

Aris Angelis, David Tordrup, [Panos Kanavos](#)
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Author: Aris Angelis David Tordrup Panos Kanavos

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**Socio-Economic Burden of Rare Diseases:
A Systematic Review of Cost of Illness Evidence**

Aris Angelis^a, David Tordrup^{a,1} and Panos Kanavos^a

^aMedical Technology Research Group, Health Research Centre, London School of Economics and Political Science, Houghton Street, WC2A 2AE London, United Kingdom

Corresponding author: Aris Angelis, London School of Economics and Political Science, Houghton street, Tower 3, W4.01D, WC2A 2AE London, United Kingdom, Tel.:+44 207955 6842

¹Present address:
World Health Organisation, Representation to the EU, Rue Montoyer 14,1000 Brussels, Belgium

Highlights

- We systematically reviewed the socioeconomic cost literature for 10 rare diseases.
- Direct and indirect costs incurred by patients, carers and society were searched.
- 77 studies were included with an unequal distribution of studies over disease types.
- Level of existing evidence is highest for diseases with available drug treatments.
- Indirect costs are in most cases of similar or higher magnitude than direct costs.

Abstract

Cost-of-illness studies, the systematic quantification of the economic burden of diseases on the individual and on society, help illustrate direct budgetary consequences of diseases in the health system and indirect costs associated with patient or carer productivity losses. In the context of the BURQOL-RD project (“Social Economic Burden and Health-Related Quality of Life in patients with rare diseases in Europe”) we studied the evidence on direct and indirect costs for 10 rare diseases (Cystic Fibrosis [CF], Duchenne Muscular Dystrophy [DMD], Fragile X syndrome [FXS], Haemophilia, Juvenile Idiopathic Arthritis [JIA], Mucopolysaccharidosis [MPS], Scleroderma, Prader-Willi Syndrome [PWS], Histiocytosis and Epidermolysis Bullosa [EB]). A systematic literature review of cost of illness studies was conducted using a keyword strategy in combination with the names of the 10 rare diseases. Available disease prevalence in Europe was found to range between 1-2 per 100,000 population (PWS, a sub-type of Histiocytosis, and EB) up to 42 per 100,000 population (Scleroderma). Overall, cost evidence on rare diseases appears to be very scarce (a total of 77 studies were identified across all diseases), with CF (n=29) and Haemophilia (n=22) being relatively well studied, compared to the other conditions, where very limited cost of illness information was available. In terms of data availability, total lifetime cost figures were found only across four diseases, and total annual costs (including indirect costs) across five diseases. Overall, data availability was found to correlate with the existence of a pharmaceutical treatment and indirect costs tended to account for a significant proportion of total costs. Although methodological variations prevent any detailed comparison between conditions, most of the rare diseases examined are associated with significant economic burden, both direct and indirect.

Keywords

Cost of illness; Rare diseases; Socioeconomic impact; Systematic review; Orphan drugs; BURQoL-RD

1. Introduction

Most rare diseases are associated with high unmet need due to the lack of available and effective treatments and the relative lack of research to discover and develop such treatments. In the European Union (EU), a rare disease is defined as one affecting less than 1 in 2,000 people, and it is estimated that over 6,000 different, life-threatening or chronic, rare diseases exist today (1). Although rare diseases are by definition associated with low prevalence, considering that 6% - 8% of the population are affected by a rare disease, the total number of patients in the EU is estimated to be between 27 and 36 million (2). With the majority of rare disease patients suffering from less frequent conditions with a prevalence of 1 in 100,000 population, and with many rare diseases being of genetic origin, there is a strong public health interest relating to their cost and broader socioeconomic impact in order to develop sustainable health policy options.

Cost-of-illness (COI) studies measure the socio-economic burden of a disease and can be used as a public policy tool to assist in prioritization and justification of healthcare and prevention policies (3). COI studies can indicate which interventions are more valuable by comparing averted economic burden, and consequently lead to shifts in distribution of public and private investments. Different stakeholders can utilise COI studies differently. Governments can estimate the financial impact of a disease on public budgets for resource allocation purposes, whereas pharmaceutical corporations can identify diseases with high management costs to direct research and development (R&D) investments towards accordingly.

In addition, COI studies provide information for other types of economic evaluations, including a framework for cost estimation in cost-utility and cost-effectiveness analyses, frequently used by policy makers (3, 4). They are increasingly cited in clinical and epidemiological research to emphasize the importance of studying a particular disease and the scale of a problem, conveying the aggregate burden of illness on society by estimating the maximum amount that could potentially be saved if a disease were to be eradicated (5, 6).

While COI studies can identify and measure all costs of a particular disease, they do not address issues of inefficiency or waste, or weigh up costs and benefits of interventions (6). Caution is also advisable when interpreting COI estimates as potential savings if a disease were systematically targeted, as not all conditions can be fully eradicated, and some proportion of economic burden will remain despite effective interventions (6). For optimal resource allocation, COI studies should be used in combination with full economic evaluations such as cost-benefit or cost-utility analyses which assess both costs and outcomes (7).

COI studies employ a wide range of different designs and methodologies, often limiting comparability and usefulness of results (8). Variations include data sources, perspectives (healthcare, societal, etc.), cost types, costing approach and discount rate(9). While standardisation of methodology through implementation of guidelines is becoming increasingly important, some flexibility may be required for diseases with special characteristics to be adequately described (3, 9).

Numerous COI studies have been conducted over the past three decades across a range of diseases, however few have addressed rare diseases. In this context, the aim of the BURQOL-RD project (“Social Economic Burden and Health-Related Quality of Life in patients with Rare Diseases in Europe”) was to provide new tools and knowledge for 10 rare diseases (RDs), including socio-economic burden and health related quality of life for patients and their caregivers (10).

The objective of this study is to systematically review the relevant literature on the socioeconomic burden of RDs and identify all costs, both direct and indirect, related to ten specifically identified RDs from the perspective of patients, families and society.

2. Data and methods

The BURQOL-RD project participants adopted a Delphi consensus approach in combination with a Carroll diagram for the selection of the 10 RDs to be studied (10). An expert panel involved 23 individuals as representatives of each associated and collaborating project partner. Initially, the selection criteria for the potential RDs were defined and were summarised under the acronym BOS CARE: these included a Broad spectrum of RDs should be suitably represented, including some ultra-rare and less

frequently researched RDs; the availability of strong and well-Organised patient associations for specific RDs in most participating Member States ensuring adequate recruitment and participation rates; taking advantage of previous Studies carried out by Eurordis and other national/regional associations, to consider at least some of the RDs included in such studies for which a minimum threshold of participation was obtained; select RDs where in the absence of effective therapies a professional network can offer integrated advice, CAre and support for the affected families; and availability of rare disease REgistries, European research networks financed by the European Union DG-Sanco or networks of reference centres. Subsequently, a two-round Delphi panel process yielded a prioritised list of diseases. A questionnaire was administered to all experts via e-mail. In the first round, the questionnaire offered the BOScare criteria and an initial set of candidate RDs; each expert was asked to select 10 diseases according to the BOScare criteria and rank them by importance. In the second round, members were provided with their own rankings as well as with the overall results of the first round for the panel, and a revision of their ranking was requested. Based on this approach a shortlist of 36 RDs emerged following the end of the first round, and a total of 33 RDs were shortlisted following the end of the second round. The following step involved a joint discussion among the expert panel, where six potential determinants were identified, notably (a) prevalence of $\geq 1/10,000$ or $< 1/10,000$; (b) age at onset and whether this was during adulthood or childhood; (c) the extent to which the disease was genetic or had other origin; (d) whether or not the disease resulted in physical impairment and/or mental impairment; (e) whether or not there exist valid diagnostic tests; and (f) whether or not there is availability of effective therapies to modify the disease course. Experts provided a ranking for the conditions based on these determinants. Finally, in the group of shortlisted conditions from the above step, a Carroll trilateral diagram was applied taking into account three determinants, namely (a) prevalence, (b) availability of effective treatments and (c) need for carer.

The final set of 10 rare conditions included Cystic Fibrosis (CF), Duchenne Muscular Dystrophy (DMD), Fragile X syndrome (FXS), Haemophilia, Juvenile Idiopathic Arthritis (JIA), Mucopolysaccharidosis (MPS), Scleroderma, Prader-Willi Syndrome (PWS), Histiocytosis and Epidermolysis Bullosa (EB). In selecting the final list of RDs for this

project, efforts were made to include both rare and ultra-rare diseases review as well as diseases that did have some pharmacological treatment versus diseases that did not.

Based on the agreed-upon disease sample, a systematic literature review of COI was undertaken using the following five keywords in conjunction with the names of the 10 RDs identified above: cost of illness; spending; financial expenditure; financial burden; costs.

PubMed and the Web of Science (WoS) databases were searched in March 2011. All studies published prior to this date were eligible for inclusion. The resulting studies were filtered to identify their suitability for inclusion based on whether they provided evidence of costs, both direct (either medical or non-medical related) and indirect (i.e. productivity loss).

All costs were converted to 2010 Euros (€). Given the limitations of the European Central Bank (ECB) Statistical Data Warehouse (does not provide currency conversion rates before 1999, which is later than some of the cost figures identified and, additionally, it does not cover European currencies prior to their accession to the Euro), exchange rates were retrieved using the PACIFIC Exchange Rate Service from the University of British Columbia (monthly averages, price notation)(11). Prices were adjusted to 2010 levels before conversion using Average Consumer Price Inflation figures (12).

<Figure 1 about here>

3. Results

3.1 Disease characteristics and prevalence in Europe

By reviewing the available evidence on disease characteristics and their prevalence/rarity, a better understanding of the burden of the different diseases can be gained. In turn, the limited availability of COI evidence suggests the need for further research on the selected RDs. Prevalence for each disease is shown on Table 1.

CF is the most frequent pediatric autosomal recessive disease in Caucasian populations (13-15), occurring in 1 in 2,500 to 3,600 births, with a European Union (EU) prevalence of 12.6:100,000 population (16). CF causes abnormalities in chloride ion transportation resulting in increased viscosity of mucus secretions within numerous organ systems. This impacts primarily the lungs and respiratory function, the pancreas, fat digestion, and, over the long-term, liver function. Respiratory failure is the primary cause of morbidity and mortality in CF patients (17). The disease was originally considered pediatric as most did not survive past adolescence, however, improvements in daily routines, medical management and pharmacological support have allowed increasing numbers of patients to survive until middle adulthood.

DMD is a recessive X-linked type of muscular dystrophy, affecting boys only. The condition appears in early childhood, resulting in muscle degeneration affecting mobility, spinal development and breathing. Life expectancy ranges from teenage to early adulthood. Treatment is largely supportive via physical therapy and medical appliances and home modifications, although some clinical trials are being performed on beta-agonists. The condition affects approximately 1 in 4,000 male infants(18), with an EU prevalence of 5 per 100,000 population (16).

Fragile X syndrome (FXS), otherwise known as Martin-Bell syndrome or Escalante's syndrome, is an X-linked dominant genetic disorder resulting primarily in autism and other mental disability (19). The prevalence of the disease is 1:3,600 males and 1:4,000-6,000 females(20) and the EU prevalence is estimated to be 20 per 100,000 population (16).

Haemophilia is a recessive X-linked disorder resulting in lowered clotting factors, which prevent coagulation and clotting from occurring. This causes difficulties in maintaining a blood clot to start the healing process and causes bleeding to last for longer. There are three types: haemophilia A, B and C (autosomal) with poorly functioning clotting Factor VIII (80% of patients), IX (20% of patients) and XI respectively. Treatment involves regular infusions of Factors VIII, IX or XI from human or recombinant blood products. The incidence of haemophilia A varies by country at 1:5,000-10,000 males while haemophilia B is 1:20,000-34,000 males (21), with an overall haemophilia prevalence in the EU at 7.7 per 100,000 population (16). Haemophilia has been divided into three

levels of severity – mild (5-40% clotting factor), moderate (1-5%) and severe (<1%). Treatment with clotting factor VIII or IX may result in the production of antibodies, known as inhibitors, causing standard treatment to become ineffective and bleeding more difficult to control. More advanced drugs have been developed to treat patients with inhibitors. Further, as treatment involves regular use of blood products, patient are exposed to the risks of Hepatitis C (HCV)/Human Immunodeficiency Virus (HIV) infection, particularly up until the mid-1990s when the virus testing window was large and before the mid-1980s when blood safety was poorer compared with current standards. As a result, a significant number of haemophilia patients are infected with HCV/HIV, making their treatment and management more difficult.

JIA is the most common form of childhood arthritis, primarily affecting knees, ankles, wrists, hand and feet. Chronic pain is commonplace, and over time joints become damaged and contracted resulting in growth retardation (also an effect of long term steroid use). There are three classifications: oligoarticular (≤ 4 joints in first 6 months; 50% of children), polyarticular (≥ 5 joints in first 6 months; 40% of children) and systemic (joint and organ involvement; 10% of children). Treatment involves physical therapy, medication (anti-inflammatory drugs, corticosteroid injections, TNF alpha blockers), surgery and occupational therapy. It has an estimated prevalence of 8-150 children in every 100,000 (22), and an overall prevalence estimate in the EU at 5.0 per 100,000 population (16).

MPS is a group of metabolic disorders where the body does not produce sufficient enzymes needed for glycosaminoglycans breakdown (long chains of sugar carbohydrates in the cells aiding bone, cartilage, tendons, corneas, skin and connective tissue growth) and are part of the lysosomal storage disease family. There are a number of MPS types, from MPS I to MPS IX each with varying incidence, sub-types and deficient enzymes (Type I, with prevalence of 1:100,000 to 1:500,000 population; Type II, 1:100,000 to 1:170,000 males; Type III, 1:70,000; Type IV, 1:200,000 to 1:300,000; Type VI, 1:250,000 to 1:600,000)(23-27). In the EU, the overall prevalence for all types of MPS is estimated to be 3:100,000 population (16). MPS Type I, also known as Hunter's Disease, is commonly differentiated into severe and attenuated types resulting in mental retardation and, often, poor cardiac and liver development. Symptoms are usually apparent early in life, at times as young as one year old (23). MPS Type VI, also

known as Maroteaux-Lamy syndrome, primarily obstructs bone development resulting in short stature, skeletal and joint deformities. While patients with the rapidly progressive phenotype tend to die before adulthood, those with a slowly progressive phenotype may live into their 40s or 50s. Recently, a new treatment, enzyme replacement therapy (ERT) (recombinant human ASB enzyme, rhASB) has been made available, potentially improving patient quality of life (28).

Scleroderma is a connective tissue disorder resulting in changes in the skin, muscles, blood vessels and internal organs due to a buildup of collagen in these organs. The cause is unknown, however, it does run in some families and some risk factors have been identified, such as industrial exposure to silica dust and polyvinyl chloride. More common in women than men, scleroderma tends to affect individuals between 30 and 50 years of age (29). The prevalence of scleroderma is estimated to be around 74:100,000 among women and 13:100,000 among men (30), with an overall EU prevalence being 42:100,000 population (16).

Prader-Willi syndrome (PWS) is a congenital genetic disease where seven genes on chromosome 15 are deleted or not expressed. This results in obesity due to hyperphagia, poor muscle tone, sex glands produce little or no hormones, as well as often below average intelligence and learning difficulties (31). Estimations of the incidence of PWS vary depending on the study and country studied, but it is in the region of 1:22,000 births (32), with an EU prevalence of 1.6:100,000 population (16). Few therapies exist for PWS. Growth hormone therapy (GHT) has been authorized by the FDA for the treatment of children with PWS (33). The use of physiotherapy, occupational therapy, speech therapy, cognitive therapy and dietetic services is a usual part of treatment to deal with muscle tone, feeding difficulties in infancy, over-eating in childhood, and learning difficulties.

Histiocytosis refers to a group of RDs resulting from an over production of histiocyte, a tissue macrophage part of the mononuclear phagocytic system responsible for tissue destruction and defense. Histiocytosis can be divided into three or more categories including Langerhans cell histiocytosis (LCH), non-Langerhans cell histiocytosis (Juvenile xanthogranuloma, Hemophagocytic lymphohistiocytosis, Niemann-Pick disease and Sea-blue histiocyte syndrome) and malignant histiocytic disorders (Acute monocytic leukemia,

Malignant histiocytosis and Erdheim-Chester disease). The individual prevalence varies across different types. Overall prevalence is estimated at 1:200,000 predominantly in children. The EU prevalence of the LCH type is estimated to be 2:100,000 population (16). The disease attacks various tissues and organs (skin, bone, muscles, liver, lungs and spleen) and forms tumours in a similar manner to cancer, but is thought to be an autoimmune disease with a genetic component for some. Treatment involves corticosteroids to suppress immune function, chemotherapy and radiotherapy, as well as physical therapy and breathing support. Niemann-Pick disease (NMD) is characterized by a number of progressive and debilitating (and fatal) neurological symptoms, including poor muscle co-ordination, impaired gait, and learning and cognitive difficulties. Symptoms present early (0-12 years) with earlier onset associated with rapid disease progression. The disease is exceptionally rare, with 67 diagnosed cases in the UK (2008) (34) and Western European prevalence estimated at 1:150,000 population (35).

EB is part of a group of rare hereditary skin diseases characterized by blisters forming on the skin spontaneously, or following minimal trauma. Due to a mutation in the keratin or collagen gene, the skin is extremely fragile, with 4 major sub-classifications. Disease severity varies from benign to deadly, with more severe forms affecting the internal gut linings and resulting in poor absorption and chronic malnutrition in addition to skin cancer development (36). The prevalence of EB is 50 children per million births, with no racial or sex prejudices (37). In the EU, the prevalence is estimated to be 2.4:100,000 population (16). The pain associated with EB has been described as third degree burns. Recent treatment developments include bone marrow transplants.

<Table 1 about here>

3.2 Evidence on costs and availability of COI evidence

A total of 1654 article titles were initially screened (Figure 1). Of these, 253 abstracts were retrieved for further investigation. Studies reporting any COI data were included,

while studies not providing concrete data (e.g. estimates based on similar conditions) were excluded. Cost-effectiveness studies were only included if they reported information on the COI or components of specific types of health care, individual or societal costs. A total of 201 full-text articles were accessed for eligibility (including cited articles), and 77 studies were included in the study. There was an unequal distribution of studies over disease types, with the largest proportion of studies covering CF (n=29) and haemophilia (n=22). For the remaining diseases 0-8 studies per disease were identified, but, overall, COI study availability was limited across most of the study RDs (Table 2). The evidence collected indicates COI data availability in terms of total lifetime costs across four RDs (CF, DMD, FXS, haemophilia), and total annual costs and indirect total costs across five RDs (CF, haemophilia, JIA, histiocytosis, scleroderma). In the sections that follow, we present the available evidence.

<Table 2 about here>

Cystic fibrosis

In total, 29 studies were found to address COI aspects of the disease, making it the most studied disease out of the ten conditions selected. Lifetime treatment costs are estimated to be lower in older studies, as prevention of progression (physiotherapy, high fat diet plus enzymes) and medications (IV therapy) were not yet universally applied. Over twenty years ago Wildhagen et al. calculated Dutch lifetime costs per patient adjusting for survival and using a 5% discount rate to €287,591 (GBP 164,365 in 1991)(38), while later estimates in Germany based on extrapolation of childhood costs suggested €477,280 (€396,000 in 1997)(15), close to the 1994 Israeli estimate of €374,173 (US\$328,431 in 1993) which includes heart- and lung transplant at age 35 (39). More recent estimates incorporating advances in disease management suggest lifetime costs in Germany are €858,604/patient, assuming a 39.7 year survival and a 3% discount rate (40) (€824,159 in 2007), while American data suggest €1,907,384 (US\$2,335,699 in 2006) assuming 37 year survivalⁱ(41). The significant differences

ⁱ This estimate was generated by multiplying average annual medical cost of US\$63,127/patient by life expectancy (37 years). No discount rate was applied.

between these estimates are primarily due to inclusion of only outpatient costs in Germany, while the American study incorporated direct costs including medication and inpatient care (though unclear whether outpatient costs were included).

Per patient average total costs (direct plus indirect) depend on age, ranging from €16,307 at age 1-9 to €68,331 at age 30-39 (DKK94,150 and DKK394,518 in 1998)(42). Pauly estimated annual indirect costs at €8,814 (US\$8,400 in 1996) based on incapacity to work, disability and premature death, corresponding to 60% of estimated direct costs (43), while the US Office of Technology Assessment based an estimate of €11,543 (US\$11,000 in 1996) on time invested by patients and relatives in CF therapy, corresponding to 94% of direct costs (44). Including time lost from paid labour, unpaid labour and leisure time for both the caregiver and patient as well as employers cost for paid sick leave, indirect costs of as much as €1,617 (CA\$2,026 in 2005) per 28 days have been reported (€21,075 per year)(45).

The estimated average annual direct treatment costs range between €7,108/patient in Canada (CA\$7,524 in 1997)(14) and €51,551/patient (US\$63,127 in 2006) in the USA (41) with a reported 7-fold difference between mild and severe cases (46), and younger children generally at the lower end of the range at €10,989 (US\$12,008 in 2002)(47). More recent estimates, although lower, may be a more accurate reflection of current treatment costs due to significant advances in CF treatment and prevention of serious infections. Baltin et al. estimate annual CF treatment in Germany at €17,938/patient (€17,219 in 2007), increasing to €22,692/patient (€21,782 in 2007) with IV therapy (40), while Huot et al. arrive at €25,781/patient (€22,725 in 2003) in Franceⁱⁱ. Concomitant *Pseudomonas* infection tends to increase medical costs significantly (15, 48) but to a lesser extent with early eradication treatment (49).

The components of treatment costs differ across studies. Baumann et al. provide a comprehensive cost breakdown: of total annual care costs (€28,913 [€23,989 in 1997]), outpatient and inpatient care account for 59% and 41% respectively – 47% of total expenditure was on outpatient drugs. A more recent French study reported annual inpatient costs of €5,730/patient (€5,051 in 2003), while home care costs were even higher at €20,051/patient (€17,674 in 2003). Drugs accounted for 45% of the total cost, and hospital care for 15% (2000) to 22% (2003)(50). An alternative breakdown based

ⁱⁱ This paragraph does not include direct cost screening estimates.

on American 2006 health insurance data estimated costs at €39,278/patient (US\$48,098 in 2006), of which 34.4% was for inpatient care, 27.2% for outpatient care and 38.4% for medications (51). An older Medicaid breakdown (1993) found inpatient costs were 47%, physician care 8%, private nursing 12%, outpatient care 5%, drugs 12%, medical equipment 8%, other 8% (52). The costs attributable to hospitalisation and drugs can be modulated by considering preventive drug regimens (53, 54) and by implementing home-based intravenous infusions (55, 56).

Drugs for CF tend to account for a large proportion of expenditure across settings. Schreyogg et al. considered inpatient hospitalization costs of 131 German CF patients by disease severity and found mean total cost was €8,098/patient (€7,326 in 2004)ⁱⁱⁱ(57), while severe cases cost 78% more than mild cases. Aside from overheads (staff costs for non-patient care and 'other'), drugs formed the largest component, particularly in severe cases. Eidt et al. found medication costs in German CF outpatient clinics were approximately €23,019 (€21,604 in 2006)(58). New rhDNase therapy is particularly costly (€9,705 [CA\$10,110 in 1996])(14) but can reduce overall direct cost (59), as are IV antibiotics given as either in- or out-patient (€4,045 [€3,565 in 2003]) (50). In earlier work pancreatic enzymes and antibiotics accounted for approximately 50% of total lifetime costs (39). The highest reported figure was 57% of direct costs attributable to drugs (60), and the lowest at 9% was recorded in an insurance claims based study from 1994 where inpatient care accounted for the majority of direct costs (59-81%) (61).

Only one study examined 'non-healthcare costs' associated with CF (including non-hospital medical care, domestic help, special facilities etc.), and estimated home-care costs to be approximately 50% of total medical and non-medical lifetime costs. Total average non-hospital costs of care were estimated at €10,826 (GBP6,657 in 1993)(13). In other studies, home-care has been estimated to be both significantly more expensive than inpatient care per patient (€12,838 [€10,865 in 2001] vs. €2,316 [€1,960 in 2001]) and significantly less expensive than inpatient care (€18,933 [GBP13,528 in 2002] vs. €31,642 [GBP22,609 in 2002]^{iv}). Differences may result from diverging methodologies, as Elliott et al. considered identical cost categories (antibiotics,

ⁱⁱⁱ In this case, total cost per case is specific to hospitalisation, not to treatment overall.

^{iv} Patients were classified as receiving care either at home or in hospital, based on the location in which they received >60% of their treatment, over the course of one year.

laboratory tests, clinic visits, days in hospital) but classified patients according to the majority (>60%) of treatment received in either location (62), while Horvais et al. directly segregated costs as either 'inpatient' or 'outpatient' (63).

Four studies estimated the costs/benefits of population wide screening, and found benefits generally outweighed the cost. For example, cost of screening in Denmark was €322,953 (DKK1,864,594 in 1998) while the net present discounted value of a CF case averted was €368,833 - €520,796 (DKK2,129,484 - DKK3,006,858 in 1998) depending on the median life expectancy of patients (30 or 40 years) (42), largely echoing previous work in the USA where treatment savings offset 74-78% of the cost of a screening programme (64). As a further benefit, average cost of treatment of children with CF diagnosed by screening have been shown to be lower (47).

Duchenne muscular dystrophy

Only three studies (the Netherlands, USA and Canada) reported treatment costs of DMD, all outdated. The Dutch study (65) identifies only total lifetime costs (1994 data). The American study (66) provides a breakdown of some direct treatment costs (equipment and rehabilitation) but a total cost figure is not calculated (1983 data). The Canadian study examines the cost-effectiveness of DMD screening and provides some estimates as costs of averting DMD (1988 data) (67).

The lifetime discounted (5%) cost of DMD treatment was estimated at €541,593/patient (US\$487,723 in 1994), however it is unclear how these costs were estimated (65).

Direct cost estimates are incomplete. The average annual equipment cost is between €1,322 (US\$800 in 1983) and €1,653 (US\$1,000 in 1983), including wheelchairs (55%), heavy equipment (ramps, lifts, hospital beds) (13%), respiratory equipment (11%), footwear (9%), spinal orthoses (7%) and seating apparatus (5%) (66). Total outpatient rehabilitation costs are €1,983/patient (US\$1,200 in 1983). Since 1983, supportive technologies including wheelchairs have advanced significantly in technology and cost, meaning these costs are likely an underestimate today. No information is available on the cost of drugs.

The cost of averting a single case of DMD is estimated to be €206,051 (CA\$172,000 in 1988), with an incremental cost per case averted of €99,552 (CA\$83,100 in 1988) (67).

Fragile X syndrome

Only a few of the studies stated which costs were included in lifetime treatment costs. A few (68, 69) commented that the most accurate estimates are those from Wildhagen et al. which are age- and sex- adjusted for survival and use a 3% discount rate resulting in a lifetime estimate of €980,057 (US\$957,734 in 1995) for a male and €546,112 (US\$533,673 in 1995) for a female (70). Per annum direct care costs are at least €31,050/patient (GBP20,000 in 1995)(68), and recent American data reveal total out-of-pocket (OOP) expenditures of €13,873/patient (US\$17,476 in 2007), of which 19% is spent on drugs. Significantly, median OOP expenditure was €1,508/patient (US\$1,900 in 2007) indicating high expenditure among a small number of families (71). This study also suggests therapy (undefined), transportation and medication are the main components of OOP care costs.

Haemophilia

In total, 22 studies were found to address COI aspects of the disease, making it the second most studied disease out of the ten, following CF.

Only one study (Mexico) estimated total lifetime discounted (5%) cost of hemophilia treatment, which differed by type of treatment from €133,024 (MXN1,408,478 in 2000) for cryoprecipitate factor treatment, to €258,025 (MXN2,731,997 in 2000) for concentrate factor treatment (72). Total annual cost was reported in two studies, ranging from €1,101 (€953 in 2002) in Sweden for on-demand (OD) treatment (73) to €178,796 (€147,939 in 2000) in Sweden for prophylactic treatment (74), though not all prophylactic regimes reported such high costs (73).

Indirect costs associated with hemophilia were negligible in some cases (€836 [DM683 in 1996] per patient, 2.8% of direct costs) (75) but significant in others, amounting to 47% of direct costs in one study, though there were significant variations between countries (73). One study comparing on-demand with prophylactic treatment estimated

indirect costs could be up to 88% (€37,582 [€31,096 in 2000]) of direct costs in on-demand treatment, though the figure was much lower (12%, €15,716 [€13,004 in 2000]) in prophylactic treatment (74).

Annual average direct medical costs range from €1,042/patient (€902 in 2002) (73) to €275,398/patient (€215,221 in 1999) (76) when inhibitors are present, to €745,376 (US\$ 884,266 in 2005) when inhibitors are present and extremely high cost patients are included (over US\$ 1 million per year) (77). High cost outliers also drove up the mean drug cost in a separate study, where median cost was found to be almost identical between inhibitor/no-inhibitor patients but the mean for inhibitor patients was 76% higher (78).

An American evaluation of a haemophilia disease management programme estimated baseline annual costs were €144,417/patient (US\$161,441 in 2003) of which the majority (91%) was outpatient factor (drug) use and 8% attributable to hospitalisation. When the disease management program was implemented, costs fell to €99,713/patient (US\$118,293 in 2005) (79). A Canadian study resulted in substantially lower costs, €53,172/patient (CA\$62,292 in 2002) (80), of which Factor VIII medication was the primary component (CA\$59,910) with hospitalization costs (including drugs, nursing care and inpatient stay) making up almost all of the balance (CA\$1,832). American, Italian and German studies also indicate anti-haemophilia drugs (including factor VIII) make up a significant proportion of total treatment costs (93.8%, 98.8% and 99.6%, respectively) (75, 76, 81), up to €275,398 per year (€17,935 per month in 1999) (76). The mean cost of drugs per patient kilogram per year was estimated to be €2,080 and €3,980 (€1,626 and €3,110 in 1999) for patients without and with inhibitors respectively (82), and elsewhere was reported per patient to be €80,780 and €165,408 (US\$80,000 and US\$141,000 in 1998), respectively (78).

The cost of drugs has been estimated per bleeding episode for activated prothrombin complex concentrate (aPCC) and recombinant activated factor VII (rFVIIa) with conflicting results. One study (Brazil) found aPCC treatment was more costly than rFVIIa per episode (both for rFVIIa alone and total treatment cost), with aPCC costing €6,935 (US\$8,227 in 2005) compared to €5,909 (US\$7,010 in 2005) for rFVIIa (83). In contrast, an American study estimated aPCC treatment cost at €17,702 (US\$21,000 in 2005), while initial treatment with rFVIIa cost €28,154 (US\$33,400 in 2005) per

episode (84). Total treatment cost with home administration has been shown to cost less than hospital administration (72).

Cost of inpatient drugs per patient was shown to be significantly influenced by a number of factors. The median cost of drugs for HIV positive patients was approximately 4 times higher than HIV negative, surgery linked to haemophilia was approximately 10 times higher than non-surgical use, costs of adults (18 years or over) were approximately 4 times higher than children, and presence of inhibitors or severe disease were approximately 2 times higher than no inhibitors or mild disease (85); however other evidence suggests there is no difference in median drug cost between patients with/without inhibitors, with a small number of high-cost patients driving up the mean cost for patients with inhibitors (86). A French study estimated the annual mean drug cost of treating a patient without inhibitors at €74,240 (€59,887 in 1997) and with inhibitors at between €67,221 (€54,226 in 1997) and €231,175 (€186,482 in 1997) depending on whether the patient was a high or low responder (87). Infection with HIV or HCV, apart from clotting factor, is also known to be associated with increased costs for prescription drugs, inpatient- and outpatient services, which is of importance due to the many infections occurring prior to blood screening in the 1980s (88, 89).

As an external factor, time to treatment has been shown to have a statistically significant upward effect on both total cost and number of doses required for resolution. As patients generally live further from hospitals than from outpatient clinics, both time to treatment, time to resolution and total cost was 3-4 times higher in hospitals than in outpatient or home treatment settings (90).

Schramm et al. examined costs incurred by patients in both prophylaxis and on-demand (OD) groups in a multi-country (France, Germany, Italy, Netherlands, Sweden, UK) analysis (73). Both France and Italy found the total cost of treating patients in the prophylaxis group was significantly higher (around 3.5 times, 3.7-4.1 times for direct costs) than in the OD group, while in Germany prophylaxis group costs were lower than the OD group. Hospitalisation costs were highest in the French OD group (64% of direct costs). A similar study by Carlsson et al. also found on-demand treatment was less costly than prophylaxis treatment (€62,264 [€51,518 in 2000] vs. €180,542 [€147,939 in 2000] respectively) (74), though the actual cost estimates were substantially higher

than any of those outlined by Schramm et al. The greatest treatment cost was for Factor VIII: 74% in OD patients and 94% in prophylaxis treatment. There is however evidence that quality of life is greater in patients on prophylactic treatment, and that prophylaxis results in fewer problems with work and other activities of daily living (75).

There appears to be no significant variation in hospitalisation costs between type A and B haemophilia (91), but annual treatment costs may vary with age, as German evidence shows paediatric patients, both with and without inhibitors, cost much less to treat than adults (by more than 4 times in both groups) (92).

Comparing mean and median costs, it is evident some of the high cost cases cause the mean cost to be significantly higher than the cost for a typical patient (77, 78, 82).

Juvenile idiopathic arthritis

Across the eight costing studies discovered and examined, study perspective, sample size (and mean age) and data reference year varied significantly. Six of the studies examined the economic impact associated JIA, while one study considered the impact on total cost of etanercept treatment (93) and another examined the cost-effectiveness of JIA hydrotherapy (94); although these focused primarily on the cost-effectiveness or effect on treatment cost of specific therapies, they are included here because they provide a comparison for standard therapies.

The mean annual total cost is estimated between €4,143/patient (€3,471 in 1999) (95) and €29,613/patient (US\$33,171 in 2000) (93, 96). Substantial variation is evident between sub-groups, however, there is a suggestion that a small proportion of patients (<12%) are responsible for 80% of overall costs, with a small number of inpatient cases accounting for 53% of direct costs (95). A small proportion of direct cost (3%) were due to devices and aids, and 14% attributable to medications (95).

Loss of income for parents was generally taken as a measure of indirect costs. In 1999, these costs were estimated at €1,870/patient annually (€1,571 in 1999), 86% of direct costs. In 2008, the same authors reported €274/patient annually (€270 in 2008), 6% of direct cost (95, 96). This reduction over time may be due to benefits of improved drug

therapy (i.e. TNF-alpha inhibitor etanercept), improving patient outcomes and enabling carers/parents to return to work. Other estimates in recent years are comparable to the latter, at €668 (CA\$837 in 2005) per year per patient, or 28% of direct costs (22), approximately €142-288 (GBP99-200 in 2000), 5-11% of direct costs (94) and €274 (€270 in 2008) or 6% of direct costs (96). Etanercept treatment was directly shown to reduce the indirect costs from €750 (US\$840 in 2000) to €373 (US\$418 in 2000) per 3-month period, 13% to 6% of direct costs, when added to the standard treatment (93).

Costs at all levels are substantially skewed towards active patients (those not in remission). For example, the mean total cost of active JIA patients at €6,763 (€5,681 in 1999) are more than seven times those in remission at €931 (€782 in 1999) (95). There is also substantial variation by subgroup with highest costs in patients with enthesitis-related, systemic JIA, extended oligoarthritis and polyarthritis (RF+^v)(95, 97), for whom the total treatment costs are almost double all JIA patients (95).

Furthermore, the introduction of new pharmaceutical therapies significantly affected both direct and indirect treatment costs according to Haapasaari et al. (2004) who estimated etanercept introduction resulted in an increase in direct annual per patient costs by €3,767 (US\$4,220 in 2000), but a reduction in indirect costs by 50% (€1,507/patient annually [US\$1,688 in 2000]) as a result of lower productivity losses accruing to parents for escorting their child to treatment (93). Total annual median costs were estimated to rise by €2,425 (US\$2,716 in 2000) with etanercept treatment.

Minden et al. performed comparable analyses in 1999 and 2008. While direct costs more than doubled over the period, indirect costs fell drastically, yielding a total differential of only €4,132 to €4,728 between 1999 and 2008 (95, 96)

Several studies estimate the mean annual direct cost of JIA per child, the most recent being €4,464 (€4,403 in 2008) (96). Other estimates range from €2,202 (GBP1,649 in 2005) (97) (secondary care provider perspective) with 11% for drugs, to €9,273 (US\$7,904 in 1992) (98) (health care system perspective) of which 22% was for inpatient care. The highest estimate was for etanercept treatment at €27,603 (US\$30,919 in 2000) (93), where drugs accounted for up to 54% of direct costs. Direct costs in turn account for 6-55% of total costs, depending on the study (95, 96). In

^v Rheumatic factor seropositive.

addition to calculating costs from a societal perspective, Allaire et al. (1992) estimated the mean annual family borne costs as €1,788 (US\$1,524 in 1992), including OOP medical costs (46%), salary loss (22%) and non-medical expenses (32%) (98).

The most recent estimate suggests healthcare costs comprise 95% of total direct costs in 2008, unchanged from 1999 (95, 96). Approximately 60% of healthcare costs are attributed to outpatient care with inpatient care making up the remaining 40%. Medication accounts for 47% of total annual direct costs (€2,097/patient [€2,069 in 2008]), physician visits 7% and non-physician visits 3% (96).

While medication comprises the largest portion of healthcare costs for JIA patients in Canada (43%), with specialist care only 12% of costs, this relationship is inverted in the UK with the specialist care cost being the most substantial cost component (45%), while medication represents only 11% of healthcare costs (97). This is potentially the effect of etanercept, or other IFN-alpha inhibitors, coming onto the market and being approved for reimbursement faster in Canada than in the UK^{vi}, raising the drug component of treatment costs (substantially), but lowering specialist costs because of improved efficacy of treatment.

A number of studies examined costs and cost-effectiveness of JIA drug treatments, focusing primarily on the IFN-alpha inhibitor etanercept. Brunner et al. (2004) estimated the mean annual costs of methotrexate therapy at €6,997 (US\$8,030 in 2004), etanercept treatment at €7,728 (US\$8,870 in 2004) and combination therapy (methotrexate and etanercept) at €11,005 (US\$12,630 in 2004), accounting for 26-54% of total mean cost (99). Earlier studies estimated the cost of drugs somewhat lower at €619 (US\$528 in 1992), or 7% of total direct costs (98).

Epps et al. (2005) indicate anti-TFN therapy annual costs (including etanercept) is approximately €11,473/patient (GBP8,000 in 2000) (94). A systematic literature review by Cummins et al. (2002) cites evidence that the annual cost per JIA patient is €12,590 (GBP8,996 in 2002) resulting in a discounted cost/QALY (Quality Adjusted Life Year) of €22,507 (GBP16,082 in 2002) (100).

^{vi}In England (2002), NICE issued a narrow reimbursement of etanercept in children (4-17y) with active poly-articular-course JIA with poor response to methotrexate.

Mucopolysaccharidosis type I and type VI (MPS I, MPS VI)

Only one study, a systematic review, was found which detailed costs and effectiveness of enzyme replacement therapies for MPS I. Information from electronic databases, pertaining to the medical costs of 41 patients in the UK, was collected from inception of treatment to mid-2004 and combined with information provided by clinical experts.

Likewise only one study for MPS VI was identified. Although it focuses on the process of marketing authorization and reimbursement for rhASB, some cost discussions are included.

The annual drug cost of treatment with Aldurazyme (laronidase) was differentiated by age with €130,451/child (GBP95,752 in 2004) assuming a weight of 20kg, and €456,581/adult (GBP335,134 in 2004) assuming a weight of 70kg. Based on the full patient cohort (n=41) on the UK Society for Mucopolysaccharide Disease registry, the total national annual cost for drugs alone for MPS I is estimated to be GBP5.1million (101). No additional costs of treatment were supplied.

Schlender & Beck (2009) estimate the annual cost of rhASB for MPS VI to be €158,295 (€150,000 in 2008) to €474,885 (€450,000 in 2008) per patient (depending on the patients' weight), with mean cost per patient per year of €369,355 (€350,000 in 2008)^{vii} (28) assuming a mean weight of 25kg.

Scleroderma (systemic sclerosis)

In total four studies were identified that addressed lifetime, direct and/or indirect costs, and one study that quantified specific drugs/therapies. The aggregate annual costs of treating scleroderma are significant. Recent work by Bernatsky et al. (2009) estimate the total scleroderma treatment cost for all patients in North America is €1.5bn (US\$1.9bn in 2007), and €3.3bn (€3.1bn in 2007) in Europe (102). Other American and

^{vii} This is based on an assumed mean weight per patient of 25kg, a recommended dose of 1mg rhASB/kg bodyweight/week and a cost of €1,400 (GBP982) per vial.

Italian estimates suggest total treatment costs are €1.6bn (US\$1.46bn in 1994) (103) and €1.4bn (€1.2bn in 2001) (104) respectively.

Annual mean total costs per patient vary across countries. Minier et al. (2010) estimate the total cost in Hungary at €12,032 (€9,619 in 2006) including direct non-medical costs (home remodeling, transportation etc.) and productivity loss (105), Canadian costs are €14,133 (CA\$18,453 in 2007) (30) and in Italy €13,502 (€11,074 in 2001) (104).

Three studies estimate indirect costs, however there is little uniformity in what is included in this category. Recent Hungarian estimates were €6,742/patient (€5,390 in 2006), of which 98% was productivity loss by disability pensioners and 2% was sick leave (105). Mean annual indirect costs were €10,275/patient (CA\$13,415 in 2007) in Canada, of which 40% was lost productivity from paid labour and 60% from unpaid labour (30). American indirect costs were differentiated as mortality losses €2,038/patient (US\$1,835 in 1994) and morbidity losses of €9,319/patient (US\$8,392 in 1994) for a total of €11,357/patient (103).

Recent estimates of direct medical cost of scleroderma are €4,128 in Hungary (€3,300 in 2006), of which hospitalization was the largest component (82%) and drugs accounted for 12% (105). Canadian total direct healthcare costs were €3,858 (CA\$5,083 in 2007), of which medication was the largest single component (31%), followed by acute-care hospitalization (28%), healthcare professional visits (15%) and diagnostic tests (14%) (30). Wilson et al. found a distribution in 1994 of 45% and 22% for hospitalization and drugs respectively out of total costs of €4,926 (US\$4,694 in 1996). A small proportion (0.3-4%) of direct costs were spent on assistive devices (30, 105), though home remodeling also accounted for a sizeable proportion (20%) of non-healthcare direct costs (105). Across these studies, direct costs generally account for approximately 1/3 of total costs.

Only Minier et al. (2010) provides estimates of average annual direct non-healthcare costs totaling approximately €1,162/patient (€929 in 2006), and comprising of transportation (ambulance travel, travel vouchers) (49%), informal care (26%), home remodeling (20%) and transportation (non-reimbursed) (5%) (105).

Prader-Willi syndrome

No studies with information on the COI related to PWS were found during the study period.

Histiocytosis

Only one study was identified explicitly quantifying costs of any of the histiocytosis syndromes, focusing on Niemann-Pick disease (NPD) with a comprehensive breakdown of direct (medical and non-medical) and indirect costs (34).

Total annual average costs of treatment for patients with NPD were estimated at €49,947/patient (GBP39,168 in 2007), comprised of direct medical costs (46.2%, €23,066 [GBP18,088 in 2007]), direct non-medical costs (24.1%) and indirect costs (29.7% of total or 64% of direct costs). Direct medical costs were made up predominantly of home visit (72.5%) and residential care (15.7%), with medications and hospitalisations accounting for only 1.6% and 1.2% respectively. Special education costs formed the primary component of direct non-medical costs (97%, €11,691 [GBP9,168 in 2007]), calculated as the incremental cost of specialist education (over and above the costs of standard school attendance borne by society for all children).

Annual indirect costs were estimated to be high. Per patient productivity losses due to reduced working hours, absenteeism and unemployment for both patients and carers were estimated at €12,762 (GBP10,008 in 2007) and €2,081 (GBP1,632 in 2007) respectively, totaling €14,842/patient annually. From a narrower National Health Service (NHS) perspective, excluding indirect costs and OOP payments, the mean annual cost was €22,969/patient (GBP18,012 in 2007). Mean annual OOP payments made by families and patients were estimated at €447 (GBP351 in 2007), comprising non-prescription medications (19%), other health services (3%) and travel costs (78%) (34).

Epidermolysis Bullosa

Overall, one study was identified that addressed cost-effectiveness aspects of screening and one that discussed specific treatments/therapies. One study examines the cost effectiveness of the 'Kozak protocol' in treating nine children in a single hospital in Ontario, Canada (1980 data)^{viii} (36). A response to this study by Ramsay (1984) indicates some serious discrepancies in the cost data, specifically which costs from the 9 patients actually pertained to EB (106). As a result, these costs have not been discussed in any depth. High-dose intravenous immunoglobulin (hdIVIg) has been used to treat a few cases of EB, however its clinical efficacy is unclear as this treatment was not undertaken within a controlled trial setting (107). No other studies were found related to costs and EB.

<Table 3 about here>

4. Discussion

4.1. Evidence and policy implications

In this review, we identified 77 studies that provide some level of information on the economic burden of ten selected RDs. An overall summary of the cost results is shown in Table 3. For some conditions (PWS and EB) no COI information was available despite relatively high prevalence (see Table 2). For other conditions (DMD, MPS I and VI, histiocytosis, FXS, scleroderma) COI information was very limited, and with the exception of MPS for which rhASB has undergone clinical trials as a treatment, none of the conditions for which little COI evidence was found are associated with a specific pharmaceutical treatment. Rather, care is based on the alleviation of symptoms, management of complications and other supportive care.

In contrast, pharmaceutical compounds are available specifically for CF (DNase) and for haemophilia (clotting factors), which between them account for 47 of the 77 studies included in this review. Overall, the availability of evidence on the economic burden of

^{viii} It is unclear from the paper what the Kozak protocol entails, or what the baseline/control therapy included.

RDs appears to be correlated with the availability of specific therapies rather than, for instance, the rarity or severity of the disease itself (Figure 2).

For the conditions with the most detailed evidence (CF, haemophilia and JIA) there are some common features. The distribution of costs over different patients tends to be skewed with either a small proportion of patients accounting for a large proportion of resource utilisation (82, 95, 96) or particular subgroups of patients incurring higher costs. For example, haemophilia patients with HIV were four times as expensive to treat as HIV negative (85), and seropositive polyarthritis was five times more expensive to treat than persistent oligoarthritis both in total and direct cost estimates for JIA patients (96).

In most studies reviewed in this study, the median cost tended to be lower than the mean, consistent with a small proportion of high-cost patients driving up average costs therefore suggesting a positive skew. As a summary of economic burden we have reported the mean rather than the median since this better incorporates the variation in severity among patients. When interpreting the results, therefore, it should be taken into account that the typical (median) patient will likely incur lower costs than reported here, while a small number of patients will incur substantially higher costs.

Apart from the direct cost of treatment borne either by insurance organisations or patients and families privately and, in most cases, on an out-of-pocket basis, the indirect COI signifies the burden on the affected patient or carer, and is higher for more debilitating conditions. When comparing the indirect cost to direct cost we find that the former can be significantly higher, e.g. up to 216% of direct costs in the case of scleroderma. All evidence on scleroderma suggests indirect exceeding direct costs (30, 105), but in all other conditions where evidence is available the indirect costs amount to less than direct costs. In some cases, direct and indirect costs can be traded off against each other, as in haemophilia care, where patients treated prophylactically incur higher direct costs as a result of factor use but avoid more hospitalizations and thus disruptions to their daily life and work pattern (75). However, most conditions examined here do not have an effective prophylaxis regime, as patients are continually affected by symptoms and must be managed on a regular basis. Importantly we note that evidence on indirect cost was only available for four out of ten diseases, and that the COI from a societal perspective for most of the diseases examined here, therefore, is

not known. As discussed earlier, indirect costs may account for a significant proportion of overall costs and as such this lack of evidence constitutes an important shortfall.

It is clear that the evidence base for the COI at individual, health system and societal level is fairly poor when it comes to understanding the pressures faced by both individuals, families and society in the context of RDs. However, the importance of RDs has long been recognised in the EU, reflected in various EU funded strategic activities, including cooperative research in the field of Health and ERA-NET programmes as well as a priority action area in the Health Programme work plan. At a higher level, the European Union Committee of Experts on Rare Diseases (EUCERD) acts as a coordinating body for member states in planning and implementing activities related to RDs. The BURQOL-RD project aims to provide new tools and knowledge on RDs unavailable in the EU, including socio-economic burden and health related quality of life for patients and their caregivers. Other activities under the EU 7th Framework Programme (FP7) and beyond are also concerned with RDs, particularly relating to clinical guidelines (Rare Best Practices) and the use of Health Technology Assessment in evaluating rare diseases (Advance HTA), which also include methodological improvements in the way evidence is produced and utilised by researchers and decision-makers.

The non-availability of COI evidence reflects the rarity of the ten diseases investigated. In contrast to other disease areas such as cancer and diabetes, the impact of these RDs on patient population and their carers is not well documented. The results of this study suggest that more could be done to study the economic consequences of RDs on society, not only accounting for direct medical costs but also for indirect costs relating to productivity losses given their significant magnitude. At a broader level, these results also point towards the need for society to invest in researching and developing new therapies, and allocating resources to ensure patient access. Nevertheless, it should be borne in mind that such decisions are always associated with important opportunity costs relating to allocation of resources elsewhere, either for the discovery and development of new treatments or the access to and provision of health care. The former is already reflected through the Orphan Medicinal Products Regulation (Regulation (EC) No 141/2000), which provides a set of incentives relating to market exclusivity, protocol assistance and access to the centralised Procedure for Marketing

Authorisation, to encourage the R&D and marketing of orphan medicines and has led to about 120 collaborative research projects relating to RDs through funded research activities on innovation and technological development. With regards to resource allocation and access to health care, most national HTA agencies have special frameworks in place to facilitate and enable the coverage of medical technologies treating RDs, taking into account their small market size, high severity of disease and poor cost-effectiveness. The findings of this study confirm the European Commission's Communication on Rare Diseases, aiming to set out an overall strategy to support Member States in diagnosing and treating rare disease patients, but also the Council's recommendation on action in the field of RDs calling for the implementation of national strategies (108).

4.2 Challenges, limitations and ways forward

A number of methodological questions and limitations need to be raised in connection with the study, its findings and their meaning. Although many of them lie outside the scope of this study they should be acknowledged and earmarked for further investigation. Most of them relate to the comparability of costing evidence across settings, individual disease areas and over time. First, despite having facilitated comparisons across countries and therapeutic areas by harmonising currencies and cost years, one limitation of this study is the wide variety of costing methodologies used, including differences in discounting, assumptions relating to life expectancy and other treatment factors, and differences in the categories of costs included. Indirect costs, largely based on measures of productivity, also differ between studies. This limits the direct comparability of costs between RDs, and, consequently, the use of such information in priority setting. Second, the approach used to compare costs across countries through exchange rate-adjusted currency units does not necessarily address differences in income across countries. Other more advanced approaches, such as adjusting figures to absolute GDP differences and variations in the GDP percentage spent on health across the different countries could be adopted instead, aiding more robust conclusions on the magnitude of costs, their differences and comparability across different settings. A third limitation is the varying discount rates applied when calculating lifetime economic burden. Although in most cases lifetime cost figures are

estimated by considering the respective life expectancy of the disease, varying discount rates can be applied across different studies therefore limiting the comparability of the results. A further limitation is that, strictly speaking, intangible costs relating to suffering of patients and carers are not considered as “costs” but, instead, as quality of life dimensions and, therefore, are not addressed by the current study. Future research might want to adopt a broader perspective and capture these costs to the extent possible. A final limitation is the relatively small sample size in most rare disease COI studies, which in many cases include approximately 100-300 subjects per study but often less than 100 subjects, a corollary of the nature and prevalence of the diseases studied. There was a relatively strong country bias towards the United States and Canada, which accounted for 21 and 9 studies respectively, though Germany, UK, France and Netherlands also accounted for 11, 10, 6 and 5 studies each, respectively^{ix}. The above limitations suggest that future research and priority setting in this area would benefit significantly from a harmonised framework for COI studies, conceptually similar to the Organisation for Economic Cooperation and Development (OECD) System of Health Accounts (109) applied for health systems more broadly.

<Figure 2 about here>

5. Conclusions

Although methodological variations prevent any detailed comparison between conditions, most of the rare diseases examined in this study are associated with significant economic burden. Indirect costs associated with loss of productivity in most cases approach or exceed the level of direct costs. The level of evidence available is highest for conditions that have specific pharmaceutical treatments available and is not necessarily associated with disease rarity. The study raises awareness about the lack of research on the socio-economic impact of rare diseases, which can be substantial, as well as methodological issues related to the comparability of the available evidence across borders which need to be addressed in future research.

^{ix} Italy: 3, Israel: 2, Brazil: 1, Denmark: 1, Finland: 1, Hungary: 1, Mexico: 1, Turkey: 1, Europe: 1, Norway/Sweden: 1

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Figure 1. Literature Search Flow Diagram for COI studies across the ten study RDs

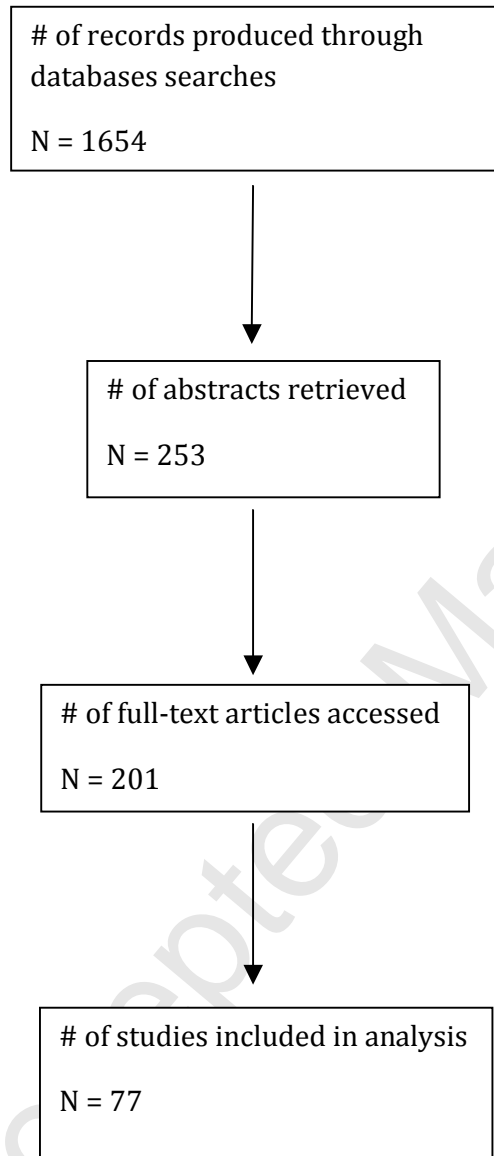


Figure 1 caption: literature search flow diagram showing the number of articles in each stage of the literature review

Table 1: EU-wide disease prevalence across the ten study RDs

	CF ¹	DMD ¹	FXS ¹	HAE ¹	JIA ¹	MPS ¹	SCL ¹	PWS ¹	HIS ¹	EB ¹
Prevalence	1:2,500 – 3,600 newborns ⁽¹³⁻¹⁴⁾	1:3,600 male infants ⁽¹⁸⁾	1:3,600 males; 1:4,000 – 6,000 females ⁽²⁰⁾	A: 1:5,000 – 10,000 males B: 1:20,000 – 34,000 males ⁽²¹⁾	8-150:100,000 children ⁽²²⁾	Type I 1:100,000; Type II 1:250,000; Type III 1:50,000 to 1:280,000; Type IV 1:75,000; Type VI 1:250,000 ⁽²³⁻²⁷⁾	74:100,000 women; 13:100,000 men ⁽³⁰⁾	1:22,000 newborns ⁽³²⁾	1:150,000 (NMD) ⁽³⁵⁾	5:100,000 ⁽³⁷⁾
Prevalence (per 100,000 population) ⁽¹⁶⁾	12.6	5.0	20.0	7.7	5.0	3.0 (all types)	42.0	1.6	2.0 (LCH)	2.4

Note: ¹ CF=Cystic Fibrosis; DMD=Duchene Muscular Dystrophy; FXS=Fragile X Syndrome; HAE=Haemophilia; JIA=Juvenile Idiopathic Arthritis; MPS=Mucopolysaccharidosis; SCL=Scleroderma; PWS=Prader-Willi Syndrome; HIS=Histiocytosis; EB=Epidermolysis bullosa

Source: The authors.

Table 2: Availability of COI evidence across the ten study RDs

	CF ¹	DMD ¹	FXS ¹	HAE ¹	JIA ¹	MPS ¹	SCL ¹	PWS ¹	HIS ¹	EB ¹
Total number of cost-of-illness studies										
Total, lifetime, direct, indirect cost	18	2	5	8	6	1	4		1	
Patient sub-groups				12						
Specific drugs/therapies	6			2	1	1	1			1
Other cost-related studies										
Screening	5									
Cost-effectiveness		1			1					1
Total studies	29	3	5	22	8	2	5	0	1	2

Note: ¹ CF=Cystic Fibrosis; DMD=Duchene Muscular Dystrophy; FXS=Fragile X Syndrome; HAE=Haemophilia; JIA=Juvenile Idiopathic Arthritis; MPS=Mucopolysaccharidosis; SCL=Scleroderma; PWS=Prader-Willi Syndrome; HIS=Hystiocytosis; EB=Epidermolysis bullosa.

Source: The authors.

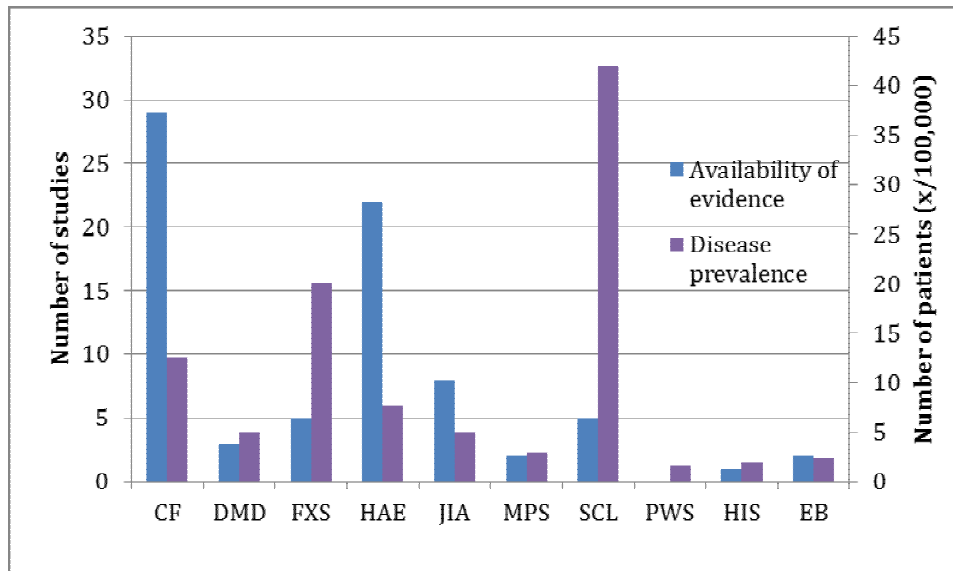
Table 3: Direct, indirect and total costs related to the ten study RDs (€, 2010)

Disease ¹	Total cost (€, 2010)		Indirect costs (€, 2010)	Direct medical costs (€, 2010)	Proportion of direct costs (per patient, annual)		
	Lifetime	Per patient, annual	Per patient, annual (% of direct cost)	Per patient, annual	Drugs	Equipment, devices, aids	Inpatient care
CF	287,591-1,907,384 ^(15,38-41)	16,307 - 394,518 ^{(a)(42)}	8,814-21,075 (60-94%) ⁽⁴³⁻⁴⁵⁾	7,108 – 51,551 ^{(b)(14-15,40-41,46-50)}	9-57% ^(14-15,50-61)	n/a	15-81% ^(15, 50-61)
DMD	541,593 ⁽⁶⁵⁾	n/a	n/a	1,983 ⁽⁶⁶⁾	n/a	67-83% ⁽⁶⁶⁾	n/a
FXS	546,112-980,057 ⁽⁷⁰⁾	n/a	n/a	>31,050 ⁽⁶⁸⁾	19% (of OOP) ⁽⁷¹⁾	n/a	n/a
HAE	133,024-258,025 ^{(c)(72)}	1,101 - 178,796 ⁽⁷³⁻⁷⁴⁾	836 (2.8%) – 37,582 (88%) ⁽⁷³⁻⁷⁵⁾	1,042 - 745,376 ^(73,76-82)	33%-100% ^(73-76,78-82,85-89)	<1%	1-64% ^(73-75,79-80,88-89)
JIA	n/a	4,143 - 29,613 ^(93,95-96)	142 (6%) – 1,870 (86%) ^(22,93-96,98)	2,202 - 27,603 ^(93,95-98)	7-54% ⁽⁹³⁻⁹⁹⁾	3% ⁽⁹⁶⁾	22-40% ^(95-96,98)
MPS	n/a	n/a	n/a	130,451 - 474,885 (drug only) ^(28,101)	n/a	n/a	n/a
SCL	n/a	12,032 - 14,133 ^(30,104-105)	6,742 -11,357 (127% - 216%) ^(30,103,105)	3,858 - 4,926 ^(30,105)	12-31% ⁽³⁰⁻¹⁰⁵⁾	0-4% ⁽³⁰⁻¹⁰⁵⁾	28-82% ^(30,105)
PWS	n/a	n/a	n/a	n/a	n/a	n/a	n/a
HIS	n/a	49,947 ⁽³⁴⁾	14,842 (64%) ⁽³⁴⁾	23,066 ⁽³⁴⁾	2% ⁽³⁴⁾	3% ^{(d)(34)}	1% ⁽³⁴⁾
EB	n/a	n/a	n/a	n/a	n/a	n/a	n/a

Source: The authors.

- Notes: ¹ CF=Cystic Fibrosis; DMD=Duchene Muscular Dystrophy; FXS=Fragile X Syndrome; HAE=Haemophilia; JIA=Juvenile Idiopathic Arthritis; MPS=Mucopolysaccharidosis; SCL=Scleroderma; PWS=Prader-Willi Syndrome; HIS=Histiocytosis; EB=Epidermolysis bullosa.
- (a) Depending on age, range limits are for 0-9 and 30-39 years(42)
 - (b) Patients with *P. aeruginosa* infection can incur >2-3x higher costs(15, 48)
 - (c) In the Mexican setting, using 5% discount rate
 - (d) One-time expense and therefore not included in annual direct cost. The 3.3% is total aids (€1,715) divided by total direct cost plus total aids (€49,947+€1,715).

Figure 2. Availability of COI evidence versus disease prevalence



Source: The authors from the literature.

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