat diseases with a prevalence of 2000 individuals or less in the Australian population (Scott et al, 2001). The designation of an orphan drug has to satisfy the combination of the criteria that the drug is not commercially viable, when used in the

[7] Orphanet: About orphan drugs [Internet]. Orpha.net. 2018 [cited 2018 Mar 9]. Available from: http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=EN&stapage=ST_EDUCATION_EDUCATION_ABOUTORPHANDRUGS_USA#policy

patient population it is indicated for, and an acceptable rationale for the drug and its indication.[8]

1.5.2 Incentives for Orphan Drugs

OD benefit from various incentives. Pharmaceutical companies seeking to develop ODs are offered incentives such as prolonged market exclusivity, reduced fees, protocol assistance and tax benefits amongst other benefits (Mariz et al., 2016). OD benefit from a period of market exclusivity where no other company can apply for marketing authorisation for another orphan product with the same indication (Simoens et al, 2012). By the Regulation (EC) No 141/2000, OD benefit from 10 years of market exclusivity which can "be reduced to six years, if, at the end of the fifth year, it is established in respect of the medicinal product concerned that the criteria laid down in Article 3 are no longer met, inter alia, where it is shown on the basis of available evidence that the product is sufficiently profitable not to justify maintenance of market exclusivity." A marketing authorisation can still be given to a competing product for the same therapeutic indication if it is "safer, more effective or otherwise clinically superior" (Regulation EC No141/2000).

Market exclusivity varies for different countries:

- EU: 10 years of market exclusivity from the year of approval
- US: 7 years of market exclusivity from the year of approval
- Japan: 10 years registration validity period (Evaluate Pharma, 2019)

[8] RESERVED I. Orphanet: About orphan drugs [Internet]. Orpha.net. 2018 [cited 2019 Mar 10]. Available from: http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=EN&stapage=ST_EDUCATION_EDUCATION_ABOUTORPHANDRUGS_AUS

OD also benefit from tax exemptions, free scientific guidance regarding issues like protocols, privilege of prioritised marketing authorisation review and programmes on compassionate use and off-label use of the OD (Gammie et al, 2015). These incentives also vary for every country:

- EU: EMA protocol assistance at a reduced fee, funding for sources
- USA: 50% tax credit on R&D expenses, R&D grants for Phase 1 to Phase 3 clinical trials
- Japan: Subsidisation of ODs' developmental costs, consultations at reduced fees, study expenses up to 12% can be registered as tax credit (Evaluate Pharma, 2019).

1.5.3 Accessibility of Orphan Drugs

The EU is the only body that has a procedure for OD designation and marketing authorisation approval which is applied in all the member states. Cross-border regulation is fundamental in the field of RD, due to limited access of OD, specialists and health care treatments and facilities to the patients (Gammie et al, 2015).

In March 2011, the EU adopted a directive which included the foundation of European Reference Networks (ERN). An ERN is defined as "an association of individuals sharing common interests and providing mutual support and information" (Evangelista et al, 2016). According to European Commission, the aim of these networks is to act as research and knowledge centres which contribute to the latest scientific discoveries, treating patients from other European member states and improving quality of care and access to healthcare.[9]

[9] European Commission. European networks of reference for rare diseases. Public Health - [Internet]. Public Health. [cited 2019 Mar 19]. Available from: http://ec.europa.eu/health/rare_diseases/european_reference_networks/erf_en

ERNs provide a structure for information sharing and synchronisation of care across the EU to improve diagnostic and treatment access and ensuring the best healthcare quality for patients.[10] According to Bearryman (2017), there are currently 24 ERNs joining approximately 1,000 health care providers across the EU.[11] The approved ERNs are supported by more than 300 hospitals and 900 specialised teams (Héon-Klin et al, 2017).

Accessibility before and after marketing authorisation

There are three ways of accessing a non-authorised OD: compassionate use, clinical trials and a prescription of medicine authorised under another clinical indication. The compassionate use of treatments is a very common practice and it has been authorised in Europe as of May 1989 (Directive 89/341/EEC). Member States have the right to deliver non-authorised medicinal products to other member states under specific circumstances such as the recommendation of a medical specialist. This type of accessibility is restricted due to prices and the lack of reimbursement by some countries. After obtaining a marketing authorisation, OD can be made available in the country via two means, either distribution to authorised pharmacies or by ordering from the mother company when requested (Alcimed, 2006).

Adaptive Licensing

Adaptive licensing is a prospective and adjustable method to regulation of drugs and biologics. "Through iterative phases of evidence gathering to reduce uncertainties followed by regulatory evaluation and license adaptation, Adaptive Licensing seeks to maximize the positive impact of new drugs on public health by balancing timely access

[10]EURORDIS. About European Reference Networks (ERNs) [Internet]. Eurordis.org. 2016 [cited 2019 Mar 7]. Available from: http://www.eurordis.org/content/about-european-reference-networks

[11] Bearryman E. Rare diseases: New steps in EU collaboration to improve citizens' lives [Internet]. Eurordis.org. 2017 [cited 2019 Mar 19]. Available from: http://www.eurordis.org/news/rare-diseases-new-steps-eu-collaboration-improve-citizens-lives

for patients with the need to assess and to provide adequate evolving information on benefits and harms so that better-informed patient-care decisions can be made" (Eichler et al, 2012).

Through Adaptive Pathways, a medicine is initially approved only for a small population of patients (based on limited scientific evidence). After more evidence is collected, the drug is made extensively available. At various points along the clinical development pathway, approved indications, coverage and therapeutic value are referred to as treatment populations are widened or limited based on new safety and efficacy data (Vella Bonanno et al, 2017).

Compassionate Use Programmes

Compassionate Use Programmes (CUPs) are "a treatment option that allows the use of an unauthorised medicine. Under strict conditions, products in development can be made available to groups of patients who have a disease with no satisfactory authorised therapies and who cannot enter clinical trials."[12] CUPs are essential in ensuring uninterrupted access to drugs until approval and reimbursement rulings are finalised (Hyry, 2015). While clinical trials are directed by protocols and participants are chosen according to certain criteria, CUPs allows patients with no consideration of any criteria. About 40% of more than 50 notifications of CUPs that have been submitted to the EMA by European countries are for the use of orphan drug.

Twenty out of 28 EU member states had set national regulations and the well-defined processes for CUPs. The national CUPs makes medicinal products available either to

[12] European Medicines Agency - Research and development - Compassionate use [Internet]. Ema.europa.eu. 2018 [cited 2018 Mar 19]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000293.jsp&mid

individuals (Named Patient Program -NPP) or groups of patients governed by every member state's legislation. NPP is not CUPs as per the EU regulations. The practitioner responsible for the treatment contacts the manufacturer directly

In Malta there is a regulatory procedure for CUPs but there is no official legislation. Compassionate use of medicines in individual patients has been documented, but it is not clear whether this is NPP or CUP (Balasubramanian et al, 2016).

Named Patient Program

Practitioners of rare disease patients may approach a manufacturer directly to request the supply of a new medicine to be used for a patient or a number of patients under their direct responsibility. Supplies are recorded by the manufacturer however there is no central register of the group of patients that are being using the NPP.[13]

Expanded Access Program

According to the Code of Federal Regulation (CFR) of the Food and Drug Administration (FDA) Expanded Access Programmes (EAPs), sometimes also called CUPs, are considered when "manufacturers make an investigational drug available for therapeutic use, outside a clinical trial, to treat patients with a serious disease in the absence of comparable or satisfactory alternative therapeutic on-label drugs that cannot either participate or have already participated in a clinical trial."

This definition of EAPs is not global. The EMA suggests that EU countries should include within EAPs, individuals who had participated in the clinical trial of the investigational drug and who wish to proceed with the treatment. It is internationally recognised that

[13] Questions and answers on the compassionate use of medicines in the European Union [Internet]. European Medicines Agency; 2010 [cited 2018 Mar 11]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/01/WC500069898.pdf

patients treated in a clinical trial can opt to carry on with the treatment for an extended period in an Open-label Extension study which generates long-term data on the drugs' efficacy, safety, tolerability and administration. Contrary to the FDA, in Europe CUPs and EAPs do not have the same meaning. EMA describes compassionate use as a means to facilitate patients' access to investigational treatments for an individual patient as Compassionate Use on a Named Patient basis, or for a group of patients as CUPs (Ludicello et al, 2016).

Figure 1. 4: Comparison of EAPs in the US to CUP and NPP in the EU.

Adopted from: Yazdani M, Boggio F. Initiating Early Access Programs in Europe: Five Things to Consider [Internet].2013 [cited 2018 Mar 15]. Available from: http://www.executiveinsight.ch/system/files/publication_pdfs/14_initiatingearly.pdf

Criteria	EAP (US)	CUP (EU)	NPP (EU)
Legislation in place	• Expanded Access Programs (FDA, 1997)	• Article 83 (1) of Regulation (EC) No 726/2004	• Article 5 of Directive 2001/83/EC
Who initiates the program?	• Manufacturer • Physician	• Manufacturer/Group of physicians (e.g. in Italy)	• Physician
Criteria to define/select target population is set by ...	• Manufacturer/FDA	• Manufacturer/CHMP	• Manufacturer/ Physician
Who can benefit from program? Limitation in use?	• Group of patients (treatment INDs & treatment protocols) • Named patients (single patients INDs)	• Group of patients i.e. more than one (permission is granted to a clinic or hospital as opposed to a particular patient)	• Only named patients for whom physician has made a request
Liability	• Manufacturer	• Manufacturer	• Prescribing physicians
Medicinal product *should* be undergoing clinical trials or awaiting market authorization?	✔	✔	✘
Is off-label use permitted?	✘	✘	✔
Are physicians paid for taking part in the program?	✔	✘	✘
Are drugs in program priced?	✘	✘	✔ (possible)

1.6 Orphan Drug Prices

An estimate of ODs as a share of the total hospital drug expenditures or total pharmaceutical expenditures has been carried out for Europe. Large revenue can be generated from orphan drugs, mainly because of their high prices (Simoens, 2011). billion In Belgium, ODs accounted for 5% of the hospital drug budget in 2008 (Denis et al., 2010). In 2014, Hutchings et al predicted that the impact of orphan drugs, as a share of the total drug expenditure in Sweden and France, would increase from 2.7%/3.2% to 4.1%/4.9% by 2020. The global orphan drug market is estimated to get to US $242 by the year 2024. The leading orphan drug therapeutic areas which contributed to more than 50% of the non-orphan drugs market are the blood, respiratory and central nervous systems (Evaluate Pharma, 2019).

Among the factors that reportedly affect OD price setting are the expenses of research and development, effectiveness of the OD, drug quality and disease prevalence (Onakpoya et al, 2014). The statement by EURORDIS regarding RD states that cost of the OD increases with the rarity of the disease although not proportionally (EURORDIS, 2009). According to a study carried out by Onakpoya et al in 2014, which involved the analysis of 74 European Medicines Agency (EMA) -approved orphan drugs, (contrary to the EURORDIS statement) it was concluded that the price of OD for the rarest diseases is lower than that for OD used for more common RDs.

Pricing of orphan drugs is problematic in that the research and development costs must be compensated for by a small number of patients. It is the limited profit opportunities, marketing exclusivity, and the shortage of therapeutic alternatives that lead to relatively expensive prices of OD, often exceeding €100,000 per patient (Gammie et al, 2015). According to a statement published by EURORDIS in 2009, the then current costs to

national healthcare systems were mainly stemmed from Glivec® which has multiple therapeutic indications for rare cancers and enzyme replacement therapies in extremely RDs. Estimates show that the remainder orphan drugs account for less than 1% of national healthcare costs (EURORDIS, 2009).

A matter of concern regarding OD prices is the issue of monopolisation. This is because considering the limited alternatives, patients would be willing to pay the manufacturer's high prices which in turn allows the manufacturer to keep prices high (Babar et al, 2015). Manufacturers may also increase prices by 'salami slicing' of a rare disease. In 1992, the FDA had vowed to limit 'salami slicing' by requiring that, for subsets of common diseases to be considered rare, they need to be 'medically plausible', a term which remained vague and unexplained by the FDA (Simoens, 2011). In 2003, the FDA then made new regulations where the manufacturer must prove why their drug is only indicated for one selected subset of the rare disease and why the drug is unintended for use outside the particular subset (Herder, 2017).

Some countries offer reimbursement to their patients; depending on if the medicinal product is approved in the country or included in the national reimbursement list. Reimbursement is also dependent on Health Technology Assessment (HTA); particularly cost-effectiveness of drugs. The high prices of OD are still limiting patient access although they might be available to them. In a study conducted by Gammie et al (2015) which analysed legislations, regulations and policies in 35 countries, 33 of the countries offered some type of compensation for orphan medicinal. A study conducted in 2019 by Stawowczyk et al, assessed the reimbursement status for 163 orphan drugs in 7 European countries. The reimbursement of orphan drugs in every country was different for every country as shown in Figure 1.5.

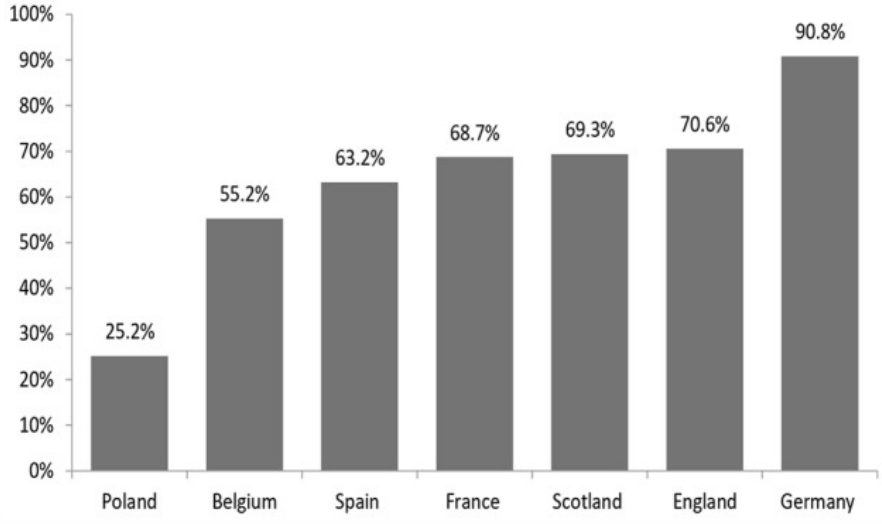


Figure 1. 5: Percentage of reimbursed orphan drugs in analysed countries.

Adopted from: Stawowczyk E, Malinowski K, Kawalec P, Bobiński R, Siwiec J, Panteli D et al. Reimbursement Status and Recommendations Related to Orphan Drugs in European Countries. Frontiers in Pharmacology. 2019;10(1279).

1.6.1 Cost-Effectiveness of Orphan Drugs

It is very challenging to conduct clinical trials for OD due to the small number of people affected by RD (Groft, 2013). Drummond et al (2007) argue that at the time of market access, clinical data is limited and the therapeutic benefit of the orphan drug tends to be moderate.

In clinical trials conducted by Onakpoya et al in 2014, it was found that over two-thirds of the EMA-approved orphan drugs at the time had clinically significant beneficial effects while one-fifth showed no significant benefits or, may do harm. It is necessary to have good access to reliable data to improve treatment alternatives and manipulate medicinal costs more efficiently (Hollak et al, 2015). One way of overcoming the lack of available

information about the clinical benefits of OD's is by the collection of long-term data via the establishment of registries (Drummond, 2008).

1.7 Treatment Protocol for RDs

Clinical practice guidelines (CPGs) are "systematically developed statements to assist practitioners and patient decisions about appropriate health care for specific circumstances" (Lohr, Fiel, 1990). CPGs for RDs are few, may be not be easy to identify by internet queries and may vary in quality depending on the source and methodology used. Several EU countries have started including CPGs in their national plans for RDs. CPGs have contributed to faster diagnosis and an improvement of the quality of care in the field of RDs (Pavan et al, 2017).

The knowledge about a particular rare disease will affect how long it takes for diagnosis and the quality of medical and social support (EURORDIS, 2005). The scarcity of information about rare disease leads to a longer period of time for the appropriate diagnosis to occur after the first symptoms. According to Engel et al (2013), it can take up to 20 years to obtain a diagnosis for a rare disease, and patients with a rare disease may visit an average of 7.3 doctors before getting the correct diagnosis for the disease. These delays may have serious repercussions on the patient's life involving risking the disease progressing to very harmful stages, financial wastages and the emotional plights the patient and their relatives have to face until diagnosis (Engel et al, 2013).

1. Off-label Treatment

With only 93 OD authorised in the EU[3] and available to the public, the off-label use of these medications and others is very common. The off-label use of OD "involves

[3] Sepodes B. Developing Medicines for Rare Diseases. Conference on the Development and Access of Medicines for Rare Diseases. Bruno Sepodes; 2017.

prescribing medications for indications, or using a dosage or dosage form, that have not been approved by the US Food and Drug Administration" (Engel et al, 2013). According to Liang et al (2010), 90% of drugs used in RD are off-label.

Off-label use of medicines carries its own risks involving quality, safety and efficacy since this type of medicine usage would have not undergone clinical tests. Although rare disease patients are greater risk-takers due to various challenges, the EU legislation declared that "patients suffering from rare conditions should be entitled to the same quality of treatment as other patients" (Regulation EC No.141/2000). In a study conducted by Kesselheim et al in 2012, it was found that of four top-selling orphan medicinals, three of them were used more commonly off-label. Although off-label use of OD might have its benefits, pharmaceutical companies should put pharmacovigilance of off-label use of the OD on their agenda (Dooms et al, 2016).

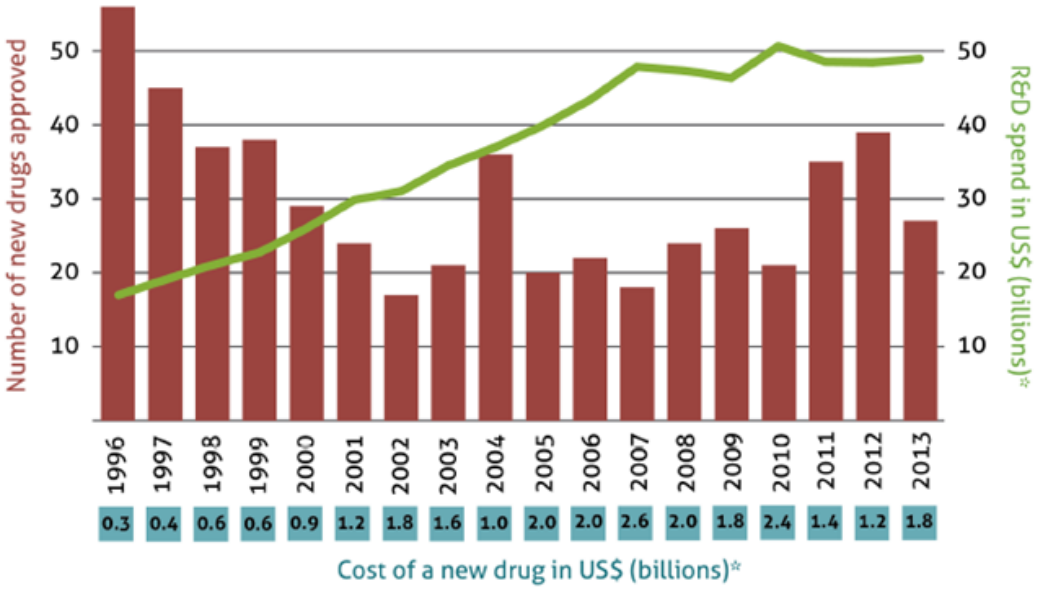
2. Repurposing Drugs for Rare Diseases

The journey from the discovery of a new drug to its release on the market is lengthy (10 years in average), expensive, risky and with a high risk of failure. Development of a drug designated for a rare disease does not allow the recovery of the funds spent in research.[14]

[14] RESERVED I. Orphanet: About orphan drugs [Internet]. Orpha.net. 2018 [cited 2019 Mar 15]. Available from: http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=EN

Table 1. 4: A comparison of cost of new drugs and the number of new drugs approved along the years.

Adopted from: Thompson R. A sustainable approach to repurposing generic drugs for generic diseases. Presentation presented at; 2017; World Orphan Drug Conference Barcelona.



Drug repurposing "is the act of taking a drug intended to treat one patient population and demonstrating its efficacy in the treatment of a completely different group of patients." Repurposing has various advantages including an established safety profile and known side effects, history of human use, known mechanism of action and reduced requirements for clinical trials.[15]

In a mini-review by Dooms in 2017, 53 EMA authorised orphan drugs whose active ingredient was a repurposed molecule were represented. No phase 1 clinical trials were required on these molecules which had well-established safety, pharmacokinetic and pharmacodynamic data. These out-of-patent repurposed active ingredients received an orphan drug designation and a ten-year market exclusivity for a RD indication without undergoing phase 1 clinical trials.

[15] Thompson R. A sustainable approach to repurposing generic drugs for generic diseases. Presentation presented at; 2017; World Orphan Drug Conference Barcelona.

Table 1. 5: EMA approved orphan drugs with repurposed molecules.

Adopted from: Dooms M. From promising molecules to orphan drugs: Early clinical drug development. Intractable & Rare Diseases Research. 2017;6(1):29-34.

No.	Product	Active ingredient	Route	Molec weight	ATC	DDD/mg	Designation	Authorization	Days	Synthesis	1ste use	Years
1	Trisenox	Arsenic Trioxide	P	197.80	L01XX27	9	2000/10/18	2002/03/05	503	1963	1996	33
2	Zavesca	Miglustat	O	219.30	A16AX06	300	2000/10/18	2002/11/20	763	1979	1994	15
3	Carbaglu	Carglumic Acid	O	190.20	A16AA05	200	2000/10/18	2003/01/24	828	1942	2004	62
4	Busilvex	Busulfan	P	246.30	L01AB01		2000/12/29	2003/07/09	922	1953	1988	35
5	Ventavis	Iloprost	B	360.50	B01AC11	0.15	2000/12/29	2003/09/16	991	1980	1994	14
6	Xagrid	Anagrilide	O	292.50	L01XX35	2	2000/12/29	2004/11/16	1418	1976	1979	3
7	Orfadin	Nitisinone	O	329.20	A16AX04	20	2000/12/29	2005/02/21	1515	1986	1992	6
8	Glivec	Imatinib	O	589.70	L01XE01	600	2001/02/14	2001/08/27	194	1996	1996	0
9	Tracleer	Bosentan	O	551.60	C02KX01	250	2001/02/14	2002/05/15	455	1992	1994	2
10	Pedea	Ibuprofen	P	206.30	C01EB16	30	2001/02/14	2004/07/29	1261	1964	1979	15
11	Prialt	Ziconotide	P	2639.10	N02BG08	0.012	2001/07/09	2005/02/21	1323	1987	1992	5
12	Cystadane	Betaine	O	117.10	A16AA06	6000	2001/07/09	2007/02/15	2047	1957	1981	24
13	Wilzin	Zinc Acetate	O	219.50	A16AX05	150	2001/07/31	2004/10/13	1170	1912	1992	80
14	Savene	Dexrazoxane	P	268.30	V03AF02	1500	2001/09/10	2006/07/28	1782	1969	2000	31
15	Litak	Cladribine	P	285.70	L01BB04		2001/09/18	2004/04/14	939	1960	1993	33
16	Onsenal	Celecoxib	O	381.40	L01XX33	800	2001/11/20	2003/10/17	696	1995	2000	5
17	Thalidomide	Thalidomide	O	258.23	L04AX02	100	2001/11/20	2008/04/16	2339	1957	1963	6
18	Diacomit	Stiripentol	O	234.30	N03AX17	1000	2001/12/05	2007/01/04	1856	1973	1978	5
19	Evoltra	Clofarabine	P	303.70	L01BB06		2002/02/05	2006/05/29	1574	1987	1999	12
20	Vidaza	Azacitidine	P	244.20	L01BC07		2002/02/06	2008/12/17	2506	1964	1972	8
21	PhotoBarr	Porfimer Sodium	P	1179.36	L01XD01		2002/03/06	2004/03/25	750	1987	1993	6
22	Lysodren	Mitotane	O	320.00	L01XX23	3000	2002/06/12	2004/04/28	686	1945	1973	28
23	Nexobrid	Bromelain	T		D03BA03		2002/07/30	2012/12/20	3796	1961	2014	53
24	Gliolan	5 Aminolevulinic Acid	O	131.10	L01XD04		2002/11/13	2007/09/07	1759	1950	1993	43
25	Firdapase	Amifampridine	O	109.10	N07XX05	40	2002/12/18	2009/12/23	2562	1935	1984	49
26	Orphacol	Cholic Acid	O	408.57	A05AA03		2002/12/18	2010/12/16	2920	1939	1990	51
27	Peyona	Caffeine Citrate	O	408.57	A05AA03	400	2002/12/18	2010/12/16	2920	1959	1975	16
28	Xyrem	Sodium Oxybate	O	126.09	N07XX04	7500	2003/02/03	2005/10/18	988	1929	1979	50
29	Tobi	Tobramycin	B	467.51	J01GB01	300	2003/03/17	2010/09/23	2747	1967	1996	29
30	Siklos	Hydroxycarbamide	O	76.05	L01XX05	250	2003/07/09	2007/06/29	1451	1869	1987	118
31	Revatio	Sildenafil	O	666.70	G04BE03	60	2003/12/12	2005/10/28	686	1992	2002	10
32	Kuvan	Sapropterin	O	314.20	A16AX07		2004/06/08	2008/12/02	1638	1963	1977	14
33	Cayston	Aztreonam	B	435.40	J01DF01	4000	2004/06/21	2009/09/21	1918	1981	1984	3
34	Mepact	Mifamurtide	P	1237.50	L03AX15	0.7	2004/06/21	2009/03/06	1719	1981	1992	11
35	Defitelio	Defibrotide	P		B01AX01		2004/07/29	2013/10/22	3372	1975	1998	23
36	Inovelon	Rufinamide	O	238.20	N03AF03	1400	2004/10/20	2007/01/16	818	1986	2005	19
37	Esbriet	Pirfenidon	O	185.22	L04AX05	2400	2004/11/16	2011/02/28	2295	1970	1995	25
38	Ceplene	Histamine	P	184.10	L03AX14	0.5	2005/04/11	2008/10/07	1275	1938	1970	32
39	Atriance	Nelarabine	P	297.30	L01BB07		2005/06/16	2007/08/22	797	1988	1998	10
40	Bronchitol	Mannitol	B	182.17	R05CB16	800	2005/11/07	2012/04/13	2349	1957	1978	21
41	Torisel	Temsirolimus	P	1030.30	L01XE09	1000	2006/04/06	2007/11/19	592	1994	2004	10
42	Plenadren	Hydrocortisone	O	362.46	H02AB09	30	2006/05/22	2011/11/03	1991	1937	1955	18
43	Vyndagel	Tafamidis	O	308.11	N07XX08	20	2006/08/28	2011/11/16	1906	2004	2011	7
44	Tepadina	Thiotepa	P	189.20	L01AC01		2007/01/29	2010/03/15	1141	1954	1968	14
45	Raxone	Idebenone	O	338.44	N06BX13		2007/02/15	2015/09/10	3129	1975	1992	17
46	Afinitor	Everolimus	O	958.20	L01XE10		2007/06/05	2009/08/03	790	1994	2006	12
47	Quinsair	Levofloxacine	B	361.37	J01MA12	500	2008/09/23	2015/03/30	2379	1986	2002	16
48	Xaluprine	Mercaptopurine	O	152.18	L01BB02		2009/04/30	2012/03/09	1044	1952	1976	24
49	Signifor	Pasireotide	P	1107.26	H01CB05	1.2	2009/10/08	2012/04/24	929	2002	2010	8
50	Votubia	Everolimus	O	958.20	L01XE10		2010/08/04	2011/09/02	394	1994	2006	12
51	Procysbi	Cysteamine	O	77.15	A16AA04	2000	2010/09/20	2013/09/10	1086	1940	1978	38
52	Granupas	p Aminosalicylic Acid	O	153.14	J04AA01	12000	2010/12/17	2014/04/09	1209	1890	1946	56
53	Ketoconazole	Ketoconazol	O	531.44	J02AB02		2012/04/23	2014/11/21	942	1978	1985	7

Elsevier, an information analytics business started a collaboration in 2016 with Findacure, a UK-based non-profit organization that conducts research to develop treatments for RDs. Findacure is building cost-of-illness models for 10 RDs, establishing the current cost of each disease to the UK's National Health Service (NHS) and demonstrating potential savings through treatment using repurposed drugs. Findacure's

repurposing approach is fixed on drugs that are off-patent, to increase savings to the NHS.[16]

3. Post-Marketing Surveillance of Orphan Drugs

Clinical studies for OD can only give a limited amount of data. Price (2016) argues that "development clinical studies would often have been uncontrolled or comparative data might have been collected from a historical control group." This results in poor data regarding safety profile of the drug. Monitoring of side effects for OD can be problematic considering that side effects usually affect a small percentage of the population and there are only a small number of patients affected by RD worldwide (Price et al, 2016). For example, if Haemophilia B affects 1 in 30,000 males[17], it would be difficult to establish the adverse drug reactions for a drug used for this indication, particularly when identifying very rare side effects.

1.8 Healthcare Professionals and Rare Diseases

General practitioners (GPs) are the healthcare professionals who have close contact with the population and are usually the first to identify peculiar patients that might have a rare disease (Zack P et al, 2006). In a study conducted by Knight and Senior in 2006, which involved children with RDs, the 73% of participating families considered their GP as responsible to coordinate the wide range of services their child required. The GPs awareness and knowledge about RDs is a distinct element for the timely and accurate

[16] Hoctor T. Repurposing Drugs for Rare Diseases: Collaboration is Key. Drug Discovery and Development [Internet]. 2016 [cited 2019 Mar 10];. Available from: https://www.dddmag.com/article/2016/11/repurposing-drugs-rare-diseases-collaboration-key

[17] Negrier C. Haemophilia B [Internet]. orpha.net. 2009 [cited 2019 Mar 8]. Available from: http://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=13896&Disease_Disease_Search_diseaseGroup=Haemophilia-B&Disease_Disease_Search_diseaseType=Pat&Disease(s)/group%20of%20diseases=Hemophilia-B&title=Hemophilia-B&search=Disease_Search_Simple

referral of patients to specialized hospitals and centres of expertise for accurate diagnosis and suitable treatment of RDs (Taruscio et al, 2007).

It is impossible for primary care physicians and medical specialists to have clinical exposure to all RDs due to their complexity, rarity and vastness. Most will not have the experience to recognise the wide clinical spectrum of every rare disease (Dudding-Byth, 2015).

Patients themselves often access the internet and look up their symptoms which may lead to their rare disease diagnosis. A vast majority of patients seek information about their rare disease. Web-based patient groups and social media groups allow individuals to contact other similarly affected individuals globally. It is the patient themselves that often successfully locate expert physicians and research centres. The customary patient-doctor encounter can be challenged due to the restricted medical expertise in conjunction with patient-sourced information. It is imperative for family doctors to empathise with their rare disease patients and respect their role in ongoing decisions regarding the management of the disease (Dudding-Byth, 2015). In a study conducted by Garrino et al in 2015, one of the aspects that emerged in the interaction between RD patient participants and health care participants, is that patients were increasingly well informed. RD patients participating in the study stated that they looked up information about the progression of the disease and the treatment available. The active participation of the RD patients proved to be helpful in building an effective strategy for treatment.

In an interview study conducted by Atherton in 1997, parents of children with rare disease, acknowledged general practitioners as their main source of help and information. A study conducted in 2018 by Boffin et al showed that delay in diagnosis by general practitioners was relatively low as 75% of the patients received a diagnosis within a year

after first suspicion of a rare disease. The GPs rated their knowledge as very good for only 29% of the RDs. Only 10 of the 64 participating GPs had used Orphanet. A study conducted in 2011 by Miteva et al showed that only one fifth of a sample population of GPs knew the correct definition of RDs (that of less than 5 in 10000).

In a study conducted by Carpenter et al in 2012, a questionnaire for rare disease vasculitis patients was developed to analyse their perception of pharmacists. In this study, participants consulted physicians and the Internet more than pharmacists for medication related information. 41.4% of the participants had used pharmacists for vasculitis medication information. Participants viewed pharmacists as less trustworthy sources of medication information than physicians and the Internet. Participants consulted physicians and/or the internet more than pharmacists for information about their medications which included adverse effects and efficacy of the drug.

In the study conducted by Garrino et al in 2015, RD patient and healthcare professionals were interviewed on their experience with RDs. Some of the interviewed healthcare professionals indicated the difficulty of speaking about RD due to the term being a general term which is based on an epidemiological criterion and that encompasses different pathologies which include broad spectrums of the respective disease.

1.9 Rare Disease Registries

Founded in 1948 by the United Nations, the World Health Organisation (WHO) strives to improve health worldwide.[18] The WHO defines a patient registry as "a file of documents containing uniform information about individual persons, collected in a

[18] World Health Organisation. The Global Guardian of Public Health [Internet]. Who.int 2016 May [cited 2019 April 20]. Available from: http://www.who.int/about/what-we-do/global-guardian-of-public-health.pdf?ua=1.

systematic and comprehensive way, in order to serve a pre-determined scientific, clinical or policy purpose." There are multiple types of registries including rare disease registries (RDR), cancer patient registries, pregnancy registries, and registries for medical devices. Planning a registry firstly requires the establishment of the registry's major purpose; what it is intended for, and the aims meant to be reached by its development. Other issues that should be kept in mind are the operation and management of the registry, authorised data access, scientific content, and ethics regarding patient data (Godard et al, 2003).

Classification of registries is in line with the objectives of the registries. Registries can be classified into three categories: public health registries, clinical registries and product registries. Based on geographic coverage, registries can be divided into population-based registries and non-population-based registries. The difference between the two registries is that population-based registries aim to register all cases in a geographically defined population while non-population-based registries are based on selected department and specific clinics where the population spread may not be specified.

"A registry should have one main general objective associated with specific secondary objectives." Objectives need to be straightforward to define the data to be collected, the patients to be registered, ethical regulations, and which analytical approached to use. Clear objective will ensure the efficacy of the registry and the fulfilment of the goal of the registry (Kodra Y et al 2018).

The registry design strategy involves the formulation of a research question and adopting a study design. Patients need to be then chosen for the study, and the registry planners need to decide if comparison groups will be set up. The data sources and the number of patients needed for the study need to be then established (Gliklich et al, 2014).

1.9.1 Rare Disease Registries in Europe

Orphanet is an online inventory which gathers information about RD and OD, with the aim to improve patients' access to good care, treatment, and fast diagnosis.[19] According to Orphanet, in Europe there are over 747 RDR (Kudra Y, 2018). Most RDR are disease-specific or include only a group of diseases. It is calculated that only 20% of RDs are covered by registration activities. Differences in RDRs may include the purpose of the RDR, disease rarities, possibilities of treatment, geographical coverage, target population, governance models, and funding sources. To overthrow this diversity of RDRs, existing RDRs need to make their data available to lighten the recruitment of patients in clinical trials, particularly for very RDs, to improve the validation of treatments for resembling diseases, and to formulate robust calculations of epidemiological indicators for registries that are population-based (Santoro M et al, 2015).

The first recognised database of RD was Orphanet was established in 1996 by the French National Institute of Health and Medical Research (INSERM) and the French Ministry of Health before becoming a Joint Action between European countries (Aymé et al, 2015). From then on, through the Research Framework and the Public Health Programmes, the EU has funded various projects to assemble EU networks of professionals in the field of RD to support RDR. In 2011, the EPIRARE project was funded to create a European Platform for RDR which was one of the strategic objectives supported by the EC with regards to RDR (Bianchi et al, 2013).

[19] Orphanet. About Orphanet [Internet]. Orpha.net. [cited 2019 Mar 10]. Available from: http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanet.php?lng=EN

1.9.2 Aspects of Rare Disease Registries

1. Role of Rare Disease Registries

The European Commission confirms the significance of registries as essential tools "for developing RD centred clinical research, enhancing patient care, and improving social, economic and quality-of-life outcomes" (Vittozzi et al, 2013).

RDR can be used to determine the natural history of a disease, including its "characteristics, management and outcomes with or without treatment". In RD of genetic origin, registries may be used to identify a genotype-phenotype correlation. The use of registries in the past was a means of assessing safety. The monitoring of adverse reactions for RDs is very challenging and the use of registers can be used to monitor side-effects particularly for off-label use of drugs which is a very common practice in RD patients (Aymé et al, 2011).

Studies can be conducted on data from RDR to establish prevalence and incidence of a disease. An ad hoc study can also be conducted for the same purpose. The results are often relevantly the same as a register. Quality of care assessments can be conducted using registries (Aymé et al, 2011). The WHO defines quality of care as "the extent to which health care services provided to individuals and patient populations improve desired health outcomes."[20] Registers can be compared to standards to identify discrepancies between health care outcomes and so find means of improvement.

RDR are now being recognised as a method of obtaining patient samples for research on RDs (Atherton, 1997). These registries serve as an inventory of patients with rare disease

[20] World Health Organisation. What is Quality of Care and why is it important? [Internet]. World Health Organization. [cited 2019 Mar 14]. Available from: http://www.who.int/maternal_child_adolescent/topics/quality-of-care/definition/en/

which is beneficial for their participation in clinical trials, epidemiological studies and for HTA to monitor the actual picture of access to treatments (Aymé et al, 2011).

2. Ethical issues in Developing Registries

The development and use of registries should be governed by ethics. Resnik (2015) describes ethics as "norms of conduct that distinguish between acceptable and unacceptable behaviour." The Belmont Report which was published after intense discussions at the Smithsonian Institution's Belmont Conference Centre after 1979 provides ethical principles and guidelines for the protection of human subjects when conducting clinical research. [21]According to the Belmont Report which outlines the fundamental guidelines of addressing ethical issues, there are three main tenants for the conduction of scientific research involving humans which is ethical. The Belmont Report describes these three principles as "respect for persons as autonomous agents (self-discrimination), beneficence (do good, no harm, protect from harm), and justice (fairness, equitable distribution of benefits, and burdens, equal treatment)." The basic ethical issues for registries circle around privacy of data and patient confidentiality, and data ownership and data access (Gliklich et al, 2014).

Informed consent is part of the common rule where persons should be well informed about the type of research that will be conducted, the condition for access and sharing of personal data, and the duration of storage. Individuals should give their consent on the creation of the registry, the use of registry data and the access to the registry data (Gliklich et al, 2014).

[21] Office for Human Research Protections. The Belmont Report. U.S Department of Human Health Services. {cited 2018 Mar 15]. Available from: https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/

3. Quality Assurance of Registries

Quality assurance of registries ascertains long-term sustainability and success of the rare disease registry (Posada et al, 2014). Registries must undergo quality assurance for collection of data, registry procedures and computerised systems. In a study conducted by Taruscio et al in 2013, 53.5% and 31.0% of data in registries came from paper or electronic formats, respectively. Of the data inputted, 43.2% of data was inputted directly by data providers. It was noted that downloading data from primary databases and online input from patients was not frequent (9.4% and 7.5% respectively). Several procedures were carried out to ensure data quality, in particular duplicate records control and data entry mistakes. Fifty percent of the RDRs showed that tests were done regularly, and quality indicators were used by only one-third of the registries (Taruscio et al, 2013).

4. Data Elements in a Rare Disease Registry

"A data element is a logical unit of data, which has a name, precise definition, and clear enumerated code values"[22]. The data elements (DEs) in a registry are dependent on the goal of the registry. Decreasing the amount of data collected has lower cost impacts, enhances the extent of fields that are completed and increases compliance of completing the data fields. Some registries fail in their original purposes due to the complexity of the data collected (Kodra et al, 2018).

According to Kodra et al, the following steps should be followed to determine the data elements used in a registry:

- The data needed for the purpose(s) of the registry

[22] Glossary Page - NINDS Common Data Elements [Internet]. Commondataelements.ninds.nih.gov. 2018 [cited 10 January 2019]. Available from: https://commondataelements.ninds.nih.gov/Glossary.aspx?term=Data+Element

- Any information models that are established that can be reused
- Determine the source of the data, whether from a primary or secondary source
- Determine what data can be extracted from other data, rather than being gathered separately
- Determine if data can be gathered and stored as part of routine clinical care
- Determine whether data can be used to assist clinical care

1.10 Current Situation in Malta

In Malta, considering limited funding patients face challenges in access to medicines. Some medicines might be centrally approved by the EMA but still not available in Malta. The Malta Medicines Authority (MMA) does not have an available list of Orphan Medicines accessible in Malta however patients can contact the MMA to ask for access of OD.

The Orphanet Report Series for Rare Disease Registries in Europe of 2016 identified 2 RD registries in Malta. A government RD register is also available which includes information from 'Congenital Anomalies Register', 'Cancer Registry', 'Treatment Abroad Registry', and 'Patient Registries'.[23]

[23]Government of Malta. Rare Diseases. Health.gov.mt [Internet]. [cited 2018 Mar 8]. Available from: https://health.gov.mt/en/dhir/Pages/Registries/Rare-diseases.aspx

Table 1. 6: Rare Disease Registries in Malta.

Adopted from: Aymé S, Kole A, Rodwell C. Rare Diseases Task Force Report on Patient registries the field of rare diseases: Overview of the issues surrounding the establishment, governance and financing of academic registries. June 2011.1-18. Available from: http://ec.europa.eu/health//sites/health/files/rare_diseases/docs/patient_registries_rev2011.pdf.

Malta – Two registries		
English Label of the Activity	Coverage	Affiliation
Malta Congenital Anomalies Registry (MCAR) – contributes to EUROCAT	National	Public
Maltese Cancer Registry – contributes to the RARECARE project	National	Public

In 2016, The Marigold Foundation which is a non-governmental organisation which offers support to patients from different causes, launched a support group for RD patients. The support group was called The National Alliance for Rare Diseases Support-Malta, also known as the Malta Alliance for Rare Diseases (MARD). The foundation is supported by the spouse of the Prime Minister of Malta, Michelle Muscat (2017). The alliance holds a patient registry which does not include all RD patients but only those

who registered voluntarily.[24] According to the alliance, there are around 25,000 RD patients in Malta suffering from an estimated 600 different RD.[25, 26]

There is currently no national plan or strategy for RDs in function in Malta (Rodwell, Aymé, 2014). A study conducted by Abbas et al in 2018, showed that there is a lack of guidelines and initiatives for RDs and OD support in Malta.

Table 1. 7: Summary of RDs and OD findings in Malta.

Adopted from: Abbas A, Vella Szijj J, Serracino Inglott A. Rare Diseases and Orphan Drug Availability in Malta. Presentation presented at; 2018; University of Malta.

RD PLAN	Not specific to Malta
CENTRE OF EXPERTISE ON RDs	No
RD REGISTERS	Four registers currently active
SCREENING AT BIRTH	No legislative mandate
GENETIC DATABASE	Malta BioBank (launched in 2017)
CLINICAL PRACTICE GUIDELINES ON RDs	No
RD EDUCATION	Annual RD colloquium
ORPHANET TEAM	No
RD PATIENT HELPLINES	No
RD INFORMATION CENTRE	No
RESEARCH FUNDS DEDICATED FOR RDs	No
OD POLICY	No
NGOs SUPPORTING RDs	Yes (Marigold foundation)

A pilot project to screen new-born babies for rare diseases was set to launch in March 2020. [27]

[24] National Alliance for Rare Diseases Support – Malta. About Us. Rarediseasesmalta.com. [Internet]. [cited 2019 Mar 9]. Available from: http://rarediseasesmalta.com/about-us/
[25] Cocks P. 25,000 Maltese citizens suffer from a rare disease. Malta Today. [Internet]. 2017 [cited 2019 Mar 9]. Available from: http://www.maltatoday.com.mt/lifestyle/health/75525/25000_maltese_citizens_suffer_from_a_rare_disease#.WPcujvl97IV
[26] Borg M. Marigold Foundation launches support group for rare disease sufferers. Malta Today. [Internet]. 2016 [cited 2019 Mar 9]. Available from:
[27] Calleja C. Pilot project to screen newborns for rare diseases. Times of Malta [Internet]. 2020 [cited 19 July 2020];. Available from: https://timesofmalta.com/articles/view/pilot-project-to-screen-newborns-for-rare-diseases.770060

1.11 Aims and Objectives

The aims of the study are:

- To put forward a new revised definition for rare diseases and orphan medicines
- To update the existing register for rare diseases by developing a new template
- To enhance the awareness of rare diseases in Malta by developing an information booklet to be made available to the general public.

The objectives of the study are:

- To disseminate two questionnaires to the general public and healthcare professionals respectively
- To extract a revised definition for ‘rare diseases’ and ‘orphan medicines’ from the results of the questionnaire for healthcare professionals
- To implement a new template for the rare disease registry belonging to The National Alliance for Rare Diseases Support Malta
- To develop an information leaflet for the general public and healthcare professionals

Chapter 2:

Methodology

2.1 Methodology Overview

The definition for rare diseases was revised, validated by the use of two questionnaires which were distributed to the general public and rare disease patients, and healthcare professionals. The questionnaires were validated by a panel of seven members. The existing register for rare diseases was updated by updating the template being used and implementing a new template which is recognised internationally. An information leaflet was developed, disseminated and validated to increase public awareness and to promote the use of the register.

2.2 Study Approvals

Prior to initiating this research, approval was obtained from the National Alliance for Rare Disease Support Malta (NARDSM) to have access to the registry belonging to the Alliance and have the approval of the Alliance's board to distribute the questionnaires to rare disease patients. Permission to access the NARDSM registry was obtained after a meeting with the NARDSM's secretary, the secretariat volunteer and the volunteer responsible for register upkeep. An approval letter was signed by the volunteer responsible for the register (Appendix 1).

An ethics proposal form was completed and together with the required approvals it was submitted to the University of Malta Research Ethics Committee (UREC). UREC approval for the project was granted (Appendix 2).

Validation panel participants were informed of the study through an information sheet and a consent form (Appendix 3).

Consent for questionnaire completion was granted by both the healthcare professionals and participants from the public. Healthcare professionals participating in the completion of the questionnaire who were recruited from pharmacies and medical practitioner clinics

gave their consent verbally. Healthcare professionals recruited online could give their consent by completing the questionnaire. Healthcare professionals were free to refuse to participate from completing the questionnaire. Participants from the general public were recruited online. Rare disease patients were recruited via the NARDSM. Consent was given by completing the questionnaire.

2.3 Validation of the Questionnaires

The two questionnaires were validated by a panel prior to dissemination (Appendix 4). The panel was comprised of two pharmacists: one community pharmacist and one medical representative, one specialist in family medicine, one basic specialist trainee in surgery, one volunteer from the National Alliance for Rare Diseases Support Malta and two lay persons. Questionnaires were analysed in terms of content, comprehensiveness, clarity and grammar. The panel was asked to rank statements about the layout and content of the questionnaires.

2.4 Study setting

The questionnaires were distributed in different pharmacies and clinics around different localities in Malta. Distribution was undertaken in all five districts of Malta. Around 4 pharmacies and/or clinics were randomly chosen from every district and healthcare professionals working at the pharmacy or clinic were asked to complete the questionnaire.

2.5 Inclusion Criteria

The inclusion criteria for all participants completing the questionnaire were: over 18 years old, both male and female gender. Additional inclusion criteria for rare disease patients recruited via the NARDSM were; having renewed their membership with NARDSM and having given their consent to participate in research.

2.6 Design and Structure of Data Collection

The two questionnaires were developed using Microsoft Office Word 2007. One questionnaire was developed for the public and rare disease patients (Appendix 5), and another questionnaire was designed for healthcare professionals (Appendix 6). A Maltese version of the questionnaire distributed to layman and rare disease patients was also developed.

A. Public Questionnaire

The questionnaire for the public and rare disease patients was divided into three sections comprised of sixteen questions:

Section A: Demographics. This section was comprised of three short-ended questions and one closed-ended question about gender, nationality, age and occupation.

Section B: Personal Experience and Knowledge of Rare Diseases. This section was comprised of nine closed-ended questions. Information about participants' experience (if any) and knowledge about rare diseases and orphan drugs was gathered including relations to rare disease patients, information about rare disease organisations, initiatives for rare diseases, and orphan medicines.

Section C: Individuals with rare diseases. This section was to be filled only by individuals with rare diseases. This section was comprised of three closed-ended questions targeting information about registration with NARDSM and the Malta Rare Disease Register, and the use of orphan drugs.

The questionnaires were distributed to lay persons online via a Google document shared on different social media platforms. Responses were recorded on Microsoft Excel 2007 and analysed via IBM SPSS Statistics 20.

Questionnaires were distributed to rare disease patients using a method with no interaction with the rare disease patients registered with NARDSM to respect the privacy of these patients. The following method was used: A volunteer at the NARDSM responsible for the NARDSM registry was contacted to determine the number of members registered with the Alliance. The volunteer was asked to allocate a number to every rare disease patient on the registry. The researcher used a random number generator to generate forty random numbers. The volunteer contacted the individuals chosen to complete the questionnaire. The volunteer either emailed the questionnaire to the participant or distributed a hard copy. If a patient declined the request to participate, another patient was chosen again using this method.

B. Healthcare Professionals Questionnaire

The questionnaire for healthcare professionals was divided into four sections:

Section A: Demographics. This section was comprised of three closed-ended questions about years of practice, nationality, occupation and specialisation.

Section B: Personal Experience and Knowledge. This section was comprised of sixteen closed-ended and four open-ended sub-questions. In this section, information about the participants' experience and knowledge was gathered. This included questions about patients with rare diseases, Orphanet, orphan drugs, the NARDSM, the Malta Rare Disease Register and learning outcomes.

Section C: Rare Diseases. Participants were presented with twelve descriptors for 'rare diseases' that were gathered from the literature review. The participants were asked to rank these descriptors according to the association and relevance to the concept of rare diseases. A Likert scale from 1 to 5 was used to rate these definitions; 1 labelled as "Least Relevant" and 5 labelled as "Most Relevant".

Section D: Orphan Drugs. In this section, the participants were presented with thirteen definitions for 'Orphan Drugs' that were gathered from the literature review. The participants were asked to rank these definitions according to the association and relevance to the concept of orphan drugs. A Likert scale from 1 to 5 was used to rate these definitions; 1 labelled as "Least Relevant" and 5 labelled as "Most Relevant".

Healthcare professionals participating in this study included community pharmacists, clinical pharmacists, industrial pharmacists, general practitioners and community nurses. Healthcare professionals participating in the questionnaire research were recruited by random and convenience sampling. Distribution of the questionnaire for healthcare professionals. Pharmacies and/or private clinics from every district in Malta (excluding Gozo) were visited and professionals working at the pharmacy or clinic (general practitioners, pharmacists, community nurses) were asked to complete the questionnaires.

The questionnaires were made available online via a Google document. The questionnaire was shared on the Facebook page 'Maltese Pharmacists and Pharmacy Students'. The responses were recorded on Microsoft Excel 2017 and analysed via IBM SPSS Statistics 20.

2.7 Analysis of Data

The statistical analysis of the data collected from both questionnaires included coding the data, descriptive statistics and other statistical analysis using IBM SPSS Statistics 20 and Microsoft Excel 2017. Frequency and statistics tests were carried out. Chi square correlation tests were carried out for both questionnaires to compare two categorical variables. The null hypothesis (H_0) was accepted if the p value exceeded the 0.05 level of significance and was rejected if the p value was less than 0.05.

H_0 = There is no significant correlation between the two variables

H_1 = There is a significant correlation between the two variables

a. Public Questionnaire

Descriptive statistics including percentages and frequencies were carried out for every question. Graphical representations of the results were developed on Microsoft Excel 2017 and IBM SPSS Statistics 20.

b. Healthcare Professionals Questionnaire

Descriptive statistics including percentages and frequencies were carried out for questions in Section A and B using Microsoft Excel 2017 and IBM SPSS Statistics 20. Mean ratings for the questions in Section C and D were calculated in IBM SPSS Statistics 20. Graphical representations of the results were developed on Microsoft Excel 2017. The average ratings for the descriptors of rare diseases and orphan medicines in Section C and D respectively were calculated by taking an average of the ratings for each descriptor. The descriptors with the highest average rating were considered the most popular amongst the healthcare professionals.

2.8 Information Leaflet

A meeting was held with NARDSM to discuss the material to be included in the information leaflet. The leaflet from the Rare Revolution Magazine entitled "Top 10 Tips for Rare Healthcare Providers"[28] was used as a guide to design the new information leaflet. Information in the leaflet included information about the European reference networks, orphan drugs available in Malta, the NARDSM, and the Malta Rare Disease Register. Three information leaflets were developed (Appendix 7) and validated by a focus group comprising of one general practitioner, one physiotherapist, two community pharmacists, two lay persons and one volunteer for the NARDSM.

2.9 Registry Template

A meeting was held with NARDSM to discuss the registry template. The existing registry data set template was analysed in terms of the data elements. Three data sets by European organisations for rare disease registries were analysed. These data sets included The Platform Set of Common Data Elements by Epirare[29], The Set of Common Data Elements for Rare Diseases Registration by the European Commission[30], The Data Set for Rare Disease Patient Registries Recommended for European Cooperation by EUCERD.[31]

A registry template was developed on Microsoft Excel 2017 by combining different elements from the three data sets used (Appendix 8). The registry template was validated

[28]Top 10 Tips for Rare Healthcare Providers. Rare Revolution Magazine [Internet]. 2020 [cited 2020 Jun 15];(006):62. Available from: https://edition.pagesuite-professional.co.uk/html5/reader/production/default.aspx?pubname=&edid=ee0a3414-bcb1-4cfc-a774-d6c8ccc3d299

[29] Taruscio D, Mollo E, Gainotti S, Posada de la Paz M, Bianchi F, Vittozzi L. The EPIRARE proposal of a set of indicators and common data elements for the European platform for rare disease registration. Archives of Public Health. 2014;72(1).

[30] European Commission Joint Research Centre. EU RD Platform CDS [Internet]. 2017 [cited 2020 Jun 15]. Available from: https://eu-rd-platform.jrc.ec.europa.eu/sites/default/files/CDS/EU_RD_Platform_CDS_Final.pdf

[31] EUCERD Joint Action WP8. Minimum data set for rare disease registries [Internet]. 2015 p. 13-17. [cited 2020 Jul 17]. Available from: http://www.eucerd.eu/wp-content/uploads/2015/03/WP8_Registries_MDS.pdf

by a focus group comprising of one general practitioner, one physiotherapist, two community pharmacists, two lay persons and one volunteer for the NARDSM. An extra section was added to the registry to enable the volunteers of the National Alliance for Rare Diseases Support Malta to register the patients with the organisation and manage their membership.

Chapter 3:

Results

3.1 Results Overview

Two hundred and twenty-eight people completed the questionnaire for the public. Out of the 228 respondents, 27 respondents were rare disease patents. Seventy-three people completed the questionnaires for the healthcare professionals.

3.2 Public Questionnaire

Section A: Demographics

The 228 respondents' ages ranged from 18 to 77 years. One hundred and eighty-three respondents were female while 45 respondents were male. Two hundred and twenty-one respondents were Maltese while 8 respondents were non-Maltese nationals.

Section B: Knowledge and Experience

Thirty-seven percent (n=85) of respondents knew or were related to someone with a rare disease. Sixty-three percent (n=143) of respondents were aware of organisations for rare disease patients while 28% (n=64) respondents were aware of the Malta Rare Disease Register. A Chi square correlation test was carried out to see if there was a correlation between age groups and the awareness on rare disease organisations.

The results of the Chi Square test are summarised in Figure 3.1.

Since the p-value of the Chi-square test is greater than 0.05 (0.359), we accept H_0 were there is no correlation between age groups and awareness of rare disease organisations.

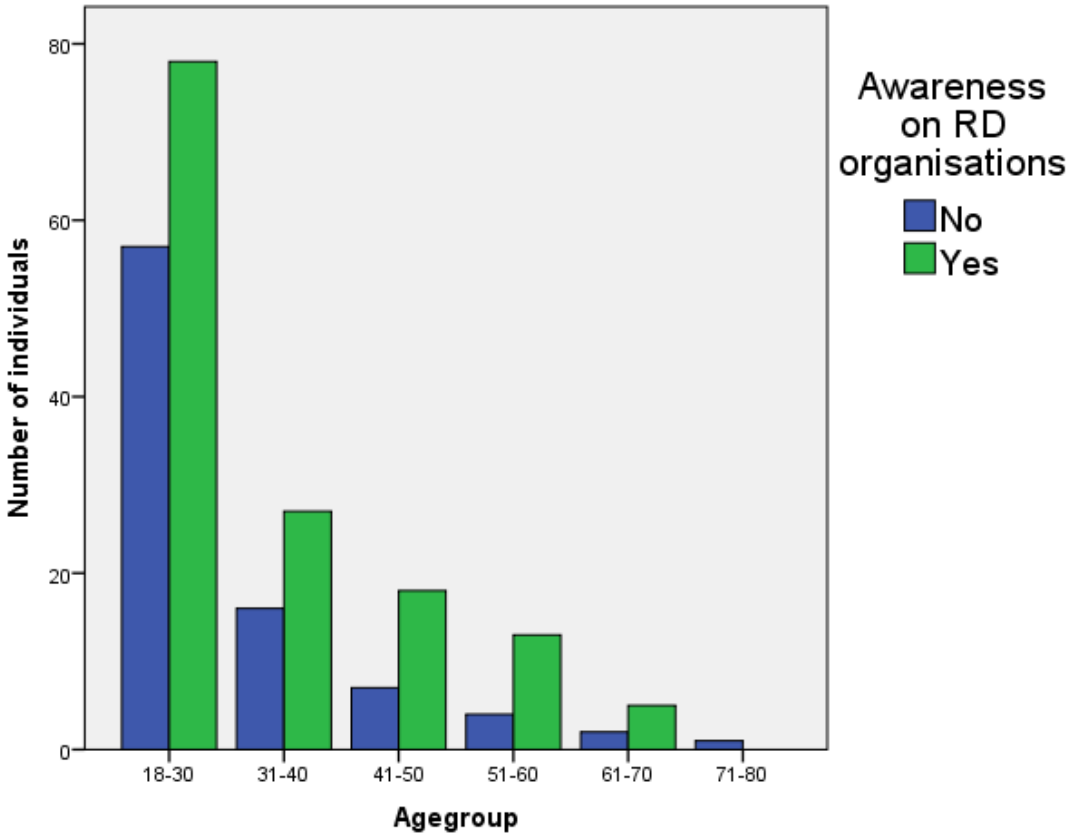


Figure 3.1: Awareness on RD organisations vs Age groups (n=228)

Figure 3. 1: Awareness on RD organisations vs Age groups (n=228)

Forty percent (n=92) of respondents had heard of governmental initiatives for rare diseases. When asked whether they wished to see orphan medicines being included in the Pharmacy of Your Choice (POYC) scheme, 98% (n=223) of the respondents agreed that they should be included. Ninety-eight percent (n=223) of the respondents wished to see more awareness being made on rare diseases while 95% (n=212) of the respondents were interested in learning more about rare diseases.

Rare Disease Patients

Twelve percent (n=27) respondents were rare diseases patients or carers of children with rare diseases. Seventy percent (n=19) of the respondents were female while 30% (n=8) of the respondents were male. The mean age was 39.51 years. The ages of the rare disease patients varied as shown in Figure 3.2.

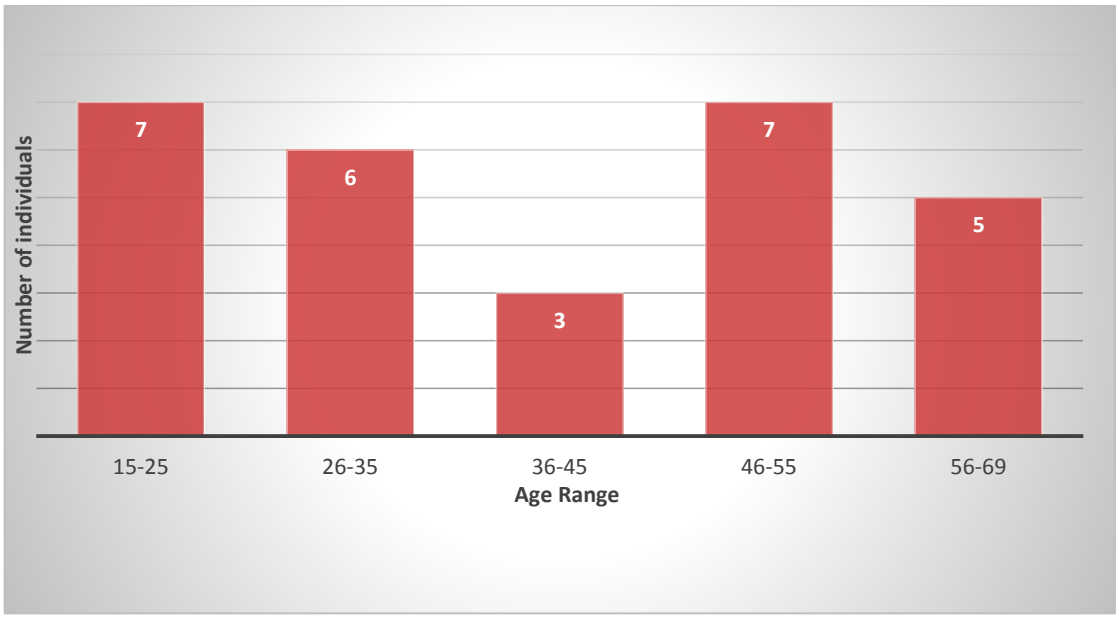


Figure 3. 2: Age range of rare disease patients (n=27)

Out of the 27 rare disease patients, 12 patients were registered with NARDSM, 1 patient was registered with the Malta Rare Disease Register and 2 patients with the Malta Rare Disease Register and NARDSM as shown in Figure 3.3.

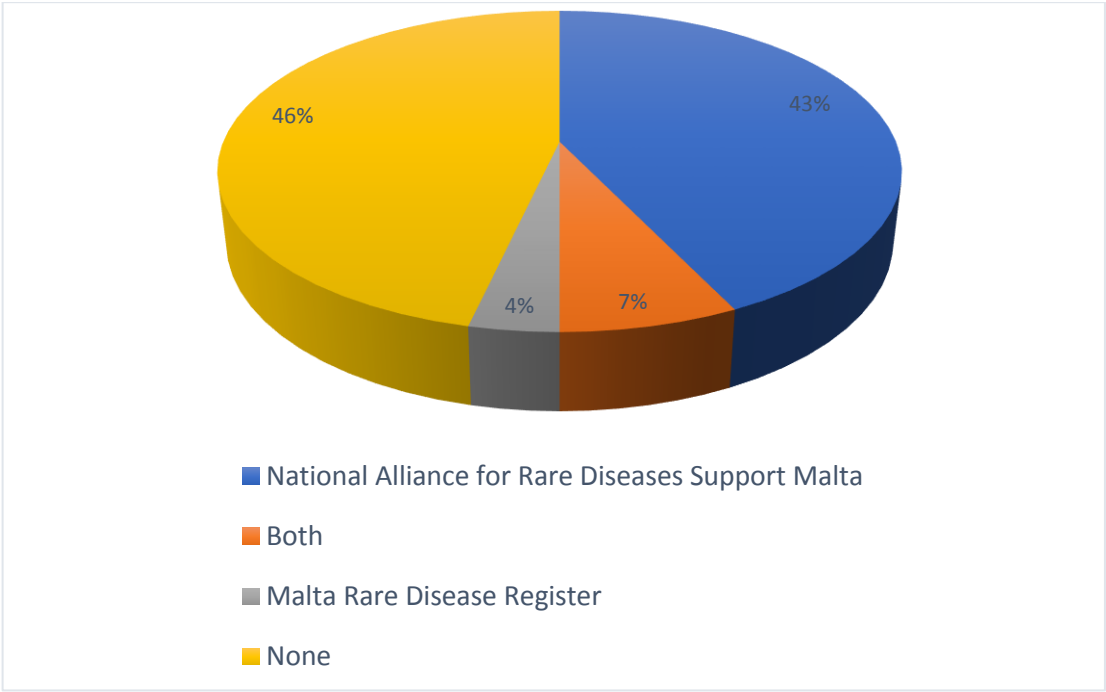


Figure 3. 3: Where are patients registered? (n=15)

Registered patients had heard of NARDSM and/or the Malta rare disease register through different sources such as newspapers articles, television programmes…etc (n=3), social media (n=2), consultant, doctor or pharmacist (n=1), word of mouth (n=2), and other means (n=3). Patients that were not registered with either of the entities, where asked for the reason on why they were not registered as shown in Figure 3.4.

Figure 3. 4: Why are patients not registered? (n=8)

Fifteen percent (n=4) patients had used an orphan drug, while 19% (n=5) patients had encountered problems while trying to obtain an orphan drug. These problems included lack of availability (n=1), lack of information(n=1), medicine was used for a different indication and not available for a rare disease (n=1) and price of the medicine (n=1).

3.3 Healthcare Professionals Questionnaire

Section A: Demographics

Out of the 73 healthcare professionals (HCPs) who responded the questionnaire for HCPs, 85% (n=62) were pharmacists, 11% (n=8) were general practitioners and 4% (n=3) were community nurses. The respondents' years of practice varied from 1 to 36 years.

Section B: Knowledge and Experience

Fifty-five percent (n=40) of the respondents had diagnosed, encountered or examined a rare disease patient at a certain point in their career while 33% (n=24) respondents had had a rare disease patient under their care at a certain point in the career. A Chi square test was carried out to determine if there was any correlation between the years of experience of the healthcare professionals and having encountered a patient during their career so far.

The results of the Chi square tests are summarised in Figure 3.5.

Since the Chi-square value is 0.402 which is more than 0.05, we accept H_0 where there is no correlation between the years of experience and having encountered a patient or not.

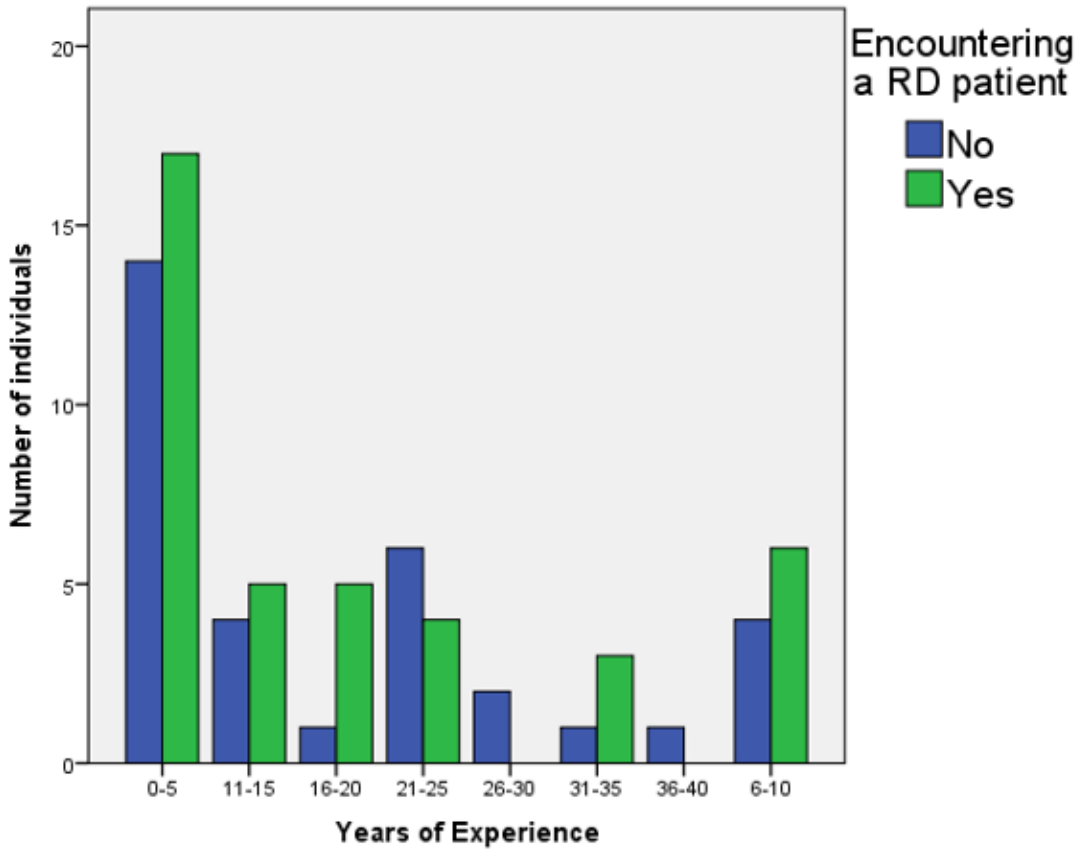


Figure 3. 5: Encountering a RD patient vs Years of Experience (n=73)

When asked about Orphanet, 21% (n=15) of the respondents had heard about Orphanet while 14 respondents knew where to access Orphanet. Only 3% (n=2) respondents had seen or used the ORPHA number system to diagnose a patient. Sixty-four percent (n=47) respondents agreed that they would like to see a section for ORPHA numbers being added to the admissions form used in hospital. A Chi square test was carried out to establish if there was any correlation between having heard of Orphanet and wishing to see the addition of ORPHA numbers to hospital admission forms.

Since the Chi-square value is 0.108 which is more than 0.05, we accept H_0 where there is no correlation between being aware about Orphanet and wishing to see the addition of ORPHA numbers to hospital admission forms.

Reasons on why ORPHA numbers should be included, easier to find information, traceability of patient history, raising more awareness and harmonisation of hospital admissions as shown in Figure 3.6.

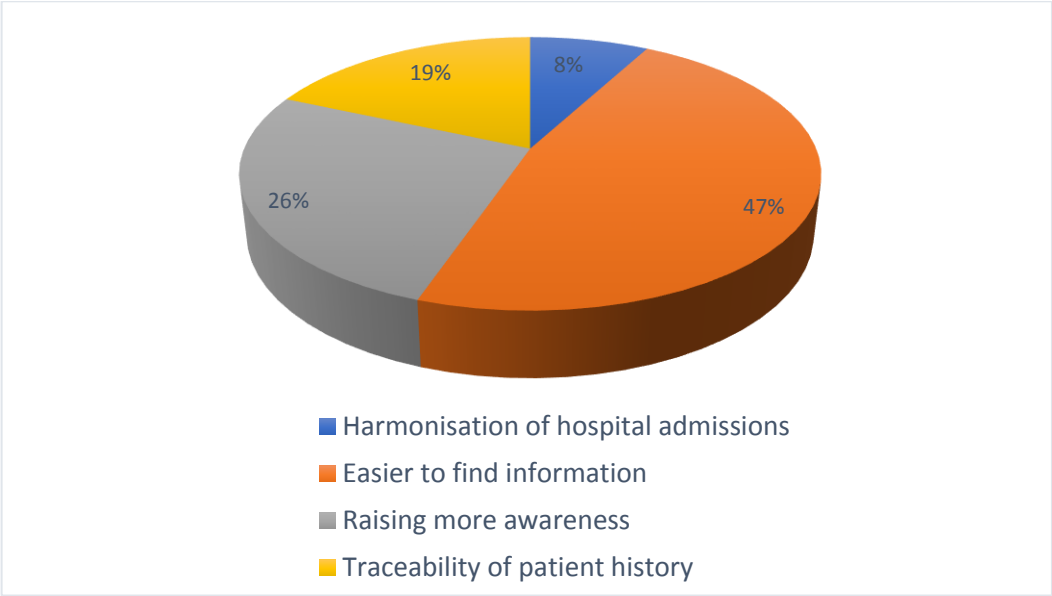


Figure 3. 6: Reasons why ORPHA numbers should be added to hospital admission forms

Thirty-three percent (n=23) of the respondents had dispensed, ordered, administered or prescribed, or tried to dispense, order, administer or prescribe an orphan drug. The respondents had obtained the drug from POYC through named patient basis, ordered through a specific agent, from the pharmacy, via a special order from Mater Dei Hospital or ordered through the Malta Community Chest Fund as shown in Figure 3.7.

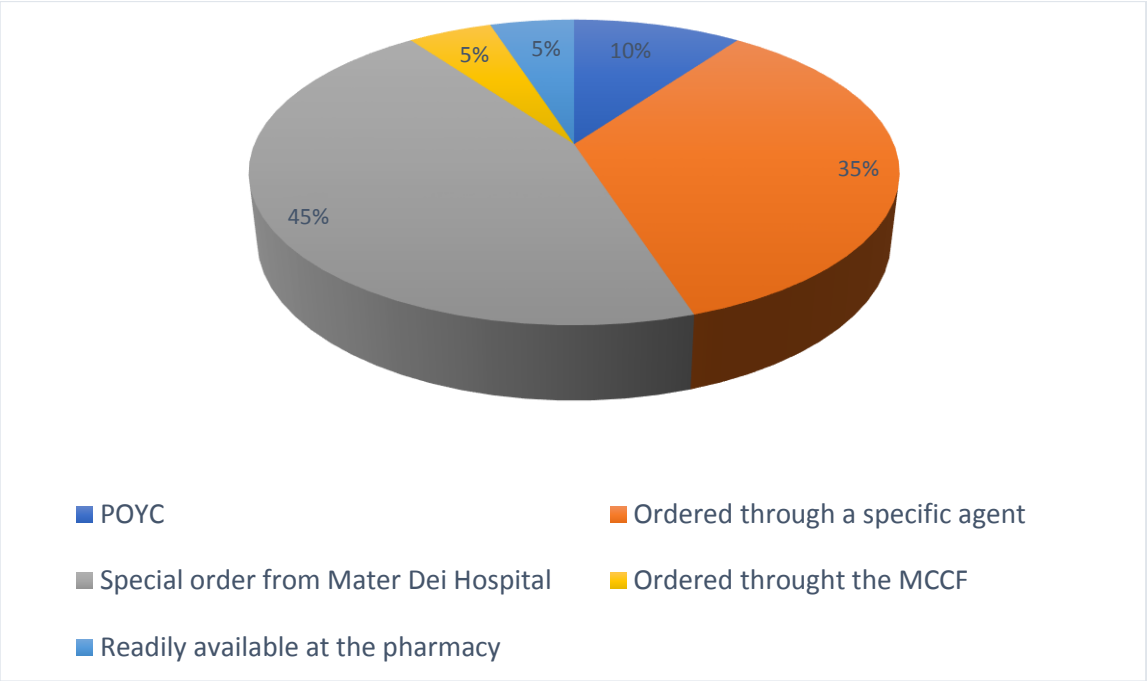


Figure 3. 7: Obtaining an orphan drug for a patient (n=20)

A Chi square test was carried out to establish if there was any correlation between having dispensed an orphan drug and the years of practice.

Since the Chi-square value is 0.573 which is more than 0.05, we accept H_0 where there is no correlation between being aware about dispensing an orphan drug and the years of experience.

Twenty-seven percent (n=20) of the respondents had encountered various problems while trying to obtain an orphan drug for patients (Figure 3.8).

Figure 3. 8: Problems encountered by healthcare professionals while accessing an orphan drug (n=20)

When asked if common drugs used for rare diseases should be also listed as 'orphan drugs'. 22% (n=16) of the respondents stated that they should be considered 'orphan drugs. Reasons on why common drugs used for rare diseases should be also listed as 'orphan drugs' included easier to access information and if these drugs are used in rare diseases therefore, they can be considered an 'orphan drug'.

Thirty-two percent (n=23) respondents agreed that common drugs (example: sildenafil used for erectile dysfunction and pulmonary arterial hypertension (RD)) used for rare diseases should also benefit from incentives (example: 10-year exclusivity period) like orphan drugs indicated exclusively for rare diseases do. Reasons on why common drugs used for rare diseases should benefit from incentives included that if these drugs are used in rare diseases therefore they can be considered an 'orphan drug', to encourage research on rare diseases and to encourage incentives on drug repurposing research. Ninety-seven percent (n=71) of the respondents agreed that an Orphan Drug Compendium of orphan drugs available in Malta should be compiled. When asked if they had heard about the

National Alliance for Rare Diseases Support Malta (NARDSM), 59% (n=43) of the respondents said yes. When asked if they were aware of the Malta Rare Disease Register, 32% (n=23) were aware of the Malta Rare Disease Register. Seven percent (n=5) of the respondents had registered or helped a patient register to the Malta Rare Disease Register. Ninety-nine percent (n=72) of the respondents agree that information sessions about orphan drugs and rare diseases should be provided to professionals and health care workers.

Section C: Rare Diseases

The respondents were asked to choose the definition which they thought was best to describe a rare disease. Seventy-eight percent (n=56) of the respondents recognised the definition for rare diseases as 'A disease that affects 1 in 2000 patients in the EU' as shown in Figure 3.9.

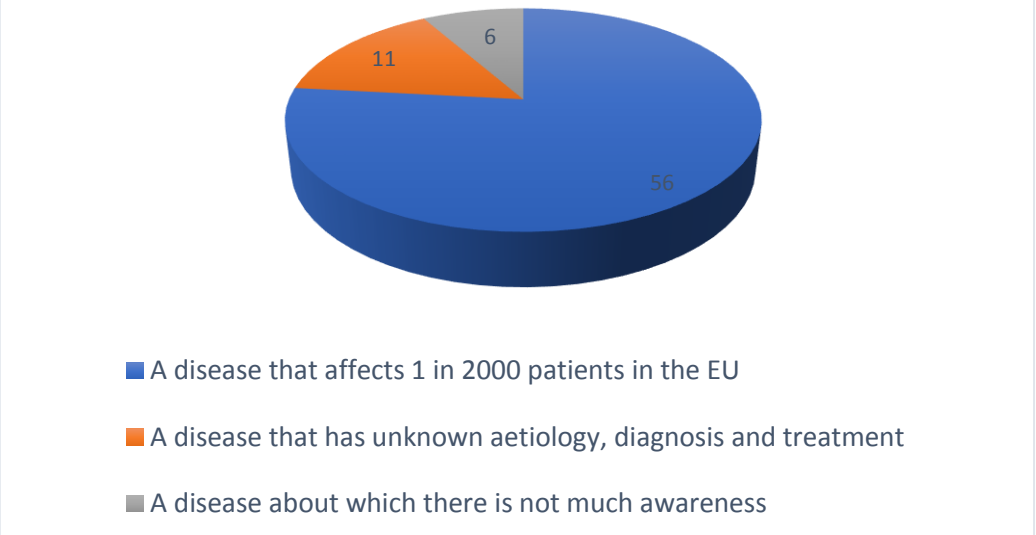


Figure 3. 9: The definition of a 'rare disease' as defined by healthcare professionals (n=73)

A Chi squared correlation test was carried out to determine if there is a correlation between the choice of the definition for rare diseases and having encountered a patient or not.

The results of the Chi square test are summarised in Figure 3.10.

Since the p-value is 0.276 which is greater than 0.05, we assume the H1 hypothesis where there is a correlation between the definition for a rare disease and having encountered a rare disease patient or not.

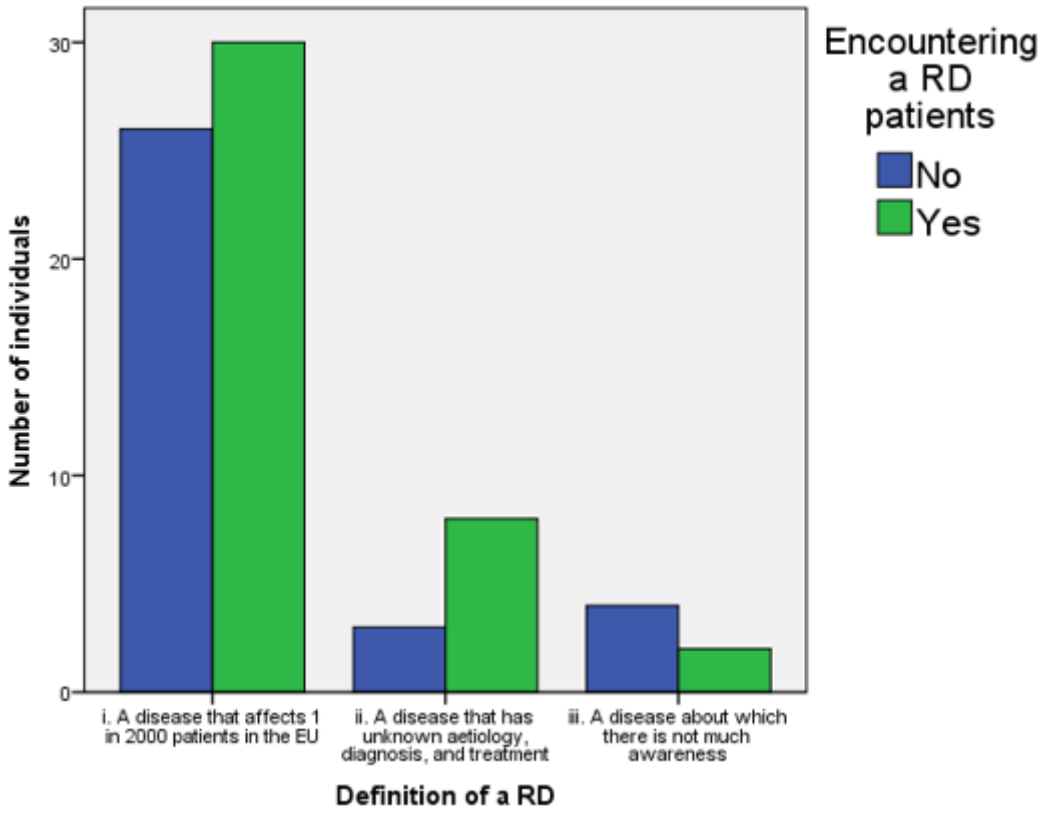


Figure 3. 10: Definition of a RD vs Encountering a RD patient (n=73)

The results for the description ratings for rare diseases are shown in Table 3.7. The three descriptors for a rare disease obtaining the highest mean rating score from the 73 HCPs were:

1.“presents a major psychological burden” – 4.12

2.“a disease with an incidence of 0.65-1%”– 3.93

3. “chronically debilitating” – 3.85

Table 3. 1: Rare Disease Descriptions Ratings

Descriptor	Average Rating
presents a major psychological burden	4.12
a disease with an incidence of 0.65–1‰	3.93
has no satisfactory method of treatment	3.77
has no satisfactory method of prevention	3.73
presents a major financial burden	3.71
chronically debilitating	3.65
seriously debilitating	3.64
is a disease of unknown aetiology	3.59
has no satisfactory method of diagnosis	3.52
life-threatening	3.29
one for which there is no reasonable expectation that the cost of developing and making available a drug for such disease or condition will be recovered from sales	3.27
has a genetic origin	3.21

Section D: Orphan Drugs

The results for the description ratings for rare diseases are shown in Table 3.8. The descriptors for an orphan drug obtaining the highest mean rating score from the 73 HCPs were:

1. “drugs used for diseases for which there is no possible alternative treatment” – 4.12

2. “intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition” – 4.10

3. “medicinal products with a significant benefit for those affected by the condition”- 4.0

Table 3. 2: Orphan Drugs Descriptions Rating

Descriptors	Average rating
drugs used for diseases for which there is no possible alternative treatment	4.12
intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition	4.10

medicinal products with a significant benefit for those affected by the condition	4.08
drugs for human use	4.01
drugs used for eradicated diseases	3.82
drugs indicated exclusively for a rare disease	3.80
medicinal products which have been identified by any doctor or dentist as an appropriate and essential remedy with no effective substitute for the treatment of a rare disease	3.67
drugs used for diseases which claim to be incurable	3.62
drugs that will not generate enough profit to cover the expenses of investment, without any incentives.	3.51
not commercially viable when used in the patient population they are indicated for	3.44
include common drugs that are also used for rare diseases (example: sildenafil used for erectile dysfunction used in also in pulmonary arterial hypertension)	3.29
drugs whose efficacy and expected safety must be excellent in comparison with other available drugs	3.26
drugs used in tropical diseases	2.26

3.4 Information Leaflets

Three information leaflets were developed and validated. The results of the validation by the focus group are included in Figure 3.11- 3.15. Results include validation for the background, font, colour scheme, overall presentation and sequence of information.

A likert scale was used to rate the validity of the information leaflet; 1 labelled as "Not Valid" and 5 as "Very Valid". 3 panel members gave the information in the leaflet a rating of "4" on the likert scale while 4 panel members gave the information in the leaflet a rating of "5" on the likert scale.

The proposed information leaflet that received the highest ratings from all the questions asked in the validation form was Proposed Information Leaflet 3.

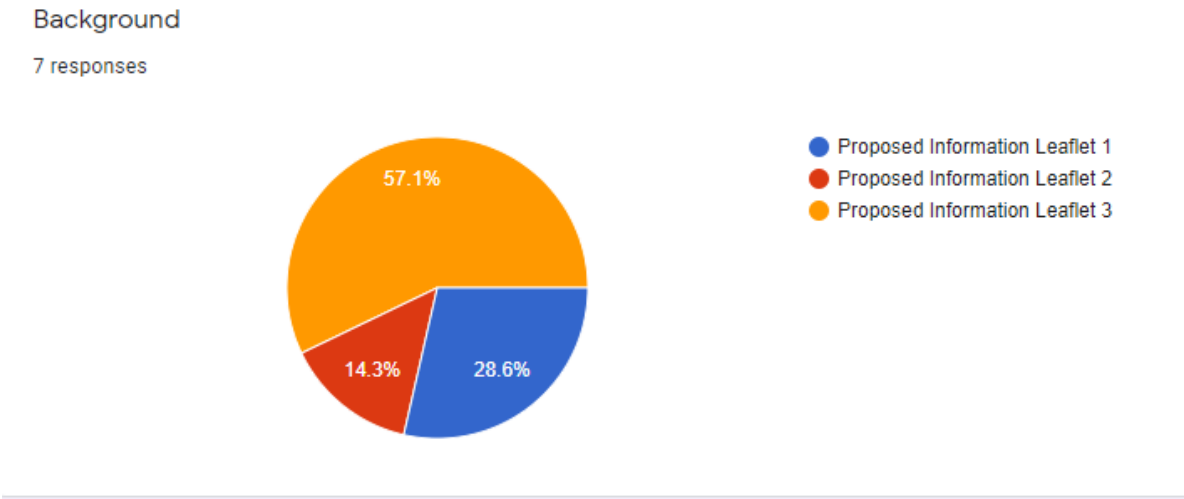


Figure 3. 11: Validation of Information Leaflet – Background (n=7)

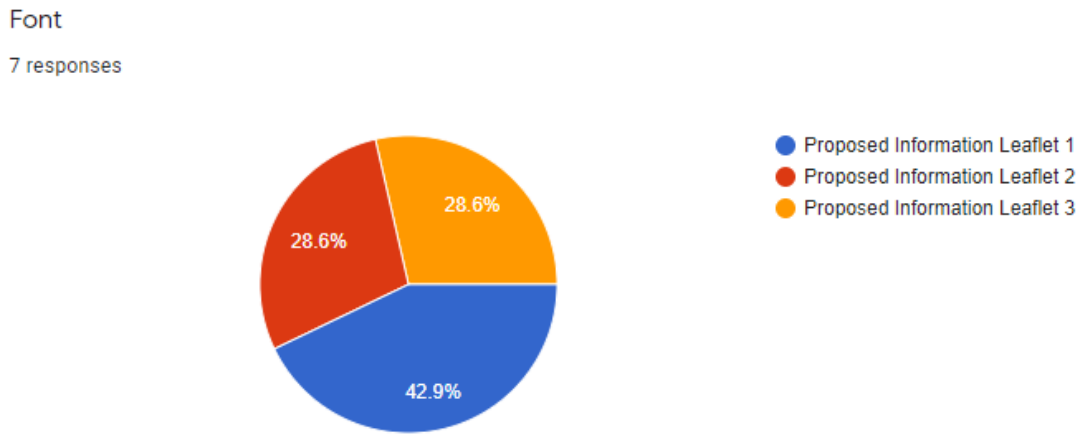


Figure 3. 12: Validation of Information Leaflet – Font (n=7)

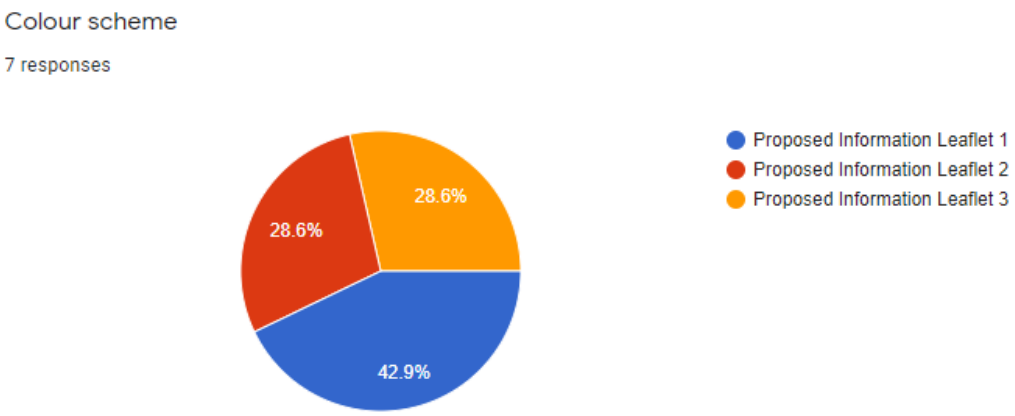


Figure 3. 13: Validation of Information Leaflet – Colour scheme (n=7)

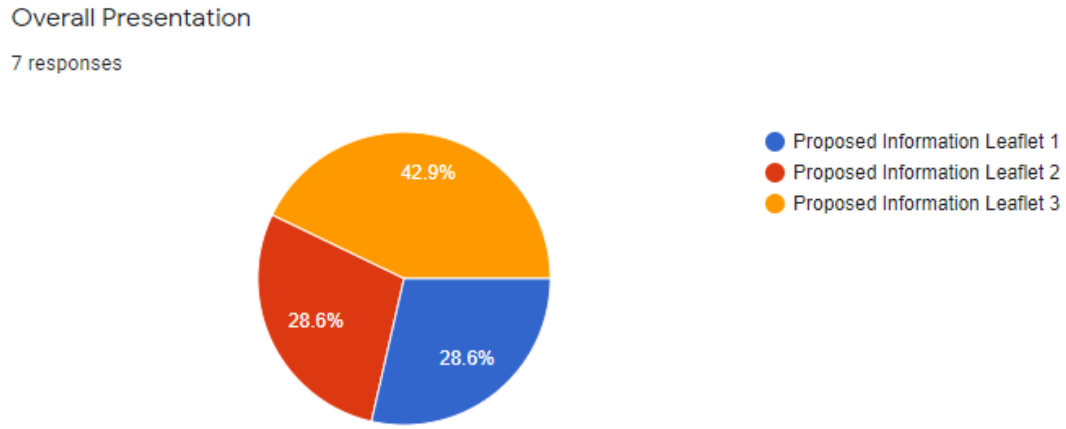


Figure 3. 14: Validation of Information Leaflet – Overall Presentation (n=7)

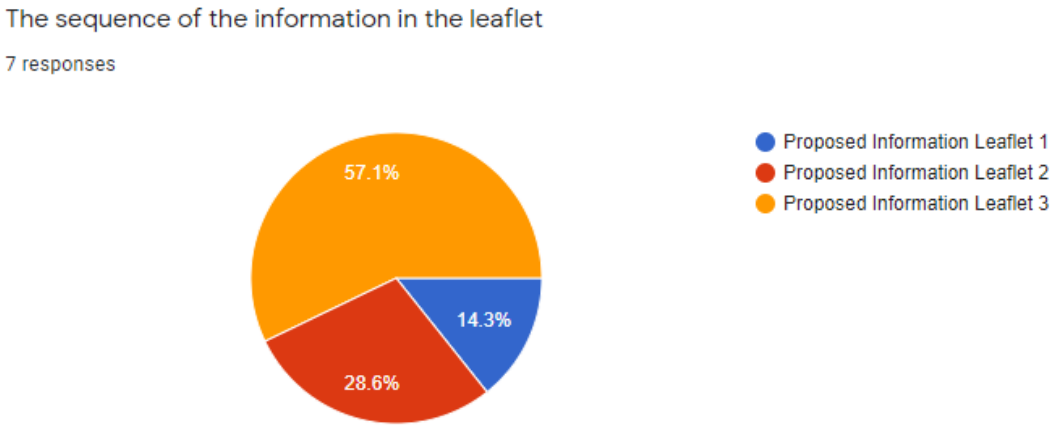


Figure 3. 15: Validation of Information Leaflet – Sequence of information (n=7)

3.5 Registry Template

Data elements included in the Rare Disease Registry template are Patient Identifier, Surname, Name, Date of Birth, Sex, Patient status, Nationality, Country of Residence, Age at Onset, Age at Diagnosis, Diagnosis of Rare Disease, ORPHA code, Generic Diagnosis, Treatment, Contact for Research Purposes, and Biological Sample.

The registry template was validated and adapted according to the validation results. The definition of a “rare disease” was added to the registry template as suggested by two of the validation panel members.

Chapter 4

Discussion

This study aimed to achieve a better perception on the situation on rare diseases and orphan medicines as regarded by the public, rare disease patients and healthcare professionals. Having identified the problems faced by these target populations, an information leaflet was developed to better target the hurdles faced by these populations. The registry template was updated to concur with European registries and to provide a more professional registration template to the National Alliance for Rare Diseases Support Malta (NARDSM).

4.1 Characteristics of the Public

The results of the study are related to Maltese characteristics such as genetics, awareness, accessibility to treatment and policies. Thirty seven percent (n=85) of the respondents knew or were related to someone with a rare disease while 12% (n=27) of the respondents were rare disease patients. These results indicate that although a rare disease by itself may be rare, collectively they are significantly numerous. In Malta, there are around 25,000-30,000 rare disease patients.[32] As 80% of rare diseases are of a genetic origin (Quinn et al, 2020), and Malta is densely populated, inbreeding may unintentionally occur, and chances of developing certain genetically inherited rare diseases become higher. As explained by Professor Alex Felice in an interview in 2016 with Think Magazine, there is a high disparity of particular mutations that are associated with some rare diseases in the Maltese population and include gangliosidosis and blood disorders such as thalassaemia.[33]

[32] 1. Calleja C. Pilot project to screen newborns for rare diseases. Times of Malta [Internet]. 2020 [cited 2020 Jul 16]; Available from: https://timesofmalta.com/articles/view/pilot-project-to-screen-newborns-for-rare-diseases.770060

[33] Wilcockson S. The Hidden History of the Maltese Genome. Think Magazine [Internet]. 2016 [cited 2020 Jul 27];(16):19. Available from: https://www.um.edu.mt/think/the-hidden-history-of-the-maltese-genome/?fbclid=IwAR19sUAqtYuIUoDcsf_2Vvd9U0YxSZrctYawDNTFdDCb8zQLtMQKbvIAcZI

A recent study conducted by Nguengang Wakap et al in 2019, showed that around 3.5-5.9% of the population in the world are suffering from a rare disease. This percentage translates to around 18-30 million individuals in the EU and 263-440 million individuals worldwide, which are suffering from a rare disease at any point in time. The chances of encountering a rare disease patient at any point in one's life are not so rare.

The results from the public questionnaire showed that 62.7% (n=143) of the public was aware about rare disease organisations. The percentage for the healthcare professionals was slightly lower at 59%. It may be postulated that the low percentage for healthcare professionals compared to the public, is due to the fact that the public comes across advertisements on television and social media about rare disease organisations more than healthcare professionals do. A recent initiative by the NARDSM, where the logo and contact information of the NARDSM is printed on Pharmacy Of Your Choice (POYC) bags used to give out medications under the Schedule V of the Social Security Act, may enhance the awareness of both the public and healthcare professionals especially pharmacists that dispense these medications.[34] A high percentage of the respondents wished to see orphan drugs being added to the Pharmacy of Your Choice (POYC) scheme (98%, n=223). Currently, there are some orphan drugs and common drugs used for rare diseases available by the Schedule V on a named patient basis.[2] The Schedule V of the Social Security Act has been amended to include clusters of diseases, so that rare disease patients can access treatment even though the disease they suffer from may not be included in the Act (European Commission, 2015).

[34] Sant Fournier M. Pharmacy support of patients with rare disease. Presentation presented at; 2018; Mater Dei Hospital. Available from: https://www.um.edu.mt/__data/assets/pdf_file/0010/348274/MsMASantFournier.pdf

Malta still lacks rare disease policies, rare disease information centres and reimbursement plans for orphan drugs (Abbas et al, 2018). A study conducted in 2019 by Stawowczyk et al, assessed the reimbursement status for 163 orphan drugs in 7 European countries. 65% of the analysed drugs were reimbursed. Malta does not yet have a reimbursement program in place for orphan drugs. In 2015, the State of Play report by the European Commission showed that Compassionate use programmes and named patient supply are available in Malta. For some years under a bilateral agreement with the UK, Malta has been providing schemes for treatment abroad for patients needing tertiary-level healthcare, including treatment for rare diseases patients.

Rare disease policies and initiatives in Malta have been boosted in recent years especially after the Maltese Presidency 2017 MMA-EURORDIS-COMP-IMI conference held in Malta where rare disease stakeholders, organisations and experts met to discuss the development of medicinal products for rare diseases.

4.2 The experience of rare disease patients

Out of the 27 rare disease patients, 12 patients were registered with NARDSM, 1 patient was registered with the Malta Rare Disease Register and 2 patients registered with both the Malta Rare Disease Register and NARDSM. Registration with an organisation and a rare disease registry is essential for research purposes. The lack of registrations to either entities was shown to be mainly due to the lack of awareness about either entity. Another reason might be that healthcare professionals are not aware of NARDSM and the Malta Rare Disease Register and so they cannot refer to their patients to get registered. This is confirmed by the fact that only 32% (n=23) of healthcare professionals had heard about the Malta Rare Disease Register and only 7% (n=5) of healthcare professionals had helped a patient register to the Malta Rare Disease Register. The printing of the information and logo of the NARDSM on POYC bags may aid in creating more

awareness on the registration of rare disease patients with rare disease organisations. Up until July 2020, the Malta Rare Disease Register has 4195 registered cases of rare disease patients. [35] This means that only 14%-16.8% of rare disease patients in Malta are registered in the Malta Rare Disease Registry when taking the estimation of 25,000-30,000 patients locally.

Five of the 27 rare disease patients had encountered problems while trying to access orphan drugs (18.5%). The three reasons for problematic access were lack of information, lack of availability and the price of the medicines. The main problem encountered was lack of availability, followed by the price of the medication. Comparing these results to healthcare professionals, 20 of 23 healthcare professionals had also encountered problems while trying to obtain an orphan drug for patients (87%). The main problem encountered was lack of availability, followed by the price of the medication. Malta does not have a compendium for orphan drugs available provides another hurdle for both healthcare professionals and rare disease patients to know what is available. Seventy-one of the 73 respondents agreed that an Orphan Drug Compendium should be compiled for orphan drugs available in Malta. Like other countries, rare diseases and orphan medicines are prioritised less due to their rarity and in the case of orphan medicines, the limited revenue they generate. This discourages stakeholders from giving attention and investing in rare diseases and orphan medicines, and instead opt to tackle issues experienced by greater masses.

There are no established guidelines for procuring orphan drugs for rare diseases for patients in Malta (Abbas et al, 2018). A study by Bourdoncle published in 2019, stated that France has an established structure for procuring and reimbursing orphan medicines.

[35] Agius F. Rare Disease Registry Numbers. 2020.

After a marketing authorisation for an orphan drug is obtained, reimbursement determinations are taken by the French National Authority for Health (HAS). A health technology assessment is carried out with mandatory criteria including clinical benefit and clinical added value. Drug access may be limited by restrictions for prescribing and/or dispensing for safety reasons. France has three routes for accessing orphan drugs for rare disease patients; from community pharmacies, from hospital pharmacies to inpatients and from hospital pharmacies to outpatients (a process known as "retrocession" in France). The National Plans for Rare Diseases is responsible for ensuring equal access to diagnosis and care throughout France. So far, Malta has not yet established a national plan for rare diseases. The funding mechanisms and reimbursement rates of a drug alternate depending on the drug access route and any opinions of the HAS.

4.3 Characteristics of Healthcare Professionals

Fifty-five percent (n=40) of healthcare professionals claimed that they had diagnosed, encountered or examined a rare disease patient at a certain point in their career (55.5%). The Chi square correlation test carried out also showed that there is no relationship between the years of practice and having encountered a patient or not. This results further shows that healthcare professionals may come across a rare disease patient at any point of their career. This percentage is very close to the percentage obtained in a study conducted by Vandeborne et al in 2019 in Belgium where 52% of general practitioners had suspected that a patient was suffering from a rare disease. This result further confirms that the chances of dealing with rare disease patients will occur more frequently than assumed.

Fifteen respondents had heard of Orphanet (20.5%). A study conducted by Vandeborne et al in 2019 in Belgium included interviews on rare disease experts. Most experts believed that only specialists, but not general specialists and general practitioners are

aware of Orphanet. These results highlight the need for better training and education of healthcare professionals on rare diseases and orphan drugs to achieve better holistic care for patients. Healthcare professionals need to be offered training on where to access information. A study conducted in Spain in 2019 by Ramalle-Gómara et al also conveyed that the challenges faced by physicians when dealing with rare disease patient were mainly due to lack of diagnostic guidelines, and lack of knowledge on where to refer patients.

Forty-seven respondents (64%) wished to see ORPHA numbers being added to the admissions form used in hospital. Reasons on why ORPHA numbers should be included, include the ease of finding information, traceability of patient history, raising more awareness, harmonisation of hospital admissions. This result may signify that current admission system at place at the national hospital might not be adequate and may be incomplete. Medical records are nowadays made available on "myHealth" which is an online portal through which patients and their can access their medical records. The addition to ORPHA numbers to hospital admission forms and subsequently patient medical records, may also increase general practitioners' awareness on rare diseases.

No correlation was found through the Chi square test between being aware of Orphanet and wishing to see the addition of ORPHA numbers to hospital admission forms. This result verifies the fact that healthcare professionals are willing to learn more about the use of Orphanet and the ORPHA numbers coding system.

Respondents identified the better need of access to information on rare diseases and orphan drugs as one of the main reasons to consider common drugs used for rare diseases as "orphan drugs" and for the same drugs to benefit from incentives like orphan drugs do. These results show that healthcare professionals yearn for better access to information on

rare diseases and orphan drugs and have identified various obstacles to dealing with rare disease patients. The lack of information may be due to the lack of coverage on rare diseases and orphan drugs while students (including medicine students, pharmacy students and nursing students) are studying at University. Currently, none of the courses at the university of Malta for medical students cover units on rare diseases or orphan drugs. Comparing these results to a study carried out in Spain, less than a third of physicians interviewed during the study had undergone training on rare diseases during their undergraduate or postgraduate years (Ramalle-Gómara, 2019). Ninety-nine percent of the respondents (n=72) respondents agree that information sessions about orphan drugs and rare diseases should be provided to professionals and health care workers.

No correlation was found through the Chi square test between having dispensed, prescribed, administered or ordered an orphan drug and the years of experience of healthcare professionals. This result further points out the fact that healthcare professionals can encounter a rare disease patient and might need to access therapy for them at any point in their career. The majority of the healthcare professionals that took part in the completion of the questionnaire had only between zero to five years of experience (42%).

4.4 Design of the information leaflet and registry template

The information leaflet developed aims to target the difficulties faced by healthcare professionals when they have a rare disease patient under their care. Information provided included information on European Reference Networks, Orphanet, a link to a list of orphan medications available worldwide, contact information of the Malta Medicines Authority, contact information of the National Alliance for Rare Diseases Support Malta and a link to the Malta Rare Disease Register.

Proposed Information Leaflet 3 was the overall preferred information leaflet from the three information leaflets. Slight alterations were adopted on the information leaflet as suggested by the participants of the validation focus group to make the information leaflet more legible and pleasant to the eye.

This information leaflet is intended for publication by the NARDSM and to be distributed to clinics and pharmacies around Malta. Through the distribution of this information leaflet, there is an aim for better holistic care for patients and to increase awareness amongst healthcare professionals. The information leaflet is also concisely built to provide healthcare professionals with the necessary information when dealing with rare disease patients.

The registry template was designed in concordance to the data sets suggested by the European organisations for rare diseases. This ensures harmonisation of rare disease registries and encourages research on rare diseases and the development of orphan drugs and other treatments for rare diseases. The definition for a rare disease was added to the registry as suggested by the validation results. The registry template is intended for use by NARDSM.

4.5 Limitations

Limitations of the study include a limited sample size for healthcare professionals and rare disease patients. The sample size of the healthcare professionals was not equally representative of all participating healthcare professional categories (pharmacists, general practitioners, and community nurses). Data available to compare the results of the healthcare professionals' questionnaire of this study was for studies conducted on physicians and not on pharmacists.

Likert scales used to validate the questionnaires, information leaflet, registry template may have not been ideal as participants of the focus group may have adopted a laid back approach when validating the questionnaire and chose random numbers on the Likert scale that were not representative of their thoughts. Another limitation of using a Likert scale is that participants using a Likert scale might not wish to conform to an extreme such as “strongly agree” and “strongly disagree” therefore results of the validation may be not be accurate. Close ended questions used in the questionnaire could have been restricting and limiting in having more representative results.

4.6 Recommendations

To achieve a better, more representative picture of the situation in Malta, a bigger sample of healthcare professionals should be used. Interviews can be conducted for healthcare workers working in the governmental sector such as Mater Dei Hospital and polyclinic to obtain a clearer view on aspects and challenges faces by clinical healthcare workers. A study is ideally carried out on the number of orphan drugs available in Malta and an orphan drug compendium developed consequently. In-depth interviews can be carried out to assess rare disease patients’ experiences when purchasing an orphan drug. The compassionate use program route needs to be studied to provide better accessibility to orphan drugs that are not readily available locally.

4.7 Conclusion

The inclusion of ORPHA numbers to hospital admission forms could have a significant benefit on the admissions system and would help improve traceability of patient history and would create greater awareness amongst healthcare professionals. The inclusion of a section in the admissions form containing the rare disease name and the ORPHA code would help healthcare professionals keep in mind the possibility of having a rare disease patient under their care, and encourage healthcare professionals to research rare diseases

and encourage the use of Orphanet. Results from the questionnaire show that more awareness should be created amongst healthcare professionals and provide them with the necessary information to be able to deal with RD patients. The information booklet is aimed to promote the use of the register in Malta and increase awareness on rare diseases and drugs amongst healthcare professionals and to offer better holistic care to rare disease patients. Rare disease research is very patient-oriented and patient involvement is beneficial. Through the information booklet, healthcare professionals are encouraged to empower their patients and take charge during their journey with rare diseases. Harmonisation of rare disease registries will encourage research and development on national and international levels. Rare disease patients are few and data for research is scarce. With the use of the new template for the rare disease register, more data which is useful for research purposes is generated.

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List of Publications and Abstracts

1. Perceptions of Rare Diseases and Orphan Medicines - 79th FIP World Congress of Pharmacy and Pharmaceutical Sciences – 22nd – 26th September 2019 Abu Dhabi, United Arab Emirates, ADNEC - Abu Dhabi National Exhibition Centre

2. Perception of Rare Diseases and Orphan Medicines – 25th European Association of Hospital Pharmacists Congress 2020 – 25th -27th March 2020 Gothenburg Sweden - The Swedish Exhibition & Congress Centre

3. Perception of Rare Diseases and Orphan Medicines – 12th World meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology – 23rd to 26th March 2020 Vienna, Austria

Appendices

Appendix 1: Approval Letter

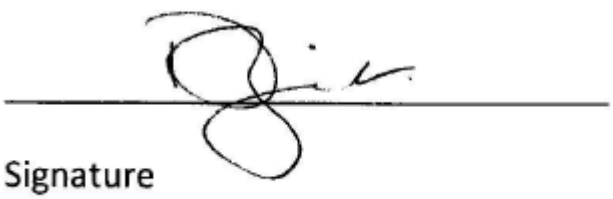
4th December 2017

Dear Ms. Vassallo,

I am writing this letter regarding your request to access data from the Rare Disease Registry for the study you are conducting entitled 'Rare Diseases and Orphan Medicines'. I am aware that the data in the registry will be very useful for your study and can yield important results that may improve the quality of life of patients with rare diseases.

I understand that data accessed from this registry will be solely used for research purposes and in no way will it be manipulated. I also understand that patients within the registry will not be contacted and their data will remain confidential.

I hereby grant you access to the Rare Diseases Registry according to the proposed, discussed and approved circumstances.



Signature

Appendix 2: UREC approval

L-UNIVERSITÀ TA' MALTA
Msida – Malta
Skola Medika
Sptar Mater Dei

UNIVERSITY OF MALTA
Msida – Malta
Medical School
Mater Dei Hospital

Ref No: **FREC MDS_1718_030**

Friday 22nd March 2019

Ms.Sharon Vassallo,
Jasmine, 68,
Freeport Street,
Birzebbugia. BBG 1807.

Dear Ms. Sharon Vassallo,

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

Rare Diseases and Orphan Medicines

The Faculty Research Ethics Committee granted ethical approval for the above mentioned protocol.

Yours sincerely,

Professor Pierre Mallia
Chairman
Research Ethics Committee

Appendix 3: Consent Form

Dear Participant,

I am a final year B.Sc in Pharmaceutical Science student studying at the University of Malta. I am currently conducting a research study entitled 'Rare Diseases and Orphan Medicines' under the supervision of Professor Anthony Serracino-Inglott. This study aims to revise the current definitions of 'rare diseases' and 'orphan medicines', analyse the current situation of rare disease knowledge and the experience of patients in Malta, create more awareness about rare diseases and to promote the use of the Malta Rare Disease Register. The revision of the definitions of 'rare diseases' and 'orphan drugs' is essential in harmonising these definitions worldwide. The updated registry template will benefit rare disease patients and NARDSM in the global effort to harmonise rare disease registries and reduce dissimilarities between existing rare disease registries.

I would kindly like to invite you to be part of a panel which is being set up for the purpose of this study. Your participation is important for the completion of this research. The panel will be meeting once in a span of six months and the discussion will last approximately 45 minutes. The panel will be meeting first to validate two questionnaires. The questionnaires will be distributed to healthcare professionals and layman individuals including rare disease patients respectively. You will be part of a heterogenous group of participants comprising of two pharmacists, one general practitioner, one basic specialist trainee, one volunteer from the National Alliance for Rare Diseases Support Malta and two lay persons.

The date of the panel will be communicated in due course. Upon your consent, the panel discussion will be recorded for data analysis purposes. Please be assured that:

- Your participation is voluntary and you may refuse to participate in the study or leave the research study at any point. If at any point, you wish to leave the panel, your data will be safely discarded according to the GDPR. Data will be discarded

in an appropriate manner and there will be no access to the data by anyone (including by the researcher) after it has been discarded.

- By participating in this study, you are not in any risk of harm or discomfort
- Participants will not be harmed or deceived in any way.
- Data collected from the panel meeting will remain confidential and used for ACADEMIC AND RESEARCH PURPOSES ONLY.
- Data will also be coded appropriately and stored with accordance to the GDPR. Under the General Data Protection Regulation (GDPR) and national legislation that implements and further specifies the relevant provisions of said Regulation, you have the right to obtain access to, rectify, and where applicable ask for the data concerning them to be erased. Data will be stored in a sealed folder in a locked cabinet which only the researcher will have access to.
- The researcher will only have access to the data and only until completion of the research. Examiners and supervisors will also have access to the data under the same terms of the researcher.
- Reporting of results will be anonymous and upon completion of the study, all data will be deleted.

If you wish to be part of this panel, kindly fill in the consent form attached. Please be assured that the results of this study are intended for publication however your identity will not be disclosed in the material that is published.

Please do not hesitate to contact me with any queries. Thank you in advance for your cooperation.

Kind Regards,

Sharon Vassallo
Mobile Number: 79986219
Email: sharon.vassallo15@um.edu.mt

Panel Participants Consent Form

Research project title: Rare Diseases and Orphan Medicines

Research investigator: Sharon Vassallo

- I agree to be part of the panel set up by Sharon Vassallo to aid with the research of 'Rare Diseases and Orphan Medicines'.
- I have read the information sheet related to the 'Rare Diseases and Orphan Medicines' and understand the aims of the project as explained to me by Ms. Sharon Vassallo. I am aware of the topics to be discussed in the panel meeting.
- Participation in this research is entirely voluntary. I am fully aware I have the right to leave the panel at any point. Data will be discarded in an appropriate manner and there will be no access to the data by anyone (including by the researcher) after it has been discarded.
- There are no foreseeable risks or discomfort to the panel participant as the study entails data collection.
- I am fully aware that data collected will be stored securely, safely and in accordance with GDPR. Under the General Data Protection Regulation (GDPR) and national legislation that implements and further specifies the relevant provisions of said Regulation, you have the right to obtain access to, rectify, and where applicable ask for the data concerning them to be erased. Data will be stored in a sealed folder in a locked cabinet which only the researcher will have access to.
- By participating in this study, you are not in any risk of harm or discomfort.
- I am fully aware that I am not obliged to answer any question, but that I do so at my own free will.

- I agree to have the panel meeting recorded (video or voice recorder), so it can be transcribed after the meeting is held.
- I understand that the results of this study may be used for medical or scientific purposes and that the results achieved from the study in which I am participating may be reported or published: however, I shall not be personally identified in any way, either individually or collectively, without my expressing written permission. I have the right to access, rectify and where applicable erase data concerning me.
- I agree to treat panel discussions as confidential, and specifically not to disclose personal details about any other participants outside the panel.
- I am aware that I will not be remunerated in any way by participating in this research study.

_____ _____

Participant's Signature Signature Date

_____ _____

Researcher's Signature Signature Date

Name of Investigator Sharon Vassallo

Email of Investigator sharon.vassallo.15@um.edu.mt

Name of Chief Supervisor Prof Anthony Serracino-Inglott

Email of Chief Supervisor anthony.serracino-inglott@um.ed.mt

Mobile Number of Chief Supervisor 99993442

Name of Supervisor Dr Maresca Attard Pizzuto

Email of Supervisor maresca.attard-pizzuto@um.edu.mt

Mobile number of Supervisor 793210973

Appendix 4: Validation Form

Validation Form for Layman and Professionals Questionnaires:

Rare Diseases and Orphan Medicines

Adopted from Bonnici H. *Proposals for Improving Patient and Pharmacist Satisfaction within the Pharmacy of Your Choice Scheme* [dissertation]; 2016

Statement	**Strongly disagree**	**Disagree**	**Neither agree nor disagree**	**Agree**	**Strongly agree**
The layout of the questionnaire is simple and pleasant to the eye					
The questions asked serve the purpose and aims of this study					
The questions are worded in a clear, simple and unambiguous way					

The questions are essential, appropriate and not repetitive.					
The sequence of the questions is coherent.					
Definitions of certain terminology (Orphanet, Rare Diseases) are clear and can be understood.					

Rate the following statements according to your level of agreement with the statement

Would you like to make any other comments of further suggestions for improvement?

_____

_____

Signature of Participant **Date**

_____ _____

Appendix 5: Questionnaire for the Public

Rare Diseases and Orphan Medicines

Dear participant,

Thank you for agreeing to participate in this research entitled 'Rare Diseases and Orphan Medicines'. This study, under the supervision of Professor Anthony Serracino Inglott aims to revise the current definitions of rare diseases and orphan medicines, create more awareness about rare diseases and to promote the use of the Malta Rare Disease Register.

Your voluntary participation is important for the completion of this research. The questionnaire takes around 5 minutes to complete. The definition of 'rare diseases' and 'orphan drugs' will be revised through the results obtained from the collection of the questionnaires. Please be assured that data collected from the questionnaire will be confidential and used for academic and research purposes only. You may refuse to complete the questionnaire or quit at any moment. Your identity will remain anonymous throughout this research study. You will not be in any form of risk or deception by participating in this study. Data will also be stored appropriately and reporting of results will be anonymous. Data will be deleted on completion of the study.

Your participation is appreciated.

Sharon Vassallo

Email address: sharon.vassallo.15@um.edu.mt
Researcher Mobile Number: 79986219
Chief Supervisor: Prof Anthony Serracino Inglott
Chief Supervisor Mobile Number: 99993442
Email address: anthony.serracino-inglott@um.edu.mt

Section A: Demographics

Gender: Male ☐

Female ☐

Other: ☐

Age: _____

Nationality: _____

Occupation: _____

Section B: Personal Experience and Knowledge

Please answer the following questions by marking with an 'X'
A Rare Disease is one that affects 1 in 2000 patients. Rare diseases are often chronic, progressive, degenerative, and often life-threatening. Rare diseases are disabling: the quality of life of patients is often compromised by the lack or loss of autonomy. There is lack of information about these diseases, and methods of diagnosis and treatment are most of the time unavailable or lengthy. - https://www.eurordis.org/sites/default/files/publications/Fact_Sheet_RD.pdf

Question	Yes	No
1. Do you suffer from a rare disease?		
2. Do you know anyone or are you related to anyone with a rare disease?		
3. Are you aware of any organisations for rare disease patients?		
4. Are you aware of the Malta Rare Disease Register?		
5. Have you ever heard of any initiatives by governmental regarding rare diseases?		
6. Have your heard of any initiatives by non-governmental organisations regarding rare diseases such as the Science in the City information stand by the National Alliance for Rare Disease Support Malta, The Prime Minister's Playlist...etc?		
Orphan drugs are medicinal products intended for diagnosis, prevention or treatment of life-threatening or very serious diseases or disorders that are rare. - https://www.eurordis.org/content/what-orphan-drug		
7. Do you agree that orphan drugs should be added to the Pharmacy Of Your Choice (POYC) scheme?		
8. Would you like to see more awareness being made about rare diseases in Malta?		

9. Would you be interested in learning more about rare diseases?		

ANSWER THIS PART OF THE QUESTIONNAIRE ONLY IF YOU SUFFER FROM A RARE DISEASE

Question	Yes	No
10. Are you registered with the Malta Rare Disease Register and/or the National Alliance for Rare Diseases Support?		

If Yes, where are you registered in?

a. Malta Rare Disease Register ☐

b. National Alliance for Rare Diseases Support Malta ☐

c. Both ☐

d. None ☐

If you are registered to either or both the Malta Rare Disease Register and the National Alliance for Rare Diseases Support, how did you get to know about them?

a. Newspaper articles, Television Programmes...etc ☐

b. Social Media (Facebook, Instagram...etc) ☐

c. Consultant, doctor or pharmacist ☐

d. Advertisement on POYC bags ☐

e. Word of Mouth ☐

f. Other: _____ ☐

If No, Why?

a. I did not hear about them ☐

b. I am not interested in being registered ☐

c. I do not feel that being registered can help my situation ☐

d. I do not wish to share my details and personal information ☐

e. Other reasons: _____ ☐

Question	Yes	No
11. Do you use or have ever used an orphan medicine?		

If Yes, please indicate the name of the medicine:

_____

If Yes, how is this medicine made available to you?

a. Bought at the Pharmacy ☐

b. Bought online ☐

c. Consultant/ Doctor/ Pharmacist ordered it from me ☐

d. Bought it from a relative that lives abroad who then sent it to me ☐

e. Other Means: _____ ☐

Question	Yes	No
12. Did you face any problems to access this medicine?		

If Yes, what kind of problems did you face in accessing this medicine?

a. Medicine was not available in Malta ☐

b. Medicine was expensive ☐

c. Consultant/Doctor/Pharmacist did not know from where to order the medicine ☐

d. Consultant/Doctor/Pharmacist did not know about the medicine ☐

e. Medicine was indicated for another condition and therefore was not made available to be dispensed for my condition ☐

f. Other problems: _____ ☐

Appendix 6: Questionnaire for Healthcare Professionals

Rare Diseases and Orphan Medicines

Dear participant,

Thank you for agreeing to participate in this research entitled 'Development of a New Rare Disease Registry'. This study, under the supervision of Professor Anthony Serracino Inglott aims to revise the current definitions of rare diseases and orphan medicines, create more awareness about rare diseases and to promote the use of the Malta Rare Disease Register.

Your voluntary participation is important for the completion of this research. The questionnaire takes around 5 minutes to complete. The definition of 'rare diseases' and 'orphan drugs' will be revised through the results obtained from the collection of the questionnaires. Please be assured that data collected from the questionnaire will be confidential and used for academic and research purposes only. You may refuse to complete the questionnaire or quit at any moment. Your identity will remain anonymous throughout this research study. You will not be in any form of risk or deception by participating in this study. Data will also be stored appropriately and reporting of results will be anonymous. Data will be deleted on completion of the study.

Your participation is appreciated.

Sharon Vassallo

Email address: sharon.vassallo.15@um.edu.mt
Researcher Mobile Number: 79986219
Chief Supervisor: Prof Anthony Serracino Inglott
Chief Supervisor Mobile Number: 99993442
Email address: anthony.serracino-inglott@um.edu.mt

Section A: Demographics

Years of Practice: _____

Nationality: _____

Occupation:

a) Medical Practitioner ☐

Area of Specialisation: _____

b) Pharmacist ☐

Area of Specialisation: (Community/Clinical/Industrial): _____

c) Community Nurse ☐

Section B: Personal Experience and Knowledge

Which one of the following would you describe as a rare disease:

i. A disease that affects 1 in 2000 patients in the EU ☐

ii. A disease that has unknown aetiology, diagnosis, and treatment ☐

iii. A disease about which there is not much awareness ☐

Please answer the following questions by marking with an 'X'		
A Rare Disease is one that affects 1 in 2000 patients. Rare diseases are often chronic, progressive, degenerative, and often life-threatening. Rare diseases are disabling: the quality of life of patients is often compromised by the lack or loss of autonomy. There is lack of information about these diseases, and methods of diagnosis and treatment are most of the time unavailable or lengthy. - https://www.eurordis.org/sites/default/files/publications/Fact_Sheet_RD.pdf		
Question	**Yes**	**No**
a. Have you ever cared for someone with a rare disease?		
b. Have you ever diagnosed/examined/encountered a rare disease patient?		
Orphanet maintains the Orphanet nomenclature of rare diseases. Orphanet was established to gather scarce knowledge on rare diseases so as to improve the diagnosis, care and treatment of patients with rare diseases. Each disease in Orphanet is attributed a unique and stable identifier, the ORPHA number. Example: **ORPHA Number** **Rare Disease**		

ORPHA:182090 Pulmonary arterial hypertension - https://www.orpha.net/consor/cgi-bin/index.php		
c. Did you ever hear about Orphanet?		
d. Do you know where you can access Orphanet?		
e. Have you ever seen or used the ORPHA number system to diagnose a patient?		
f. Would you like to see a section for ORPHA numbers being added to the admissions form used in hospital? If Yes, comment on your answer: _____ _____ _____		
Orphan drugs are medicinal products intended for diagnosis, prevention or treatment of life-threatening or very serious diseases or disorders that are rare. - https://www.eurordis.org/content/what-orphan-drug		
j. Did you ever dispense/order/prescribe/administer an orphan drug? If Yes, how did you obtain the orphan drug? Was it readily available from the pharmacy? _____ _____ _____		

k. Have you ever had problems accessing an orphan drug for your patient? If Yes, what was the problem you encountered? a. Lack of availability ☐ b. Price ☐ c. Lack of information about the drug ☐ d. Other: _____ ☐		
l. Do you agree that common drugs used for rare diseases should be also listed as 'orphan drugs'? If Yes, Why? _____ _____ _____		
m. Do you agree that common drugs used for rare diseases should also benefit from incentives (example: 10 year exclusivity period) like orphan drugs indicated exclusively for rare diseases do? If Yes, Why? _____ _____		
n. Do you agree that an Orphan Drug Compendium of orphan drugs available in Malta should be compiled?		
o. Have you heard about the National Alliance for Rare Diseases Support Malta?		

p. Are you aware of the Malta Rare Disease Register?		
q. Have you ever registered or helped a patient register to the Malta Rare Disease Register?		
r. Do you agree that information sessions about orphan drugs and rare diseases should be provided to professionals and health care workers?		

Section C: Rare Diseases

The following are terms used in various definitions of rare diseases used globally. Rank the following terms (1 being the least and 5 the highest) according to association and relevance to the concept of rare diseases. Which terms do you think should be included in the definition of rare diseases? **Mark your answer with an 'X'.**

Statement : A Rare Disease is	**1 Least Relevant**	**2**	**3**	**4**	**5 Most Relevant**
a. one for which there is no reasonable expectation that the cost of developing and making available a drug for such					

disease or condition will be recovered from sales					
b. life-threatening					
c. chronically debilitating					
d. seriously debilitating					
e. has no satisfactory method of diagnosis					
f. has no satisfactory method of prevention					
g. has no satisfactory method of treatment					
h. is a disease of unknown aetiology					
i. presents a major financial burden					
j. presents a major psychological burden					
k. has a genetic origin					
l. a disease with an incidence of 0.65–1‰					

Section D: Orphan Drugs

The following are terms used in various definitions of orphan drugs used globally. Rank the following terms (1 being the least relevant and 10 the most relevant) according to association and relevance to the concept of orphan medicines. Which terms do you think should be included in the definition of orphan medicines?**Mark your answer with an 'X'.**

Statement : Orphan drugs are	**1** **Least Relevant**	**2**	**3**	**4**	**5** **Most Relevant**
a. drugs for human use					
b. intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition					
c. drugs that without incentives it is unlikely that the marketing of the					

medicinal product in the community would generate sufficient return to justify the necessary investment d. drugs that will not generate profit to cover the expenses of investment, without any incentives					
e. medicinal products with a significant benefit for those affected by the condition					
f. biologics, medical devices and medical foods, particularly parenteral nutrition and nutraceuticals					

g. drugs used for diseases which claim to be incurable					
h. drugs used for diseases for which there is no possible alternative treatment					
i. drugs whose efficacy and expected safety must be excellent in comparison with other available drugs					
j. medicinal products which have been identified by any doctor or dentist as an appropriate and essential remedy with no effective substitute for the treatment of a rare disease					

k. not commercially viable when used in the patient population they are indicated for					
l. drugs used in tropical diseases					
m. include common drugs that are also used for rare diseases (example: sildenafil used for erectile dysfunction used in also in pulmonary arterial hypertension)					
n. drugs indicated exclusively for a rare disease					
o. drugs used for eradicated diseases					

Appendix 7: Information Leaflets

Treasure Exceptions - A Guide to Rare Healthcare Providers

1. Listen and Learn

Research has shown that a vast majority of patients seek information about their rare disease. This may challenge the traditional patient-professional approach. Help patients feel that their opinions, experiences and information are valued. It is a learning experience for both!

2. Be Honest

There are an estimated 8000 rare diseases worldwide. It is impossible to be knowledgeable on each and every one. Don't be afraid to admit you don't have the answer to the patient's questions. Be transparent about research and its future for your patient.

3. Collaboration and Research

In 2011, European Reference Networks (ERN's) were set up to facilitate the sharing of information between professionals and expertise centres. There are currently 24 ERNs joining approximately 1000 healthcare providers over the EU. Collaboration is key for the patient's holistic care.

GET IN CONTACT WITH ERN'S

RARE CONNECT: https://www.rareconnect.org/en

ORPHANET: https://www.orpha.net/consor/cgi-bin/index.php

4. Know what's available

In the EU, there are around 93 orphan drugs with a marketing authorisation. A number of orphan drugs are available in Malta even through the Pharmacist of Your Choice Scheme (POYC). Some medications can be made available through Named Patient or Compassionate Use Programmes.

YOUR GUIDE TO WHAT'S AVAILABLE:

List of Orphan drugs available in the EU:

https://www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_drugs_in_europe.pdf

Malta Medicines Authority: http://www.medicinesauthority.gov.mt/home?l=1

E-mail: info.medicinesauthority@gov.mt

5. Register your Patient

Rare Disease Registries are the essentials for research and development, improving patient care and also quality of life. Registering your patient should be one of your main priorities.

WHERE TO FIND THE NARDSM:

Website: http://rarediseasesmalta.com/

Phone: +356 99912373

Email: info@rarediseasemalta.com

6. Empower your Patient

The National Alliance for Rare Diseases Support Malta (NARDSM) is a local NGO which offers patient support to rare disease patients. According to NARDSM, there are around 25,000 rare disease patients suffering from an estimated 600 different rare diseases. Encourage patients to involve themselves and be active in their journey with rare diseases.

FOLLOW THE LINK TO REGISTER YOUR PATIENT

https://deputyprimeminister.gov.mt/en/dhir/Pages/Registries/Rare-diseases.aspx

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4. Register your Patient

Rare Disease Registries are the essentials for research and development, improving patient care and also quality of life. Registering your patient should be one of your main priorities. You can register your patient with the National Alliance for Rare Diseases Support Malta (NARDSM) and the Malta Rare Disease Register.

Follow the link to register your patient:

https://deputyprimeminister.gov.mt/en/dhir/Pages/Registries/Rare-diseases.aspx

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Your Guide to What's Available:

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https://www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_drugs_in_europe.pdf

Malta Medicines Authority: http://www.medicinesauthority.gov.mt/home?l=1

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Follow the link to register your patient:

https://deputyprimeminister.gov.mt/en/dhir/Pages/Registries/Rare-diseases.aspx

Appendix 8: Rare Disease Registry

PROPOSED RARE DISEASE REGISTRY TEMPLATE					
Group	**Element Number**	**Element Name**	**Element Description**	**Coding**	**Comment**
Personal Information	1.1	Patient Identifier	Number associated with Input	(1,2,3…)	
	1.2	Surname	Patient's Surname		
	1.3	Name	Patient's Name		
	1.4	Date of Birth	Patient's date of birth	(dd/mm/yy)	
	1.5	Sex	Patient's sex at birth	Female	
				Male	
				Undetermined	
	1.6	Patient Status	Patient Alive or Dead	Alive	
				Dead	Include date of Death in Comments if applicable
				No longer a member	
	1.7	Nationality	Patient's Nationality	Maltese	
				Other	Specify other nationality if applicable
	1.8	Country of Residence	Country where patient is currently residing	Malta	
				Gozo	

				Other	State other country
Disease History	2.1	Age at onset	Patient's age at which first symptoms and signs appeared	Antenatal	
				At Birth	
				Date	
				Undetermined	Unknown
	2.2	Age at diagnosis	Patient's age at which diagnosis was made	Antenatal	
				At Birth	
				Date	
				Undetermined	
Diagnosis	3.1	Diagnosis of the Rare Disease	Name of Rare Disease as stated on Orphanet		A rare disease is defined as a disease that affects 1 in 2000 patients in the European Union. Orphanet is a European website providing information about orphan drugs and rare diseases.Orphanet maintains the Orphanet nomenclature of rare diseases, essential in improving the visibility of rare diseases in health and research information systems: each disease in Orphanet is attributed a unique and stable

					identifier, the ORPHAcode.
	3.2	ORPHA Code	ORPHA code corresponding to rare disease	ORPHA Code	Each disease in Orphanet is attributed a unique and stable identifier, the ORPHAcode.
	3.3	Genetic Diagnosis (If Applicable)	Genetic diagnosis retained by specialised centre		
Treatment	4.1	Treatment	State what kind of treatment the patient is receiving; Choose from:		
			Surgeries	Yes/No	If Yes state type of surgery undergone and date of surgery
			Transplantation	Yes/No	If Yes state type of transplant undergone and date of transplant
			Orphan Drug Treatment	Yes/No	If Yes state active ingredient, available from the ORPHANET list
			Other treatment	Yes/No	If Yes state active ingredient
			No treatment	Yes/No	

Research	5.1	Contact for research purposes	Consent to be contacted for research purposes	Yes	
				No	
	5.2	Biological Sample	Patient's Biological sample stored in a biobank	Yes	If Yes provide link to Biobank
				No	