Can the Consideration of Societal Costs Change the Recommendation of Economic Evaluations in the Field of Rare Diseases? An Empirical Analysis

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ABSTRACT

Objectives: To analyze whether the adoption of a societal perspective would alter the results and conclusions of economic evaluations for rare disease-related healthcare technologies.

Methods: A search strategy involving all the active substances considered as orphan drugs by the European Medicines Agency plus a list of 76 rare diseases combined with economic-related terms was conducted on Medline and the Cost-Effectiveness Registry from the beginning of 2000 until November 2018. We included studies that considered quality-adjusted life years as an outcome, were published in a scientific journal, were written in English, included informal care costs or productivity losses, and separated the results according to the applied perspective.

Results: We found 14 articles that fulfilled the inclusion criteria. Productivity losses were considered in 12 studies, the human capital approach being the method most frequently used. Exclusively, informal care was considered in 2 articles, being valued through the opportunity cost method. The 14 articles selected resulted in 26 economic evaluation estimations, from which incremental cost-utility ratio values changed from cost-effective to dominant in 3 estimates, but the consideration of societal costs only modified the authors’ conclusion in 1 study.

Conclusions: The presence of societal costs in the economic evaluation of rare diseases did not affect the conclusions of the studies except in a single specific case. In those studies where the societal perspective was considered, we did not find significant changes in the economic evaluation results due to the higher costs of treatments and the low quality-adjusted life-years gained.

Keywords: rare diseases, societal costs, informal care, productivity losses, healthcare costs, economic evaluation, health technology assessment.

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Introduction

Rare diseases (RDs) have lower rates of incidence or prevalence than other acute or chronic illnesses. There is no worldwide accepted definition or even a unique prevalence threshold yet. In the European Union (EU), RDs are defined as those serious, life-threatening, or chronically debilitating diseases that affect less than 5 out of 10 000 people. In the United States, a disease is considered rare when it affects less than 200 000 people (equivalent to a prevalence rate of 62 per 100 000 inhabitants), in Japan when it affects less than 50 000 people (39/100 000 inhabitants), and in Australia when it affects less than 2000 people (9/100 000 inhabitants). Although, when considered one by one, these diseases affect few people, it is estimated that there are between 5000 and 8000 different rare diseases. This implies that the joint prevalence of all RDs can amount to 6% of the EU population, that is, 30 million European citizens.

At least 80% of RDs have an identified genetic origin, and 50% of new cases are in children. The other RDs are composed of rare onco-hematological diseases, autoimmune diseases, genetic diseases, or toxic and infectious diseases. Despite their variety, some common patterns of these diseases are their chronicity and severity, and they are often degenerative and fatal. These diseases profoundly affect the quality of life of patients and compromise their autonomy, generating great suffering and psychosocial burden, on both patients and their relatives. Many of these diseases lack an effective treatment, are complex to diagnose (they are unknown by the health professionals themselves and there are significant delays in diagnosis), and require management and multidisciplinary follow-up, including support for families.

From the economic point of view, there is evidence of the high impact caused by these diseases both to patients and relatives. A monographic issue analyzed the economic impact of 10 rare diseases (such as cystic fibrosis, Duchenne muscular dystrophy, or...
The main component of non-healthcare resources was the cost related to the nonprofessional time of care (informal care) in case of Duchenne muscular dystrophy (that could represent around 75% of the total cost in Italy and 65% in Spain).\textsuperscript{11} Similar values were observed in Fragile X syndrome (Italy 69%, Spain 80%, or France 35%).\textsuperscript{12} Even in countries such as Sweden that have well-established social services, the time of informal care in these diseases was aligned with those in Italy and Spain, at levels of 67% and 57% for Fragile X syndrome and Duchenne muscular dystrophy, respectively.\textsuperscript{11} Likewise, and despite the different degrees of development of long-term care systems in the participating countries, the societal costs (mainly informal care and labor losses) were those that carried the greatest weight within the total cost in all countries.

In fact, in those diseases where the treatment might be quite expensive, there are other challenges to consider. The high financial burden due to the research and development processes jointly with the narrow market due to the small number of patients cause high prices in many orphan drugs (ODs).\textsuperscript{13-17} These high prices have motivated an important debate as to whether the usual measurements of health outcomes adequately capture the benefits of these therapies. Whether ODs receive or should receive special consideration by society\textsuperscript{18} and, if so, the reason for this (due to its rare nature, its extreme severity, or the fact that in some diseases there are no effective alternative treatments).\textsuperscript{19-22}

It is within this context that the debate about the perspective that should be considered in the economic evaluations of rare diseases requires special attention.\textsuperscript{15,13-17} Although other authors have evaluated the methodological quality of economic evaluations,\textsuperscript{21} or whether orphan drugs could meet the usual reimbursement thresholds,\textsuperscript{23} to our knowledge there is no evidence in the RD field that has assessed the relevance of the perspective chosen for the performance of economic evaluations. In this study, we aimed to assess whether the choice of the societal perspective versus the healthcare payer’s perspective in the economic evaluation of healthcare technologies used in the treatment of RDs changed the results and conclusions of the economic evaluations performed on RD interventions.

Methods

We conducted a systematic review of the literature. We focused on economic evaluations of any healthcare technology (eg, diagnostic devices, drug treatment) carried out in rare-disease patients from 2000 to November 2018. We used 2 databases to identify potential references for the review: (1) Medline (PubMed) and (2) the Cost-Effectiveness Analysis Registry from Tufts University.\textsuperscript{17,24} This registry uses an algorithm that has been launched on Medline to retrieve references of economic evaluations. Other authors have used this database,\textsuperscript{25,27} and more details about the registry are provided on the website of the Tufts Medical Centre.\textsuperscript{21}

Search Strategy

The search strategy included both formal terms (MeSH terms) and natural language, with the following economic terms: “cost” “cost analysis”; “cost-effectiveness”; “cost-utility”; “cost-benefit”; “economic evaluation”; “economic analysis”; “QALY”; “quality-adjusted life years.”

For the identification of rare disease patients, we used the list of ODs listed on the website of the European Medicines Agency (EMA) on May 2018 (https://www.ema.europa.eu/en/medicines/download-medicine-data), and we selected the 104 active substances considered by the EMA as authorized orphan drugs (see Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.10.014). We then combined these terms with the aforementioned economic terms in Medline. Additionally, we used the Cost-Effectiveness Analysis Registry of active substances to retrieve any economic evaluation carried out in rare disease–related healthcare technologies to avoid losing sensitivity in the search strategy launched in Medline. For the same purpose, we also used the active-substance indication approved by the EMA plus the economic terms in Medline to recall studies where the active substance did not appear in the title or abstract. Finally, 20 RD terms suggested by the authors (see Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.10.014) were also combined with the economic terms and launched in Medline.

Inclusion Criteria

This systematic review focused on economic evaluations of RD healthcare interventions. Hence, only studies that applied a full economic assessment design in rare disease were included. We also applied the following inclusion criteria: (1) the study should be published in a scientific peer-reviewed journal, (2) the perspective of the study should include informal care costs or productivity losses, (3) it should be written in English, (4) it should use quality-adjusted life years (QALYs) as one of the outcomes for the analysis, and (5) it should provide separately the results of the cost-effectiveness analysis according to the perspective applied, if not provided, it should be possible to extract such information from the available data. We included the QALY as an outcome owing to its homogeneity and wide use in RDs that allows for comparison between treatments indicated for different diseases. Some active substances designated as OD by the EMA (eg, budesonide, cinacalcet hydrochloride, or eculizumab) are also used for other non-rare diseases or health conditions. The indications used in the economic evaluations were reviewed within the rare-disease database provided by the Orphanet collaboration website.\textsuperscript{29} We excluded those references where the active substance was assessed in non-rare-disease patients (eg, chronic obstructive pulmonary disease, asthma, use in patients after an organ transplantation).

Definitions of Costs

In this study, direct healthcare costs included all medical resources. The societal costs concerned mainly the economic evaluation of informal (provided by nonprofessional caregivers) and productivity costs due to loss of productivity. We adopted the definitions provided by the Organisation for Economic Co-operation and Development’s “System of Health Accounts.”\textsuperscript{30} Briefly, the loss of productivity was defined as the economic valuation of paid worktime lost by the patients as a result of the disease. Thus when the healthcare costs were included, we called it the “healthcare perspective,” and when the estimate of loss of production and/or informal care cost was included in the cost analysis, we called this the “societal perspective,” as suggested in the international guides on the performance of economic evaluations in healthcare.\textsuperscript{31}

Extraction of Data

We collected the following data from the references that fulfilled the inclusion criteria: the first author, the type of disease, the year of publication, the type of analysis carried out (cost-utility or cost-effectiveness plus cost-utility), the country, the type of intervention assessed in the economic evaluation (eg, drugs, nonpharmaceutical therapy, diagnostic or screening device, or a medical procedure), the perspective stated by the authors and the
threshold assumed for the economic evaluation, the discount rates used for costs and outcomes, the time horizon, the type of sensitivity analysis performed, which costs were included in the economic evaluation, and the incremental cost-utility ratios (ICURs) resulting from the new intervention compared with the alternative.

Three researchers (I.A.R., B.R.S., L.P.L.) carried out the first screening, reviewing the title and abstract of the references, and the same 3 researchers performed the second review of full-text references. The discrepancies were resolved by another researcher (JOM/JLB).

Results

After excluding duplicates and reviewing the title and abstract of the references retrieved from the search strategy, 2306 records from both databases were identified. We evaluated the full text of 319 articles (Figure 1), but, finally, we identified 249 economic evaluation articles of healthcare interventions for rare disease from the year 2000 to November 2018. From these, only 11% (n = 27) of the 249 economic evaluations included informal care costs or productivity losses in the assessment. However, 2 studies were excluded from this review because QALYs were not included as an
Table 1. Characteristics of the studies included in the review.

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Disease</th>
<th>Intervention type</th>
<th>Discount rate: Costs; Outcome</th>
<th>Country</th>
<th>Time horizon</th>
<th>Costs included in the economic assessment</th>
<th>Elements included in the productivity losses and method applied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheng (2017)</td>
<td>Chronic myeloid leukemia</td>
<td>Care delivery</td>
<td>3%; 3%</td>
<td>China</td>
<td>Lifetime</td>
<td>Healthcare cost: adverse event costs, outpatient visits, hospital stays, tests, transplantation, monitoring. Social costs: productivity losses and informal care costs†</td>
<td>HC</td>
</tr>
<tr>
<td>Landfeldt (2017)</td>
<td>Duchenne Muscular dystrophy</td>
<td>Diagnostic</td>
<td>3.5%; 3.5%</td>
<td>UK</td>
<td>Lifetime</td>
<td>Healthcare cost: hospital admissions, visits to physicians and other healthcare professionals, medical tests and assessments, medications, emergency and respite care, and costs associated with nonmedical aids. Social costs: productivity losses and informal care costs†</td>
<td>HC HC</td>
</tr>
<tr>
<td>Park (2016)</td>
<td>Multidrug-resistant tuberculosis</td>
<td>Pharmaceutical</td>
<td>5%; 5%</td>
<td>Korea</td>
<td>20 years</td>
<td>Healthcare cost: drug costs, clinical and laboratory tests, inpatient and outpatient care, surgery, end-of-life palliative care. Social costs: productivity losses</td>
<td>HC</td>
</tr>
<tr>
<td>Borg (2016)</td>
<td>Multiple Myeloma</td>
<td>Pharmaceutical</td>
<td>3%; 3%</td>
<td>Sweden</td>
<td>Lifetime</td>
<td>Healthcare cost: medication, laboratory tests, monitoring and adverse events. Social costs: productivity losses</td>
<td>HC**</td>
</tr>
<tr>
<td>Wilson (2014)</td>
<td>Idiopathic pulmonary fibrosis</td>
<td>Pharmaceutical</td>
<td>n.a.; n.a.</td>
<td>UK</td>
<td>1 year</td>
<td>Healthcare cost: drugs, primary and secondary care, other health professionals, social services, out-of-pocket expenditure. Social costs: productivity losses and informal care costs</td>
<td>HC</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Disease</th>
<th>Intervention type</th>
<th>Discount rate: Costs; Outcome</th>
<th>Country</th>
<th>Time horizon</th>
<th>Costs included in the economic assessment</th>
<th>Elements included in the productivity losses and method applied</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Dussen (2014)</td>
<td>Type 1 Gaucher’s disease</td>
<td>Pharmaceutical</td>
<td>4%; 1%</td>
<td>The Netherlands</td>
<td>Lifetime</td>
<td>Healthcare cost: inpatient hospital day, in-hospital day-care treatment, diagnostic tests, drugs, outpatient hospital care, GP, specialist consultations, social carer, alternative healer. Social costs: productivity losses</td>
<td>HC</td>
</tr>
<tr>
<td>Kulpeng (2014)</td>
<td>Chronic Myeloid Leukemia</td>
<td>Pharmaceutical</td>
<td>3%; 3%</td>
<td>Thailand</td>
<td>Lifetime</td>
<td>Healthcare cost: aspolymerase-chain reaction testing, complete blood count, cytogenetic analysis, bone marrow aspiration, other laboratory tests, transport costs. Social costs: productivity losses</td>
<td>n.a</td>
</tr>
<tr>
<td>Kanters (2014)</td>
<td>Pompe’s disease</td>
<td>Pharmaceutical</td>
<td>4%; 1.5%</td>
<td>The Netherlands</td>
<td>Lifetime</td>
<td>Healthcare cost: the cost of the drug alglucosidase alfa, infusion-related costs, costs related to other healthcare use. Social costs: informal care</td>
<td>HC</td>
</tr>
<tr>
<td>Rombach (2013)</td>
<td>Fabry-Anderson disease</td>
<td>Pharmaceutical</td>
<td>0 and 4%; 0 and 1.5%</td>
<td>The Netherlands</td>
<td>Lifetime</td>
<td>Healthcare cost: inpatient hospital day, inpatient hospital intensive care unit day, in hospital day-care treatment, drugs, kidney treatment and transplantation, other diagnostic and therapeutic procedures, outpatient hospital visits, out-of-hospital visit. Social costs: productivity losses</td>
<td>HC</td>
</tr>
<tr>
<td>Ghatnekar (2010)</td>
<td>Chronic Myeloid Leukemia</td>
<td>Pharmaceutical</td>
<td>3%; 3%</td>
<td>Sweden</td>
<td>Lifetime</td>
<td>Healthcare cost: hematologist visit, inpatient stay, laboratory tests and diagnostic procedures, transfusion, drugs. Social costs: productivity losses</td>
<td>HC</td>
</tr>
</tbody>
</table>

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outcome in the assessment, and 11 did not provide separate results according to both perspectives so it was not possible to extract the data from the results. Hence, 14 articles satisfied all the inclusion criteria and were finally included.

With respect to the perspective used in the studies included in the review, half of the studies used both that of the healthcare provider and the wider perspective (the societal approach) in the analyses. However, 5 studies used the societal perspective as the main perspective, but the healthcare provider’s perspective could be extracted from the tables. On the other hand, 2 studies used the healthcare provider’s perspective as the main perspective but included the societal perspective in the sensitivity analysis. More details of the characteristics of the selected studies can be found in Table 1.

Informal care costs were included in only 5 studies, and the opportunity cost method was used in 4 of them; however, Wilson et al did not state clearly the valuation method used. Landfelt et al used a Markov model to carry out the economic evaluation, and they estimated the burden of informal care by avoiding the double accounting of the cost of care provided via nurses’ visits and by allowing an unadjusted estimate of indirect costs due to the loss of productivity of the main informal caregiver. To do that, the authors estimated the number of hours devoted to informal caregiving tasks using outcomes from the lost productivity questionnaires obtained in a previous cross-sectional study and data from the Organisation for Economic Co-operation and Development about the mean daily number of hours of leisure time for an adult in the United Kingdom. The leisure time was valued at 35% of the country-specific national mean gross wage and was estimated to be between 33 and 44 hours per week. However, Kanter et al used the responses of a small (n = 12) survey sample in which the consumption of healthcare and non-healthcare resources was recorded. The mean number of informal care imputed in the economic evaluation was not provided in either study. Finally, Risebrough et al assumed (based also on the results of a previous survey completed by clinical nurses and hematologists) 16 hours of informal care per week owing to the care needed by the patients when bleeding episodes occurred, and they used national mean gross wage to assess that time of care. Some differences were also observed between the authors: although Landfeldt et al did not specify the unit cost, they did include paid and unpaid informal care by the primary caregiver. Kanter et al explicitly state the unit cost (9€ per hour), but the authors did not include any additional information about how caregiving time was valued or recorded. Risebrough et al mentioned that the 171 Canadian dollars per day corresponding to informal care time represented 2 off-work days employed by the parents to care for their child.

Productivity losses were considered in 12 articles, and the human capital approach was used in most of them, although the authors from one study did not provide the method used in the assessment of productivity losses. Regarding the inclusion of production lost in the productivity losses, in 3 studies the caregivers’ absences from work were also included in these estimates. In 2 studies, either the data were obtained from the literature or...
<table>
<thead>
<tr>
<th>EST</th>
<th>First author (publication year) (ref)</th>
<th>Brief description of the comparison</th>
<th>Healthcare payer perspective: ICUR (Cost/QALY)*</th>
<th>Societal perspective: ICUR (Cost/QALY)*</th>
<th>Do the conclusions change? (YES/NO)</th>
<th>Threshold value ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sheng 2017 (32)</td>
<td>Medical insurance vs no medical insurance</td>
<td>93 401</td>
<td>50 641 (IC = 68.46% healthcare costs; 18.27% productivity losses; 13.27% informal care)</td>
<td>YES</td>
<td>74 000 (RMB)</td>
</tr>
<tr>
<td>2</td>
<td>Landfeldt 2016 (33)</td>
<td>Model 1 was based on a new patient-reported outcome instrument</td>
<td>1 442 710 (IC = 97.27% intervention costs; 1.68% direct medical costs; 1.07% direct nonmedical costs)</td>
<td>1 266 510 (IC = 97.27% intervention costs; 1.68% direct medical costs; 1.07% direct nonmedical costs; 0% productivity losses; 0.66% informal care)</td>
<td>NO</td>
<td>£100 000</td>
</tr>
<tr>
<td>3</td>
<td>Landfeldt 2016 (33)</td>
<td>Model 2 used the international clinical care guideline</td>
<td>1 939 590 (IC = 97.90% intervention costs; 1.45% direct medical costs; 0.65% direct nonmedical costs)</td>
<td>1 760 650 (IC = 97.53% intervention costs; 1.44% direct medical costs; 0.65% direct nonmedical costs; 0% productivity losses; 0.38% informal care)</td>
<td>NO</td>
<td>£100 000</td>
</tr>
<tr>
<td>4</td>
<td>Landfeldt 2016 (33)</td>
<td>Model 3 was based on patient's ventilation status</td>
<td>3 574 770 (IC = 98.40% intervention costs; 1.44% direct medical costs; 0.16% direct nonmedical costs)</td>
<td>3 121 890 (IC = 98.22% intervention costs; 1.43% direct medical costs; 0.16% direct nonmedical costs; 0% productivity losses; 0.19% informal care)</td>
<td>NO</td>
<td>£100 000</td>
</tr>
<tr>
<td>5</td>
<td>Park 2016 (34)</td>
<td>Drug A vs drug B</td>
<td>11 638 656</td>
<td>3 002 817 (IC = 79.49% healthcare costs; 20.51% productivity losses)</td>
<td>NO</td>
<td>£26 000 000 KRW</td>
</tr>
<tr>
<td>6</td>
<td>Borg 2016 (35)</td>
<td>Drug A vs drug B</td>
<td>533 382 (IC = 88.14% drug costs; 10.97% resource use, laboratory tests and monitoring; 0.88% adverse events costs)</td>
<td>537 713 (IC = 58.87% drug costs; 7.33% resource use, laboratory tests and monitoring; 0.59% adverse events costs; 33.21% productivity losses)</td>
<td>NO</td>
<td>Not provided</td>
</tr>
<tr>
<td>7</td>
<td>Diel 2015 (36)</td>
<td>Drug A vs no drug (placebo)</td>
<td>5084</td>
<td>Dominant (IC = 37.21% healthcare costs; 62.79% productivity losses)</td>
<td>NO</td>
<td>£10 000 (£)</td>
</tr>
<tr>
<td>8</td>
<td>Wilson 2014 (37)</td>
<td>ITT (unadjusted analysis)</td>
<td>1567</td>
<td>Dominant</td>
<td>NO</td>
<td>£20 000-30 000</td>
</tr>
<tr>
<td>9</td>
<td>Wilson 2014 (37)</td>
<td>ITT (adjusted analysis with missing data imputation)</td>
<td>6818</td>
<td>22 012</td>
<td>NO</td>
<td>£20 000-30 000</td>
</tr>
<tr>
<td>10</td>
<td>Wilson 2014 (37)</td>
<td>Protocol (unadjusted analysis)</td>
<td>993</td>
<td>Dominant</td>
<td>NO</td>
<td>£20 000-30 000</td>
</tr>
<tr>
<td>11</td>
<td>Wilson 2014 (37)</td>
<td>Protocol (adjusted analysis with missing data imputation)</td>
<td>4849</td>
<td>11 400</td>
<td>NO</td>
<td>£20 000-30 000</td>
</tr>
<tr>
<td>12</td>
<td>van Dussen 2014 (38)</td>
<td>Drug A vs no drug (usual care): discounted</td>
<td>432 540</td>
<td>428 096 (IC = 98.82% healthcare costs; 1.1% productivity losses)</td>
<td>NO</td>
<td>€10 000 000</td>
</tr>
<tr>
<td>13</td>
<td>van Dussen 2014 (38)</td>
<td>Drug A vs no drug (usual care): undiscounted</td>
<td>884 994</td>
<td>874 456 (IC = 98.98% healthcare costs; 1.02% productivity losses)</td>
<td>NO</td>
<td>€10 000 000</td>
</tr>
<tr>
<td>14</td>
<td>Kulpeng 2014 (39)</td>
<td>Drug A vs control (high dose in first line treatment)</td>
<td>Dominant</td>
<td>Dominant</td>
<td>NO</td>
<td>THB 120 000</td>
</tr>
<tr>
<td>15</td>
<td>Kulpeng 2014 (39)</td>
<td>Drug B vs control (high dose in first line treatment)</td>
<td>11 115</td>
<td>83 426</td>
<td>NO</td>
<td>THB 120 000</td>
</tr>
<tr>
<td>16</td>
<td>Kanters 2014 (40)</td>
<td>Drug A vs drug B</td>
<td>1 013 825 (IC = 96.89% ERT costs; 3.11% infusion costs)</td>
<td>1 043 868 (IC = 94.72% ERT costs; 3.04% infusion costs; 2.24% informal care)</td>
<td>NO</td>
<td>€10 000 000</td>
</tr>
<tr>
<td>17</td>
<td>Rombach 2013 (41)</td>
<td>Drug A vs usual care (discounted)</td>
<td>3 282 252</td>
<td>3 284 265</td>
<td>NO</td>
<td>€20 000-100 000</td>
</tr>
<tr>
<td>18</td>
<td>Rombach 2013 (41)</td>
<td>Drug A vs usual care (undiscounted)</td>
<td>6 065 529</td>
<td>6 073 006</td>
<td>NO</td>
<td>€20 000-100 000</td>
</tr>
</tbody>
</table>

*continued on next page*
the authors used data from the literature plus the opinion of a panel of experts, but most of them included data from face-to-face interviews or regular visits of patients and/or caregivers. In 3 studies the authors took into account the production lost due to temporary or permanent disability because of the disease, and one of them also included the cost of premature deaths due to the illness. However, the authors assumed only 1 year and 2 years of productivity losses for permanent disability and premature death, respectively, instead of considering the time left until retirement. Only 1 study included a tool for estimating the cost due to the presenteeism because of the illness, and only in 1 study did the authors assume a compensation effect. Specifically, this means that due to the patient’s absence from work, the authors assumed 50% productivity compensation by an increase in the productivity of the remaining employees and replacement by other workers. Lastly, we should consider that the Swedish studies included a particular issue related to the loss of productivity. Apparently, the Swedish authorities recommended including patients’ consumption of public resources while alive when assessing the loss of productivity. The application of the human capital approach was found to be the only valuation method used in the 12 articles that considered the inclusion of such costs. It should be highlighted that variations with respect to the way in which productivity losses were estimated were also found between studies. For example, Landfeldt et al did not state the unit cost used but mentioned that both absenteeism and presenteeism were considered, which contrasted with Wilson et al and Miners et al, who only included absenteeism. Borg et al specified that the value of production was adjusted not only by the proportion of patients who work, but also by the value of lifetime consumption. Park et al, apart from using the mean hourly wage as the unit cost, specified the mean labor time in a cycle (hours/month) and the employment ratio. The latter was also specified by Ghatnekar et al, as were the payroll taxes. Nevertheless, Diel et al included productivity losses due to morbidity and due to mortality if treatment was unsuccessful.

### Economic Evaluation Results

Table 2 and Figures 2 and 3 summarize the results from the 26 full economic evaluations found in the 14 studies included in this systematic review, comparing the results obtained in terms of ICURs.

The changes observed when considering the societal perspective instead of the healthcare one led to changes in the ICURs and changes in the conclusions in 1 study. From the healthcare payer’s perspective, 1 out of the 26 economic
evaluations reported that the new alternative dominated the comparator (negative incremental costs and higher utility values). Moreover, 8 positive ICURs, when compared to the applied threshold, led to the conclusion that the intervention was not cost-effective and was therefore not preferred to the comparator. From the societal perspective, 4 out of the 26 cost-utility analyses included in the review showed that the new intervention dominated the comparator.

When the societal perspective was considered, the conclusion from 1 economic evaluation changed with respect to the healthcare payer’s perspective (Table 2, estimate number 1). In this economic evaluation, incorporating societal costs into the economic evaluation made the assessed intervention cost-effective against the comparator. In another 3 estimates (Table 2, estimates numbers 7, 8, and 10), the inclusion of societal costs converted the ICUR from cost-effective to dominant, as the new intervention led to cost savings. However, the conclusions did not change, as the new intervention was already preferred to the comparator, from the healthcare payer’s perspective. But from the societal perspective, the assessed intervention became not only cost-effective, but also a dominant strategy.

We found 8 estimates in which the ICURs from a societal perspective increased denoting higher incremental costs than from the healthcare payer’s perspective, whereas 18 estimates were in the expected direction (ICURs lower than healthcare payer’s perspective when a societal perspective was considered). Most of these differences seem to be due to clinical aspects of the new interventions and methodological aspects of the statistical

Figure 2. Incremental cost-utility ratios per quality-adjusted life year (<€100 000): healthcare and societal perspectives comparison. The numbers in the x-axis refer to the number of estimations. See Table 2 for more details.

Figure 3. Incremental cost-utility ratios per quality-adjusted life year (≥€100 000): healthcare and societal perspectives comparison. The numbers in the x-axis refer to the number of estimates. See Table 2 for more details. *Threshold value was 26 000 000 Korean won. †Threshold value was not provided by the authors.
analysis. In the study by Wilson et al.,27 we only found ICURs that were higher from a societal perspective than from the healthcare payer’s perspective when the adjusted analysis plus a missing-data imputation was applied. Rombach et al and Kanters et al assessed an enzyme replacement therapy, and besides the higher direct medical costs, this therapy expected that more informal care would be needed, and more productivity loss due to the therapy and its expected related complications.60,44 Finally, in Kulpeng et al, direct nonmedical costs included costs for transport, meals, accommodation, facilities, and productivity loss.59 The authors did not provide these costs separately, preventing knowing how much costs were due to transport, meals, and so on and how much to productivity losses. Finally, in the study carried out by Gulbrandsen et al, the authors only included the lost productivity in the new intervention arm.45

Discussion

Economic evaluations of treatments or health interventions in the field of rare diseases have to address numerous challenges. Some of them are shared with other health technologies, but others are typical of the special conditions in which the research into such interventions is carried out, including the small sample size of the trials and studies involved.58-53 Additionally, once the treatment has been developed and its inclusion in the health system requested, its high price often exceeds the thresholds commonly used by those countries that include economic evaluations in their decision-making processes.52,54,55 This situation results in a relative increasing impact on the healthcare budgets when RDs are considered individually. However, this impact on budgets could be scarcely significant when all RDs are considered together.52,56-58 So it is not surprising that considerable uncertainty surrounds the decision making about the financing and the price of these treatments.59,60 Keeping in mind the small health benefits that such therapies might provide in the long term compared with its high costs. In this regard, it should be noted that, given the results usually achieved by the economic evaluations of health interventions in rare diseases, an appeal has been made to the use of other methods that complement or even substitute the previous ones, and that help either to expressly include elements that should be present in the decision making about financing and prices, or to introduce innovative reimbursement schemes to reconcile the patients’ access to treatments with the requirements of good value for money,16,61-65 and affordability. However, it should be noted that, first, the substitution of some of the proposed methods instead of the usual economic evaluations is not exempt from criticism either,66,67 and second, that although theoretically there are convincing arguments to justify a special societal consideration for treatments used on rare diseases, there is no solid empirical evidence that “rarity” is a basic element that is valued more intensely by citizens than other factors that also affect this type of treatment, such as the severity of the disease, the potential gain in health, or the absence of alternative treatments.20,68-72

Given this framework of complexity and uncertainty, comparing the results achieved from the societal perspective with those from the perspective of the healthcare payer could be of potential utility in the decision-making process. Countries such as Sweden, The Netherlands, or France52-75 recommend the use of the societal perspective in the economic evaluation of health interventions, including medicines. Other countries recommend using both the societal perspective (Spain, Italy) and the health payer,16,77 and there are countries that have opted for the perspective of the health payer also allowing to include, as a supplementary analysis, the societal perspective. But the recommendation for including resources as the time provided by informal caregivers or the loss of productivity still remains out of most of the national guidelines.

In other previous reviews, Picavet et al found that only 11% of the studies included in the systematic review applied the societal perspective compared to 86% that applied that of the healthcare provider.23 Similar figures were also reported by other authors21,78 in relation to expensive drugs, where only about 9% of the studies included production costs related to paid work. In the field of Alzheimer’s disease, a recent study found that about 65% of interventions included societal costs.79 Therefore, although the existing literature on cost-of-illness suggests that the impact of societal costs on rare diseases is very relevant,8 this does not seem to have been translated into a greater interest in including these costs in economic evaluations, as the results drawn from this literature review show.

Our results showed that the inclusion of societal costs can modify the results in the economic evaluations carried out in rare-disease patients, but rarely modify the authors’ conclusions from the evaluations. Only in 1 study did the author’s conclusions change the recommendation, after applying a societal perspective, about whether the assessed alternative provided a value of efficiency32 when compared to the applied threshold. Krol et al, taking into account a threshold of €40 000 per QALY, found that the cost of lost productivity could alter the decision making in 31% of the economic evaluations analyzed.78 In the same way, Peña-Longobardo et al found that the inclusion of societal costs in Alzheimer’s disease influences the results, as in 37% of the economic evaluations included this became the dominant strategy after including societal costs when they were already cost-effective from the healthcare perspective. Even more relevant is the fact that in about 11% of the interventions, the conclusions changed when societal costs were included.79 In this sense, the threshold for acceptability could play an important role. Although the rarity of the disease is one of the variables that are normally mentioned in the literature to consider higher than usual thresholds, Adkins et al did not identify country-specific guidance and health technology assessment (HTA) documentation for recently evaluated ODs.80 None of these countries were found to have explicit HTA criteria for the assessment of ODs; therefore, ODs are assessed through the usual HTA process. As far as we know, only the National Institute for Health and Care Excellence seems to consider a higher threshold linked to the NICE’s Highly Specialised Technologies Programme. This consideration might be related to rarity (prevalence).81 This is consistent with the few studies of elicitation of societal preferences carried out in its area of activity.82

In brief, our work indicates that the adoption of a societal perspective would not modify the results and conclusions that had previously been reached from the perspective of the healthcare payer, giving the high ICURs identified. Therefore, although it could be deduced that using the societal perspective would be a useless exercise, at least 3 nuances should be noted and taken into account. First, the very small number of the studies that include societal costs on rare diseases is very relevant,9 this does not seem to have been translated into a greater interest in including these costs in economic evaluations, as the results drawn from this literature review show.

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such as the patients’ caregivers. Third, there is great methodological heterogeneity in the studies reviewed in relation to the measurement and assessment of non-healthcare costs.

Thus, it is necessary to significantly increase the number of economic evaluations that include a double perspective—society, healthcare payer—and it is necessary to advance with greater methodological homogeneity in the evaluations performed in this field.

Supplemental Materials

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