Access to Orphan Medication and Quality of Life in Rare Diseases

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To my parents Nada and Ibraheem

and to my two sisters Rand and Reem

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Abstract

Over 7000 rare diseases (RD) affect around 60 million patients living in the European Union (EU) and the United States (US). Research on RDs focuses on treatment and care of RDs with limited focus on health related quality of life and accessibility to Orphan Drugs (ODs).

The aims of this study were to 1) analyse and compare regulations and policies related to accessibility of ODs in the EU and US 2) describe OD accessibility and the health needs of the Maltese RD population and 3) create a health related quality of life (HRQOL) assessment tool for RD patients and caregivers. The HRQOL tool explores issues of diagnosis, mental health, use of health and support services and general quality of life.

The methodology included (1) assessment of OD accessibility policies in 29 countries based on 6 themes (national OD policies, OD designation, marketing authorisation, marketing exclusivity, incentives and pricing) identified during retrospective analysis of literature (2) identifying issues encountered by Maltese RD patients by (i) interviewing policy makers (ii) conducting literature review (iii) and analysing data from RD registers (3) development, validation (by 7 experts) and administration of HRQOL tool to patients and caregivers (N=225) in the EU (n=137) and the US (n=88). The tool included 30 close ended Likert scale questions divided into four sections collecting information on the demographics, personal care and independence, mental and social health and access to treatment.

The results showed that out of the 29 countries assessed, 17 EU countries had OD policies and 6 countries (including the US) had financial incentives for OD development. OD designation, marketing authorisation and market exclusivity were centralised in both the EU and US by the EMA and FDA respectively. Malta had no

OD plans in place and RD patients in Malta had poor access to ODs when compared to other EU countries.

Statistical analysis of the HRQOL indicated a significant difference ($p<0.05$) between RD patients in the EU and US. A significant difference was observed when RD patients were asked to report how they felt during everyday activities such as dressing ($p=0.001$), eating ($p<0.001$) or participating in everyday activities ($p=0.014$) with the US RD patients scoring lower in all areas. The financial burden of RDs was significantly higher ($p<0.001$) in the US as the Likert mean score was 3.00±1.065 while EU RD patients reported 4.44±0.512 on the Likert scale (1 = Financial burden, 5 Not a burden). Poor OD accessibility was reported by both groups with 44 (32%) EU respondents and 27 (31%) US respondents reporting it is 'almost impossible' to receive treatments for their RD. EMA has granted 140 ODs with market authorisation compared to 415 approved ODs in the US.

There are differences between countries on the degree of accessibility, pricing and reimbursement. Poor HRQOL may be related to issues of accessing medicines, diagnosis, psychosocial support, and coping with stigma and uncertainty. US based RD patients scored poorly when compared with their EU counterparts in relation to mental health, personal care and independence and ability to afford ODs.

Keywords

Accessibility –European Medicines Agency – Food and Drug Administration - Orphan Drugs – Quality of Life –Rare Diseases

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List of Abbreviations

APS	Accelerated Procedure Scheme
CHMP	Committee for medicinal products
COE	Centre of Expertise
COMP	Committee for Orphan Medicines
CPGs	Clinical Practice Guidelines
DPS	Drug Payment Scheme
ERNs	European Reference Networks
EU	European Union
EURORDIS	European organisation for Rare Diseases
FDA	Food and Drug Administration
FI	Financial incentives
HTA	Health Technology Assessment
HRQOL	Health Related Quality of Life
ICER	Incremental Cost Effectiveness Ratio
MA	Marketing Authorisation
MEAs	Managed Entry Agreements
NFI	Non-Financial Incentives
NGOs	Non-governmental Organisation
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NRDPs	National Rare Disease Plans
OD	Orphan Drug
ODD	Orphan Drug Designation
QOL	Quality of Life
US	United States of America

CHAPTER 1

INTRODUCTION

1.1 Background

Rare diseases (RDs) afflict millions of people worldwide of all ages, genders and ethnicities. Over 80% are serious and life-altering and life-threatening genetic conditions (Hudson and Breckenridge, 2012). Due to the number of people affected with any one specific RD being relatively small, a number of challenges complicate the development of effective medications and medical devices to prevent, identify, treat, or cure these RDs. In the last three decades, scientists, activists, policy makers, and the public have highlighted the challenges of RDs. Despite these efforts, only 5% of RD patients have effective treatment (Tambuyzer, 2010).

More than 7000 RDs are prevalent worldwide; the majority (80%) are of genetic origin and affect the paediatric population mostly (Westemark and Llinares, 2012). RDs increase the mortality rate and are chronically incapacitating (Bogershausen and Wollnik, 2013). Examples of rare diseases include genetic diseases, rare cancers, infectious tropic diseases and degenerative diseases (Caldwell et al, 2004).

RD classification differs between countries (Table 1.1). In the European Union, for a disease to be classified as a RD, a disease must affect less than 5 patients per 100,000 patients, have an effect on mortality and have chronic debilitating effects. The United States defines an RD as one that affects less than 200,000 patients out of the total population (Schieppati, 2008). RDs exist in every disease area and affect every age and may range from ultra-rare diseases such as Ribose-5-phosphate isomerase deficiency to more widespread RDs such as cystic fibrosis and Tourette's syndrome (Wamelink, 2010).

Table 1.1 Rare Disease Classification

Country/Region	Definition (by affected number of population)	Prevalence per population
European Union	<2,000	1.1
European Union (Ultra RD)	<50,000	-
U.S.A	<200,000	7.5
U.K. (Ultra RD)	<1,000	0.1
Japan	<50,000	4.1

Adapted from: Da Silva EN, Sousa TR. Economic evaluation in the context of rare diseases: is it possible? Cad. Saúde Pública, Rio de Janeiro, 2015; 31(3):496-506.

1.2 Access to medicines

Access to medications is considered a basic human right under the World Health Organisation constitution (WHO).[1] The human right declaration specified that:

> *'The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition'*[2]

[1] World Health Organisation constitution 1946 [Cited 2018 May 30] can be accessed through URL: http://apps.who.int/gb/bd/PDF/bd47/EN/constitution-en.pdf?ua=1

[2] Universal Declaration of Human Rights [Cited 2018 May 30] can be accessed through URL: http://www.who.int/medicines/areas/human_rights/en/

A human rights framework also emphasises the importance of non-discrimination for marginalised and vulnerable groups such as RD patients (Yamin, 2003).

Accessibility to medicines is defined as the ability to receive medications and treatments when required (Gulliford et al, 2002). The degree to which a patient 'gains access' relies on financial, organisational and social or cultural barriers which contradicts the human rights declaration mentioned above (Zucker and Rago, 2007).

1.3 Orphan Drugs

Orphan drugs (ODs) are medicines or vaccines formulated to treat, prevent or diagnose a RD.[3] The '1983 Orphan Drug Act' in the US recognised the importance of pharmaceutical research in RDs and allocated special incentives for drug companies and researchers to help develop new treatment.[4] Soon after this act was passed, Japan and the European Union followed (Gahl and Tifft 2011).

Owing to the low prevalence of RDs, pharmaceutical companies viewed the development of medications for RDs as economically unworthy, and this resulted in a situation of imbalanced access between RD patients and patients with more common ailments (Stakisaitis et al, 2007). Due to the small population size of RD patients, the cost of research and development of ODs is covered by a small number of the population (Dear et al, 2006). The cost of development of ODs is much smaller than that which is actually reported due to the small size of participants in clinical trials (Hyde and Dobrovolny, 2010). The small population number can reduce the quality of

[3] Orphanet: the portal for rare diseases and orphan drugs. About rare diseases [Cited 2018 May 30]. Available from URL: http://www.orpha.net/consor/cgibin/Education_AboutRareDiseases.php?lng=EN

[4] The Orphan Drug Act. United States Public Law No 97-414 1983 [Cited 2018 May 30]. Available from URL: http://www.fda.gov/orphan/oda.htm

epidemiological data which leads to a less reliable safety and efficacy profile. The lack of clinical data information can prevent decision makers and payers from incorporating ODs into their health systems (Tiwairi, 2015).

1.4 Orphan Drug Legislations

ODs follow a similar regulatory development process as is the case with any other pharmaceutical medicine; establishing efficacy, safety, pharmacokinetics, pharmacodynamics, dosing and stability (Murakami, 2016). Due to the low number of RD patients, the number participating in Phase III clinical trials is low, and as a result some of the statistical requirements are lessened to maintain development momentum (Uguen et al, 2014).

Due to the small market and limited indications of ODs, some countries and regions, decided to intervene to encourage pharmaceutical companies to develop ODs.[5] These interventions can be in the form of:

- Tax exemptions
- Market exclusivity
- Financial research grant (Kiran et al, 2012)

1.5 United States Orphan Drug Legislation

Until the 1980s, few drugs had been developed for the treatment of rare diseases, leaving patients with only palliative treatment in nearly all cases, and when the drugs were in supply, the pharmaceutical companies suffered financial losses (Wellman-

[5] Orphan drug report 2014 [Cited on 30 May 2018] can be accessed from URL: http://info.evaluategroup.com/rs/evaluatepharmaltd/images/2014OD.pdf

Labadie and Zhou, 2010). In 1982 the U.S. Food and Drug Administration (FDA) created a specific sector for these drugs, and in 1983 the U.S. Congress passed the Orphan Drug Act, which not only defined "orphan" diseases but also created incentives for the development of drugs and other related technologies, in the form of special government credit lines and reduced taxes.[6] The orphan drug act also provides for special research protocols and rapid approval, in addition to guaranteeing seven-year market exclusivity for the approved drugs.

1.6 European Union Orphan Drug Legislation

The European member states voted and adapted Reg (EC) no 141/2000 [the orphan regulation] in December 1999[7]. The primary aim of this act was to set a procedure for OD designation and establish what incentives are to be offered for OD developers. The Committee for Orphan Medicinal products (COMP) was established and created a centralised authorisation procedure.[8]

The European orphan drug status grants 10-year post approval market exclusivity, tax exemptions (although taxation varies from one-member state to another); research grants and guidance on orphan designation application process (Gerke et al, 2017).

[6] U.S. Department of Health and Human Services - FDA. Report: Complex Issues in Developing Drugs and Biologic Products for Rare Diseases and Accelerating the Development of Therapies for Paediatric Rare Diseases Including Strategic Plan: Accelerating the Development of Therapies for Paediatric Rare Diseases. 2014. [Cited on 30 May 2018] can be accessed from URL: http://www.fda.gov/downloads/RegulatoryInformation

[7] EU ORPHAN DRUG ACT 1999 [Cited on 30 May 2018] can be accessed from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000552.jsp&mid=WC0b01ac058061ecb7

[8] Eurordis Statement. Orphan drugs: Rising to the challenge to ensure a better future for 30 million patients in Europe. [cited on 30 May 2018] can be accessed from URL: http://www.eurordis.org/sites/default/files/publications/Statement_Future_of_Orphan_ Drugs_14_October_09.pdf.

In 2004 the bill was amended to include guidelines on the compassionate use programme. The compassionate use programme is a treatment programme that allows the use of unlicensed ODs under strict conditions. The pre-approved/licensed medicine can be made accessible to a patient with a RD when no other licensed medicine can be used. The compassionate use programme is regulated by the Committee for Medicinal Products for Human Use.[9]

1.7 Orphan Drug Designation

The Orphan Designation is a legal procedure that allows for the designation of a medicinal substance with therapeutic potential for a rare disease, before its first administration in humans or during its clinical development. The specified therapeutic indication is defined at the time of marketing authorisation.[10]

These new laws allowed for a decrease of regulatory fees, extra regulatory counselling and a marketing exclusivity period of seven years (US) or ten years (EU) after approval of the product. As of January 2017, the FDA has 3963 orphan designations assigned, and over 590 medicines approved for marketing[11]. In 2015 the European medicines Agency had more than 114 ODs authorized and over 1000 orphan designations.[12] These figures from both continents reveal how successful both agencies have been in

[9] Guideline on aspects of the application of Article 8(1) and (3) [Cited on 30 May 2018]. Can be accessed from URL: https://ec.europa.eu/health//sites/health/files/files/orphanmp/doc/c_2008_4077_en.pdf

[10] EU commission on public health [Cited 2018 May 30]. Can be accessed from URL: https://ec.europa.eu/health/home_en

[11] U.S. food and drug admistration. Orphan drug database [Cited on 30 May 2018]. Can be accessed from URL: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/

[12] EMA orphan drug designation database [Cited on 30 May 2018]. Can be accessed from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/orphan_search.jsp

providing incentives and encouraging pharmaceutical companies to find new ODs (Schieppati, 2008).

The EU has a centralised procedure applied and regulated by the European Medicines Agency (EMA). EMA has a designated body, the Committee for Orphan Medicinal Products (COMP) which deals exclusively with Marketing Authorisation for all member states to ensure equal access of ODs (Denis et al, 2010c).

1.8 Access to Orphan Drugs

In recent years, the issue of accessibility to ODs has gained needed recognition due to increasing pressure from RD patients and the general public. ODs are pharmaceutical products formulated to treat or manage RDs. More than 7000 RD conditions all share a common feature of affecting a 'small or ultra-small' proportion of the population. These characteristics of RDs raise the question of how public healthcare systems prioritise, source and allocate funds for RDs and ODs (Trama et al, 2010).

The question, 'should a person with a RD be given the same level of care as a patient affected by diabetes?' has been answered by the EU regulation on ODs in 1999.[10] It proclaimed that a 'patient living with a rare disease should be entitled to the same level of care as other patients'. In 2009 the European Council emphasized that 'the principles and overreaching values of universality, access to good quality care, equity and solidarity' are of paramount value for RD patients.[10]

The EU member states aimed to implement these statements throughout the last two decades and develop a national plan for RDs. Social justice and accessibility to equal level of care helped in creating many policies.[13]

On a global level, the 'Right to Health' and 'Universal Health Coverage' are among 17 Sustainable Development Goals (SDG) issued by the UN. It highlights the importance of 'ensuring the healthy lives and promoting the well-being for all at all ages' as essential to achieve any progress towards socio-economic justice. All SDGs published used the motto 'leave no one behind' and emphasised the need to start with those most vulnerable, referring to RD patients (Tsai, 2014).

1.9 Orphan Drugs Pricing

It is a fact that the majority of ODs carry a higher price tag than medications used for common conditions. Traditionally, the high cost of ODs has been linked to two factors; the first being the complexity of developing therapies for RDs, while the second being the 'ultra small' population size of patients set to receive treatment (Iskrov and Stefanov 2014). The latter of the two factors explains why payers and health insurance companies have generally covered the cost of ODs for RD patients. This is primarily because, despite the price tag of an OD being high, the low number of RD patients receiving the said OD means that the overall impact on the health budget was of a reasonable magnitude when compared to common medications for chronic conditions (Rice et al, 2000).

[13] European Commission. Research & Innovation. Key Research Areas: Rare Diseases. [Cited on 30 May 2018] can be accessed from URL: https://ec.europa.eu/research/health/index.cfm?pg=area&areaname=rare

High price tags for novel non-OD therapies for widespread conditions such as HIV, Hepatitis and different cancers have put tremendous pressure on healthcare systems and budgeting. Such drugs have an exceptionally high price as a reflection of their legitimate value, particularly when they come with the promise of cure (as is the case with Hepatitis C) and shorter interval of treatment with fewer side effects when compared with available medicines. These factors have lead payers and policy makers to develop a concern that high prices, when applied to diseases that affect the wider population would heavily impact the budget (Rosenberg-Yunger et al, 2011).

This concern can be challenged, as it is a fact well known that competition between pharmaceutical companies can lead to significant decrease overtime in both the price and the budget impact on healthcare systems (Michel et al, 2012). This indicates that for common conditions, economic regulations through fair market competition can prove beneficial in reducing drug price (Dear et al, 2006). The same cannot be said for ODs, as the orphan drug designation gives patent rights to the marketing authorisation holder for a set number of years which leads to a price which is controlled by the drug developer (Barak and Nandi, 2011).

With the above in mind, policy makers and payers in the EU and USA have a challenging situation where the limited resources available have to be prioritised and used to procure cost effective medications with proved benefits for common conditions (Dunoyer, 2011). In this context, one can see why ODs have been constantly pushed aside and marginalised by many countries worldwide.

The question, 'should high prices of ODs be accepted as legitimate indication of their value?' has been asked many times policy makers within Europe (Denis et al, 2012). Three different scenarios can be used to help answer this question:

- Is it acceptable to repurpose an existing, cheap and safe hospital preparation into a new product subject to orphan drug designation and new market authorisation and ask for a price hundreds of times higher than the true value? Humira®, which was approved by the FDA in late 2002 to treat millions of people who suffer from rheumatoid arthritis (Scheinfeld, 2003). Three years later, the marketing authorisation holder asked the FDA to designate it as an orphan to treat juvenile rheumatoid arthritis, which, they told the FDA, affects between 30,000 and 50,000 Americans. That paediatric use was approved in 2008, and Humira subsequently was approved for four more rare diseases. The designation has led to Humira to sell for more than $8.41 billion.[14]

- In the case of truly novel ODs, this usually is the addition or inclusion of a new indication to an already available drug to gain OD status. This is accompanied by an increase in price tag which is said to be due the costs of clinical studies in the condition to be included.[12]

- ODs carry the highest price tag of any medication; little evidence is provided by pharmaceutical companies to justify the asking price.[12]

[14] NPR USA [Cited on 30 May 2018] can be accessed from URL: https://www.npr.org/sections/health-shots/2017/01/17/509506836/drugs-for-rare-diseases-have-become-uncommonly-rich-monopolies

1.10 Issues of Orphan Drug Pricing

It would be inaccurate to claim that the prices of all ODs are questionable and that they are the primary contributing factor to a failing health system. Recent studies have shown that the majority of ODs approved by the European Medicines Agency (EMA) range in annual cost between €800 and €385,000. Although the figure in the higher range is significant, the study showed that the annual median cost to be €35,000 which is reasonable. The study showed that around 25% of all ODs investigated in the review had an annual cost of less than €12,000 while only 17.6% had a cost superior to €100,000 (Dunoyer, 2011).

ODs can be categorized into different areas for RD treatment. Rare cancers ODs, such as Gleevec©, has shown to improve the patient's survival and QOL and as a result its indication extended to different types of cancer. These extensions lead to an increase in the target population which in turn increased the demand and price. These raises in price brought up great controversy and the question of price control was discussed by payers and policy makers.

1.11 Orphan Drug Market

As of 2017, there were 310 authorised ODs and over 450 orphan drug designations in clinical trials most of which (60%) are biologics.[15] Pharmaceutical companies in the United States were spearheading the market with more than 350 orphan drugs in clinical trials(Table 1.2) [13]. Drugs for rare cancers were the most approved and researched with more than 35% of ODs in clinical trials.[13]

[15] Global orphan drug market to reach US$ 120 billion by 2018 (press release), New Delhi: Kuick Research, [Cited on 30 May 2018] can be accessed from URL: https://www.prnewswire.com/news-releases/global-orphan-drug-market-to-reach-us-120-billion-by-2018-244195511.html

Table 1.2 Current US orphan drug market[16]

ODs in clinical trials	600
ODs in phase II	231
ODs in United States clinical trials	350
OD sales in the United States	$44 billion dollars

A 2012 study (Gaze and Breen, 2012) on the 'economic power of ODs' found that there was an increasing investment in the OD market particularly in research driven by the legislations issued in the EU and the United States which offer many incentives. Between 2001-2011, the OD market had its 'most productive decade in the history of OD development, designations and approvals' (Kiran, 2012). During this period, the Compound annual growth rate, (this is a business and investing specific term for the geometric progression ratio that provides a constant rate of return over the time period (Mark J et al, 2010), for ODs grew to 26% (Gaze and Breen 2015).

'The revenue-generating potential of orphan drugs [was] as great as for non-orphan drugs, even though patient populations for rare diseases are significantly smaller. Moreover, we suggest that orphan drugs have greater profitability when considered in the full context of developmental drivers including government financial incentives, smaller clinical trial sizes, shorter clinical trial times and higher rates of regulatory success' (Gaze and Breen, 2012).

[16] EvaluatePharma OD report 2017 [Cited on 30 May 2018] can be accessed through URL: http://info.evaluategroup.com/rs/607-YGS-364/images/EPOD17.pdf

The OD market has become more lucrative for pharmaceutical companies for two reasons (Andreas, 2014):

- The cost of conducting a clinical trial is very low when compared to non ODs.
- The competition is low due to lack of ODs.

Incentives in the form of tax exemptions lower the drug development cost (Andreas H, 2014). It is estimated that the cost per patient for ODs is '6 times higher than non-ODs, a clear indication of their pricing power' (Gaze and Breen, 2012).

The 2017 OD report declared that OD sales has been increasing and the market will continue growing rapidly, with sales expansion prediction at 11% per year, more than double the rate predicted for non-ODs.[17] It is estimated that the sales of orphan drug will almost double between 2016 and 2022, to hit €200 billion.[14] This rapid market expansion and current enthusiasm of payers to pay the high price tags are two of the major reasons why the industry has become increasingly lucrative to some of the biggest pharmaceutical industries. Through legislations such as the Affordable Care Act in the United States, more pressure will be placed on budgets as more people with rare diseases will be eligible for subsidies (Kontoghiorghe, 2014).

Pharmacovigilance or post market surveillance of an OD is a vital step to ensure the safety and clinical benefit of the OD (Bate et al, 1998). Pharmacovigilance is utilised to establish if the OD is clinically efficacious and if it is found that the OD is not, the medication is withdrawn from the market (DuMochal, 1999).

[17] Orphan drug report 2017 [Cited 2018 May 30]. Can be accessed by URL: http://info.evaluategroup.com/rs/607-YGS-364/images/EPOD17.pdf

1.12 Market Abuse

Incentives offered for drugs designated as ODs have led drug developers to attempt to get OD status (Simones and Steven, 2011). An example of this is the AstraZeneca cholesterol controlling drug Crestor (Rosuvastatin) which was initially filed as an OD to treat familial hypercholesterolemia in paediatrics. After Crestor received financial and research assistance and was approved for OD designation, AstraZenca gained approval for the drug to be used in all types of hypercholesterolemia (Kontoghiorghe, 2014).

1.13 Pharmacoeconomics of Orphan Drugs

The pharmacoeconomics of ODs became more established and was used for every OD prior to designation and approval by 2007.[18] The quality adjusted life years (QALY) was used in cost utility analysis (CUA) to establish the ratio of cost to QALY saved by using an OD in a particular RD. The UK's National Institute of Clinical Excellence (NICE) will pay up to a maximum of €35,000 per QALY for a medication. It is important to note that most ODs appraised had cost effectiveness 'well within the accepted level, and will be reimbursed' (Loopstra et al, 2016). NICE held a meeting with patient groups, health professionals and pharmaceutical companies to discuss the need for more research and OD cost effectiveness.[19]

"model of pharmaceutical research and development, the expectations that companies and patient groups have about how risk and reward is shared between the industry and

[18] Drummond MF, Grubert N. (2007), International Trends in the Use of Health Economic Data, Spectrum Report, Decision Resources, Waltham MA [Cited on 30 May 2018]. Can be accessed from URL: http://apps.who.int/medicinedocs/documents/s20976en/s20976en.pdf

[19] "NICE calls for a new approach to managing the entry of drugs into the NHS", NICE, 18 September 2014 [Cited on 30 May 2018] can be accessed from URL: https://www.nice.org.uk/news/press-and-media/nice-calls-for-a-new-approach-to-managing-the-entry-of-drugs-into-the-nhs

a publicly funded NHS, and in the arrangements for commissioning expensive new treatments."

— NICE 2014[19]

1.14 Quality of life

The term Quality of Life (QOL) existed when Aristotle (384-322 BC) asked the questions "what does life mean" and "what is the best way of life" in order to explain the association between happiness, 'well-being' and a good life (Chung et al, 1997). QOL can be defined as the 'individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, values and concerns'.[20] The primary areas of assessment in QOL are mental, physical and social aspects of a person. A health-related quality of life assessment (HRQOL) is an evaluation of how a person's daily life is affected over time by a condition or a disability.

In 1948, the WHO defined health as a 'state of complete physical, mental and social well-being and not merely the absence of infirmity and disease'[17]. Thus, health can be considered in a multidimensional way, including physical, psychological and social health status and well-being in the context of disease (Fairclough 2002; Carr et al, 2003; Sirgy et al, 2006). As a result, the feeling of 'good health' may be with or without disease. For example, an individual may have a disease but is able to cope with difficult situations, may still report a feeling of good health. Additionally, if this person has strong social support s/he may be psychologically healthy (Bowling 2005). Therefore,

[20] WHO Quality of life measurement. [Cited 2018 May 30]. Can be accessed through URL: http://www.who.int/healthinfo/survey/whoqol-qualityoflife/en/

satisfaction and happiness may be experienced not only with health but also with disease.

1.15 Measuring Health Related Quality of Life

The advancement in medical diagnostic procedures as well as medical and surgical interventions have given many patients a chance of survival and have increased their life expectancy (Sirgy et al, 2006), particularly among patients with rare diseases. Although many are genetic and a cure is not available for over 95% of RDs, the available medical interventions can save patients' lives and improve their longevity. However, a chronic disease can suddenly cause life threatening complications, e.g. disability, which can affect the patients' QOL negatively. It is therefore important to assess their QOL. Bowling (2005) maintained that a medical model is no longer enough; particularly in cases of chronic or life threatening diseases.

Using only clinical data to treat patients can be considered dehumanising, because healthcare providers forget to ask patients about their feelings of 'well-being' (Fallowfield, 1990). Bowling (2005) declares that '*What matters is how the patient feels; rather than how professionals think they feel'.* For example, feelings of pain and discomfort or perceptions of change in daily physical functioning or emotions are indicators of ill health, not only pathological abnormalities (Bowling, 2005). Thus, the traditional medical model that focuses on a clinical outcome becomes insufficient to understand the patients' health problems because 'there are multiple influences upon patient outcome, and these require a broad model of health to incorporate them' (Bowling, 2005).

Measuring HRQOL can provide unique data for tracking individuals' physical and psychological health over time, and for identifying unmet health needs to improve their biopsychosocial health (Taylor, 2000). Szende et al, (2003) argue that 'Assessment of health-related QOL has become a recognized and important part of the evaluation of the health status of patients with chronic diseases'.

1.16 Areas of Assessment

There are numerous but similar definitions of HRQOL. For example, Anderson and Burckhardt in 1999 have stated that HRQOL is the patients' subjective perception of the impact of their disease and/or its treatment on their daily life, and their physical, psychological and social functioning. Also, Bowling (2001) defined HRQOL as 'an optimum level of mental, physical, role (e.g. work, parent, career, etc.) and social functioning, including relationships, and perceptions of health, fitness, life satisfaction and well-being. It should also include some assessment of the patient's level of satisfaction with treatment, outcome and health status and with future prospects'. Both these definitions clearly acknowledge that HRQOL is a multidimensional concept. It is theoretically based on the WHO definition of health, which integrates physical, psychological, social functioning and well-being (Bowling, 2001) as well as the individuals' subjective perceptions about their health status, capacity and performance.

Strong interest in cost and broader socio-economic impact grew in the last decade with rare diseases effecting 6-7% of the EU population.[21] Recent cost of illness studies (COI) are focusing on building public policy tools to aid with prioritisation and allocation of

[21] European Commission on Rare diseases - what are they? [Cited on 30 May 2018]. Available from: http://ec.europa.eu/health/rare_diseases/policy/index_en.htm

health budget. COI research aids governments to estimate the financial burden of a disease on its budget. The research and development sectors in pharmaceutical companies utilise COI studies to direct its investment.

One important issue with COI analysis is that they cannot measure inefficiency, misuse, or evaluate costs and benefits interventions. It is important to note that COI studies should be combined with other economical evaluation methods, such as cost benefit analysis or cost utility analysis, to achieve an accurate decision on resource allocation (Aris et al, 2015).

COI studies use a various array of designs and methodologies, which results in limiting comparability and reliabilities of results. Methods such as data sourcing, prospective (society, government etc.) type of costs, and rates of discount are commonly used. Recently published studies are showing more adherences to guidelines and standardisation of COI studies. However, it is important to note that many rare diseases, due to their chronic type, require special consideration and flexibility to sufficiently express the economic burden (Rice et al, 2000).

While many COI studies have been carried out in the last decade, very few have focused on rare diseases.[22] This study aims to give a brief overview of the COI studies carried out in relation to rare diseases. Relevant studies will be analysed and the socioeconomic burden of rare diseases, direct and indirect, will be summarised.

[22] Cost of illness in Rare Disease [Cited 2018 May 30] Available from URL: http://www.imf.org/external/ns/cs.aspx?.id=28

‘The social economic burden and health related quality of life in patients with rare diseases in Europe’ (or BURQOL-RD) project was the first of its kind to try and quantify the RD problem in the EU. The main aim of BURQOL-RD is to generate a model to measure the socio-economic costs and health related quality of life issues, of both patients and caregivers, for ten rare diseases in eight European member states.

The selection of 10 RDs was carried out by a panel of experts from different RD organisations across the EU. The diseases were selected based on commonly researched RDs, availability of patient associations, previous studies, EURORDIS information, and availability of professional care networks. This selection criteria list is known as BOSCARE. The search terms; spending, financial expenditure, financial burden and cost were searched in combination with all of the selected RDs individually (Aris et al, 2015).

1.17 Quality of Life in Rare Disease

Much of the current research on RDs focuses on systematic review of the available literature. The number of QOL tools have increased in the past ten years as more researchers have recognised that alongside physical disabilities, emotional and psychological health are an integral part of QOL. QOL tools are used to assess and measure cost effectiveness, which is a requirement for approval of a treatment in the EU and the US (Martin, 2015).

One example of a RD which has a direct impact on QOL is Fabry disease (FD) (Arendes et al, 2015). An OD approval in 2014 has significantly improved the QOL of FD patients (Arendes et al, 2015). The prevalence of the condition is 1:170,000 births

globally, however, non-classical FD is estimated to be more prevalent than previously thought. Early signs of FD include angiokreatoma, anhidrosis, GI symptoms and nerve pain (Martin et al, 2015). At later stages of the condition renal and heart failure are classical symptoms which results in a shorter life expectancy for most patients[23]. Available FD treatment include two enzyme replacement therapy (ERT), Agalsidase-α, and Agalsidase-β (Martin et al, 2015). Both drugs showed positive outcomes in clinical trials, however, cardiac and renal complications still occur as the disease progression is not stopped, but delayed.

The Quality of life of FD patient's is reduced compared to healthy individuals. According to a recent systematic review of QOL in FD (Maaren et al 2015), pain and anhidrosis are two of the symptoms that affect patients at early stages of the disease. Published studies show correlation between improved QOL of FD patients and ERT (Hughes-Wilson et al, 2012). Different measures of QOL were used by these studies and patient samples were small.

Eleven studies that examined QOL in FD only discussed whether or not QOL was better or worse when compared with the healthy individuals, no exact scores were provided to support claims (MacDermott et al, 2001).

1.18 Social Support for Rare Disease

Several research studies have assessed the association between social support and HRQOL among patients with different RDs. Social support has been found to be a vital

[23] Medicine NET [Cited on 30 May 2018) can be accessed through URL: https://www.medicinenet.com/fabrys_disease/article.htm

factor in improving HRQOL among patients with chronic RDs, particularly mental health. For example, Arestedt et al, (2012) found that there was a significant positive association between perceived social support after controlling for age and gender among elderly patients with chronic RDs and HRQOL. Social support was associated specifically with mental health but not associated with physical health. Karnell et al, (2007) showed that with increasing social support there was a decline in symptoms of depression and improvements in mental health but there was no significant difference in the physical health of patients with head and neck cancer. Social support may be an important factor in perceived mental health in patients with chronic illness.

The link between social support and survival rate has been investigated in numerous longitudinal studies, which showed that social support, especially perceived emotional support, is significantly related to improved psychological and physical health outcomes as well as a decrease in the mortality rate (Lyyra and Heikkinen 2006). Lack of social support can cause psychological symptoms such as anxiety or depression, which may have a negative influence on an individual's health status.

1.19 Aims

The study aims were to:

(1) analyse and compare regulations and policies related to accessibility of ODs in the EU and US and,

(2) describe OD accessibility and the health needs of the Maltese RD population and,

(3) create a health related quality of life (HRQOL) assessment tool for RD patients and caregivers and explore issues of diagnosis, mental health, use of health and support services and general quality of life.

CHAPTER 2

METHODOLOGY

2.1 Methodology

The methodology included (1) assessment of OD accessibility regulations and policies in 29 countries (2) identifying issues encountered by Maltese RD patients by (i) interviewing policy makers (ii) conducting literature review (iii) and analysing data from RD registers (3) development, validation and administration of a Health Related Quality of Life (HRQOL) assessment tool to patients and caregivers in the EU and the US.

Accessibility of ODs and management of RDs in the EU and the US were evaluated. The EU and US were selected as they have an established health system, medicines regulatory bodies and have legislations and policies regarding ODs and RDs.

2.2 Accessibility to Orphan Drugs

A comprehensive literature review was carried out utilising available electronic databases (PubMed, Orpha.net, EURORDIS, EMA, FDA etc.), available European policy documents, and disease specific websites. The PRISMA[24] flow chart method was utilised. The literature review took place between January 2017 and December 2017 and aimed to focus on English peer reviewed articles and journals.

Journals accessed included: 'Health Policy', 'Pharmaeconomics', and 'Orphan Drugs: Research and the Orphanet Journal of Rare Diseases'. A search strategy was developed and keywords included the following: ("Rare" or "Orphan" or "neglected" (diseases))

[24] The 27 checklist items pertain to the content of a systematic review and meta-analysis, which include the title, abstract, methods, results, discussion and funding [Cited 2018 May 30] Can be accessed from URL: http://prisma-statement.org/PRISMAStatement/Checklist.aspx

(“Access” or “Availability” or “Accessibility”) and (“Orphan” or “High Cost”) and (“Orphan Medicines” or “Orphan Drugs” or “Orphan Pharmaceuticals”) and (“Drugs” or “Medicines” or “Pharmaceuticals”) and (“Regulation” or “Policy”) (“FDA” or/and “EMA”).

A total of 20,120 articles were identified using the search methods. The articles included mentions of accessibility and legislations, regulations and governmental policies. Additional records were identified using other sources such as RD websites and OD policies specific to certain regions.

Figure 2.1 shows the process of literature review. The initial step involved searching for the relevant articles and journals using appropriate search terms. The search yielded a total number of articles of over 20,000. The second step was removing duplicates and articles which were not relevant to the title (n=177). Only 137 articles were assessed by reading the abstracts to see if they are eligible for the inclusion criteria.

The selected articles were then assessed for bias and misinformation which resulted in the elimination of 1 article. The PRISMA method yielded a total of 68 articles that were deemed relevant to be included in the study(Figure 2.1).

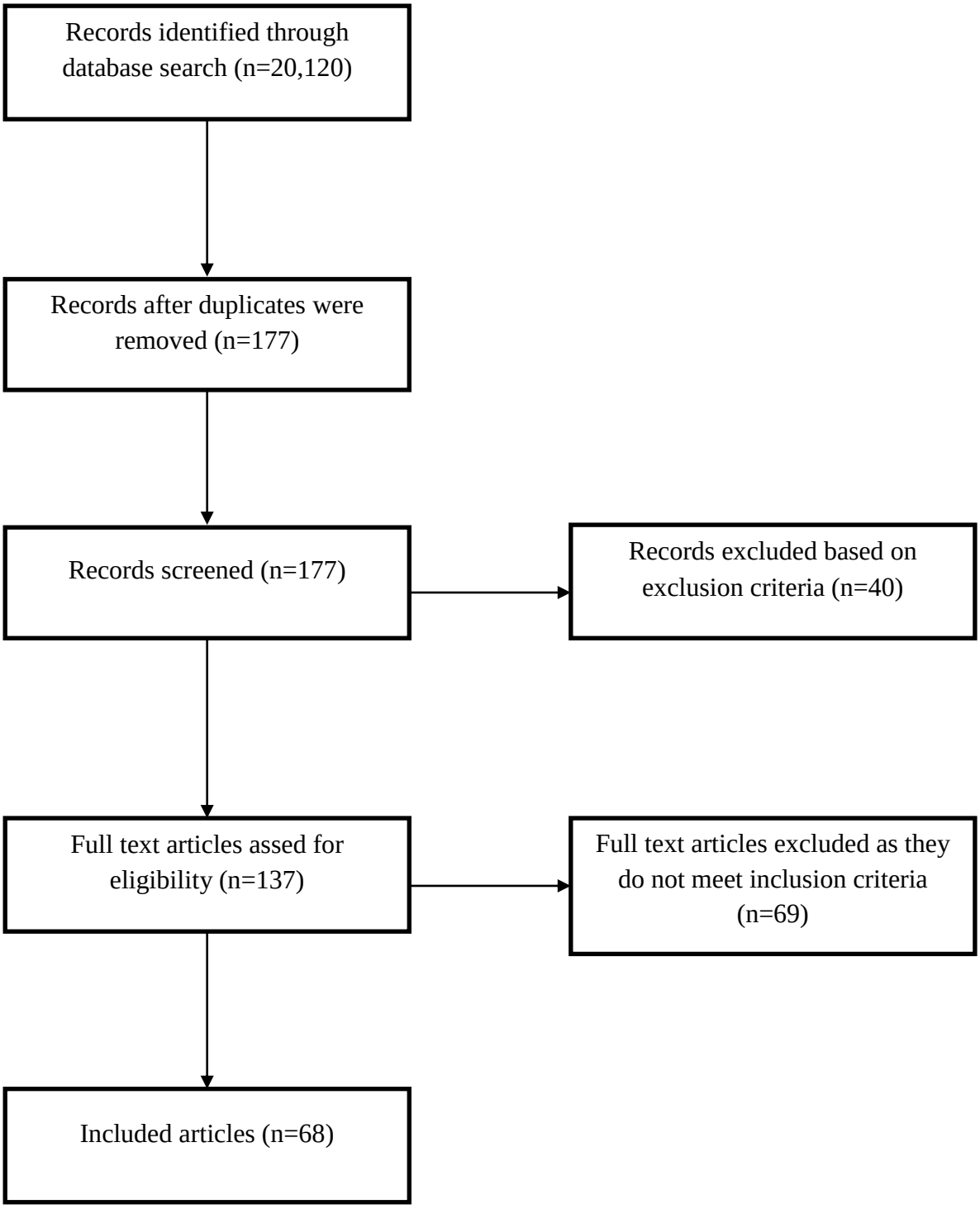


Figure 2.1 PRISMA method used for the systematic analysis of rare disease literature

Table 2.1 Summary of the inclusion and exclusion criteria

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Population	Studies on RD patients access issues to ODs	Studies that do not address both RDs and ODs access issues
Publication	○ English language article ○ Peer reviews ○ Full length article	○ Articles not available in English ○ Non-original data
Publication date	2000 - 2017	Articles which were published before 2000 and after December 2017 were excluded
Regions	○ Any region with a policy or a system in place specific for RDs and ODs ○ Countries with a publicly funded national health service	Any region without an RD or OD specific legislation or policy
Investigating	Accessibility of ODs (Available marketing authorisation, regulation, licensing, economic and social effect of ODs, reimbursement and pricing)	N/A
Bias	N/A	Issues with study design, records, or political agenda

2.3 Inclusion and exclusion criteria of literature review

Table 2.1 gives a summary of the study characteristics, the inclusion and exclusion criteria that were applied to the selected journals. The dates of published literature ranged from 2000-2017. The year two thousand was chosen as it was the date when the first OD legislation was approved in the EU parliament.

2.4 Data Analysis

The literature included in this study was systematically reviewed to ensure that a narrative could be similar to that of other scientific publications. Study classification was based on 6 different themes adapted with the permission of Gammie et al, 2015 (Appendix 1). The 6 themes were:

- OD policies
- Marketing Authorisation
- Incentives
- Pricing
- Reimbursement
- Pharmacovigilance

These themes were used to describe the different policies and regulations found in each of the countries or regions included in this study.

2.5 Rare Disease Management in Malta

Malta is a member of the EU and has adopted the EURORDIS definition of a RD. RD Action[25] RD-Action is 'European Health Programme' funded Joint Action, promoting implementation of recommendations on policy, information and data for RD. The RD action committee has issued a series of themes to examine RD action in a country in different EU countries. Eight themes to assess RD management in Malta were adapted from RD-action plan and another 5 themes were identified through literature concerning RDs in other EU countries. Themes used to assess the management of RDs and accessibility of ODs in Malta included:

[25] RD action plan: ORPHANET [Cited 2018 May 30] can be accessed through URL: www.rd-action.eu

1. RD national plan
2. Centre of expertise on RDs
3. Registers specific to RDs
4. IT support for RDs
5. NGOs to support RDs
6. Screening at birth
7. Clinical practice guidelines
8. RD education
9. Orphanet team
10. RD patient helplines
11. RD information centres
12. Research funds dedicated for RDs
13. OD policies for patient access

2.6 Accessibility of Orphan Drug in Malta

The 13 themes were used to formulate interview questions prior to meeting policy makers in the Department of Health Information and Research Malta. The Department for Health Information and Research in Malta was contacted to obtain data and information on accessibility to medication and treatment. This directorate lead the collection, analysis and delivery of health related information in Malta and provided access to EU data. An official request was sent to the head of the Department of Health Information and research to access available data regarding RD patients. The request was granted as per Health information laws in the EU[26], which allowed access for

[26] Data Protection in the EU [Cited 2018 May 30] available online from URL: https://ec.europa.eu/health/data_collection/data_protection/in_eu_en

policy and decision makers, for the public in general, interested institutions and any other who may have required it.

Available RD registries and statistical data extracted were analysed and the 10 most common RDs in Malta were classified. ODs for the 10 RDs in Malta were researched using the EMA OD data base and the 'portal for RDs and ODs' on Orphanet[27] to investigate their availability in the EU. Availability of the ODs associated with the 10 RDs in Malta were then researched in Malta using the Malta Medicines Authority data base[28]. The Maltese National Hospital Formulary[29] was searched to check for ODs available in hospitals only. The Medicines Access Unit at the Malta Medicines Authority was contacted to provide a list of medications available on the Maltese market.

RD researchers in the Malta BioBank project were interviewed to assess their opinion and to attain more information on RDs and OD accessibility issues. Other groups contacted included clinicians, policy-makers, advocacy groups, and industry leaders to gather information on the management of RDs and access to ODs.

[27] Orphanet OD portal [Cited 2018 May 30] can be accessed through URL: https://www.orpha.net/consor/cgi-bin/Drugs_Search

[28] Malta Medicines Authority database [Cited on 30 May 2018] can be accessed through URL: http://www.medicinesauthority.gov.mt/search-medicine-results?modSearch=sim&field=93EE9EB8B044EFED

[29] Hospital Formulary List Malta [Cited on 30 May 2018] can be accessed through URL: http:/deputyprimeminster.gov.mt/en/pharmaceutical/document/GFL/hop_gfl_may2018.pdf

2.7 Literature Review on Rare Diseases and HRQOL

Literature review about health related QOL issues was conducted between January and May 2017. A comprehensive search was done using available electronic databases and available online information.

2.8 QOL Assessment

A health-related quality of life (HRQOL) assessment tool was developed to focus on four different areas related to Rare Diseases (RDs) and their management (Appendix 2).

2.9 Design of HRQOL Tool

The HRQOL tool consisted of 30 questions. The tool contained 27 closed ended questions with specific response options. The remaining 3 questions required that the participant give written information, for which a text-box was provided. The data reported was quantitative and qualitative. The HRQOL was published online using the Google Forms (Google Corp. USA) platform in December 2017.

2.9.1 HRQOL Areas of Investigation

The HRQOL consisted of four main sections which included:

- Section A: Demographics and background information
- Section B: Personal care and independence
- Section C: Mental and social health
- Section D: Accessibility to orphan drugs

These four areas were chosen after extensive literature review showed these are the areas most lacking in research in RDs.

2.9.2 Section A: Demographics

Section A included background information about the respondent. Apart from demographic data, respondents could include information about their condition and diagnosis in this section. Questions in section A included information about misdiagnoses, length of time it took to receive the correct diagnosis, medical tests carried out to confirm the presence of a RD and if the condition was of genetic origin or not.

2.9.3 Section B: Personal Care and Independence

Section B of the HRQOL aimed to investigate personal care and independence of RD patients. Respondents were asked to rate everyday activities that impacted the QOL of the RD patient. These included information about how difficult daily activities such as 'bathing, washing and general hygiene' were in the past four weeks. A 5 point Likert-scale was utilised in which the rating system was from 1 to 5; where 1 rated the activity 'almost impossible' and 5 indicated that performing the activity was 'not a problem at all'. Participants were then asked questions about difficulty in mobility and independence and how this affected their QOL using Likert scale.

2.9.4 Section C: Mental and Social Health

Section C of the HRQOL investigated the mental and social health of RD patients. Participants were asked to reflect on how different day to day activities made them feel. Using the 5 point Likert scale, participants were asked to rate their experiences on how they felt while eating or being fed, dressing or undressing and lying in bed.

Participants were then asked questions designed to gather information on difficulty in communication and social interactions. Questions investigated if participating in recreational activities affected by their condition and if the RD has had an impact on their mental health.

2.9.5 Section D: Accessibility to Orphan Drugs

Section D examined access to ODs (if relevant). Four out of the five questions in this section were in a multiple choice style. Participants were asked to reflect on their ability to access medication and whether they can afford to buy their medication.

Questions asked in section D aimed to find if the RD patient was receiving a treatment, and if the medication was easy to access. Participants were given the choice of selecting an option stating 'There are currently no treatments for my condition' if there was no available treatment for their RD.

The patient's ability to source and afford the medication or treatment was investigated. Options such as 'there is currently no medication for my condition' and 'medication is available but not in my country' were included.

The final part of section D, investigated the financial and economical burden associated with RDs. Respondents were asked whether they experienced difficulties to buy their medication due to the price of the OD. Three options were given in a multiple choice question (yes, no and not applicable). The respondent was asked to rate the financial burden of their condition using a Likert scale (1 being not a burden at all and 5 being high burden).

The final question of the HRQOL tool aimed to find out whether respondents were willing to participate in future studies related to RDs.

2.10 Validation of HRQOL Tool

A validation tool was formulated based on the work of Lynn (1986). Permission for using this method was obtained from the author (Appendix 3). This validation method was chosen as it was quick and easy to use.

The validation tool started with a brief letter designed to inform the validator about the research. Brief background information on the researcher (name, address, email, study site) was included. Participation was voluntary and validation experts were informed that they may choose to withdraw their participation at any point prior to completion of the study.

The process began with special instructions to be followed by the validators. A screen-shot of an example of a question and a table for the representation of answers were included to aid the process (Table 2.2). Validators were asked to choose a number representing relevance of question (1 to 4); where option 1 was chose if the validators found the question to be ‘not relevant’ and option 4 was chosen if the validators found the question to be ‘very relevant and succinct’.

Table 2.2 Validation process table

Please select one answer / number based on the relevance of the questions provided in the questionnaire:	
Numbers	**Relevance interpretation**
1	Not relevant
2	Unable to access relevance without item revision
3	Relevant but needs minor alterations
4	Very relevant and succinct

For each of the 30 questions in the HRQOL tool, validators were asked to rate the question and if applicable comment. Depending on the rating they gave each question, they were given different instructions. For example, if for question 1, they chose option 2 or 3, they were asked to leave a comment or provide a suggestion to help in the selection of the question structure. All answers and comments were to be included in the spaces provided.

If option 1 was chosen for any of the questions by one of the validators, the question was omitted from the survey as per guidelines of the validation tool used. If the validator selected option 4, then the question was deemed 'very relevant and succinct'. This process applied to all 30 questions. A sample of the validation tool was attached (Appendix 4).

2.11 Validation Panel

The HRQOL tool was validated in order to establish the:

- Simplicity and viability of the questions included
- Reliability and precision in the words used
- Adequacy of the questions related to the problem intended to measure
- Ability of the questions to reflect underlying theory or concept to be measured
- Capability of the questionnaire to measure change (Edwards, 2010)

Selection criteria were put in place to identify validators for the HRQOL tool. Individuals identified had to have:

- Experience in scholarly research
- Recent experience in research
- QOL research
- General attributes of higher education and faculty
- Adequate knowledge on the measurement of demographic attributes

A list of possible validators was drawn and a formal participation invitation letter was formulated. The letter gave a brief description on the main researcher, background of the study and an official request for completion (Appendix 5). Each participant was contacted via email and received; the HRQOL questionnaire, letter of recruitment, validation tool and instructions.

The validation panel consisted of 7 members. These included 3 pharmacists, 2 researchers, 1 clinician and 1 RD patient. Responses were received and comments and suggestions were applied to the HRQOL tool.

2.12 Need for revalidation

After the validation of HRQOL tool, suggestions and feedback were collected and the HRQOL tool was altered as suggested. One of the questions received a rating on 1, therefore deemed irrelevant and removed from the HRQOL tool as per validation tool guidelines. The phrasing of 3 questions in sections A and C were changed as per recommendation of one of the validators. There was no need to revalidate the HRQOL assessment tool.

2.13 Testing for Validity and Reliability

The validity and reliability of the tool was tested by the main researcher using the Collingridge six step validation method.[30] The aim of Collingridge method was to ensure the questionnaires face value was established by experts, the HRQOL was pilot tested on a 27 participants, and analysis included using Principal component analysis and Cronbach Alpha methodology.

Step 1 and 2 of the Collingridge method involved 'running a pilot study'. The tool was reviewed again following the pilot study and questions deemed irrelevant or weak were omitted.

Step three of this method involved 'Cleaning collected data'. Data was reverse coded; meaning that if participants had filled out the HRQOL carefully, their answers to questions that were phrased in a negative manner had to correlate to answers of similar questions that were phrased positively.

[30] What it takes to validate a survey [Cited 2018 May 30] Can be accessed from URL: http://www.mtab.com/validating-a-survey-what-it-means-how-to-do-it/

Step 4 involved 'Principal components analysis' which validated what the questionnaire is actually measuring.

The next step was 'checking for internal consistency'. This method focused on reviewing the consistency of questions in the same section by ensuring the consistency of the answers. The Cronbach Alpha test allowed for this detection. Values of this step ranged from 0 to 1.0, and a result of 0.6 and higher indicated internal consistency while a value lower than 0.6 indicated inconsistency.

The final step for checking validity and reproducibility of the HRQOL tool, involved 'revising the survey' based on the feedback and information obtained using the six step reliability and validation method.

2.14 Inclusion and Exclusion Criteria for HRQOL Tool

The inclusion and exclusion criteria for participation were included in the introduction section of the HRQOL tool. RD patients or their guardians or carers who could read and write in English, who gave consent and were above the age of 18 years, were invited to take part in the HRQOL questionnaire. Participants under the age of 18 years who were not diagnosed with a rare disease as classified by EURORDIS[31] were excluded.

2.15 Ethics Approval

The University of Malta Research and Ethics Committee (UREC) approval was granted prior to the commencement of the study (Appendix 6).

[31] The complete list of Rare Disease as classified by the European Organisation of Rare disease [Cited on 30 May 2018] can be accessed from URL: http:/www.eurodis.com/raredisease/classification

2.16 Obtaining Consent

Prior to filling in the questionnaire, respondents were given a brief background of the study and its aims. Respondents were assured of their anonymity and were informed about aggregation of data for reporting purposes.

Respondents were then asked to choose to give or refuse consent to participate in the study. Respondent had to confirm that they read and understood the introduction before proceeding to fill out the questionnaire. The introduction section also included the email address of the main researcher for the participants to communicate with the researcher.

2.17 Dissemination of HRQOL Tool

RD alliances and support groups were contacted locally and internationally by email to request them to disseminate the HRQOL to their patients. An official request email template was drafted to be forwarded to all (Appendix 7).

A list of all rare disease alliances and support groups was drafted (Table 2.3). Electronic search tools were utilised to find the organisations. The search terms included; 'Rare Disease organisation', 'rare disease support group or rare disease alliance'. The search strategy included 'Rare disease or organisation or alliance in…'; this search was then combined with a country or a region. One Hundred and Fifty organisations were identified to work with RD. A list of 12 of the most popular RD organisations in the US and the EU was drafted.

An email request was sent out to the organisations with background information on the research and a copy of the HRQOL tool attached. Instructions on how to fill out the HRQOL were also included.

Table 2.3 RD national organisations and patient groups contacted to disseminate HRQOL tool

Organisation contacted	Region
EURORDIS	Europe
NORD	North America
Marigold Foundation	Malta
Genetic alliance	US
Rare disease UK	United Kingdom
National organisation For rare diseases	US
Global Genes	US
Genetic Alliance UK	United Kingdom
Genetic and rare disease disorders organisation	Ireland
ESPERare foundation	Switzerland
Rare Disease Foundation of Poland	Poland
NVACP	The Netherlands

2.18 Analysis of HRQOL Data

The IBM Statistical Package for Social Sciences (SPSS), Edition Standard v24 was used for data analysis and tabulation. Descriptive statistics including frequency for nominal and categorical variables; and mean ± standard division and median for

continuous variables were computed. Parametric statistical techniques such as the independent sample t-test were used to assess the difference between group mean scores. Independent t-tests were used to compare and to find the differences between the mean scores of the US and EU groups. A non-parametric statistical technique, chi-square for independence (cross table), was used to compare the frequencies of nominal variables for the two groups. All statistical tests were two tailed with $p < 0.05$ as the significance level.

2.18 Publications

The following work has been published (Appendix 8):

Posters and abstracts

- Abbas A, Vella Szijj J, Serracino-Inglott A. Impact of RDs on quality of life. 9th European Conference on Rare Diseases & Orphan Products (ECRD, 2018, Vienna) *Poster*
- Abbas A, Vella Szijj J, Serracino-Inglott A. Accessibility issues associated with Orphan Medications. Orphan Drug Congress (2017, Barcelona) *Abstract*

Invited speaker

Abbas A, Vella Szijj J, Serracino-Inglott – Rare Diseases and Quality of Life

Oral presentation at Malta rare diseases colloquium - 2015

Abbas A, Vella Szijj J, Serracino-Inglott – What are orphan medications and why do we need them? *Oral presentation at the Malta rare diseases colloquium* – 2016

Abbas A, Vella Szijj J, Serracino-Inglott – Access to orphan medications and quality of life in rare diseases *Oral presentation Malta rare diseases colloquium* – 2017

Abbas A, Vella Szijj J, Serracino-Inglott – The rare disease landscape in Malta *Oral presentation Barcelona Orphan Drug Congress* - 2017

Abbas A, Vella Szijj J, Serracino-Inglott – Rare Diseases and Quality of Life *Oral presentation Marigold foundation annual rare diseases day* - 2017

Future publications

- Abbas A, Vella Szijj J, Serracino-Inglott A. Issues associated with Orphan Medications Access in the EU and US. FIP (2018, Scotland) *Poster*
- Abbas A, M, Vella J, Serracino-Inglott A. Access to Orphan drugs in Rare Disease (ACCP poster presentation, 2018, USA) *Poster*

CHAPTER 3

RESULTS

3.1 Accessibility of Orphan Drugs

Sixty-eight articles relating to 29 countries were included in this study (28 European member states and the United States). No reports, legislations or regulations were included from countries other than the EU and US as the inclusion criteria was not met. Six themes for assessing the accessibility of ODs were identified and used for a systematic literature review. The six themes were:

1) OD policies
2) Marketing Authorisation
3) Incentives offered
4) Pricing of ODs
5) Reimbursement
6) Pharmacovigilance

The six themes explain the political or regulatory mechanism utilised and the relevant influence with regard to patient access to orphan medicines (Grammie et al, 2015). The 6 themes identified generated subthemes (Figure 3.1). The accessibility of ODs in each country is included as an appendix (Appendix 9).

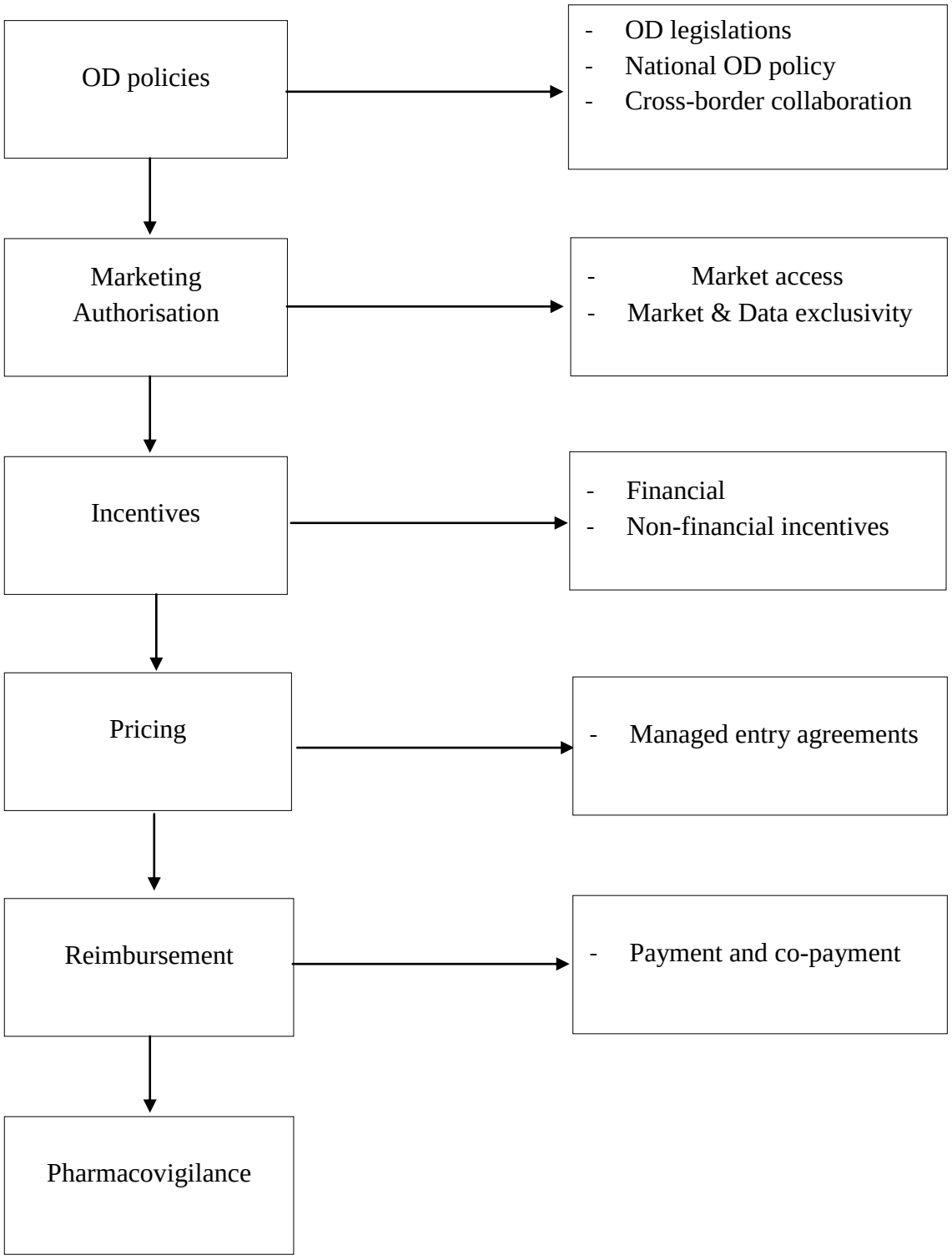


Figure 3.1 Themes and subthemes used to assess accessibility of orphan drugs in the EU and US

Through literature review, it was found that subthemes of OD policies included:

- OD legislations
- National OD policy
- National RD policy
- Cross border regulation
- OD designation

3.1.1.1 Orphan Drug Legislations

The United States introduced an OD policy in 1983 under the OD Act. Australia followed by issuing the Australia Therapeutic Goods Act in 1990 and they included a section on ODs in 1997[32]. The EU followed with the EU legislation [Regulation (CE) N°141/2000] for orphan drugs in 2000. Taiwan introduced a small section on ODs in their Medicines Act Chapter 176a Section 9 and Singapore's Rare Disease and Orphan Drug Act which specified special incentives for ODs (Song et al, 2012). All OD legislations examined aimed to ease the burden of cost on patients and make OD development a lucrative decision for pharmaceutical companies (Blankart et al, 2011). The EU and US legislations contained incentives for research and development of ODs. The incentives included:

1. Tax exemptions
2. Tax return for research cost
3. Free scientific advice and;
4. Market exclusivity

[32] Federal Register of legislation [Cited on 30 May 2018] Can be accessed through URL: https://www.legislation.gov.au/Details/F2017C00528

Some OD legislations differed from others in terms of incentives offered (Table 3.1). In the EU, fast track for marketing authorisation of ODs and pre-licensing use for selected RD patients is available (Feltmate et al, 2015).

Table 3.1 Overview of incentives offered by orphan drug act in the EU and US

Legislation and provisions	**US**	**EU**
OD legislation/policy	Orphan Drug Act (1983) FDA[33]	Regulation No. 141/2000 (2000) (European Medicines Evaluation Agency)[34]
Marketing exclusivity	7 years	10 year (extended for ODs used in paediatric patents)
Accelerated evaluation availability	Yes	Yes
Application or regulatory fee reduction	Yes	Yes
Scientific advice	Yes	Yes
Tax Incentives	50% tax credits for clinical research cost	Tax credit depending on country (Appendix 9)

[33] FDA OD act [Cited on 30 May 2018] can be accessed from URL: https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm364750.htm

[34] EU Regulation on OD [Cited 2018 May 30] can be accessed from URL: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2000_141_cons-2009-07/reg_2000_141_cons-2009-07_en.pdf

3.1.1.2 National Rare Disease Plans

The primary goal for National Rare Disease Plans (NRDPs) is to produce policy that promotes research, improves access to healthcare and ODs and increase awareness on RDs (Michel and Toumi, 2012). Unlike OD legislations, NRDPs do not have a specific legislation in place instead; NRDPs show the 'readiness' of a country or a region to take action in the RD field (Denis et al, 2010b). NRDPs are documents with a vision on how to improve health outcomes for RD patients (Table 3.2). Three EU countries, (Bulgaria, Greece and Romania) established joint NRDPs which helped outline the needs of RD patients and may particularly impact OD purchasing power and affect government budgeting, pricing and reimbursement (Stefanov and Taruscio, 2012).

Table 3.2 Aims of national rare disease plans

Ensure that RDs are appropriately coded and categorised in OD registers
Promote research on RDs
Create a centre of expertise on RDs
Promote pooling of expertise at a European and a global level
Empower patients by involving them in policy and decision making

3.1.1.3 Cross-border Regulation

The EU has a centralised procedure for OD approval and OD designation for all its member states. The centralised procedure aims to improve uniformity in terms of OD accessibility for everyone living within a member state (Trama et al, 2009). The 2011/24/European directive states that patients within the EU have a right to gain cross border treatment. The 2011/24 directive allows RD patients within any member state the right to access healthcare within any EU healthcare service if their national

healthcare system cannot provide treatment required regionally within an appropriate time span (Feltmate et al, 2015). Due to differences in OD pricing and reimbursement laws across EU member states patients face differences in OD pricing and reimbursement.

3.1.1.4 Orphan Drug Designation

Orphan Drug Designation (ODD) is usually granted under four criteria; these include:

- Severity of RD
- Unfulfilled treatment needs (no treatment available for the RD)
- Pharmacoeconomics
- Prevalence of the RD (Barak and Nandi, 2011)

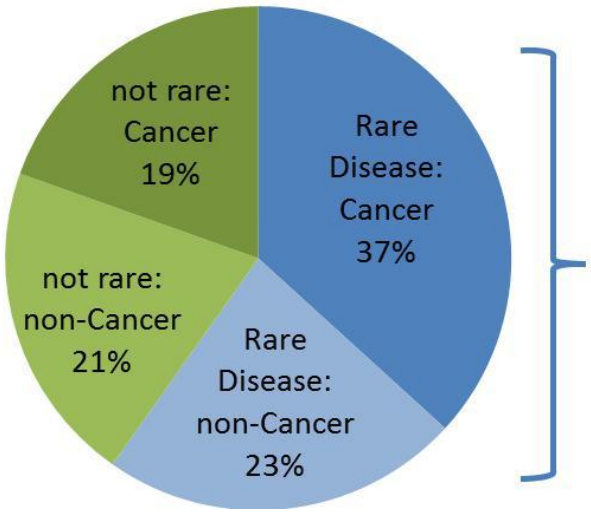
The prevalence of RD is dependent on the regions definition of what a RD is (Table 3.3). The pharmacoeconomics approach is considered if the OD will yield a profit and cover development costs. Due to the limited number of RD patients, there are few ongoing clinical trials involving ODs which can lead to a lack of robust clinical data (Rosenburg-Younger et al, 2011). ODD permits drugs to gain some exemptions from clinical trials or in the case of the EU, get research help throughout the OD development programme (Iskrov and Stefanov, 2014). It is estimated that the United States has the highest number of ODDs of which 37% (n=69) are for rare cancers (Cheng et al 2012).

Table 3.3 Number of orphan drug designations in the EU & US

Region	Number of designated OD (January 2000 to December, 2017)
EU (refer to appendix 7 for individual country analysis)	1952[35]
US	3642[36]

The FDA has two types of ODD.

1. **Breakthrough Therapy Designation (BT):** is a form of designation for medicines used to treat RDs where clinical data indicate that the drug may substantially improve the RD. Most approvals were granted for rare cancer ODs.



Over 60% (n=107) of BTs approved in the US are to treat RDs

Figure 3.2 FDA breakthrough therapy designation approvals (2013 to 2017) (N=179)

[35] EMA OD Section II [Cited 2018 May 30] Can be accessed from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp&mid=WC0b01ac0580b18a41

[36] FDA Data Access [Cited 2018 May 30] can be accessed from URL: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/listResult.cfm

2. **Priority Review Designation (PRD):** is a scheme applied to medicines to treat a life threatening condition. The drug must demonstrate significant improvement to the condition to remain designated after being granted ODD.

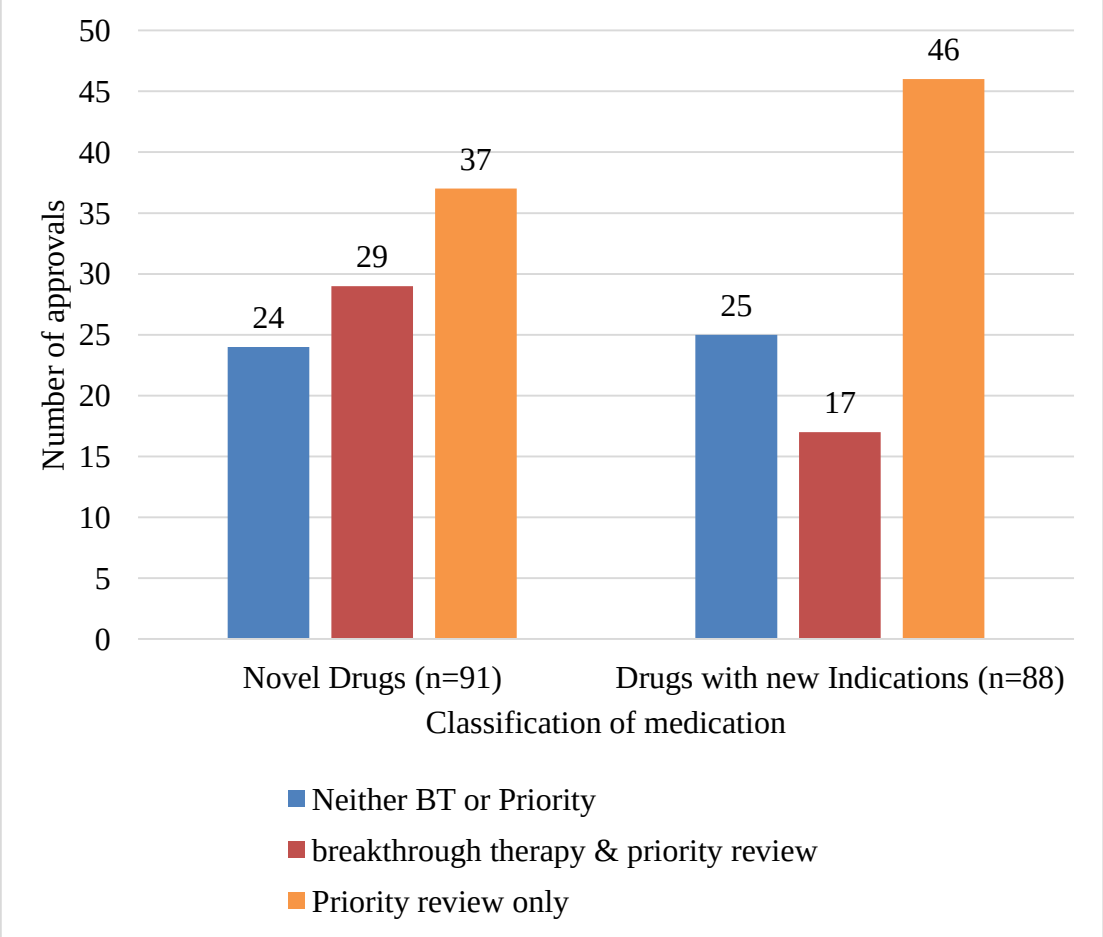


Figure 3.3 Comparison of FDA ODD approvals (2013 to 2017) (N=179)

Figure 3.3 shows the number of novel drugs approved as ODs and the number of existing medicines that were given ODD.

3.1.2 Marketing Authorisation

Accessibility and availability of ODs correlates with Marketing Authorisation (MA). MA assessment in the EU is different to the United States, where the FDA deals with OD authorisation in a manner similar to that of non-OD (Russell et al, 2014).

Other non-member European countries such as Serbia and Macedonia grant MA for ODs based on information from the EU (Blankert et al 2016). The granting of MAs can impact access to ODs in small states (such as Serbia and Macedonia) as pharmaceutical companies are inclined to apply for approval in the US or the EU before applying for MA in other countries. It was evident that non-EU and US countries rely on EMA and FDA clinical studies to assess efficacy of ODs (Joppi and Garattini, 2013).

ODs are evaluated by examining the RD severity and unmet medical needs of the population. Differences in the interpretation of the results of these studies may determine MA for ODs (Morel et al, 2013). The number of ODs that obtain MA after receiving an ODD was shown to be lower than 11% of all ODDs approved in member states in the first decade of EU OD legislation (2000–2010). The US had a similar rate of MAs as only 16% of ODs with ODD received MA approval in the last three decades (Blankart et al, 2011). Low MA approval rate can be attributed to the differences in authorisation criteria for ODDs vs. those for MA. Research and development incentives for ODs push many pharmaceutical companies to try to gain ODD. In recent years both the FDA and EMA have demonstrated that gaining ODD does not mean automatic approval for MA (Mariz et al, 2012). Figure 3.4 and Figure 3.5 show the OD MA in the EU and US.

Table 3.4 Number of ODs with marketing authorisation in the EU and US

Region	Number of approved ODs (January 2000 to December, 2017)
EU	140 (Giannuzzi et al, 2017)
USA	415 (Giannuzzi et al, 2017)

Table 3.4 shows the number of approved ODs by the EMA and FDA.

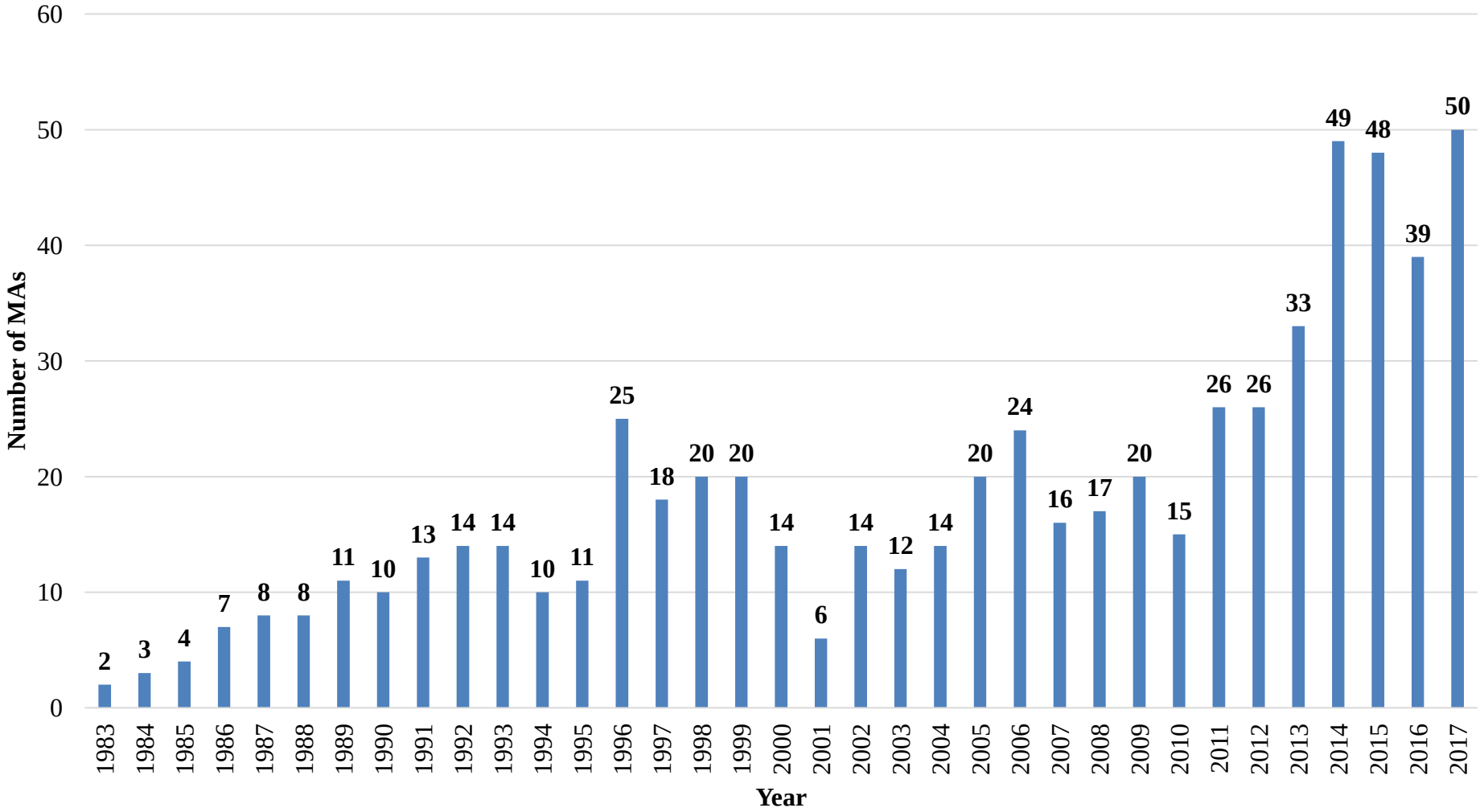


Figure 3.4 Number of marketing authorisations for orphan medicinal products granted by FDA

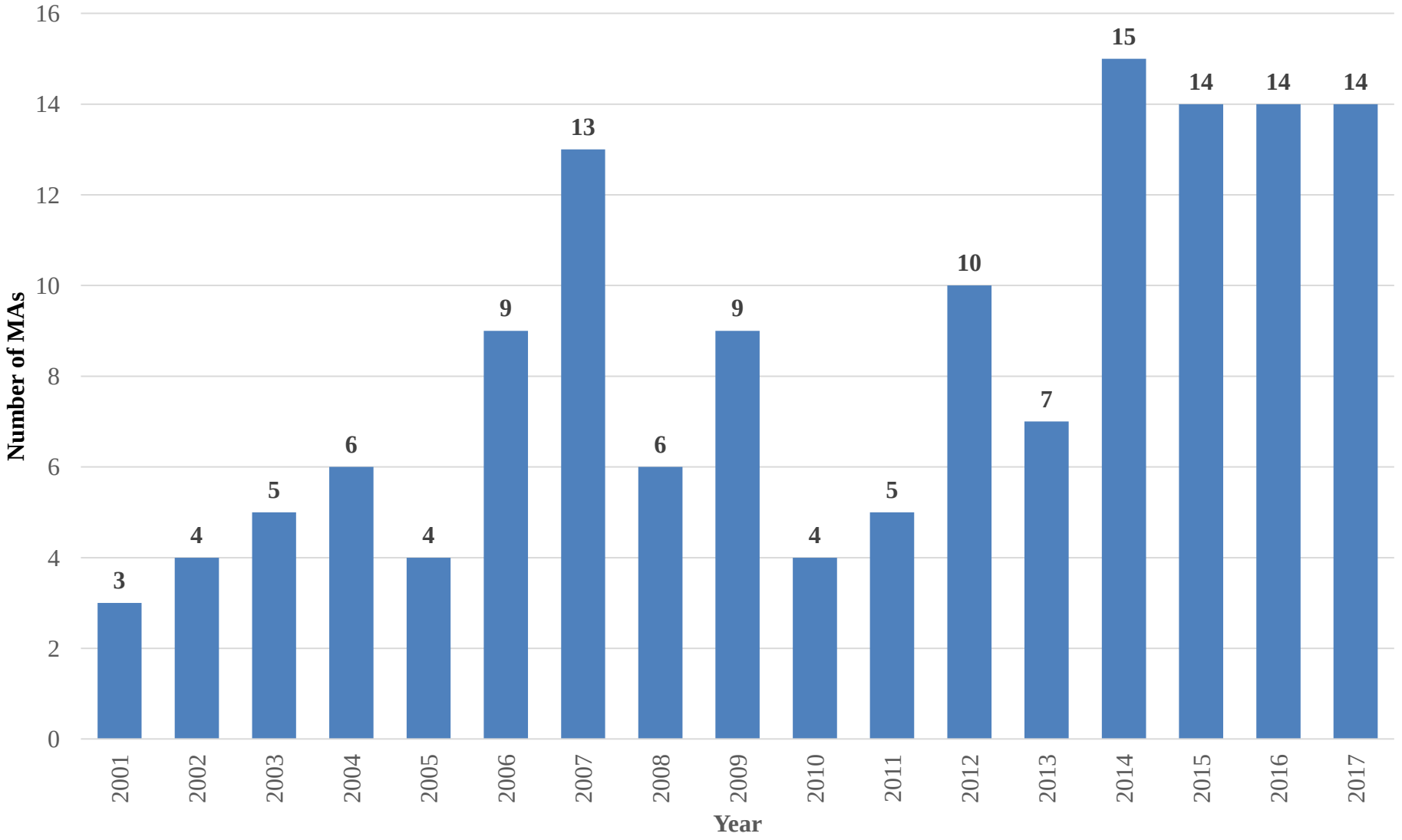


Figure 3.5 Number of marketing authorisations for orphan medicinal products granted by EMA

3.1.2.1 Early Marketing Authorisation and Market Access

Both the US and the EU have an Accelerated Procedure Scheme (APS) to help improve OD accessibility for RD patients (Kesselheim, 2012). APS takes an average time frame of 6 months, about half of that for a normal marketing procedure (Kesselheim, 2012). APS incentives include (Table 3.5):

- Priority review
- Fast tracking approval
- Accelerated approvals for certain RDs

APS is available for both ODs and non-ODs; however, ODs likely to be considered for APS. An urgent need for the drug, unmet medical needs and high evidence of therapeutic benefits can help with granting of APS.

There are considerable crossovers in terms of objectives and features (Table 3.5) between the FDA and EMA APS programs and they may be used in combination (Mariz et al, 2013). ODs that qualify for fast track schemes in the US may be eligible for accelerated approval and priority review. In the EU, a medicinal product benefitting from PRIME[37] (Early access tool, supporting patient access to innovative medicines) scheme may also qualify for Conditional Marketing Authorisation (CMA). ODs benefitting from early access are also eligible to the EMA centralised licensing procedure (Russell et al, 2014). Early accessibility is applicable to both ODs and non-ODs in both the EU and US, although the schemes are more favourable for ODs. ODs

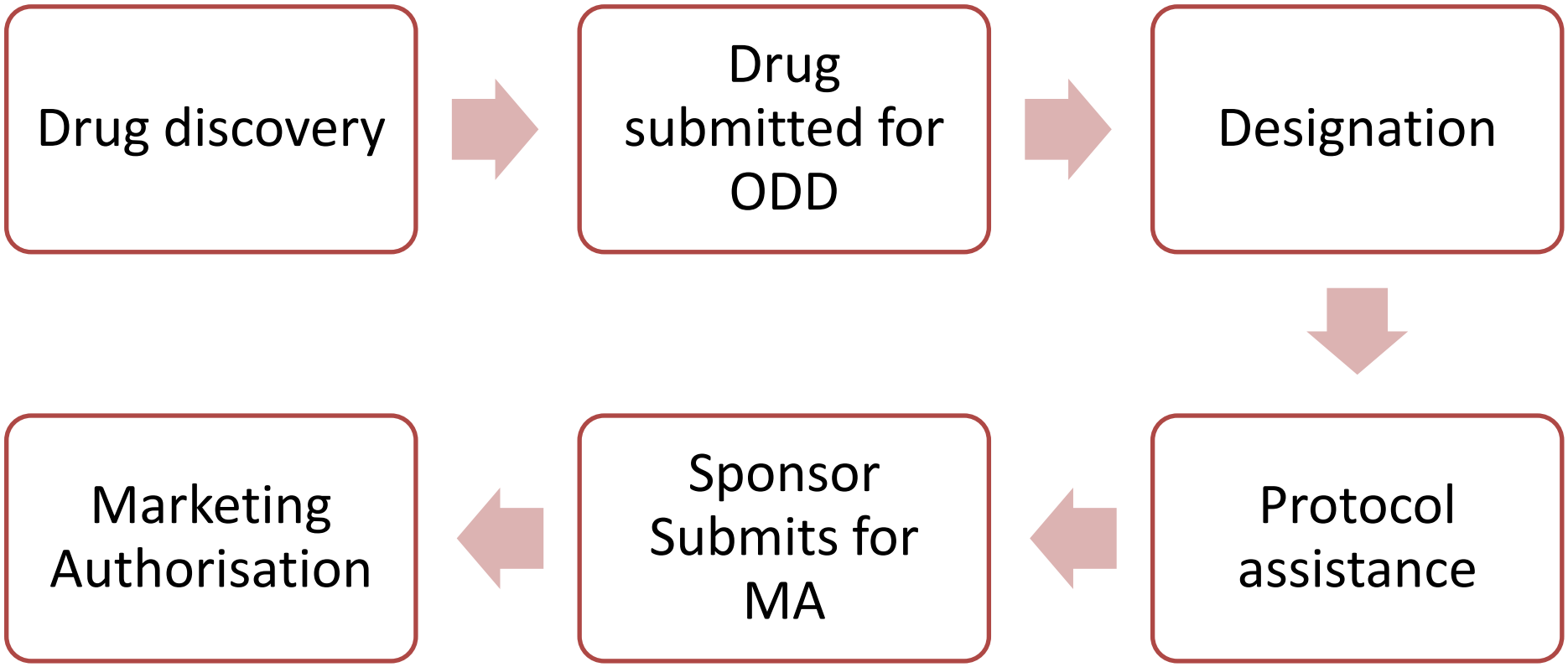
[37] EMA R&D [Cited on 30 May 2018] can be accessed through URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000660.jsp&mid=WC0b01ac05809f8439

do not automatically qualify for accelerated procedures but are more likely to qualify for early access (Michel and Toumi, 2012).

Table 3.5 Features contributing to early marketing authorisation for orphan drugs

Features	FDA	EMA
Enhanced early agency interaction	Fast track designation	PRIME (Priority Medicines scheme), Adaptive Pathways (AP)
Dedicated agency	Breakthrough therapy designation, Regenerative Medicine Advanced therapy Designation (RMAT)	Support for SMEs, Support for ATMPs (CAT), PRIME early rapporteur
Earlier market authorisation and access	Accelerated Approval Scheme	Conditional Marketing Authorisation (CMA) Exceptional circumstances scheme Compassionate use programme (CHMP)
Accelerated review of MA	Priority review (<180 days, the usual is 300 days)	Accelerated assessment (<150 days, the usual is 210 days)

Figure 3.6 Orphan Drug regulatory process in the EU and US



3.1.3 Incentives

OD legislations, acts and policies influence pharmaceutical companies to encourage OD development.

3.1.3.1 Financial Incentives

Financial-Incentives (FIs) offered by both the EU and the United States consist of:

- Funding of research
- Tax exemptions
- Fee reductions
- Market exclusivity

Incentives are in place to allow OD manufacturers to recover costs of research and development (Simoens, 2011). Blankart et al, found that less than 12% of OD clinical trials would have still been conducted without the financial incentives offered by OD legislations.

Whole or part exemptions from the payment of fees for ODD application designated for human use are granted based on the decision made by the Executive Director on the usage of the contribution from the EU (Table 3.6), provided for by Article 7(2) of Regulation (EC) No 141/2000[38] taking account of the advice of the COMP (Michel and Toumi, 2012).

[38] EU legislation council [Cited 2018 May 30] can be accessed from URL: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2000_141_cons-2009-07/reg_2000_141_cons-2009-07_en.pdf

Table 3.6 Overview of financial and non-financial fee reduction types processed in 2017 by EMA

Procedure/Type of Application	No. of transactions 2017	Fee reductions 2017	
		Euro	% of total
Protocol Assistance (including follow-up)	164	8,395,750	63.3%
Initial Marketing Authorisation	26	3,051,520	23.0%
Inspections	63	1,275,900	9.6%
Type IA / IB Variations	7	41,200	0.3%
Type II Variations	4	294,600	2.2%
Transfer	1	7,100	0.1%
Annual fees	2	202,400	1.5%
Total	**267**	**13,268,470.00**	**100.0%**

3.1.3.2 Non-Financial Incentives

Non-Financial Incentives (NFIs) found include:

- Accelerated procedure schemes,
- Off label use scheme (for pre-licensed ODs)
- Research advice
- Scientific and regulatory consultation (Protocol assistance) (table 3.6)

Certain EU countries allow pre licensing use of ODs given that there is some clinical evidence (Garau et al, 2014). This allows better accessibility for RD patients living in countries where MA has not been granted yet for the OD. The off label use scheme is usually the most applied procedure used to assist patients in accessing unlicensed ODs. It is important to note that the off label scheme is reserved for RDs that have a serious morbidity and mortality ratio with no alternative treatment available. In countries such

as The Netherlands, the physician and the patient must submit an application with highlighted evidence for the required OD therapy (Grammie et al, 2015).

3.1.3.3 Market and Data Exclusivity

Market and data exclusivity (ME) is granted once a medicine is designated. Orphan designation is an incentive that allows the OD developer 7 years of ME in the United States and 10 years in the EU. The designation translates to the company being the sole producer of the OD molecule for that frame and the regulatory agency (FDA or EMA) cannot authorise another molecular entity to treat the same indication. The designated OD can 'expand' its indication. Picavet et al, highlighted in a study that OD regulations in the EU will not adhere to the 10-year market exclusivity incentive if the OD does not prove clinical efficacy. No withdrawal of market exclusivity in both the EU and the US have been found.

Data exclusivity refers to a period of time during which a company cannot cross-refer to the data in support of another MA[39]. The EMA uses the 8+2(+1) exclusivity formula (Figure 3.7). The first 8 years the data of the OD is protected and the last 2 years ME is guaranteed. The decision for the addition of the 1 year ME is offered to paediatric formulations with support of significant clinical data.

[39] FDA Chronicles [Cited 2018 May 30] can be accessed from URL: https://www.fda.gov/downloads/drugs/developmentapprovalprocess/smallbusinessassistance/ucm447307.pdf

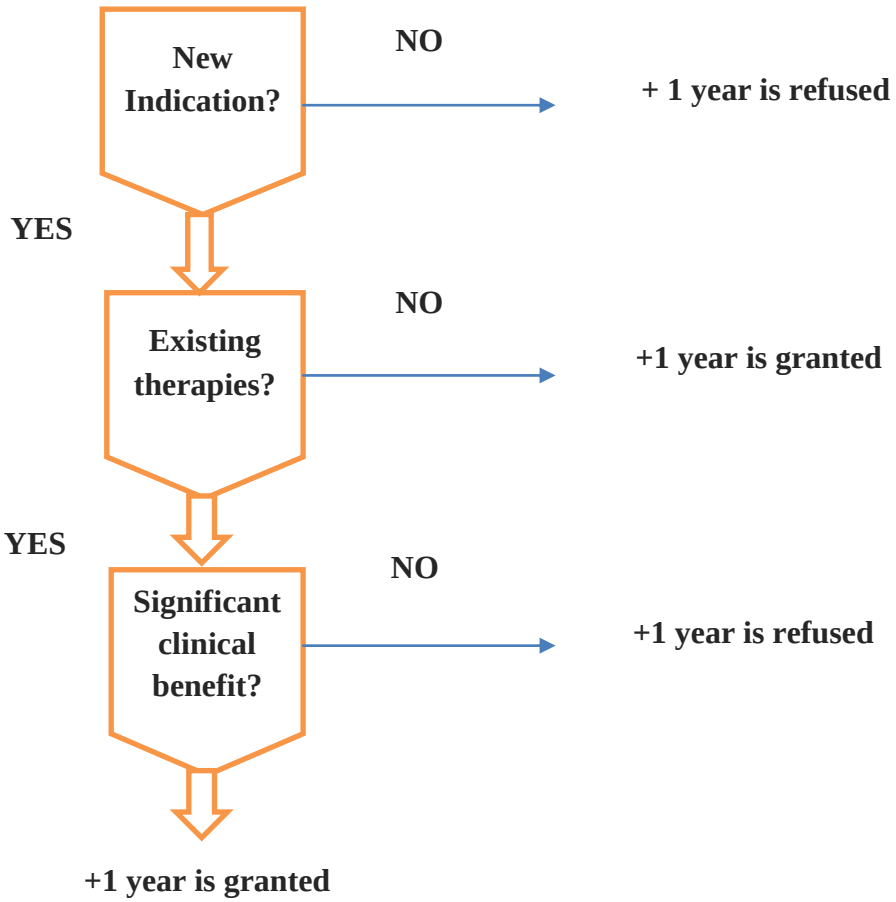


Figure 3.7 Decision tree for EMA +1-year market exclusivity for paediatric formulations

Due to the incentives offered for drugs designated as ODs, many manufacturers attempt to gain orphan status for drugs which are not intended to treat RDs (Grammie et al, 2015). Patients with RDs have a high willingness to pay, which can put manufacturers in a position to elevate and inflate the prices of ODs. This can cause inequality in access and can put high pressure on payers and health budgets.

3.1.5 Pricing of Orphan Drugs

There are no reference prices issued by sponsors in the case of ODs. Due to the small RD population size and high cost of research and marketing process, OD prices typically exceed €100,000 per patient annually (Arends et al, 2015). The newly developed Agalsidase alfa for the treatment of Fabrys Disease, costs around €250,000 annually per patient in the US (Arends et al, 2015). Prices of ODs are generally comparable in the EU and the US, but differences in re-imbursement and co-payment are a factor that can affect accessibility. US based patients face a higher cost of ODs due to co-payment and reimbursement issues (Simoens and Steven, 2011). ODs with multiple RD indications, for chronic RDs or for which an increase in overall survival or health related quality of life has been demonstrated, are associated with higher annual cost of illness. There were no associations found between annual cost of illness of ODs across countries and the different pricing and reimbursement systems (Pivcat et al, 2014). Prices of ODs are influenced by elements such as accessibility to an alternative drug treatment, repurposing and reimbursement (Drummond et al, 2007).

Unlike the US, most EU member states have adapted a fixed pricing method. The fixed pricing method involves having a reference price set by the manufacturing company and involves 2 methods. The first method involves examining the requested OD price by the manufacturer with the price requested in other regions and the second involves a set price agreed on by the government or health body. These two examples of fixed pricing ensure equality between countries in access to ODs. The United States and Germany has a free pricing market which allows the manufacturer to name the price (Simoens and Steven, 2011).

3.1.5.1 Managed Entry Agreements

Managed entry agreements (MEA) are contractual agreements between the marketing authorisation holder and payers (Bouvy et al, 2018). MEAs are used when a 'yes' or 'no' decision on the prices and reimbursements are not concluded due to one of clinical or financial uncertainty on the OD (Bouvy et al, 2018). MEAs are used to fund high cost ODs (Grammie et al, 2015). Financial uncertainty agreements allow the payer and manufacturer to agree that if the OD shows low cost effectiveness, then the manufacturer would reduce the price or reimburses the payer. It was found that 7 EU countries had MEAs in place, the highest number of MEAs were in Italy (N=25) (Garattini et al, 2015). The number of MEAs in the United States could not be found.

3.1.6 Reimbursement of Orphan Drugs

An important barrier to RD patient access to ODs is the reimbursement factor. ODs that are expensive, not paid for by the patients' insurance or the government are inaccessible to RD patients (Trama et al, 2009, Denis et al 2011, Simoens and Steven, 2011).

The pharmacoeconomical values of ODs are assessed by the Health Technology Assessment (HTA) in both the EU and the US. The cost effectiveness of the OD is assessed by the HTA under two themes; quality adjusted life years (QALY) and incremental cost effectiveness ratios (ICER) (Trama et al, 2009). Due to the lack of clinical data for ODs, it is difficult to conduct HTA. As a result of this lack of information, many countries make exemptions when it comes to OD assessment.

Most ODs assessed do not meet the usual cost effectiveness criteria of the FDA or EMA. Payers take into account factors, such as unmet medical needs and added QALY (Simoens et al, 2012). Other factors taken into account by the US and the EU are; clinical impact, medical ethics, impact of the OD on the budget, number of patients affected and political pressure. Italy and France would reimburse 95% of the ODs available in the EU market, while Sweden would reimburse 70% due to differences in HTA (Barak and Nandi, 2011). Countries in the EU do not rely completely on clinical data by the manufacturer; rather they take into account cohort studies and published literature on these ODs. France looks into the value of reserving a patient's mortality regardless of cost of the OD (Grammie et al, 2015).

3.1.6.1 Payment and Co-payment

Co-payment or co-insurance has a major impact on accessibility to ODs (Reider, 2000). Co-payment in the US can be significant and average around $100 per OD per patient or on average 35% co-insurance of the OD cost (Grammie et al, 2015). The US has a co-insurance cover (Medicare) that would cover up to 95% of drug cost when the patient reaches the threshold out of pocket payment of $4350[40] annually (Table 3.7) (Grammie et al, 2015). Only 7 of the reviewed countries had a reference figure of co-payment.

[40] CMS website [Cited on 30 May 2018] can be accessed through URL: https://www.cms.gov/Medicare/Eligibility-and-Enrollment/LowIncSubMedicarePresCov/Downloads/StateLISGuidance021009.pdf

Table 3.7 Percentage expenditure on orphan drugs from total health budgets

Year	Percent expenditure	Country	Reference
2006	1.2%	Netherlands	Kanters et al, 2014
2007	1.9%	European Union	Orofino et al, 2010
	4.9%	United States	Divino et al, 2016
2010	3.2%	European Union	Schey et al, 2011
	21%	Global	Meekings et al, 2012
	11.2%	Global	EvaluatePharma[41]
2012	4.3%	Netherlands	Kanters et al, 2014
2013	2.7%	Sweden	Hutchings et al, 2014
	3.1%	France	Hutchings et al, 2014
2014	8.8%	United States	Divino et al, 2016
	1%	Latvia	Logvis et al, 2016
2016	4.7%	European Union	Schey et al, 2011
2018	9.7%	United States	Divino et al, 2016
	4%	Sweden	Hutchings et al, 2014
	4.4%	France	Hutchings et al, 2014
2020 predicted	5%	European Union	Schey et al, 2011
	4.5%	Sweden	Hutchings et al, 2014
	4.4%	France	Hutchings et al, 2014
2022 predicted	21.7%	Global	EvaluatePharma[41]

[41] EvaluatePharma [Cited 2018 May 30] can be accessed through URL: https://onlinelibrary.wiley.com/doi/full/10.1002/ddr.21176

3.1.6.2 Pharmacovigilance

The FDA, unlike the EMA has a Pharmacovigilance plan (PP).[42] The FDA plan is to gather information on three areas specific to ODs:

1. Important identified risks
2. Important potential risks
3. Important missing information

A specific plan would be developed for the OD by the sponsor to monitor the drug safety and is discussed with the FDA prior to approval for ODD (Edwards, 2001). The plan must contain information on:

- Safety issue related Pharmacokinetics
- Objective of proposed action(s)
- Action(s) proposed on how Pharmacovigilance will be conducted
- Rationale for proposed action(s)
- Monitoring by the sponsor for safety issue and proposed action(s) related to ODs[43]

Routine Pharmacovigilance monitoring is carried out which include adverse drug reactions (ADRs) and periodic safety update reports (PSURs) (Venning, 2000).

[42] FDA pharmacovigilance plan [Cited 2018 May 30] can be accessed through URL: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073107.pdf

[43] Guidelines for Good Pharmacoepidemiology Practices (GPP), International Society for Pharmacoepidemiology, [Cited on 30 May 2018] can be accessed through URL: http://www.pharmacoepi.org/resources/guidelines_08027.cfm,

3.2 National Orphan Drug Policy Malta

This section deals with the local (Maltese) findings on RDs and ODs. Through assessing local data and interviewing key figures and policy makers in the RD scene in Malta, the following findings were obtained; As of November 2017, Malta has not yet adopted a national policy or plan for RDs.[44]

The Malta congenital anomaly register showed that over 70% of all registered cases annually are classified as a RD. It has an annual registry of 100 to 120 cases annually. The Malta National Cancer Registry yields around 12% (n=240) of incident cases matching RDs diagnosis as registered on Orphanet. Treatment Abroad List Malta revealed that over 60% (n=210) of all patients sent for treatment outside Malta and Gozo have a documented RD.

The management of RDs and accessibility of ODs were assessed under 13 themes (Table 3.8).

[44] RD action plan EU [Cited on 30 May 2018] can be accessed through URL: http://www.rd-action.eu/wp-content/uploads/2017/10/Malta-Report-09.10.2017.pdf

Table 3.8 Summary of the RD & OD findings in Malta

RD plan	Not specific to Malta
Centre of expertise on RDs	No
RD registers	Four registers currently active
Screening at birth	No legislation to 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)

3.2.1 Rare Disease Plan

Malta has no RD plan or strategy. Policy makers in Malta have established that there is a need for a strategy to be implemented which focuses on:

- Establishing a local RD register for clinicians to register RD cases on
- Creating a 'treat abroad' scheme for specialised cases of RD
- Establishing a Pathology Database

3.2.2 Centre of Expertise on Rare Diseases

Malta has no centre of expertise (COEs) for RDs and there are no formal plans in place to establish one. Since it is a requirement for EU member states to establish a COEs prior to joining European Reference Networks (ERNs), policy makers in Malta are working towards a plan to establish COEs to allow participation in ERNs.

3.2.2.1 European Reference Networks

Policy makers in Malta are working towards implementing a 'formal process of designation' for COEs in order to participate in ERNs. To date, no Health Care professional in Malta has taken part of an ERN application, either as a coordinator, member or affiliated member.

3.2.3 Rare Disease Registration

There is 1 RD specific register in Malta and 3 other registers which contain reports on RDs (Table 3.9). The RD register is available for the general public is available on the Ministry of health website but is not updated or promoted. No specific legislation was enacted in this regard until September 2016. 'All epidemiological registers are kept

within the remit provided by data privacy legislation for the protection of public health and management of health services'. Data collected through the RD register available showed that:

- Only 3,258 people living with RDs in Malta have been registered which represents only 13% of the total RD population in Malta (28,000).
- Over 550 different RDs have been registered within the population, although estimates indicate there are > 600 RDs within the Maltese population.

Table 3.9 Registers currently available or being developed in Malta

Register	**Status**	Data
Cancer register	Launched (2005)	240 cases of rare cancers annually
Congenital anomaly	Launched (2002)	100-120 cases recorded annually
Malta RD register	Launched (2013)	25 reported cases (2017)
Treated abroad RD register	Launched (Data kept from 2000 onwards)	350 documented RDs annually
Clinician specific register	In development	-
RD Genetics data	In development	-
RD Pathology data	In development	-

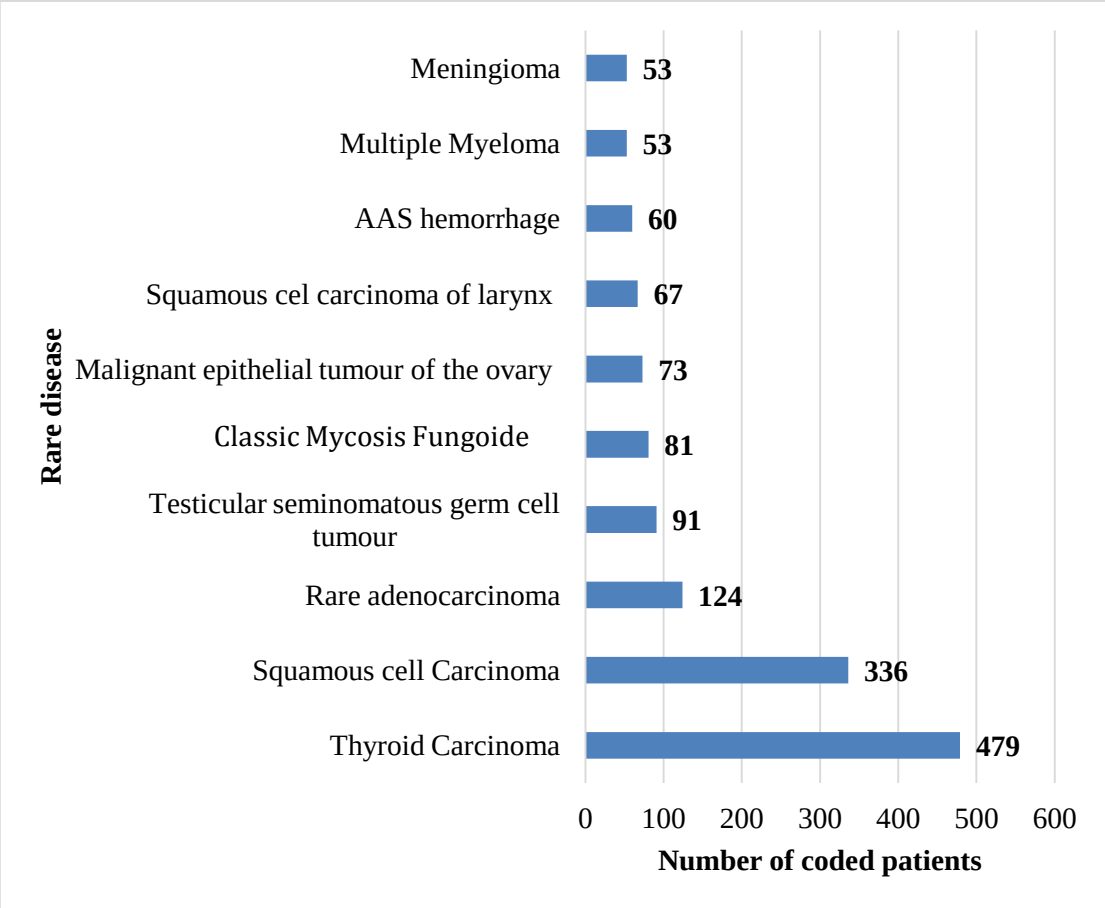


Figure 3.8 Ten most reported RDs in Malta from 2015 to 2017 (N=1417)

Figure 3.8 shows the number of coded RDs extracted from 3 active registers. Eight out of the 10 most reported RDs in Malta are cancers. The data was gathered from 4 different registers, and combined by the department of health information Malta.

There were 405 new cases of RDs registered in 2017 by the Department of Health Information and statistics. The Department of Health Information and Statistics reported that 25% received a delay in diagnosis and 40% were misdiagnosed.

Table 3.10 shows the available OD treatments in the EU and in Malta.

Table 3.10 Orphan drugs availability to treat top 10 registered rare diseases

Rare Disease	Orphan drugs centrally authorised by EMA	Orphan drugs available on the Maltese market
Meningioma	N-hydroxy-4-(3-methyl-2-(S)-phenyl-butyrylamino)benzamide	Not available in Malta
Multiple myeloma	Bortezomib Hospira Caelyz Darzalax Empliciti Farydak Imnovid Introva Kyprolis Mozobil Ninlaro Revlimid Velcade	Bortezomib (hospital only)
Haemorrhage with amyloidosis, arctic type	No OD available	Not available in Malta
Squameous cell carcinoma of the larynx	Eribitux Opidivo Taxotere	Not available in Malta
Malignant epithelial tumor of ovary	Avastin Caelyx Hycamtin Lynparza Mvasi Yondelis Zejula	Not available in Malta
Classic mycosis fungoides	Adcetris Ledaga Mozobil Targretin	Non available in Malta
Testicular seminomatous germ cell tumour	No OD available	No OD available
Rare adenocarcinoma of the breast	No OD available	No OD available
Squamous cell carcinoma	No OD available	No OD available
Thyroid carcinoma	Caprelsa Cometriq Lenvima Nexavar Thyrogen	Not available in Malta

3.2.4 Immediate Action Plan in Malta

According to health information department, there are areas requiring immediate action.

Table 3.11 Department of health information immediate action plan outline

Malta RD Issue	Status
• Registers - to increase awareness amongst healthcare professionals and the public in utilising registers.	Progressing
• The need for an IT system in the creation of registers and the improvement in data interpretation.	Urgent (progressing)
• Improvement in the area of data protection, legal administrative issues focused primarily on ownership and sharing of data between EU member states.	Urgent (collaborating with EURORDIS)
• The empowerment of NGOs and patient groups to take charge of the RD community and ensure their needs and opinions are a public issue.	Progressing

Currently, there are no designated funds for RD registers in Malta and as a result the development and launch of registers has been hindered (Table 3.11). Orphacoding is currently in use to encode data obtained from registries. There is a plan to integrate data from hospitals, pathology laboratories and genetic laboratories.

3.2.5 Screening at Birth for Rare Diseases

Currently there are no legislations designated for neonatal screening at birth in Malta. The Maltese ministry of health requires that neonates are tested for 2 particular diseases: Neonatal Congenital Hypothyroidism (NCA) and Haemoglobinopathies (HGI).

3.2.6 Clinical Practice Guidelines

Clinical Practice Guidelines (CPGs) are written to define drug entitlement in Malta. There are national guidelines for the development, adoption and implantation of CPGs.

3.2.7 Rare Disease Education

A RD symposium is held annually on the National RD day (held in February) organised by the Malta BioBank and the University of Malta.

3.2.8 Orphanet Malta

Malta does not currently have a national Orphanet team.

3.2.9 Helplines

No helplines specific to RDs are currently in place, although there are plans between NGOs and the ministry of health to start a RD helpline.

3.2.10 Information Centre

There is no official RD information centre in Malta, there are no plans in place to start one

3.2.11 Research Funds

There is no specific programme to fund RD research in Malta and there are currently no plans in place to have such programmes.

3.2.12 Orphan Drug Plan

There are currently no specific policies or regulations on ODs in Malta.

3.2.13 NGOs for Rare Diseases

At the beginning of 2014, with the support of a RD NGO in Malta (Marigold Foundation), the first official RD alliance was set up. The alliance has closely worked with EURORDIS and has brought the RD issue to the agenda of the Maltese presidency of the EU in 2017. The primary aim of the alliance was to bring together patients, caregivers, researchers and policy makers to support patients and raise awareness of RDs.

The RD Alliance of Malta collaborated with the Marigold Foundation and the Ministry of Health to establish a national directory in 2016 to trace RDs genetically on the Maltese islands.

There are policies and regulations in place to enable RD patients to access social and disability programs in Malta which are provided to patients who suffer from disabilities due to RDs. There is also a specific employment programme for people with a disabilities but not specific to RD patients.

3.2.14 Rare Disease Events

The Alliance and the Marigold Foundation, both organise charity and fund raising events throughout the year. The national RD day is held on the 27th of February every year. The Alliance is currently collaborating with EURORDIS to bring the RD issue on a United Nations level.

Table 3.12 Results on OD and RD specific findings by country

Country	OD or RD plan	Financial incentives	Non-financial incentives	Pricing of ODs	Reimbursement procedure
Malta*	No	No	No	Free under POYC scheme	Reimbursed for ODs listed in Maltese national formulary

Table 3.12 is a summary of the OD and RD findings in Malta compared with other EU member states and the US.As ODs are centralised, all EU member states have the same OD legislation, OD designation and market authorisation carried out by the EMA Information about the other 28 countries (EU member states and the US) can be found in appendix 9.

3.3 Validation of the HRQOL Tool

Non-random sampling was used in the recruitment of the panel members. Purposeful sampling was viewed as the most suitable recruitment method in the case of this study. Seven validators participated in the validation process. These included 3 pharmacists, 2 researchers in the field of RDs, 1 clinician and 1 RD patient.

3.3.1 Amendments to section A: Background information

Feedback on Section A involved grammatical and question structure suggestions. Two validators suggested changing the wording of question 4 from '*please select what ethnic group you belong to'* to *'Ethnicity origin (or race)'*. Another suggestion by one of the validators for this section was to exclude one of the questions that were initially included which investigated the income of the participant. As per guidelines of the Lynn validation method, the question was omitted from the HRQOL tool.

One validator suggested the removal of two questions that aimed to gather information on the socio-economic status of the RD patient or care. These question were:

'Please state your level of education'

'Are you currently employed or unemployed'

The two questions were omitted as per the Lynn validation method guidelines.

3.3.2 Amendments to section B: Personal care and independence

Three validators chose option 2 on the Lynn scale which meant that the question needed rephrasing. The phrasing of question 13 was changed from '*getting up in the morning'* to '*getting in and out of bed'*.

No amendments were required for section C and D. There was no need for revalidation.

HRQOL Tool

Statistical results from 225 responses were gathered and analysed using SPSS and Microsoft Excel.

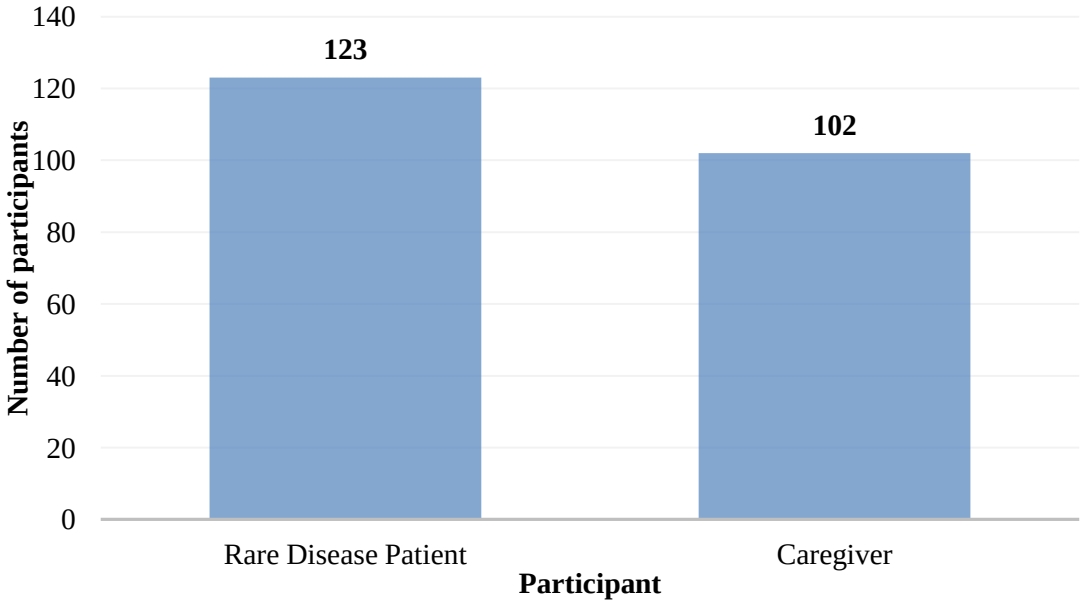


Figure 3.9 Status of Participants (N=225)

Figure 3.9 shows that 123 (54.7%) of the participants were RD patients while 102 (45.3%) were caregivers or parents.

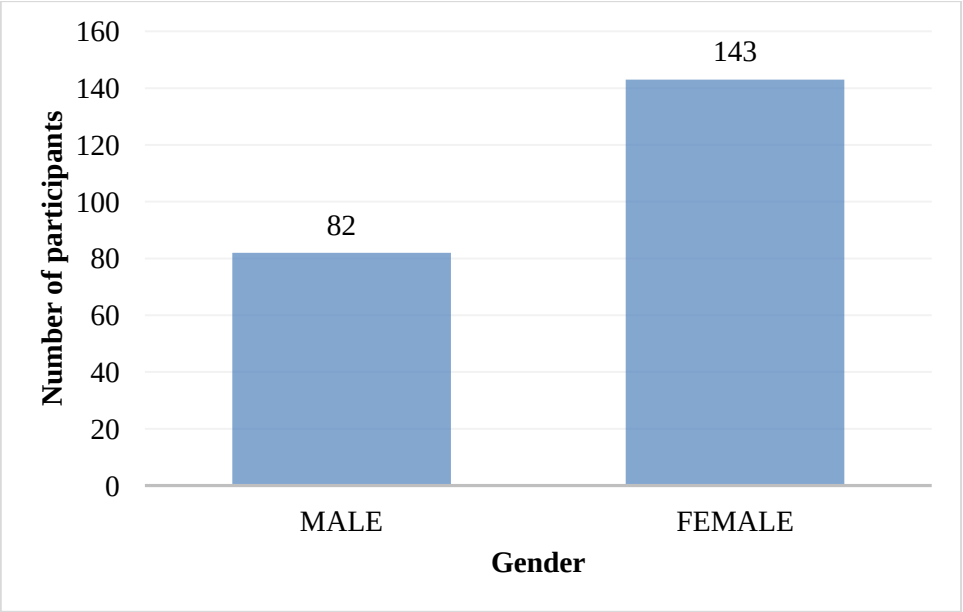


Figure 3.10 Gender of the Rare Disease Patient (N=225)

Figure 3.10 showed that the majority of the participants were female.

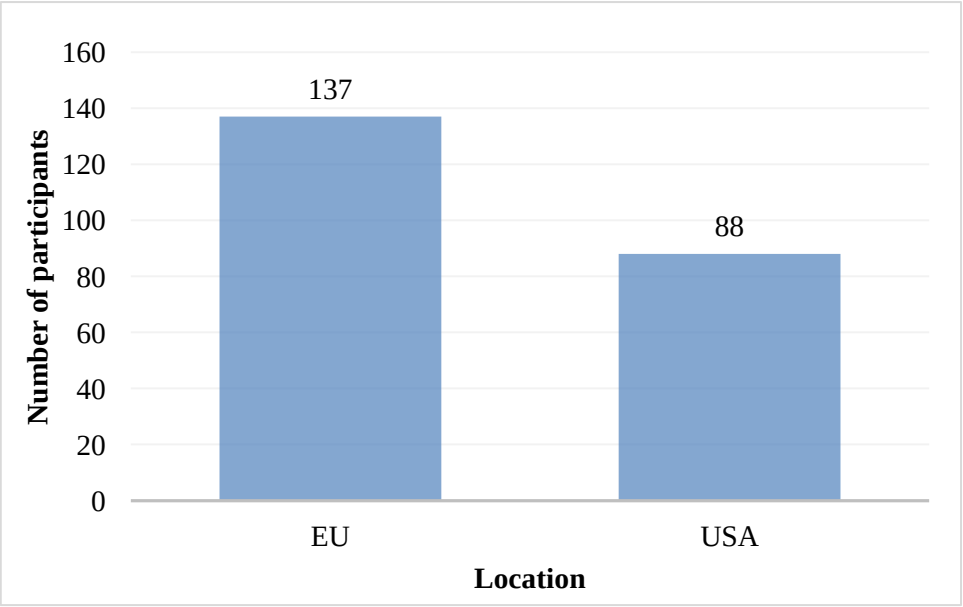


Figure 3.11 Residence or Location of the Rare Disease Patient (N=225)

Figure 3.11 shows that 137 (60.9%) of the participants in this study were from an EU country and 88 (39.1%) are from the USA. The majority of the EU participants were from Malta (55, 41%) and Germany (21, 16%).

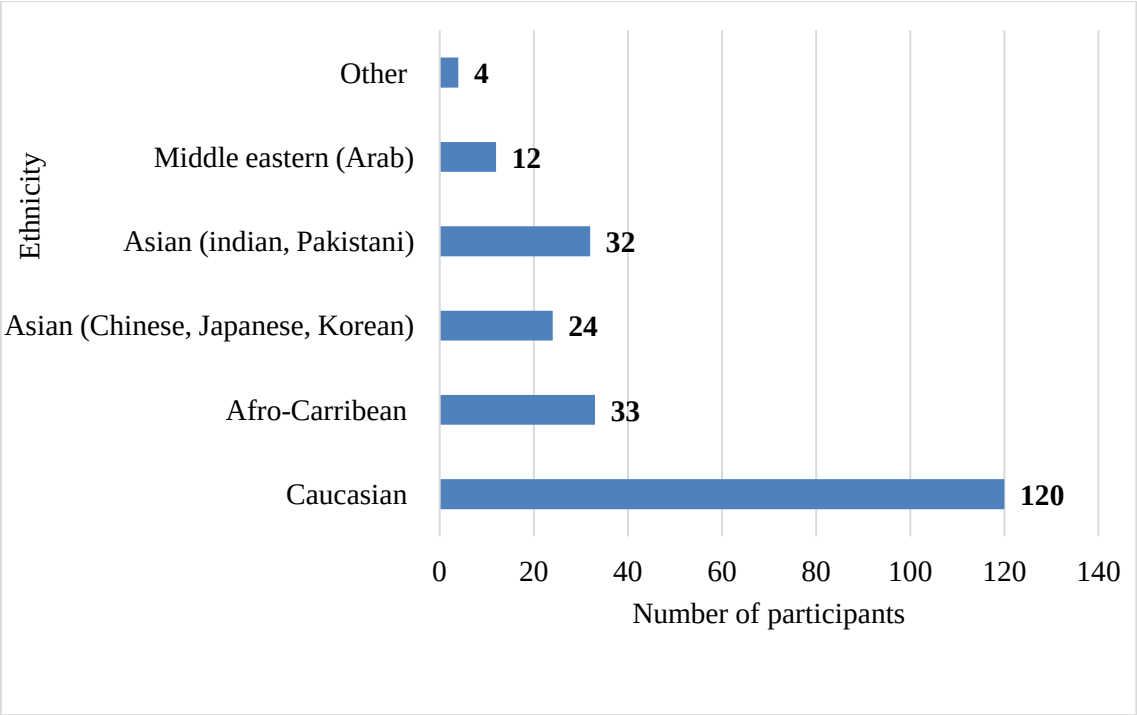


Figure 3.12 Ethnicity (N=225)

Figure 3.12 shows that 120 (53.4%) of the participants were Caucasian, 33 (14.6%) were of Afro-Caribbean origin while 24 (10.7%) were of Asian (far east) origin. South east Asian participants were 32 (14.3%) while 12 (5.4%) participants were of Middle Eastern (Arab) origin.

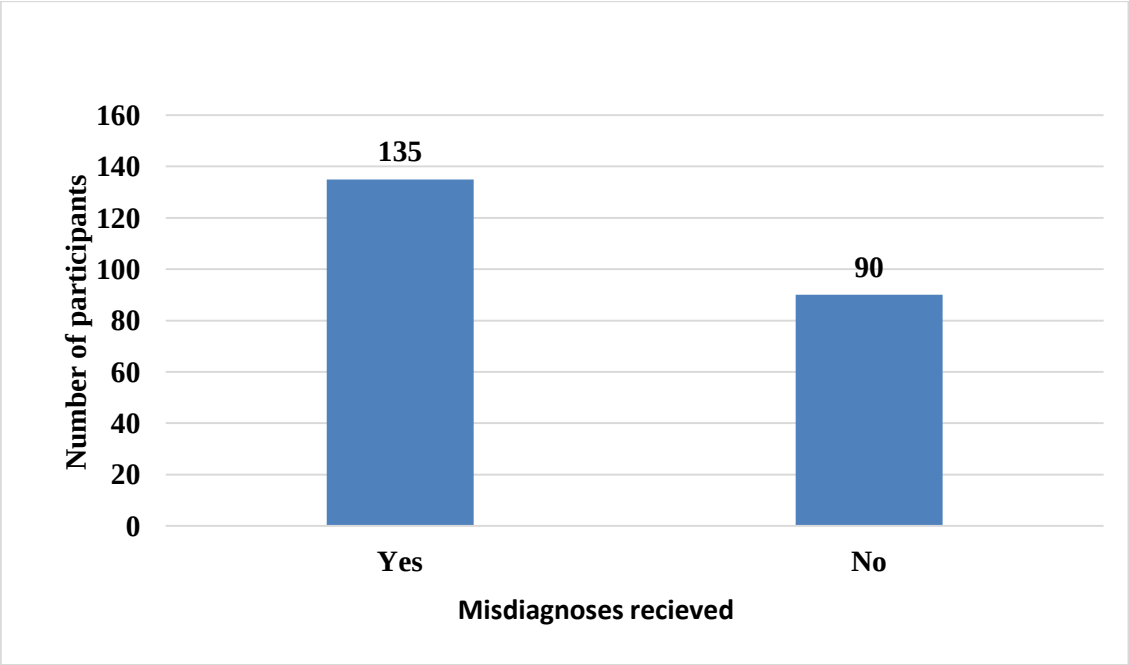


Figure 3.13 Number of misdiagnoses (N=225)

Figure 3.13 show that RD patients reported a high rate of misdiagnoses (135, 65%).

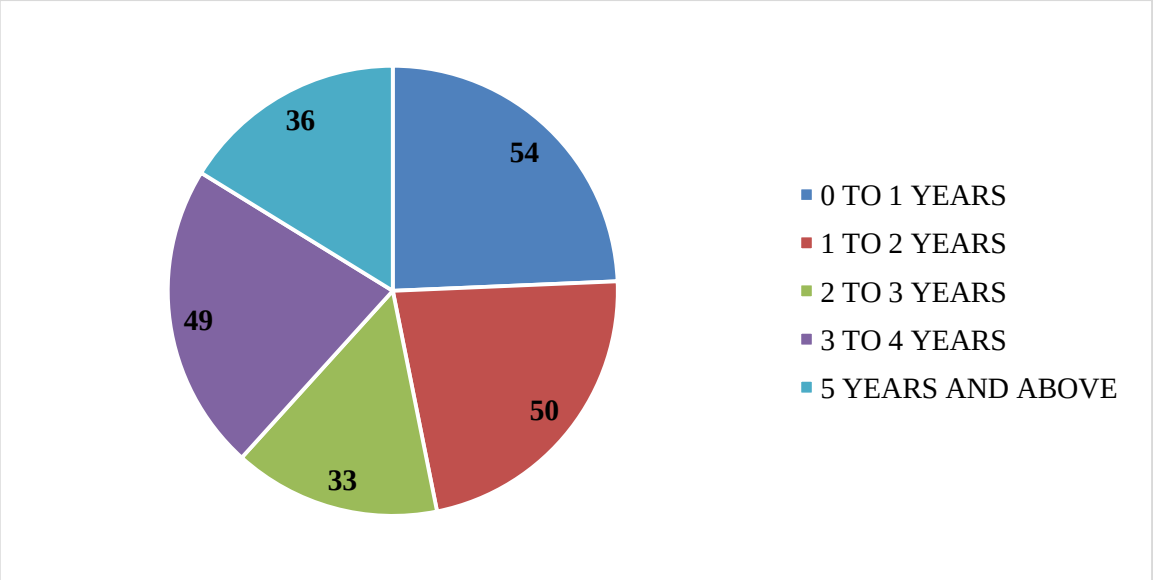


Figure 3.14 Time to receive correct diagnosis (N=225)

Figure 3.14 indicates that the majority (n=54) of RD patients received their diagnosis at birth. Fifty patients received their diagnosis within 1 to 2 years and only 33 patients

received their diagnosis after 2 to 3 years while 49 reported that they received a diagnosis after 3 to 4 years.

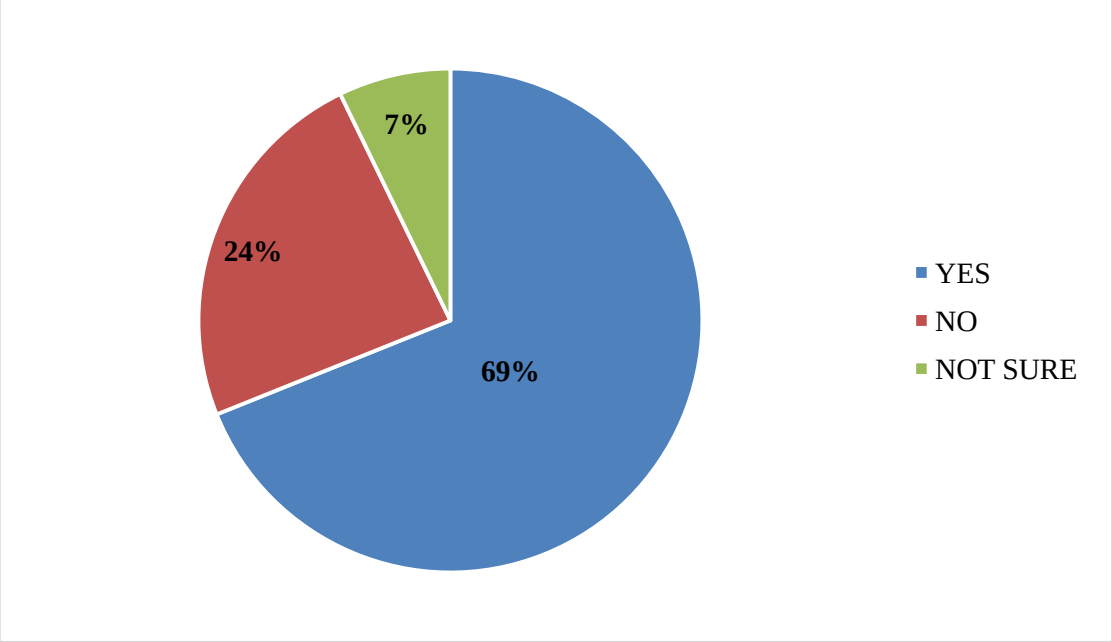


Figure 3.15 Origin of rare disease (N=225)

Figure 3.15 shows that 69% of the participants reported that their RD is genetic in origin. Around 24% stated that their condition is not genetic and 7% were not sure if their RD is genetic or not.

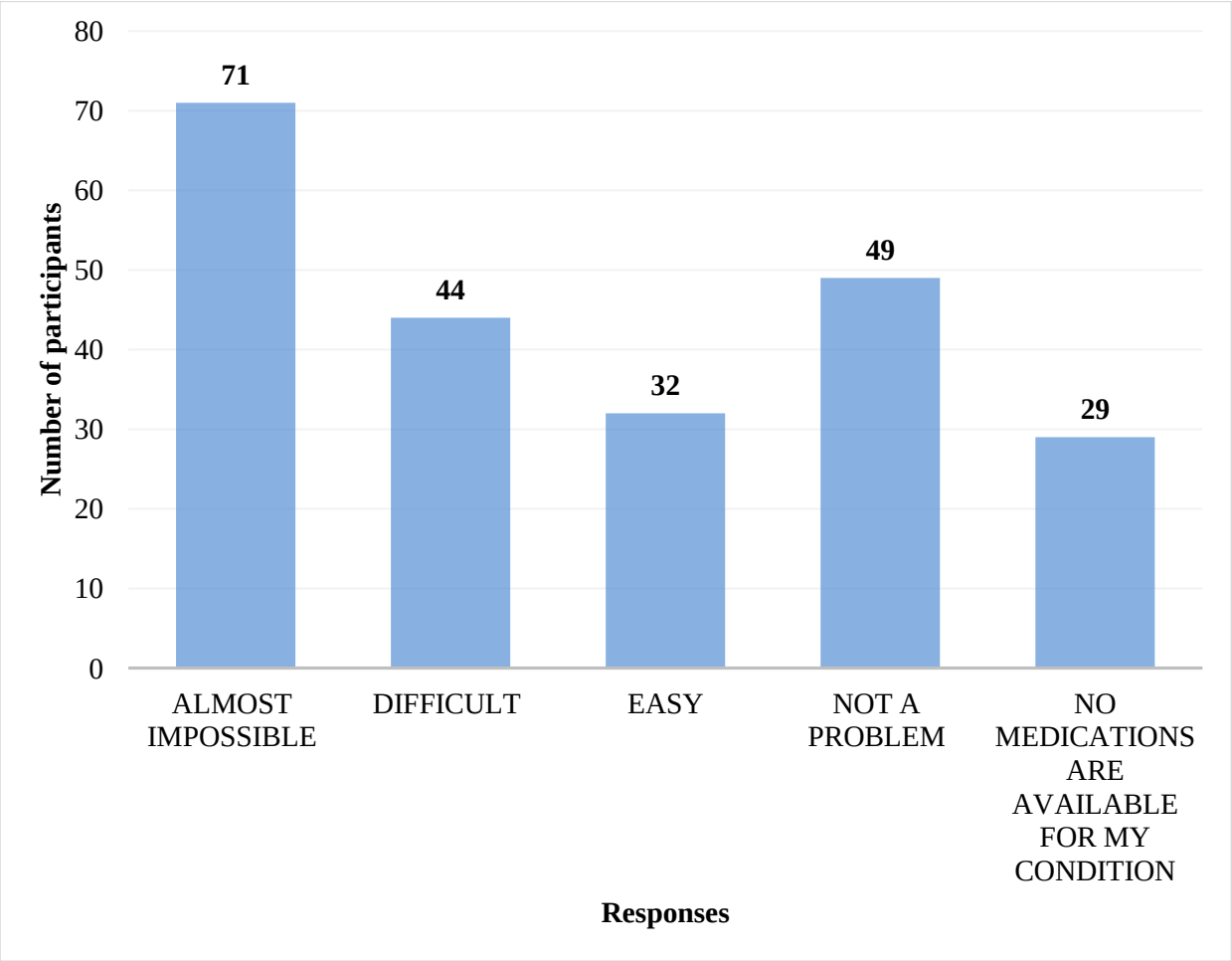


Figure 3.16 Affordability of orphan drugs (N=225)

Figure 3.16 shows responses obtained for the question 'how difficult was your ability to afford medications if applicable'. The majority stated that it was almost impossible (71, 31.6%) to afford medications while 44 (19.6%) stated that it was difficult. Thirty-two (14.2%) and 49 (21.8%) stated that it was easy or not a problem at all to access medications respectively. Twenty-nine (12.9%) respondents stated that there were no medications available to treat their condition in their country or region.

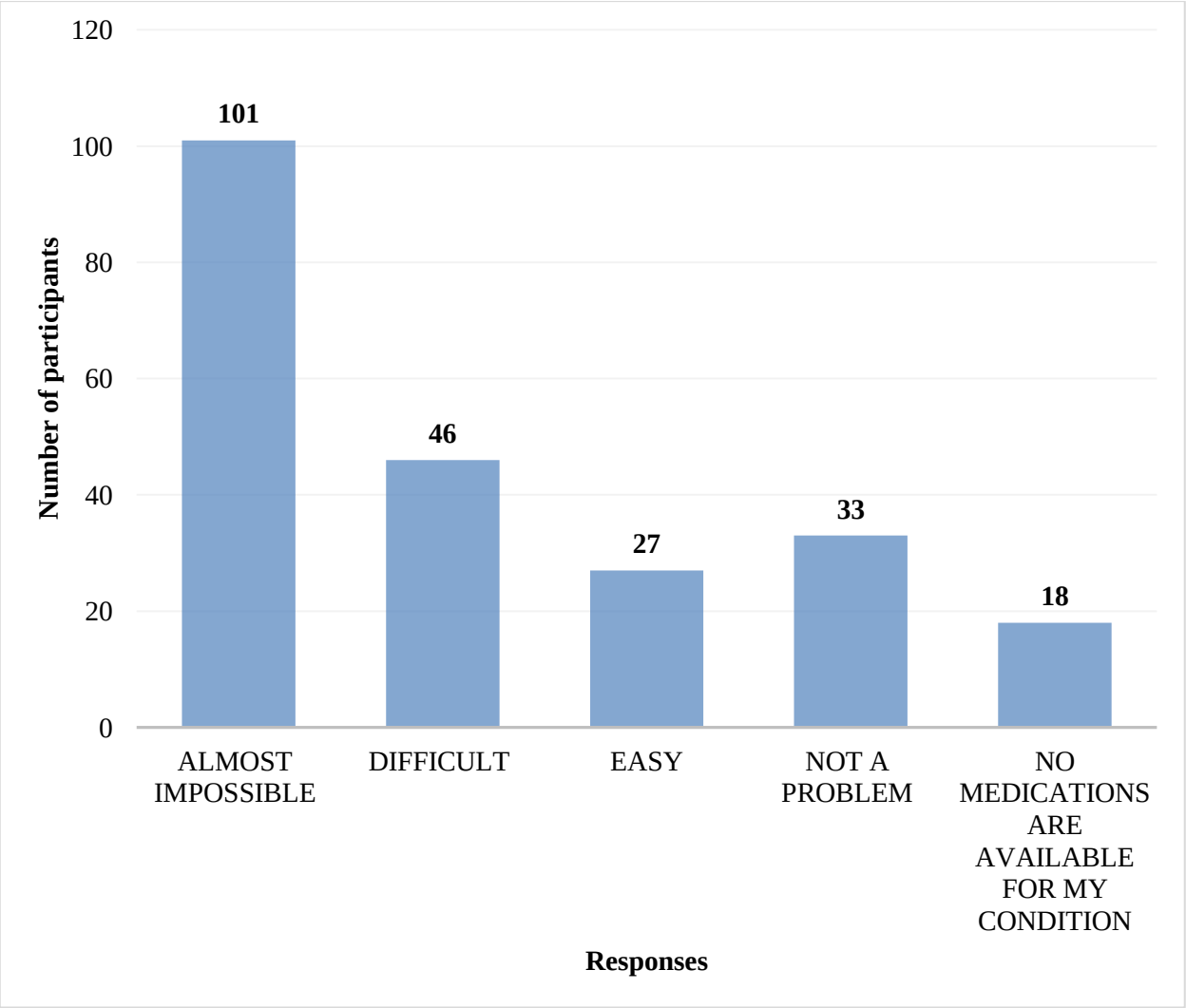


Figure 3.17 Patient's ability to source medication (N=225)

Figure 3.17 shows the responses obtained for the question how difficult was sourcing the ODs, if applicable. The vast majority (101, 44.5%) of the respondents stated that it was almost impossible to afford the medication, while 46 (20.4%) stated that it was difficult. Only 27 (12%) and 33 (14.6%) stated that it was ‘easy’ or ‘not a problem’ respectively. Eighteen (8%) participants stated that there were no medications available for their condition.

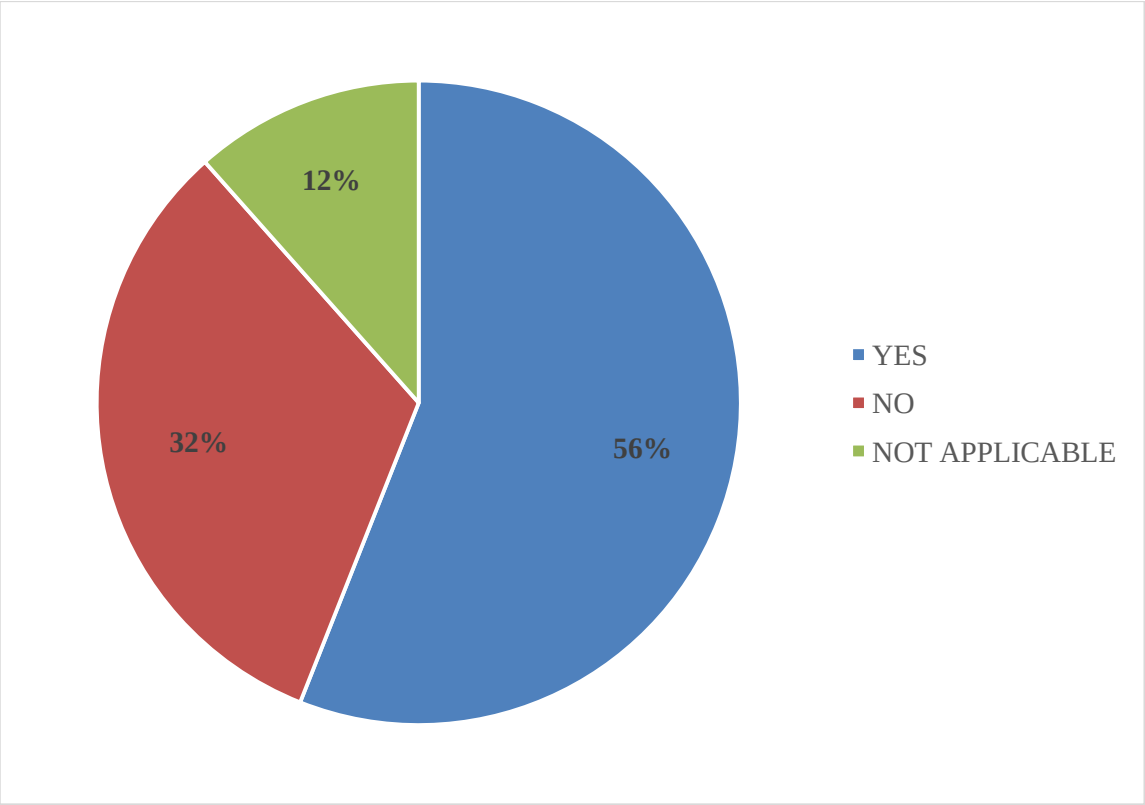


Figure 3.18 Financial burden due to orphan drugs (N=225)

Figure 3.18 represents a pie chart which depicts answers to the question 'did you struggle financially due to the price of your treatment'. Over 56% of the respondents stated that they struggled while 32% stated that they had no financial struggle due to the price of their medication. Only 12% of the respondents selected the not applicable option

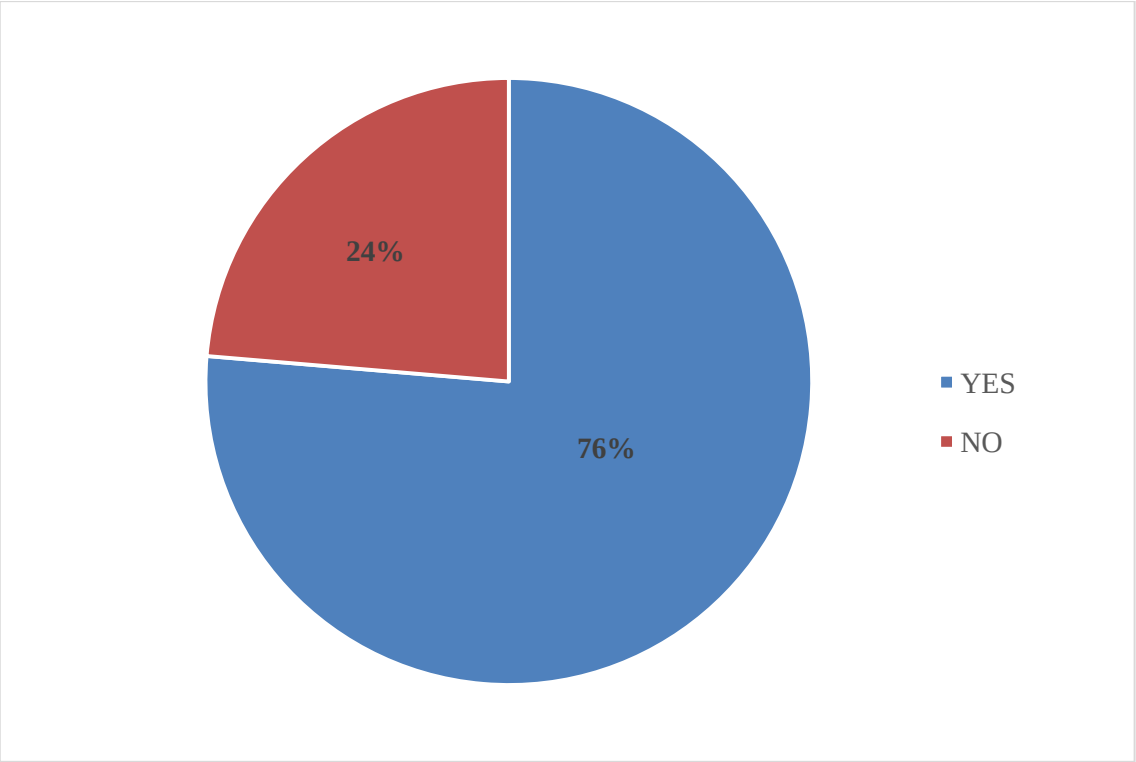


Figure 3.19 Willingness to participate in future research

Figure 3.19 shows the willingness of participants to participate in future rare disease research. The vast majority (76%) stated that they are willing to participate while only 24% stated that they would not like to participate in future research.

Table 3.13 Patients views on their QOL related to personal care and independence (Likert scale; 1 = not possible, 5 = not a problem)

How difficult was the following	Group	Mean (Likert scale score)	Std. Dev.	p-value
Eating, drinking or being fed	EU	3.58	0.502	0.000*
	US	2.38	0.500	
Bathing, washing or general hygiene	EU	3.44	0.512	0.116
	US	2.94	0.998	
Getting in or out of bed	EU	4.44	0.512	0.000*
	US	2.84	0.454	
Moving about in the home	EU	3.56	0.512	0.000*
	US	2.19	0.946	
Visiting public places	EU	2.50	0.516	0.232
	US	2.68	0.909	
Understanding parent, caregiver or people around you	EU	4.50	0.516	0.463
	US	4.61	0.495	

***p value <0.05**

RD patients in the EU and US were asked to rate their personal care and independence by use of the Likert-scale which was used for all the questions and consisted of 1 to 5 rating (where one is not possible and 5 not a problem). Table 3.13 shows a comparison using the Mann-Whitney U test between two independent groups (EU and US).

Questions 1, 3 and 4 revealed that there is a significant quality of life difference between EU and US RD patients as the p-value was <0.05 (0.000). The mean score from table 3.1 reveals that European RD patients reported having less difficulty carrying out daily activities such as eating, moving about and getting in or out of bed than their US based counterpart. Question 1 shows that EU patients scored a mean of 3.58 (with a standard deviation of 0.502) on the Likert-scale while the US RD patients scored 2.38 (std. deviation of 0.500).

Questions 2, 5 and 6 showed that both groups had a similar experience when it came to hygiene, being in public places and understanding caregivers.

Table 3.14 Patients views on their QOL related to mental health (Likert scale; 1 = very upset, 5 = happy)

How did you feel during the following?	**Group**	**Mean (Likert scale score)**	**Std. Dev.**	**P-value**
Eating, drinking or being fed	EU	4.44	0.512	0.000*
	US	2.84	0.454	
While dressing or undressing	EU	5.00	0.000	0.001*
	US	4.50	0.894	
Being understood by people around you	EU	4.55	0.506	0.000*
	US	2.06	0.854	
Communicating with those around you	EU	3.44	0.512	0.061
	US	2.97	0.836	
Participating in recreational activities	EU	4.31	0.479	0.014*
	US	3.65	0.950	

***p value <0.05**

RD patients in the EU and US were asked to rate their mental health by reporting how they felt during daily activities. Table 3.14 shows a comparison using the Mann-Whitney U test between two independent groups (EU and US). A Likert-scale was used for all the questions which consisted of 1 to 5 rating (where one is very upset and 5 happy).

Questions 7, 8, 9 and 11 reveal a significant difference between the two groups as the p-values for these questions are below the significance level (<0.05). The mean score from table 3.14 reveals that European RD patients reported having less difficulty managing mental health issues associated with RDs than their US based counterparts. Question 1 shows a mean score of 4.44 on the Likert-scale for EU based RD patients, while US respondents scored a mean of 2.84.

Questions 10 showed that both groups had a similar experience when it came to communicating with people around them. A mean score of 3.44 and 2.97 was obtained on the Likert-scale for EU and US based RD patients respectively.

Table 3.15 Patients views on the financial burden of their rare disease (Likert scale; 1 = significant burden, 5 = not a burden)

Rate the following	Group	Mean (Likert scale score)	Std. Dev.	P-value
Financial burden of the disease	EU	4.44	0.512	0.000*
	US	3.00	1.065	

***p value <0.05**

RD patients in the EU and US were asked to rate financial burden they faced due to their RD. Table 3.15 shows a comparison using the Mann-Whitney U test between two independent groups (EU and USA). A Likert-scale was used for this question which consisted of a 1 to 5 rating (where 1 significant burden and 5 not a financial burden).

The differences between the two groups (EU and USA) was significant as the p-value was below the significance value of <0.05. Question 12 reveals that USA based patients face a larger financial burden than EU RD patients. EU patients scored a mean of 4.44 on the Likert scale while USA based RD patients scored a mean of 3.0.

Table 3.16 Patients views on the financial burden of their rare disease

Have you ever experienced any of the following since you became aware of your condition?		Region		Total
		US	EU	
Stress	No. of respondents	34	55	89
Anxiety	No. of respondents	33	44	77
Depression	No. of respondents	14	31	45
Frustration	No. of respondents	9	16	25
Decreased interaction	No. of respondents	8	5	13
Sleeping problems	No. of respondents	13	21	34
Fear of the future	No. of respondents	1	8	9
None of the above	No. of respondents	6	4	10
Total	**No. of respondents**	**86**	**134**	**220**

$X^2(7) = 9.351, p = 0.228$

RD patients in the EU and US were asked to select mental health conditions that they experienced since becoming aware of their RD. Table 3.16 shows that 89 (40.4%) of the respondents stated that they experienced stress since they became aware of their condition. A total of 77 (35%) of patients experienced anxiety and 45 (20.45%) reported having depression. Frustration, fear of the future and decreased interaction were the least reported outcomes as they scored 25 (11.4%) and 9 (4%) respectively. The p value was not significant (<0.05).

Table 3.17 Gender and mental health

Have you ever experienced any of the following since you became aware of your condition?		Gender		Total
		Male	Female	
Stress	No. of respondents	34	55	89
Anxiety	No. of respondents	36	41	77
Depression	No. of respondents	23	22	45
Frustration	No. of respondents	9	16	25
Decreased interaction	No. of respondents	6	7	13
Sleeping problems	No. of respondents	20	14	34
Fear of the future	No. of respondents	5	4	9
None of the above	No. of respondents	7	3	10
Total	**Count**	**82**	**162**	**220**

$X^2(7) = 8.371$, p = 0.085

Table 3.17 shows that more females participated in this study. Females reported higher frequencies of stress (n=58) and anxiety (n=24) than males. The p value was above the significance level of 0.05.

Table 3.18 Patients views on receiving the correct treatment for their rare disease

How difficult was receiving the correct treatment?		Region		Total
		USA	EU	
Almost impossible	Count	27	44	71
Difficult	Count	15	29	44
Easy	Count	16	16	32
Not a problem	Count	21	28	49
No treatment	Count	9	20	29
Total	**Count**	**88**	**137**	**225**

$X^2(4) = 3.177, p = 0.529$

Table 3.18 shows that 31.6% (n=71) of the respondents stated that is almost impossible to receive the correct treatment. Twenty-one (n=49) stated that it is not a problem at all to receive the correct treatment while 19.6% (n=44) stated that it is difficult. Over 14% (n=32) stated that it is easy to access the correct treatment while only 12.9% (n=29) stated that there are currently no treatments for their condition.

RD patients in the US reported slightly better accessibility to ODs as they have scored lower in the 'almost impossible', 'difficult' and 'no treatment' categories. Since the p-value (0.528) exceeds the 0.05 level of significance; there is no regional discrepancy to be noted. Both US and EU based RD patients have reported similar experiences in receiving the correct treatment.

Table 3.19 Comparison of rare disease diagnosis in the EU and US

Have you received a misdiagnoses?		Region		Total
		USA	EU	
Yes	Count	59	76	135
No	Count	29	61	90
Total	**Count**	**88**	**137**	**225**

$X^2(1) = 1.267$, p = 0.261

Table 3.19 shows a comparison on the misdiagnoses of EU and US based RD patients. Sixty percent of the respondents reported that they have received misdiagnoses while 40% stated they have not. The p-value exceeded the 0.05 level of significance that indicates that there is no difference in the misdiagnoses of RDs between the EU and the US.

CHAPTER 4

DISCUSSION

This section will discuss the key findings to answer the research question in two separate sections: section I will discuss the regulations and policies available in the EU and US and their impact on patient access to orphan drugs; and section II will discuss the results obtained through the Health-Related Quality of Life (HRQOL) tool and its associated factors. This chapter discusses the limitations and strengths of the study, recommendations for future research and a conclusion.

4.1 Access to ODs (EU &US)

One of the aims of this research was examining the regulations and policies on Orphan Drugs (ODs) in 29 countries (EU member states and the US). Findings were reported in the results section. Similar research was conducted in the past, however it either discussed or examined OD and RD regulations in one country or region (Franco, 2013). This research aimed to give a more detailed comparative analysis between different EU countries regulated by the EMA and compare their practices to that of the FDA. The summary of different legislations and policies in each country identified can be used to address the deficiencies and better address the accessibility of ODs.

The 28 EU countries included had 4 common themes and incentives which included; (i) Marketing Authorisation (ii) Orphan Drug Designation (iii) Market exclusivity and (iv) Research Assistance. There were differences in pricing and re-imbursement within the EU. This, may affect the RD patient's experience within different member states on equal access to treatment.

Although all of the 29 countries in this study had an OD legislation, only 16 EU countries had an orphan drug plan in place. The US does not have a national plan for ODs. Countries lacking a national OD plan such as the United States, have incorporated their plan for ODs in the national Orphan Drug Legislation (Feltmate et al, 2015). A reason why certain EU countries lack a national plan for ODs might be due to the fact that they are not enforced by the EU and the EMA (Denis et al, 2010). Having a national plan remains a topic that the individual EU country deals with independent of other EU member states.

The EU and US have a centralised marketing authorisation procedure for ODs. Both the EU and the US had a designated procedure to apply for OD designation. The US and the EU had in place accelerated authorisation procedures which depended on the severity of the RD and unmet medical needs of the patient. Accelerated access procedures helped decrease the authorisation timeframe by 6 months.

Financial incentives were offered by all the countries examined in this study (N=29). Research suggested that the countries struggled to fulfil or implement these incentives due to budgetary issue or the price of the OD. The US and 14 EU member states had pre-licensing or compassionate use programmes in place to allow patients to access unlicensed medications for their RDs. Compassionate use programmes are not usually reimbursable by the insurance or public healthcare. Pre-licensing access does not mean that the drug is available for everyone. Compassionate use programmes are carried out on an individual named patient basis.

Both the EU and FDA offer a market exclusivity for ODs. The EU offers a 10-year market exclusivity while the United States offers a 7-year exclusivity. This incentive is highly lucrative for the OD manufacturer as it gives them full market control where no other medicine for the same indication can be licensed. This market exclusivity essentially gives the OD manufacturer full control over the price of the OD. OD designation should not be used to hinder the development, licensing and marketing of other products for the same condition which have demonstrable clinical potential.

Accessibility is hindered by the inflated prices of ODs. The fixed price model was implemented by some of the countries investigated in this research (9 countries). The model of fixed pricing can cause certain limitations, for example, the fluctuation of prices can be 'attributed to international purchasing power parity differences'.

A significant factor that may affect accessibility to ODs is the reimbursement of ODs. The pharmacoeconomics and the cost effectiveness factor, of the Health Technology Assessment (HTA) has the primary decision on reimbursement. All of the EU countries and the United States consider cost effectiveness when carrying out assessment on ODs. Countries like Sweden and The Netherlands considered other factors such as the benefit of improving the quality of life by making an OD available, unmet medical needs, and demand from patient groups. Some EU member states such as Hungary have set up a separate authority to deal with the assessment of ODs. It can be concluded that ODs are sometimes made available even with minimal clinical evidence when compared with non ODs.

RD patients in the United States are faced with the co-payment barrier which can pose a high financial burden. Although the US has the highest OD designation worldwide, RD patients often face significant barriers to accessibility due to the cost of ODs. When observing the US OD market, it becomes clear that availability does not mean access. All 29 countries offered some form of co-payment or re-imbursement for ODs. The re-imbursement depended on whether the OD is approved or is listed in the drug formulary for re-imbursement.

It was found that 5 EU member states and the United States have a maximum co-payment (MCP) scheme to protect RD patients against excessive financial burden. For example, in the Republic of Ireland, the Drugs Payment Scheme (DPS) placed a cap on the amount patients and their families have to pay for a medication (€134 per month).

One of the most commonly used approaches for access of ODs, is the Managed Entry Agreements (MEAs). MEAs are applied to patients who seek an OD that lacks satisfactory clinical evidence.

The role that patient groups and alliances play is paramount, as the US and EU OD Acts were passed after heavy campaigning. The US based National Organisation for Rare Diseases (NORD) and its European counterpart EURORDIS focus on improving the care of RDs by improving access to information and on some occasions improving access to ODs. Patient advocacy groups often lobby third-party payers or governments funding healthcare, to provide full reimbursement of orphan drugs, regardless of their high price. Patient advocacy groups may form partnerships with regulatory agencies, for example, EURODIS with the European Medicines Agency (EMA).

The access part of this study had limitations. Although an attempt was made to limit bias by using the PRISMA method, the literature used might have included outcome and publication bias. Two journals were eliminated as a result of bias in reporting.

Another limitation faced was that the study included literature published in English only. This limited our review process as only 4 of the countries included in this study had English as a first language. There was difficulty translating certain legislation whose policies were not published in English and as a result only studies conducted in English were relied upon. What made the process of reviewing more challenging was that that only articles published in peer-reviewed journals were included. 'Grey-Literature' was excluded, to ensure that only a factual academic level of information was included.

The impact of the OD regulations and policies can be seen from the results obtained from the Health Related Quality of Life Tool (HRQOL). Patients living within the United States had an access to wider number of ODs, however, these patients struggled more frequently with the financial impact of their RD due to prices and insurance issues. Most of the EU RD patients struggled with the availability of the ODs. Many have stated that they know of an OD used abroad but it is not available in their country.

It is a limitation that our research was limited to two regions, United States and the European Union member states. Future research should compare legislations from Asia, such as Japan, China and India, Africa and Latin America. Future research should focus on countries that have had success when dealing with RDs and ODs and propose a

strategy that can be applied to improve equality when dealing with access and pricing of ODs.

Overall most of the countries in developed nations have adapted policies and regulation on RDs and ODs. The RD scene has witnessed an increase in research and development of treatments and care since the introduction of OD legislations in the United States and, 17 years after, in the EU. The issue of accessibility, availability and pricing remain a problem for RD patients. Some of the incentives given in the United States and the EU have brought some controversy. For example, marketing exclusivity has been viewed to be problematic for research and development of new ODs, as both EMA and FDA protect new ODs for the same indication from entering the market. This can cause monopolisation in the OD market.

4.2 Rare Disease Management and Access to Orphan Drugs In Malta

The RD community in Malta is faced with challenges like other RD patients worldwide. Since joining the EU, Malta had developed in areas related to RDs and ODs. Although Malta lacks an official RD plan like 18 of its EU counterparts, policy makers and government officials have highlighted the need to implement an immediate action plan. Dharssi et al, (2017), highlighted the widespread implementation and application of RD plans designed to more adequately address the comprehensive needs of RD patients. Countries with RD or OD plans have improved harmonisation of care, diagnosis resources, access to medicines, patient education and support, and quality of RD research (Dharssi et al, 2017).

RD registers in Malta are the primary source of statistical information. With only 1 RD specific register, Malta ranks amongst the lowest in the EU[45]. France has 151 RD specific registers while Germany has 145. The lack of RD specific registers can lead to many RDs not being coded which in turn can affect the QOL of patients afflicted by these RDs. The EU plan 'Building Consensus and Synergies for the EU Registration of RD Patients' aims to outline a model platform for EU RD registers (Vittozzi et al, 2013). A plan for a joint EU RD registry is in motion under EURORDIS (Vittozi et al, 2013).

EU member states are implementing screening for RDs at birth and Malta currently screens for 2 RDs in new-born infants (Neonatal Congenital Hypothyroidism and Haemoglobinopathies). Screening for RDs at birth is an important issue to ensure early diagnosis and management. In a 10-year observational study carried out in Germany, Lindner et al, (2011), established that screening of infants for metabolic RDs significantly decreases physical and cognitive disability.

Clinical Practice Guidelines (CPGs) are written in Malta to establish medication entitlement. Although there are no RD specific CPGs, Malta has in adapted a national policy for the development, adoption and implantation of CPGs. Access to RD information is one of the priorities adopted in most national RD plans in Europe (Pavan et al 2017). Alfonso-Coello et al, 2010 found a link between misdiagnoses and mismanagement of conditions in countries with no CPGs. In the UK, the National

[45] Orphanet report series [Cited on 30 May 2018] can be accessed through URL: https://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf

Institute of Clinical Excellence (NICE) is responsible for CPGs for both RDs and non-RDs.[46]

RD patients in Malta reported: delays in diagnosis, struggle to find information about their RD and poor access to expert medical care. RD education is a vital part of helping the patient and the public understand the challenges. The concept of RDs is not covered in the medicine, pharmacy or nursing curricula at the University of Malta[47]. In a study assessing the knowledge of health care professionals on RDs, 88% of the 270 medical professionals recruited scored poorly independent of their experience (Jonas et al, 2017). Malta holds a public annual RD colloquium for researchers, health care professionals and the general public.

Malta has no centre for RD information or helpline for RD patients. Lewis et al, 2017, found that having an RD information centre and helpline can significantly help with patient education and in turn improve their HRQOL. RD information centres fill a critical void by providing the RD patients with vetted, evidence-based material that empowers patients (Lewis et al, 2017). RD patients who use information centres or helplines reported high levels of satisfaction.

Orphanet is a global organisation that aims to improve the QOL for RD patients. National Orphanet teams are responsible for the gathering of information from RD expert centres, medical laboratories, researchers and patient advocacy groups locally

[46] NICE guidelines [Cited on 30 May 2018] can be accessed through URL: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-guidelines/types-of-guideline

[47] UOM Medical school [Cited 2018 May 30] can be accessed through URL: https://www.um.edu.mt/ms/medicine/studyunits

and report findings in the local language the teams are based (Rath et al, 2012). Malta is one of three countries in the EU with no Orphanet team.[48]

In recent years, Malta is becoming more aware of the issues of RDs. During the EU presidency, Malta highlighted the issues of OD accessibility and RD research. The Malta summit highlighted the need for cross border collaboration to guarantee that RD patients throughout the EU have equal opportunity for access to diagnosis, therapies, and care. To reach this level of cooperation, the EU has to develop a strategic and structured way to tackle the issue of RD. A series of proposals were given by many member states representatives, researchers and policy makers (Appendix 10).

Malta is still falling behind on the market availability of ODs. Only 1 out of the 10 registered RDs in Malta have an OD available while the UK in comparison has the ODs to treat 7 of the top 10 registered RDs in Malta. This lack of access may be due Malta lacking an OD plan to help with access to EMA licensed ODs.

4.3 HRQOL Tool

The third objective of this study was to define the characteristics of HRQOL, both physical and mental, of European and Americans (USA) rare disease patients. Table 4.1 presents the research questions and highlight the findings associated with them. It is important to note, that no local study has previously investigated the HRQOL of RD patients. This is the first study to compare HRQOL of EU patients with that of the US.

[48] Orphanet teams [Cited 2018 May 30] can be accessed through URL: https://www.orpha.net/consor/cgibin/Education_AboutOrphanet.php?lng=EN&stapage=ST_EDUCATION_EDUCATION_ABOUTORPHANET_NATIONAL_WEBSITES

The RD patient's perception of HRQOL will depend on their individual experience with their condition.

To aid in the formulation of the HRQOL tool, Australian RD communities, researchers and NGOs were contacted to gather information related to areas that need to be addressed. The information gathered indicated that the most important areas for Australian RD patients were:

- Fast and accurate diagnosis
- Information provision at the time of diagnosis
- Services available for specific cases
- Coordination between healthcare providers to ensure there are no gaps in management of the patient
- Access to support groups and registries
- Access to medications (if available)

Only two previous studies held in the UK and Europe highlighted the impact of delay in diagnosing, misdiagnosing, uncoordinated care, lack of information provision and incorrect treatment (Nutts et al, 2011).

The HRQOL was similar in design and sections as that of the UK (Nutts et al, 2011). The HRQOL was self-administered and available for patients over the age of 18 years with a RD. Over 800 participants responded with which 92% had a confirmed diagnosis. Results obtained showed a high rate (45%) of misdiagnoses and insufficient information (72%) at the time of diagnosis (Molster et al, 2016).

Points of discussion	Question
HRQOL of RD patients	How do RD patients perceive their Physical health and independence?
Mental and social health	How do RD patients perceive their overall mental and social health?
Accessibility to Orphan drugs	What affects accessibility to treatment for RD patients?

Few studies analysed factors related to the HRQOL in RD patients. Most of these factors focused on patients with chronic genetic RDs at the late or end stages e.g. Fabrys disease (Van der Plas et al, 2004; Gutteling et al, 2006; Sobhonslidsuk et al, 2006; Dan et al, 2008; Haag et al, 2008; Afendy et al, 2009; Hsu et al, 2009; Liu et al, 2012; Arendes et al, 2015).

It is challenging to attempt a comparison of all the reviewed papers, because HRQOL is a multidimensional idea that is measured by diverse tools in different researches. Due to this, only the studies that (1) observed QOL in RDs, (2) investigated perceived HRQOL as a chief outcome and (3) used a validated tool, were included. Additional studies investigating mixed disease stages were included to support the discussion about the link between independent variables and HRQOL, if relevant.

4.3.1 HRQOL Section A: Demographics and Background Information

Limited research has been conducted on the association between HRQOL and RDs. It was noted that factors that affect HRQOL for RD patients include; gender, ethnicity, region where patient lives and socioeconomic factors. These factors will be discussed.

Studies had conflicting findings about the association between age and gender and HRQOL. Afendy et al, (2009) and Basal et al, (2011) established that age had a significant association with poor physical health domains. Elderly RD patients were more likely to experience poorer physical health than younger RD patients (Basal et al, 2011). Dan et al, (2008), likewise, indicated that older patients suffered poorer physical health than younger RD patients. It is important to note that age was not significantly linked to poorer mental health domains (Basal et al, 2011). Kim et al, (2006) found that HRQOL and psychological distress in RD patients was not linked to the age. It can be concluded that age has an effect on personal care and independence and less effect on mental health (Afrendy et al, 2009). There was no link found between age and HRQOL found in this study.

Studies suggested that females had poorer physical and mental health (Afendy et al, 2009, Karaivazoglou et al 2010). It was found that women were more likely to have poor HRQOL, particularly in physical health (Sobhonslidsuk et al, 2006; Afendy et al, 2009; Karaivazoglou et al, 2010). More female RD patients participated in the HRQOL assessment. There was no significant correlation between poor HRQOL and gender. This might be due to the sample size included in the study

The socio-economic status of RD patients was not investigated in this study. The validators suggested the removal of all questions that investigated occupation, employment, education level and income. This can be seen as a limitation of this study. There is strong association between QOL and socio-economic factors (Basal et al, 2011). A study by Molster (2016) showed that RD patients who did not have an occupation reported poor mental health but their physical health was not significantly different to working RD patients. The level of education was also significantly linked with physical health, but not with mental health (Molster, 2016). Additional research is required to develop finite association between education level and mental health in RD patients of this association.

Patients with RDs had a higher probability of having financial problems (Molster, 2016). Over 33% of male RD patients reported that paid employment was the aspect most affected in their daily life (Marchesini et al, 2001). Around 40% of patients under 50 years old perceived their RD as a hindrance for employment (Marchesini et al, 2001). The income of the RD patient did not seem to have an effect on their mental or physical health (Basal et al, 2011).

Unemployed RD patients or carers were reported poorer QOL than employed patients (Molster, 2016). Molster, (2016) suggests that RD patients or carers who were unemployed experienced poorer mental health than patients who were able to work. These findings imply that RD patients are more likely to have lower socio-economic status, which accordingly affects their overall HRQOL health. Further in-depth studies are necessary to assess socio-economic status in RD patients using a dedicated valid tool to determine the effect of socio-economic status on HRQOL.

In this study, most of the participants were Caucasian. No correlation was found between ethnicity and HRQOL. The vast majority of participants in this study (n=120) were Caucasian. This can be attributed to the fact that the EU and US consist primarily of Caucasian. Savey et al, (2014) found that ethnicity was a factor that had direct impact on HRQOL. The study investigated the association between ethnicity and its effect on HRQOL in patients suffering from a RD known as Behcet's disease (Savey et al, 2014). The study reported ethnicity-related variances with respect to phenotype of Bahcet disease patients and reported that Sub-Saharan African patients exhibited the worse prognosis out of all ethnicities.

A HRQOL of healthcare experiences for patients living with RDs was conducted in 2015 (Molster et al, 2016). Molster et al, (2016) focused on issues of accessibility of diagnosis, access to medications and use of health and support services in their localities. The HRQOL questionnaire was published online for RD patients living in Australia to participate in.

4.3.2 HRQOL section B: Personal care and independence

One of the primary components of the HRQOL tool was personal care and independence. Most RDs are chronic and are physically debilitating which is big concern for RD patients and their carers. EU RD patients reported higher QOL related to Bogart and Irvin (2017) suggested that personal care and independence are the most important aspect of HRQOL as it directly impacts mental health.

4.3.3 HRQOL section C: Mental health

The HRQOL is significantly lower for patients suffering from a RD compared to patients who are healthy; the QOL is particularly low for patients with no ODs available. Mental health was assessed using the HRQOL tool as it has a direct impact on quality of life. Factors that can lead to the deterioration of mental health of a RD patient include; delays in diagnosis fear of the future, pain, finance and dependency (Bogart and Irvin, 2017).

The Shire report (2014), conducted a mental health comparative study between the UK and the US. The shire report (2014) found that 81% and 89% of US (N=178) RD patients reported having depression and anxiety respectively. UK (N=288) RD patients reported slightly lower depression (75%) and anxiety (82%).

The most reported mental health issues in this study were stress (40%) and anxiety (35%). Rothrock et al, (2010) indicates that the most common cause of anxiety, stress and depression in chronic conditions can be attributed to delays in diagnosis and worrying about the future. We found that 24% of the participants received their diagnosis at birth and 22% had to wait 5 years or longer to get diagnosed with their RD. Shire report (2014), indicated that it took 7.6 years in the US to get a RD diagnosis while the UK it was about 5.6 years (Shire, 2014).

Rothrock et al, (2010) found that patients with genetic RDs had a lower quality of life when it came to mental health. Biesker and Erby (2008), reported that patients suffering from chronic diseases such as RDs can adapt to their new QOL if they are provided with appropriate support (such as mental counselling). Beisker and Erby defined

adaptation as '*the process of coming to terms with the implications of a health threat and the observable outcomes of that process'*. Mental adaptation in response to RDs has been reported by Bogart and Irvin, (2017) and they found that RD patients who received a diagnosis early in life were better able to adapt to their HRQOL. RD patients who an received early diagnosis and less misdiagnoses reported less HRQOL issues than those who received multiple misdiagnoses (Resta et al, 2006).

Molster (2016) links mental health problems such as frustration, sleeping problems and fear of the future to misdiagnoses where an average of 2 to 3 misdiagnoses is received by RD patients. In this study, 135 patients reported receiving misdiagnoses. Shire (2014) reports that 55% of US RD patients have incurred direct medical expenses not covered by their health insurance due to misdiagnoses of their RD. Misdiagnoses resulted in 37% of US RD patients borrowing money from family or friends to cover expenses of their misdiagnoses (Shire, 2014).

4.3.4 HRQOL section D: Accessibility to Orphan Medicines

Accessibility to ODs remains an issue for RD patients although both the EU and US have granted approvals for over 600 ODs combined over the last decades. Less than 5% of RDs have treatments available which has a direct impact on RD patients HRQOL. The number of RD patients and the high cost of ODs pose a substantial economic burden for the patient and payer. Patients living in the EU and the US reported differences in accessibility to ODs.

This study found that 44.5% (n=101) of participants reported that it was impossible to source or access ODs to treat their condition with 8% reporting that there are no ODs

available to treat their condition. In a EURORDIS survey on OD access in the EU, similar results were found. The survey included 480 RD patients of which 22% did not know of any treatment available for their RD and 8% reported no ODs available for their RD[49]. Detcek et al, (2018) found that out of 125 ODs, between 71 (64%) and 101 (90%) ODs were accessible in Germany, the UK, France, Italy and Scandinavia. Only 27% to 38% of authorised ODs were available in Ireland, Bulgaria, Greece and Romania (Detcek et al, 2018).

Affordability of ODs is another barrier that was examined in this study. It was found that 31.6% of the participants reported that it was impossible to afford their ODs while 19.6% reported some difficulty in affording the ODs. Around 13% reported no medication available for their RD. Hughes and Poletti-Hughes (2016) reported that affordability of ODs depended on the pricing of the OD by pharmaceutical company and the national health systems willingness to pay or co-pay. OD market authorisation holders reported 9.7% higher revenue returns when compared to non-ODs (Hughes and Poletti-Hughes, 2016). A survey on payers' willingness to pay for ODs in the US showed that patients are paying higher co-payments than their EU counterparts (Hyde and Dobrovolny, 2010). Hyde and Dobrovolny (2010), found that affordability of ODs in the US will continue to fall due to the rising cost of ODs. This correlates with this study findings as US patients reported lower access and affordability to ODs than EU based RD patients with over 56% of the participants reporting financial struggle due to the price of their medication.

[49] EURORDIS survey on Access to Orphan Drugs in the EU [Cited 2018 May 30] can be accessed through URL: https://www.eurordis.org/content/survey-patients%E2%80%99-access-orphan-drugs-europe

Financial struggle due to RDs was examined using the HRQOL tool. Mann-Whitney test revealed that US based patients experienced a significantly higher (p-value <0.05) financial burden due to their RD. Shire survey (2014) reported that ODs, diagnostic tests, visits to specialists and access to mental health support were the primary causes of financial struggle in the US and the UK. Shire (2014) revealed that although 90% of patients surveyed in the US had health insurance, they faced a significantly higher financial burden due to their RD. Access to appropriate healthcare practitioners is an essential part of good HQOL.

4.4 Limitations

Accessibility to ODs was assessed only in EU countries (n=28) and the US. Countries like Canada, Australia and Japan were not included due to time constrains. A review of OD and RD regulations and policies in languages other than English was not possible. Only peer reviewed journals were included and grey literature was excluded. Bias in the literature could have led to incorrect assumptions related to the accessibility of ODs in different countries included in this research.

Regardless of this study being the first to assess HRQOL in RDs and accessibility of ODs in Malta, EU and US, limitations must be acknowledged. The HRQOL part of the study was cross-sectional. Cross sectional studies cannot be used to analyse QOL over a period of time and can be an inaccurate representation of the population pool due to variables. Seers and Critelton (2001), and Ligthelm et al, (2007) reported that an appropriately formulated cross-sectional study can support evidence based practice for patient management. The cross-sectional part of this study did not allow for

investigation on how RD patients perceived their HRQOL over time to assess their health transition.

The HRQOL tool used closed-ended questions which might have created bias as the participant responses were limited to the available options. The tool contained questions with a five-point Likert-scale which might have limited the participants by providing them with 5 options. The responses might have not reflected the real views of RD patients, as carers could have filled the answers on their behalf.

Randomised sampling is the most accurate way of sampling as it reduces bias and provides individuals with an opportunity to partake in the study and reduce the chance of sampling errors (Meadows 2003). The participants in the HRQOL tool were predominantly Maltese (n=64) making data gathered not truly reflective of the EU RD population.

4.5 Recommendations for future research

Replicating this study with a larger sample of countries included to assess accessibility is recommended. Larger sample of RD patients at different stages of RDs needs to be recruited in the HRQOL study. A longitudinal approach should be used to examine the predictive factors of HRQOL to confirm the hypothesis of the model of Wilson and Cleary (1995) and develop causal relationships between factors assessed using HRQOL tool.

- It is important to assess policies and regulation associated with accessibility to ODs in regions other than the EU and US.

- Research is needed to compare the cost of ODs and the numbers of ODDs against number of approved ODs in light of the differences in legislations, regulations and policies across various countries.
- Effective RD intervention programmes in Malta are important to enhance the social support of RD patients.
- A HRQOL tool is needed to investigate the impact of specific RDs on QOL.
- A study on the pharmacist knowledge and intervention in RD patients management is needed.
- RD patients should be assessed regularly to identify and treat symptoms of depression, anxiety and other mental health issues.
- An investigation is needed to identify the link between socio-economic factors and HRQOL in RDs.
- Interventional studies with the aim of developing a programme to relieve manageable symptoms associated with RDs and encourage social support.
- Healthcare providers in Malta should be encouraged to register patients with RDs.
- There is a need for a future study that specifically investigates the use of RD registers in Malta.
- A future longitudinal study is recommended to examine the relationship between independent and dependent factors.
- Policy makers in Malta should consider establishing a data base with HRQOL data on specific RD and non-RD diseases which can be accessed by clinicians and researchers.
- There is a need for a study to investigate the HRQOL among RD patients living in regions other than the EU and the US (e.g. Canada, Australia, New Zealand, Japan etc.).

- An investigation needs to be conducted on whether the socio-economic factors impact HRQOL in RDs.

4.6 Conclusion

This study helps healthcare professionals and health policy makers locally and internationally better understand the healthcare needs of RD patients, particularly in terms of QOL and access to treatment. This study gives a critical appraisal of how different countries are dealing with RDs and ODs. It is the first of its kind in Malta and the only study that compares HRQOL in RDs and OD accessibility in the EU and US.

Both the EU and US have undertaken a mixture of policies and regulations to improve OD accessibility in the last twenty years. There are critical differences between countries in the types of policies and regulations implemented and these regulations and policies can enable the accessibility and availability ODs. The existence of marketing exclusivity remains a critical incentive for the research and development of ODs but poses risks, most importantly drug monopolisation and over pricing for ODs, which impacts RD patients accessibility to these appropriate treatments.

Malta has no RD plan, centre of expertise or clinical practice guidelines when it comes to RDs. Just over 3000 patients are registered out of the estimated 28,000 (8%) RD patients living on the islands. There is only one OD available to treat one out the ten registered RDs in Malta. Policy makers in Malta need to focus on establishing an RD plan and increasing access and availability of ODs.

The findings from the HRQOL tool indicate that physical and mental health of European RD patients is higher than that of the US. Analysis of responses showed that US RD patients have poorer mental, physical and social health than their European counterparts. These results are consistent with other observational studies conducted on RD patients (Marchesini et al, 2001).

There is a growing interest in investigating the perceived HRQOL and QOL in patients with RDs. Studies that have been carried out reached the same conclusion that patients with RDs have a poorer generic and disease specific HRQOL than the normal population. The literature is not clear about which dimensions of HRQOL are most affected, which may be related to differences in the cultural background and healthcare systems. Common factors that influence HRQOL have been identified, including demographic factors, socio-economic status, and clinical factors such as comorbidities. The heterogeneity of the participants in most of the previous studies is problematic regarding the generalisability of these studies findings on patients living with RDs particularly relating to perceived poor HRQOL.

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Appendix 1

Permission to adapt Grammie themes

Dear Amar

Many thanks and please feel free to use the themes, kindly let me know if I could be of any further help.

Kind Regards
Zaheer

Zaheer-Ud-Din Babar, PhD
Professor in Medicines and Healthcare
Department of Pharmacy, University of Huddersfield, Queensgate, HD1 3DH
Huddersfield, United Kingdom
Tel (office): +44 1484471471
https://www.hud.ac.uk/ourstaff/profile/index.php?staffid=1610

Editor-in-Chief
Journal of Pharmaceutical Policy and Practice
www.joppp.org

Secondary Affiliation: School of Pharmacy, Faculty of Medical and Health Sciences, University of Auckland, Private Mail Bag 92019, Auckland, New Zealand.

From: Abbas Amar at Medicines Authority [mailto:amar.abbas@gov.mt]
Sent: 12 March 2018 15:18
To: Zaheer Babar <Z.Babar@hud.ac.uk>
Subject: Research
Importance: High

Dear Dr. Babar,

I am a final year Doctorate student conducting my research in the field of Rare Diseases and Accessibility to Orphan Drugs at the university of Malta and university of Chicago (College of Pharmacy),

I would be very grateful if i can get your permission to adapt the themes you used for table 3. (Legislations, Regulations and Policies for Orphan Drugs by Country in your published article -**Access to Orphan Drugs: A Comprehensive Review of Legislations, Regulations and Policies in 35 Countries. PLoS ONE 10(10): e0140002**.) .

I will fully credit you in the research.

Awaiting your response,

Kindest regards
Amar

Appendix 2

Health Related Quality of Life Assessment tool

Health Related Quality of Life Assessment in Rare Disease Patients

This Doctorate research questionnaire is investigating areas of care to possibly help improve the quality of life of individuals. Our research group is investigating the area of rare diseases and accessibility of relevant medications, exploring the experiences of rare disease patients worldwide. The diagnosis, information provision at the time of diagnosis, use of health and support services, economic burden and general quality of life will be observed. The information provided by you in this questionnaire will be used solely for research purposes and will not be used in a manner which would allow identification of your individual responses.

Do you agree to participate in this study? *

Mark only one oval.

- ◯ Yes - continue to survey
- ◯ No- I don't want to take part

I confirm that I am over the age of 18 years * *Mark only one oval.*

- ◯ Yes - continue to survey
- ◯ No

Contact Amar Abbas with any queries on amar.abbas@gov.mt

SECTION A - BACKGROUND

This part aims to gather background information on the participant

1. You are a: *
   Mark only one oval.
   - ◯ RARE DISEASE PATIENT
   - ◯ CAREGIVER/PARENT/GUARDIAN

2. Please state your country of residence

   _____

3. Please state the name of your condition below:

   _____

4. Ethnicity origin (or race)
   Mark only one oval.
   - ◯ Caucasian (white)
   - ◯ African or Afro Caribbean (Black)
   - ◯ Asian (Chinese, Korean, Japanese)
   - ◯ Asian (Indian, Pakistani, Bangladeshi)
   - ◯ Middle Eastern or North African
   - ◯ Other: _____

5. Gender of patient
   Mark only one oval.
   - ◯ Female
   - ◯ Male
   - ◯ Prefer not to say

6. Age of patient (years)
   Mark only one oval.
   - ◯ 0-10
   - ◯ 11-20
   - ◯ 21-30
   - ◯ 31-40
   - ◯ 41-50
   - ◯ 51-65
   - ◯ 65+

7. Have you received a misdiagnosis of the condition? *Mark only one oval.*

- Yes
- No

8. How long did it take to receive the correct diagnosis since you first approached a healthcare professional about the symptoms?

Mark only one oval.

- 0 to 1 year
- 1 to 2 years
- 2 to 3 years
- 3 to 4 years
- 5 years and a bove

9. Is your condition genetic in origin? *Mark only one oval.*

- Yes
- No
- Not sure

10. Which of the following tests did you carry out? (Check all that apply): *Check all that apply.*

- [ ] Genetic testing
- [ ] Blood testing
- [ ] Colonoscopy
- [ ] Bone density testing
- [ ] MRI scan
- [ ] CAT SCAN
- [ ] None
- [ ] Other: _____

SECTION B - Personal care and independence

During the past four weeks, how difficult was the following: (If you're not the patient please answer to the questions below to the best of your knowledge)

11. Eating/drinking or being fed?

Mark only one oval.

	1	2	3	4	5	
Almost impossible	◯	◯	◯	◯	◯	Not a problem at all

12. Bathing / Washing/General hygiene?

Mark only one oval.

	1	2	3	4	5	
Almost impossible	◯	◯	◯	◯	◯	Not a problem at all

13. Getting in and out of bed?

Mark only one oval.

	1	2	3	4	5	
Almost impossible	◯	◯	◯	◯	◯	Not a problem at all

14. Moving about in the home? (in whatever way possible) *Mark only one oval.*

	1	2	3	4	5	
Almost impossible	◯	◯	◯	◯	◯	Not a problem at all

15. Visiting public places? (shopping, commuting, sightseeing, etc) *Mark only one oval.*

	1	2	3	4	5	
Almost impossible	◯	◯	◯	◯	◯	Not a problem at all

SECTION C - Mental and social health

During the past four weeks, how did you feel during the following: (If you're not the patient please answer to the questions below to the best of your knowledge)

16. While eating/drinking or being fed?

Mark only one oval.

	1	2	3	4	5	
Very upset	◯	◯	◯	◯	◯	Happy

17. While dressing/undressing?

Mark only one oval.

	1	2	3	4	5	
Very upset	◯	◯	◯	◯	◯	Happy

18. While lying down in bed?

Mark only one oval.

	1	2	3	4	5	
Very upset	◯	◯	◯	◯	◯	Happy

19. Understanding your parent/ caregiver/people around you? *Mark only one oval.*

	1	2	3	4	5	
Almost impossible	◯	◯	◯	◯	◯	No problem at all

During the past four weeks, how did you feel during the following: (If you're not the patient please answer to the questions below to the best of your knowledge)

20. Being understood by your parent/ caregiver/people around you? *Mark only one oval.*

	1	2	3	4	5	
Almost impossible	◯	◯	◯	◯	◯	No problem at all

21. Communicating with those who don't know you well?
Mark only one oval.

	1	2	3	4	5	
Almost impossible	◯	◯	◯	◯	◯	No problem at all

22. Participating in recreational activities (swimming, interacting with family and friends, etc.)?
Mark only one oval.

	1	2	3	4	5	
Almost impossible	◯	◯	◯	◯	◯	No problem at all

23. Have you ever experienced any of the following since you became aware of your condition?
Check all that apply.

- [ ] Stress
- [ ] Anxiety
- [ ] Depression
- [ ] Frustration
- [ ] Decreased interaction with family/friends
- [ ] sleeping problems
- [ ] Fear of the future
- [ ] None of the above
- [ ] Other: _____

SECTION D - Accessibility to Orphan Drugs

Since your diagnosis, how difficult was the following: (If you're not the patient please answer to the questions below to the best of your knowledge)

24. Receiving the correct treatment

Mark only one oval.

- ◯ Almost impossible
- ◯ Difficult
- ◯ Easy
- ◯ Not a problem at all
- ◯ There are currently no treatment for my condition
- ◯ Other: _____

25. Ability to source the medication

Mark only one oval.

- ◯ Almost impossible
- ◯ Difficult
- ◯ Easy
- ◯ Not a problem at all
- ◯ There are currently no medications for my condition

26. Ability to afford the medication

Mark only one oval.

- ◯ Almost impossible
- ◯ Difficult
- ◯ Easy
- ◯ Not a problem at all
- ◯ There are currently no medications for my condition

27. Did you struggle financially at any stage due to the price of medications/treatment? *Mark only one oval.*

- ◯ Yes
- ◯ No
- ◯ Not applicable

28. Please rate the financial burden of the condition *Mark only one oval.*

	1	2	3	4	5	
Significant burden	◯	◯	◯	◯	◯	Not a burden at all

29. Would you be willing to participate in clinical research studies? *Mark only one oval.*

- ◯ Yes
- ◯ No
- ◯ Maybe

THANK YOU FOR YOUR PARTICIPATION

Appendix 3

Permission to adapt the Lynn validation method

Adaptation of Lynn Validation method into a tool

Actions

To:

Abbas Amar at Medicines Authority

Attachments:

Heather final.docx (315 KB)[Open as Web Page]

Inbox

11 April 2018 15:08

Dear Mr. Abbas,

You are free to use and adapt the Lynn validation method,

Please don't forget to reference the author in your study.

Best of Luck in your research

Regards

M.Lynn

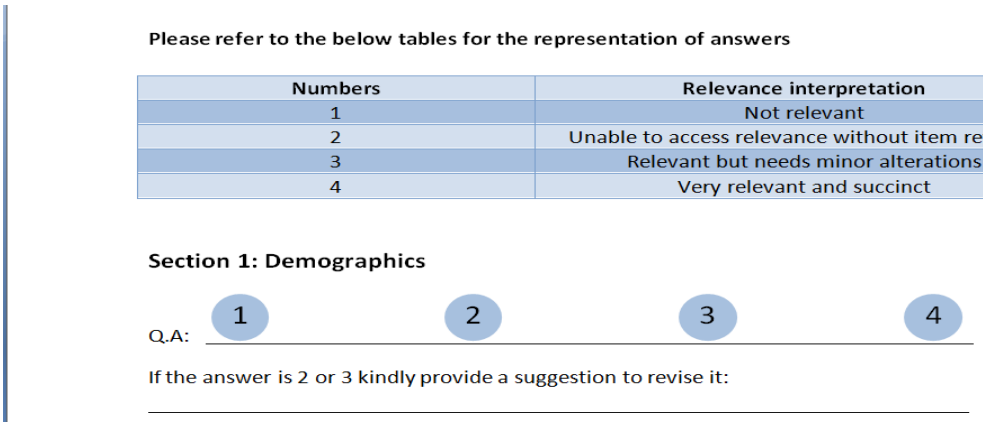
Appendix 4

Validation Tool

Instructions/directions

1. The following task will take approximately 10 to 15 min to complete
2. Kindly use the table below to refer for each answer / number to be selected.
3. Example: If you find the question 1 (identity of participant) valid and relevant to the context of my research then you would select one option/ number from the provided validation document (B) to rate its relevance.

B.



4. If 1 is selected then the question will be considered irrelevant and will be removed from the questionnaire
5. IF 2 or 3 is selected then those questions will be changed according to your suggestions provided below that particular question
6. If number 4 is selected then the question will be considered valid and relevant to my research and will be part of the questionnaire without any changes.

Please select one answer / number based on the relevance of the questions provided in the questionnaire:

Please refer to the below tables for the representation of answers

Numbers	Relevance interpretation
1	Not relevant
2	Unable to access relevance without item revision
3	Relevant but needs minor alterations
4	Very relevant and succinct

Section A: Background

Q.1: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q.2: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q.3: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q.4: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q.5: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q.6: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q.7: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q.8: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q.9: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q.10:

1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Section B – Personal care and independence

Q.11:

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q.12:

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q.13:

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q.14:

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q.15:

1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q.16:

1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Section C – Mental health and social life

Q.17:

1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q.18:

1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q.19:

1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q.20:

1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q.21:

1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q.22:

1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q.23:

1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q.24:

1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Section D – Accessibility

Q25: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q26: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q27: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q28: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q29: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q30: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Appendix 5

Letter to Validators

Dear Expert,

I hope this email finds you well.

I am a third year Doctorate student, currently conducting the study entitled ***"Management of Rare Diseases and access to Orphan medications"***. The study aspires to provide data that aims to evaluate the quality of life and socio-economic factors relevant to rare diseases.

To enable me to obtain the required data, I humbly request your expertise for the validation of my questionnaire. Below you will find instructions on the validation process of the four sections of assessment tool.

Your participation will be important to my academic endeavor and is highly appreciated.

I am looking forward to your positive response.

Yours truly,

Amar Abbas

3rd year Doctorate of Pharmacy student

University Of Malta

Appendix 6

Ethics (UREC) Approval

L-Università ta' Malta

Faculty of
Medicine & Surgery

www.um.edu.mt/ms

Ref No: **54/2017**

Wednesday 3rd January 2018

Mr Amar Ibraheem Abbas
Flat 11, Classic Flats
Misrah il-Barrieri
Msida

Dear Mr Amar Ibraheem Abbas,

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

The Management of rare diseases and access to Orphan medications

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

Yours sincerely,

Dr. Mario Vassallo
Chairman
Research Ethics Committee

Appendix 7

Request for dissemination of HRQOL tool

Dear Sir/Madam,

I am a Doctorate of Clinical Pharmacy student conducting my research in the area of Rare Diseases at the University of Malta. My study will explore the issues of diagnosis, information provision at the time of diagnosis, use of health and support services and general quality of life.

Our research group has published a validated self-administered questionnaire online. We would appreciate your help with making members of your organisation aware of our questionnaire.

It can be accessed through the following link:

https://docs.google.com/forms/d/e/1FAIpQLSdh7ymzEccgPPvY_5TGXTltNX410Gca7H0Zm7i3VWT9de3Omw/viewform?c=0&w=1

Your help is greatly appreciated,

Kindest regards,

Amar

Amar Abbas (MPharm),

Fellow of the Malta Medicines Authority

Inspectorate and Enforcement Directorate

Medicines Authority

Phone: 23439102

Mail: Sir Temi Zammit Buildings, Malta Life Sciences Park, San Gwann SGN 3000

E-mail: amar.abbas@gov.mt

Appendix 8

Publications

ACCESS TO ORPHAN DRUGS AND QUALITY OF LIFE IN RARE DISEASE

Amar Abbas, Janis Vella Szijj, Anthony Serracino-Inglott Department of Pharmacy

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Background: Over 7000 rare diseases (RD) affect around 300 million patients worldwide. The majority of RDs are genetic and appear early in life, resulting in a 30% mortality in children diagnosed before their fifth birthday. To date, there has been no locally conducted study about the healthcare needs of people living with RDs. Purpose: (1) To retrospectively analyse regulations and policies related to Orphan Drugs(ODs) accessibility in the EU and The US and propose methods to improve patient access(2) To create a Quality of Life assessment tool specific to RD patients and explore issues of diagnosis, information provision at the time of diagnosis, use of health and support services and general quality of life Methodology: A retrospective analysis was carried out to extract features of various OD policies to help identify areas that can improve accessibility. A self-administered Health Related Quality of Life (HRQOL) Assessment tool was created, validated by seven experts, and published online. Different patient groups in European Union countries the United States of America were contacted to invite their members to participate. Results: There were OD specific legislations in all of the EU countries and in the US. Accessibility of ODs depended on pricing, re-imbursement policies and product availability. Two hundred and twenty-five responses given by RD patients were analysed. Accessibility issues were a hurdle for RD patients as 52% reported that medication is available in other countries but not in their country. Forty percent received a misdiagnosis and 34% were waiting over 1 year to receive a diagnosis. In terms of mental health, 74% complained of stress and anxiety problems. Discussion: Although all the countries examined in this study had an OD regulation in place, there were differences between countries in pricing, licensing and reimbursement of ODs which have an impact on accessibility. There is a need for improvement in the quality of life of RD patients given the high cost of illness, mental health problems and poor accessibility to medications.

ODC -Barcelona

Quality of life in rare diseases

Research Question: What are the regulations and policies related to Orphan Drugs (ODs) that exist locally and internationally and how is the Quality of Life of RD patients?

Methods: A retrospective analysis was carried out to observe features of OD policies in RD patients locally and internationally. A self-administered Health Related Quality of Life (HRQOL) Assessment tool was developed, validated and published online. The HRQOL tool explored issues of diagnosis, information provision at the time of diagnosis, use of health and support services and general quality of life of RD patients including mental health issues. Different patient groups in Asia, Europe, Africa and America were contacted to invite their members to participate.

Results: There were OD specific legislations in 29 countries. Accessibility of ODs depended on pricing, re-imbursement policies and drug availability. One hundred and thirty responses given by RD patients were analysed. Sixty percent (n=78) of responses gathered were from Malta, 20% (n=26) from Ireland and 10% (n=13) from the USA. Accessibility issues were a hurdle for RD patients as 50% (n=65) reported that medication is available in other countries but not in their country. Forty percent (n=52) received a misdiagnosis and 30% (n=39) were waiting over 1 year to receive a diagnosis. Seventy percent (n=91) of patients complained of stress and anxiety problems.

Conclusion: All the countries in this study had an OD regulation in place,.There were differences between countries in pricing, licensing and reimbursement of ODs which have an impact on accessibility. There is a need for improvement in the quality of life of RD patients.

Appendix 9

Orphan drug and rare disease policies by country

Table 3.1 Results on OD and RD specific findings by country					
Country	**OD or RD plan**	**Financial incentives**	**Non-financial incentives**	**Pricing of ODs**	**Reimbursement procedure**
Austria	No	No	Scientific advice, compassionate use access	Reference pricing	Reimbursed under the national law for life saving drug access
Belgium	Yes	Exemption from tax	No	Price negotiated with supplier	Reimbursed after approval by the ministry of social affairs
Bulgaria	Yes	No	Compassionate use access	Reference pricing	Reimbursed by Ministry of Health
Czech Republic	Yes	No	No	Fixed pricing method	Reimbursed for ODs on national formulary

Table 3.1 *(Continued)*					
Country	**OD or RD plan**	**Financial incentives**	**Non-financial incentives**	**Pricing of ODs**	**Reimbursement procedure**
Denmark	No	No	Compassionate use, free scientific advice	Free	Reimbursed for ODs on national formulary + a co-payment
Estonia	Yes	No	Free administrative advice	Free – must be justified	Reimbursed from 50-100% by the Estonian health insurance scheme
Finland	No	No	No	Fixed pricing method	Reimbursed for ODs on national formulary
France	Yes	Tax exemption	Compassionate use, free scientist advice	Price negotiation method	60-100% reimbursement by

					health ministry

Table 3.1 (*Continued*)

Country	**OD or RD plan**	**Financial incentives**	**Non-financial incentives**	**Pricing of ODs**	**Reimbursement procedure**
Germany	Yes	No	Compassionate use access	Free – must be justified	Reimbursed for ODs on national formulary after a cost analysis
Greece	Yes	No	Compassionate use access	Reference pricing	Reimbursed for ODs on national insurance system
Hungary	No	No	Compassionate use access	Free	Reimbursed under legal equity procedure
Ireland	Yes	No	Compassionate use access	Free – must be justified	Reimbursed for ODs on national formulary after

					a cost analysis

Table 3.1 *(continued)*

Country	**OD or RD plan**	**Financial incentives**	**Non-financial incentives**	**Pricing of ODs**	**Reimbursement procedure**
Italy	Yes	No	Compassionate use access, scientific advice	Reference pricing	Reimbursed under law 658 though the government
Latvia	Yes	No	Scientific access	Free	Reimbursement for ODs on formulary
Malta	No	No	No	Free under POYC scheme	Reimbursed for ODs listed in Maltese national formulary
Poland	Yes	No	Compassionate use access	Reference pricing	Reimbursed if passes HTA through the

					therapeutic programme scheme

Table 3.1 *(continued)*

Country	**OD or RD plan**	**Financial incentives**	**Non-financial incentives**	**Pricing of ODs**	**Reimbursement procedure**
Portugal	Yes	No	No	Free	Reimbursed through the ministry of health
Romania	Yes	No	Compassionate use access	Reference pricing	Reimbursed if passes HTA through the therapeutic programme scheme
Slovakia	No	No	Compassionate use access	Free	Reimbursed with a co-payment of €0.16
Spain	Yes	Reduced tax	Compassionate use access	Fixed	Reimbursed if on the Formulary

Switzerland	No	Tax exemption	No	Free	Reimbursed with a 10% co-payment

Table 3.1 *(continued)*

Country	**OD or RD plan**	**Financial incentives**	**Non-financial incentives**	**Pricing of ODs**	**Reimbursement procedure**
Netherlands	Yes	Fee waivers	Compassionate use access	Price negotiation	Reimbursed if on the Formulary
United Kingdom	Yes	No	No	Fixed - decided by PPRS	Reimbursed by NHS if on the ICER is met
United States*	No	Reduced tax (50%), fee waivers	Compassionate use access, scientific and administrative advice	Free	Reimbursed by 95% by Medicare

*the US has an OD legislation but it does not have an OD or RD plan in place

Appendix 10

The Malta Summit on Rare Diseases

RDs are gaining more European and international recognition in the last two decades. There has been a global call for strategies to tackle the social and economic burden that RD patients are living with. Since 1999, the EU started to recognize and better deal with RDs by cross-country collaboration in the fields of clinical trials, access to medications and the founding of EURORDIS. Individuals living with an RD encounter considerable challenges. Just 5% of RDs are treatable or manageable - a small number of curative, several transformative, but the majority of treatments are improving or extending QOL. Few scattered RD patient groups, limited researchers and little attention from policy makers marginalised RD patients; however, the aim of the conference in Malta was to mitigate challenges faced by bringing all these groups together.

The significant technological and scientific progress in the past decade paved the way for better diagnostic tools for RDs and presented an opportunity for researchers to better understand and develop novel therapy to target rare conditions. These fresh opportunities personify hope for patients; however, they come with concern to policy makers as issues of accessibility and availability are present. Development in the data collection and sharing between nations has improved cooperation to help with budgeting and highlighting areas of need with the RD pool however, there is still room for better cooperation to address the ethical and legal matters that come with accessibility of RDs.

The Malta summit highlighted the need for cross border collaboration to guarantee that RD patients throughout the EU have equal opportunity for access to diagnosis, therapies, and care. To reach this level of cooperation, the EU has to develop a strategic

and structured way to tackle the issue of RD. A series of proposals were given by many member states representatives, researchers and policy makers.

One of the proposed ways of cooperation was the introduction of the 'European reference networks' (ERNs). ERNs allow a clear governance structure for cross border data sharing and care harmonization, connecting over 900 healthcare providers in the European Union. This allows for easier access of information and sharing of knowledge for either the RD patient or healthcare professionals involved with these patients. ERNs encourage clinical excellence by leaving no one behind. Allowing the healthcare professionals to see how certain RDs are being treated by other member states and connecting patients with other RD sufferers breaks the barrier of isolation that many feel.

EURORDIS gave a clear and concise message at the Malta conference. 'ERNs are the most important step forward in improving QOL in RD patient'. This declaration encouraged policy makers and researchers to participate in ERNs, through sharing of knowledge. ERNs can be a training ground for healthcare professionals and a source of hope for patients of RDs. EURORDIS made an official request for all EU member states to facilitate and aid in the establishing of ERNs in their respective countries. Systematic education, workforce exchange and other 'emerging opportunities are to be utilised in all workforces, from clinical specialists to nurses, paramedics to research assistants, IT specialists to managers, and centres coordinators to patient representatives'.

RD Patients must be given appropriate information to make them in charge of their condition whenever appropriate. National health systems must be able to fund and provide suitable care to these patients. Centres of care for RD patients must be established for the patients throughout the EU as the next step in easing the burden of rare conditions. The proposed ERNs will have a common data base to be used for all EU citizens. The summary of EURORDIS was:

- Voluntary cooperation and education is voluntary and should be designed to ensure that the patient is at the heart of ERNs
- Twenty four ERNs were established on the 1st of march of 2017 and is a revolutionary point in RD care
- Healthcare professionals who are involved in RD management should be trained to ensure uniform care throughout the EU
- ERNs should be integrated into the national health service of all EU member states
- It is important to ensure that data collected by ERNs is accessible to be used by healthcare professionals and researchers to aid in the development of new therapies

Structured cooperation in research for rare diseases

Understanding of RDs has changed drastically since the completion of the human genome project in 2003. It was confirmed that in fact most of RDs are genetic in origin and thus treatment and diagnosis should take into account genetic sequences of the RD. With these scientific and technological advances in the last 20 years, many issues of ethics and inequality have risen. The most important in regards to RDs, is the issue of

accessibility. The question of is an RD patient born in Malta receiving the same care as an RD patient living in England is a hot topic within the RD community.

The Rare disease connect project was also in discussion at the Malta RD conference. EURORDIS commented on the lack of Expertise on RDs in the EU. This makes it difficult for both patients to be diagnosed and appropriately treated, and for researchers conducting projects in this field. The RD connect project aims to to connect the EU RD community by sharing 'RD databases, registries, biobanks and clinical bio-informatics data' in a central resource and make it accessible worldwide. If RD connect was to come to practice within memeber states, it would vastly impact research and give EU policy makers great insight into area of need in RDs. This project will help limit duplication of research and data and will be used for funding allocations.

Projects such as the E-RARE and IDRiRC have helped with data collection and sharing in the past Initiatives contributed in the reduction of fragmented RD data. Lack of funds and interest in these projects in the past prevented them from progressing further.

In regards to RD connect, the most important information discussed were;

- Cooperation between researchers can improve results obtains
- Integrated networks should be the first step
- Public and national funding at EU level would ease the burden of RDs
- Structured drug access plan for the EU

The last two decades have seen a large increase of interest in RDs within member states, and as a result, a stronger cooperation between the EU has taken place. Member states have recognised the financial and social problem faced by RD patients. An agreement for information sharing and joint HTA and uniform pricing of ODs are the

primary focus of member states. The Malta summit confirmed that all member states were willing to cooperate In this area and they recognised:

- The importance of fast tracking OD process and controlling the price of the ODs.
- That a collective EU approach is needed to facilitate procurement of ODs for all member states.
- iii. that this unified European approach shall facilitate the negotiation of fairer prices, better related to the real value of a medicine, and to its level of clinical uncertainty; public authorities in all Member States, and most particularly the 22 Member States with a population of less than 20 million, are encouraged to give their consideration to this proposal.

The congress concluded with a remark from EURORDIS to identify the efforts of the Maltese presidency to enhance the well-beings of RD patients in the EU.

Appendix 11

World Orphan Drug Conference

World Orphan Drug Congress

The World Orphan Drug Congress is an annual marketplace for orphan drug professionals looking at the complete value chain of orphan drug development, from clinical development and research and development to corporate development and market access. The 8th Annual Orphan Drug Congress took place in Barcelona Spain with around 1000 attendees and 150 speakers. The conference started on the 13th of November with a Pre-Congress Workshop focusing mainly on the pricing, reimbursement and market access challenges for orphan drugs and cell and gene therapies. The President of MME Europe, Dr. Renato Dellamano addressed the need for better accessibility of orphan drugs to the patients. The MME (Medical Marketing Economics) is a global leader in the development of value-based strategies and market research for health care goods and services. It was emphasised that "an orphan drug that does not reach the patient is a failure". Since 2001, MME has developed value-based marketing strategies for large and emerging bio/pharmaceutical clients. MME's areas of expertise include biotech, market access, oncology, orphan drugs and hospitals. MME provides clients with:

- unique combination of manufacturer and customer perspectives combined with solid academic theory
- Strategy development and tactical execution to support informed decision making
- Assessment and planning of opportunities and competitive situations at every stage of the product life cycle.

The MME has completed over 125 US and EU launch price strategies in the last 3 years. One of the issues that were brought up by MME was the discrepancy of the time

to launch post regulatory approval in the US and the biggest countries in the EU for the same sample of products. The calculated number of weeks for the US was found to be 2.4 while for example the launch in the UK took 28 weeks. (second photo of the 13/11).

There are two ways to obtain therapies before the product is granted a marketing approval:

- Special license sales that provide the opportunity for patients to get access to innovative therapies in high need areas more quickly, and for clinicians to gain experience with the product
- Compassionate use: the medicinal product is made available to patients with "a chronically or seriously debilitating disease, or a life-threatening disease, and who cannot be treated satisfactorily by an authorised medicinal product in the EU." [50]

Enzyme replacement therapies (ERTs) used in rare diseases also face multiple challenges. One of these challenges is that rare diseases are often characterised by multiple phenotypes that imply completely different clinical response to the new treatment. ERTs usually have a weight dependent dose, so the cost to treat an adult patient is usually higher compared to the cost of treating a child, and is often the opposite in terms of therapeutic effectiveness. The HTA bodies in Europe often do not consider these features and in addition to that, the caregivers and families' burden is not well contemplated.

The difference between Advanced Therapy Medicinal Products (ATMPs) and Enzyme Replacement Therapy (ERTs) was highlighted. ATMPs are not considered as medicinal

[50] EMA website [Cited 2018 May 30] can be accessed through URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000293.jsp

products in all EU countries, are usually one-off treatments and have an extremely limited shelf-life. ERTs are considered to be traditional pharmaceutical products, are used for chronic treatments and have an extended shelf life.

There are various drug development issues for orphan drugs, mainly:

- Very small patient populations, often with severe diseases
- No alternative treatment available
- Clinical trials are very difficult to run
- Unmet patient need may necessitate product use pre-approval
- Need for additional observational data both pre- and post- approval

Orphan Drug development first starts by identifying the need for a new drug and recognising the small patient population that needs the drug. This is followed the Phase 1 trials where the pharmacokinetics of the drug are established. In phase 2a trials, determines the dose ranges that can be administered. Phase 1 and phase 2a trials may be combined in a single study of patients.

Phase 2b studies follow, where the drug effect is monitored. The drug is then ready to obtain a MA or may undergo expanded access programs to provide pre-approval access and evidence of safety pre-approval. Post approval observational studies provide long-term safety and efficacy data. This data may be obtained by the use of registries. This is where the concept of real world data comes in. EMA defines 'Real World Evidence' as 'evidence coming from registries, electronic health records (EHRs), and insurance data where studies may be required by regulators through scientific advice, CHMO or ORAC and the subsequent results are used to inform regulatory and potentially HTA-

decision making."[51] It is a term used to describe healthcare related data that is collected outside of randomised clinical trials. Real World Evidence in rare diseases has multiple benefits including the identification of patients for clinical trials, interactive communication and data reporting to investigators and the launch of evidence-based medicine for outcomes and reimbursement. Real world study can be retrospective therefore based on historical cohorts or prospective, dealing with qualitative studies such as interviews, focus groups and observational studies. Real world data is very beneficial in orphan and rare disease research mainly to establish patient population size and describe safety and efficacy of the orphan drugs.

Expanded and Compassionate Use programs can provide pre-approval information on real world drug safety and clinical effectiveness. They are also intended to improve access to investigational drugs for patients with serious or immediately life-threatening disease or conditions who do not have comparable or satisfactory alternative therapies to treat the disease or condition. They enable patients to access products that are still in development for treatment purposes.

Registries play a very important role in the provision of real world data. Registries can be patient-centred of physician-centred. Patient-centred registries are usually available at a single centre per country and contain data reported by patients. Patients may be paid a nominal fee for participation. Patient-Centred registries may involve the participation of patient advocacy groups. Physician-centred registries can be found in

[51] EU committee EC [Cited 2018 May 30] can be accessed through URL: https://ec.europa.eu/health//sites/health/files/files/committee/stamp/201603_stamp4/4_real_world_evidence_ema_presentation.pdf

multiple sites across the country and usually contain medical records provided by physicians. Physician-centred registries usually require patient consent.

Regulators in both EU and Us are opening up assessment pathways that are faster to address unmet medical needs, particularly in rare and difficult to treat diseases. One of these pathways is the newly introduced adaptive pathway. "Adaptive pathways can be defined as a prospectively planned, iterative approach to bringing medicines to market. The iterative development plan will initially target the development to a well-defined group of patients that is likely to benefit most from the treatment. This is followed by iterative phases of evidence gathering and progressive licensing adaptations, concerning both the authorised indication and the potential further therapeutic uses of the medicine, to expand its use to a wider patient population as more data become available."[52]

Due to the limited resources and data, patient participation in clinical trials and drug development is very highly requested. MAPI, which was one of the sponsors organising the conference, is a leading Patient-Centred Research company serving academia, life science researchers, and the pharmaceutical industry. Ms. Kelly Franchetti, Vice President of Global Patients Insights and Engagement at Mapi Group led a hands-on workshop that represented the actual workshops carried out by advocacy groups for patients with rare diseases. Through this interactive workshop, Ms. Franchetti aimed to demonstrate how to assess their physical, social and emotional needs, and identify their motivators, barriers and influencers as they relate to clinical study participation.

[52] European Medicines Agency [Cited 2018 May 30] can be accessed through URL: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/08/WC500211526.pdf