Improved methods and actionable tools for enhancing HTA

Deliverable D4.1: Revising the methodological aspects applied to the identification, measurement and valuation of social costs in economic evaluations

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LIST OF ABBREVIATIONS

AB – Absenteeism

CA - Conjoint analysis

CarerQoL – Caregiver Quality of Life

CAS - Caregivers Activity Survey

CATS - Caregiver Activity Time Survey

CBA - Cost benefit analysis

CCA - Cost consequences analysis

CEA – Cost-effectiveness analysis

CIIQ - Caregivers Indirect and Informal care Cost Assessment Questionnaire

CM - compensation mechanisms

CMA - Cost minimisation analysis

COI – Cost of Illness

CUA – Cost-utility analysis

DM – Diabetes Mellitus

EE – Economic Evaluation

EEHT - Economic Evaluation of Health Technologies

EQ-5D – EuroQol 5 Dimensions

FCO – Friction Cost Approach

GDP – Gross Domestic Product

HCA - Human Capital Approach

HLQ - Health and Labour Questionnaire

HPQ -Health and Work Productivity Questionnaire

HRPQ-D - Health-Related Productivity Questionnaire Diary

HRQoL - Health-Related Quality of Life

HTA – Health Technology Assessment

HUI – Health Utility Index

ICHA-HC - Functional Classification of Health Care

iPCQ - iMTA Productivity Cost Questionnaire

ISPOR - International Society for Pharmacoeconomics and Outcomes Research

MeSH - Medical Subject Heading

MIDAS - Migraine Disability Assessment instrument

NPAF - New Product Assessment Form

OECD - Organisation for Economic Co-operation and Development

PAF – Population Attributable Fractions

PBAC - Pharmaceutical Benefits Advisory Committee

PR – Presenteeism

PRODISQ - Productivity and Disease Questionnaire

QALY – Quality Adjusted Life Years

QQ - Quantity and Quality Method

RD – Rare Diseases

RUD - Resource Utilization in Dementia

SF – Short-Form Six-Dimension

SHA - System of Health Accounts

SPS-13 - Stanford Presenteeism Scale 13

UP - Unpaid

USA – United States of America

VOLP - Valuation of Lost Productivity Questionnaire

WLQ - Work Limitations Questionnaire

WPAI - Work Productivity and Activity Impairment Questionnaire

WPSI - Work Productivity Short Inventory

WTA – Willingness to Accept

WTP – Willingness to Pay

ZIN - Zorginstituut Nederland

Executive summary

Economic evaluations are becoming of utmost importance to help policymakers in the allocation of scarce health care resources. One of the areas of greatest methodological discussion, with potential implications for decision making regarding reimbursement, pricing and rational use of health technologies, is the type of perspective to include in such evaluations. Although some countries have decided to restrict economic evaluations to the healthcare payer perspective, others consider that not taking into account a wider perspective could mean leaving out of the analysis costs and effects relevant to individual and societal well-being and then could bias health policies.

If a societal perspective was adopted, two main areas of controversy would exist to whether and how to value the time of patients and caregivers. The debate on the inclusion of social costs in economic evaluations also relies on the methods used, with no actual consensus on productivity loss valuation methods in national guidelines. On the other hand, while the strengths and weaknesses of the methods used to value productivity losses have been widely discussed in the literature, the debate for informal care assessment is less widespread, being the methods applied in constant development.

Thus, in this report, we aimed to, first of all, provide with an overview of how social costs are usually defined in the literature of economic evaluation of health care technologies (Section 2), taking an in-depth look at the valuation of paid and non-paid time of the person affected by any specific illness or injury (Section 3) and of non-professional (informal) caregivers (Section 4). Then, in Section 5, we will review whether, if so, international guidelines recommend the application of a societal perspective in economic evaluations and the recommendation on how social costs should be included. In Section 6, we perform a systematic review of the existing literature to test whether social costs are included in applied economic evaluations and which methods are used. In Section 7, we conclude summarizing the main findings identified in the report.

Throughout this document, we confirm that, with respect to the valuation of patient´s paid time, the debate about whether the human capital approach or the friction cost method is preferred is still far from being over. However, according to the applied literature, the human capital approach is the most commonly used method. One of the reasons behind might be its greater simplicity in terms of application, whereas the friction costs method requires an adaptation to country-specific

characteristics and an update to each stage of the economic cycle, which makes its use more complicated. Although the theoretical debate has not progressed in recent years, there are advances in other lines such as the identification and incorporation of presenteeism. In contrast with the valuation of paid time, the evidence on methodological aspects related to non-paid time is very scarce.

In the case of informal caregiving time valuation, the debate about the different available methods has been less intense. However, it seems to be an agreement on the easiness of application of the opportunity cost method as it has been the most commonly used approach to value informal care costs in cost of illness studies and the review of economic evaluations. The applied literature identified that, within the number of studies including informal care costs (n = 46), almost 74% of the articles used the opportunity cost approach to value informal caregiving, 10% applied the replacement cost method and 16% used both methods.

The debate around which is the most appropriated perspective (the health care financer perspective; the societal perspective; or both) and the methods that should be applied if the inclusion of social cost is considered relevant is also present in international guidelines and the applied literature. Consensus has not actually been reached. When the societal perspective is recommended, some guidelines explicitly recommended a method of productivity loss valuation. When informal care consideration is explicitly mentioned, only a few guidelines establish recommendations on how to be valued. In general terms, it is identified the need for clarification and general consensus on social costs inclusion, identification and valuation, which has also been reflected in the applied literature review. We identified 980 articles applying an economic evaluation to assess any healthcare intervention, from which 170 (more than 17%) included either productivity losses, informal care costs or both social costs.

1. Introduction

The economic evaluation of health technologies (EEHT) has reached a strong development in Europe in the last decade. The main cause of this flowering is the driving role that public authorities are playing in their development, using these tools as a key element in the adoption and dissemination strategies of health innovations. Economic evaluations try to respond to the pressure between the need to incorporate therapeutic novelties, generally more effective and, therefore, with an added value or promise of improvement of health, and the greater budgetary effort that their inclusion usually imply for the health care system. Faced with this complex situation, health decision-makers have the duty to get balance between the access to their citizens with therapeutic advances that help improve their health and considering the financial sustainability of public health systems, a fact that could threaten the indiscriminate adoption of health innovations.

A necessary element to facilitate the application of economic evaluation in decision-making is that the agents that carry out these evaluations have clear methodological rules and, as far as possible, agreed upon. In this regard, it should be underlined that there is a strong degree of agreement in the guidelines of the most outstanding countries for the practical application of the EEHT in the decision-making process on some essential features of any economic evaluation (choice of comparators, subject population to study, time horizon to be used, application of discount rates, the need to perform sensitivity analyses, the need to present the results in incremental terms). However, there are other aspects in which, because they are closer to the normative scope than to the technician or because they have experienced notable methodological advances in recent years, there is no such degree of agreement.

In this sense, a long-discussed aspect is the most appropriate **perspective** from which the analysis should be carried out (Brouwer et al., 2006; Jönsson, 2009; Johannesson et al., 2009; Claxton et al., 2010). This is a key element in any economic evaluation since it must reflect the most relevant point of view from which the evaluation must be considered, and this determines the type of costs and results to be considered. Thus, there are different perspectives that could be applied in economic evaluations. Firstly, the healthcare financer perspective, in which all healthcare resources (hospitalizations, general practitioner and specialist visits, drugs, etc.) would be included but other

resources used or lost would not be relevant, such as social services or labour productivity losses. Secondly, the perspective of the public financier, where all resources financed from public budgets would be relevant; followed by the perspective of the provider (for example, a hospital centre; in which non-health costs would be irrelevant but those that are not the responsibility of the centre); and the patient's or the family's (since they may have to assume significant monetary and non-monetary burdens caused by an illness or injury). And, finally, the broader perspective, the societal perspective, in which any resource employed or lost as a result of an illness or injury must be taken into account.

Secondly, even when it has been concluded that the perspective of analysis should not be limited solely to the assessment of the healthcare costs, the approach to the consideration, identification, measurement and valuation of other social costs does not lack of difficulties. In fact, it can be affirmed, without fear of committing any incorrectness, that, on the one hand, this area has been one of the most methodological discussions of the last two decades in the field of economic evaluation of healthcare interventions and, on the other hand, that the methodological debates are still far from being closed.

This document does not seek to resolve issues where dozens of brilliant researchers have devoted time and effort over the years, but seeks to capture precisely those debates, in order to synthesize and clarify the existing methodological options and analyse how they are applied in practice.

Therefore, in this report we do not discuss what kind of perspective is the most appropriate or in which situations one or the other should be used. Neither do we propose which non-health costs must be included or not in the economic evaluations, but how they can be valued in case that a positive decision is made about their inclusion. Likewise, we will not focus on how the paid or non-paid work time of the patients or the time of the carers should be identified or measured, although we will inevitably refer to these aspects in specific places of the document. Our main objective is to show the different ways of assessment of social costs and, more precisely, **the assessment of the time of patients and carers**.

The document is ordered as follows. After this brief introduction, we will include a brief consideration on the concept of social cost that we are going to consider. Next, the main methodological debates focused on the assessment of the time of patients and carers will be analysed. The next step will be to observe how the inclusion of social costs in the methodological guides of economic evaluation of different countries is considered, to later review how these costs are included in the economic evaluations published in the scientific literature. The document closes with some concluding remarks.

2. On the concept of social cost and its identification

As Anthony Culyer rightly points out in his excellent work (Culyer, 2018), the costs (and, therefore, the benefits) cannot be defined without taking into account the specific context of the decision. Therefore, the costs of the resources considered, and the opportunities lost will depend on the uses that were to be given to those resources and the scope of influence that we want to analyse. This conception of the cost will have important effects in the methodological approaches that we will show later in this report and is behind the fact that there are intense unresolved debates about the most appropriate methods to apply in the valuation of the social costs associated with illnesses and injuries.

As explained in the introduction, we will focus on the monetary valuation of social costs. The definition of social cost is not at all obvious or simple, but the first step is to identify and limit the concepts of health care and social costs. For this purpose, we are going to follow the System of Health Accounts (SHA) methodology proposed by the Organisation for Economic Co-operation and Development (OECD) in 2000 and revised in 2011 (OECD 2011).

The System of Health Accounts 2011 "provides a standard for classifying health expenditures according to the three axes of consumption, provision and financing. It gives guidance and methodological support in compiling health accounts[1]". "The functional classification of health care (ICHA-HC) delineates the boundaries of health care activities from an international perspective. Following the concept underlying the design of the ICHA-HC classification, the boundary contains all activities with the primary purpose of improving, maintaining and preventing the deterioration of the health status of persons and mitigating the consequences of ill-health through the application of

[1] "More specifically, the purposes of the System of Health Accounts 2011 are:

- to provide a framework of the main aggregates relevant to international comparisons of health expenditures and health systems analysis;
- to provide a tool, expandable by individual countries, which can produce useful data in the monitoring and analysis of the health system;
- to define internationally harmonised boundaries of health care for tracking expenditure on consumption."

qualified health knowledge." "This primary purpose is pursued by the following groups of health care activities:

- Health promotion and prevention;
- Diagnosis, treatment, cure and rehabilitation of illness;
- Caring for persons affected by chronic illness;
- Caring for persons with health-related impairment and disability;
- Palliative care;
- Providing community health programmes;
- Governance and administration of the health system."

Also, according to the SHA 2011, "Total long-term care consists of a range of medical/nursing care services, personal care services and assistance services that are consumed with the primary goal of alleviating pain and suffering or reducing or managing the deterioration in health status in patients with a degree of long-term dependency".

The definition of social costs considered in this report is those that takes into account the valuation of non-health resources that the presence of an illness or injury cause. Although there are several possibilities of classification of these resources, the most valuable element that is modified is the **time of the people affected by the illness or injury and the time of their affective social environment**. In this sense, health care and long-term care resources are out of the scope of this report.

Of course, there are non-health care resources associated with adaptations in the housing and the transportation vehicle and that may be of great relevance to the budgets of the families that have to face their payment. Moreover, for the analysis of some specific health problems other external costs can be very relevant. For instance, in the case of addition to illegal drugs, the costs impose to the justice system, private legal defence, police protection, penitentiary costs, property damage for victims, programs of dishabituation and social reinsertion, etc. However, given that the identification of these resources in specific situations may be unrelated, but the general principles of valuation of these resources are not complex (market prices, usually, in the case of adaptations), or given that they

are related to very specific problems, which have been treated in other works (Harwood et al, 1998; Collins et al., 2006), our report is not going to focus on these situations and on these social resources.

Thereby, focusing in the time of the people affected by the illness or injury, the term commonly used in the economic evaluation literature to refer to any change in time use is "indirect costs". However, the practical application of this concept has focused in most cases on the identification, measurement and assessment of the paid work time. Therefore, in this report we have decided not to use the term "indirect cost" and analyse each of the components separately. Then, a negative shock in the health status of an individual could cause undesired effects on the following concepts:

- Labour (paid) productivity lost by patients.
- Labour (paid) productivity lost by caregivers (e.g., partner/spouse family and friends).
- Domestic (unpaid) productivity lost by patients (also called non-labour or unpaid productivity).
- Domestic (unpaid) productivity lost by caregivers.
- Leisure time lost per patient.
- Leisure time lost by caregivers.

Thus, the proposed classification differentiates between the person directly affected by the illness or injury considered (patient) and the people of the affective social environment responsible for their care (carers). In the first case, a distinction will be made between paid time and unpaid time[2].

[2] This distinction is not made in the case of personal caregivers due to the different approaches to consider the valuation of this time, as we see in section 4

3. Assessment of the time of the person affected by the considered illness or injury (the patient)

In relation to the assessment of the **patient's time**, we will consider two fundamental elements: **paid and unpaid work time** (table 3.1.). **Unpaid time** is a resource dedicated to the production of goods and services that are not exchange on the market like household work (cooking, cleaning, shopping…but also care activities) and to develop leisure activities. In some circumstances is very complex to separate unpaid labour from leisure time. Cooking, for instance, can be a household work but it can increase the utility of people who enjoy this activity. Therefore, it is not clear to what extent it is a domestic activity and to what extent it is a leisure activity. The 'third person criterion' can in some situation be useful to separate unpaid production from leisure (Krol and Brower, 2015). This criterion implies that all elements replaceable by a third person would be considered unpaid labour and all non-replaceable elements (related to the enjoy in the process of the activity) would be considered leisure. However, even applying this criterion, the distinction between unpaid labour and leisure will not evident for all situations. In any case, for practical purpose, we will maintain the distinction between unpaid work and leisure activities.

In relation to the **paid time**, it is usual to find assessments of this resource in two main concepts: **costs derived from morbidity and costs associated with mortality**. The former corresponds to losses or restrictions on the ability to perform paid work, **temporarily or permanently**. In the second case, it would be the permanent loss of productivity caused by premature deaths. Based on these two components, at least three main items can be identified: **labour losses associated with premature mortality, labour losses associated with permanent sick leave and labour losses associated with temporary sick leave**. The first two are permanent work time losses, while the third one involves a temporary leave that finishes when the worker returns to the workplace. There are two additional items to consider regarding this temporary leave: the reduction of the abilities of the person who performs a paid activity, also known as "presenteeism", and the early retirement from the labour market.

We are focusing on labour losses associated with premature mortality and labour losses associated with the permanent and temporary sick leave as their consideration in economic evaluations that

incorporate labour productivity losses is more common. "**Presenteeism**" is defined as the situation in which a person is not as productive as expected due to a reduction in her/his abilities caused by a chronic disease or injury and premature retirement pose additional methodological challenges. The first one may be relevant in diseases that incapacitate the person to perform their usual tasks but do not necessarily imply a physical absence from the job. Meanwhile, **premature retirement** could be biased due to issues not strictly related to the disease (i.e. in patients close to the retirement age an early retirement could be attractive, regardless of their health status because there are financial or social incentives). A health shock can be the catalyst for retirement. However, to demonstrate the cause-effect relationship, it is necessary to have very rich databases, which is usually beyond the reach of the researcher in the field of EEHT.

Table 3.1 Time of patients. Components considered for assessment.

Paid time (labour productivity losses)	Premature death
	Temporary sick leave/absenteeism
	Permanent sick leave
	Presentism
	Early retirement
Unpaid time	Domestic time
	Leisure time

3.1 Valuation of the remunerated time of the person affected by the considered illness or injury (patient)

There are few areas in the field of economic evaluation where there has been a methodological debate as intense as that experienced in the 90s of the last century in relation to the most appropriate method for estimating labour productivity losses caused by an illness or injury. The two main assessment methods that focused these debates - **human capital approach and friction costs approach** - are still

the methods commonly used in the valuation of labour productivity losses without these debates being concluded or having ended with a consensus reached on which method is the most appropriate. We can only affirm that both approaches start from very differentiated methodological assumptions (Grossman, 1972; Koopmanschap & Ineveld, 1992; Liljas, 1999; Grossman, 2000; Zhang et al., 2011; Krol et al., 2013; Lensberg et al., 2013; Krol & Brouwer, 2014) and this translates into important differences in the estimation of results (Hutubessy et al., 1999; Lofland et al., 2001; Marcotte et al., 2001; Oliva et al., 2005).

Although this document focuses on the economic assessment of time, it is important to recognize the difficulty in identifying and measuring time, in this case, that of paid work, and the productivity associated with it. First, from a practical point of view, the identification of negative health shocks in people who are performing paid work is not always easy. The optimal would be to have labour records or surveys specifically designed for that purpose. However, if the source is clinical records, the information on whether a person was working or not at the time of suffering a negative health shock may not be available. Or, on the other hand, in the case of premature mortality data, the information collected by the National Statistics Institutes does not usually include the occupational status of the deceased. This implies that assumptions should be established about the degree of labour participation and the employment rate of people who have died as a result of a certain disease, being aware that the models applied will try to approximate or estimate the losses, but they will be subject to some measurement error due to lack of starting information.

Likewise, in the case of certain pathologies, such as mental disorders, it has been observed in numerous studies (Evers & Ament 1995; Oliva-Moreno et al., 2006; Cornwell et al., 2009; Fritjers et al., 2010) that the labour participation of these people is much lower than that of the general population. This supposes, for example, in the case of people suffering from schizophrenia, that the administrative figures for sick leave are very low in relation to the prevalence and severity of the disease. This is due to the fact that access to the labour market for these people is strongly conditioned by their illness and that, therefore, we will observe absence of work activity rather than sick leave. These practical aspects are complex to handle in the assessment of paid time of the people affected

by health problems, but they should be kept in mind as limitations in the application of the theoretical approaches that we show below.

Additionally, it is very complex to observe the individual productivity of a worker in a context of teamwork processes, with the possibility of sharing out burdens on other workers (which would entail other opportunity costs that would have to be considered), with possible multiplier effects derived from the absence of a member over the rest of colleagues (Krol et al., 2013), with the possibility of substitution after a certain time and in a context of labour markets that are far from responding to the pattern of "perfection" that is assumed as a starting point in numerous analyses.

On the other hand, it is necessary to consider that we are discussing the valuation of the remunerated time of the people from the social perspective, not from the perspective of individual agents (the affected person, the company, insurers or the public sector). According to the postulates of welfare economics, this means excluding from the analysis transfers that take place between an insurer (usually the public system, although there may also be situations of private insurance) and the person who suffers from the disease, when we value the loss that causes the time of illness. Thus, from the perspective of the individual, an illness, in addition to the loss of direct well-being that it causes, would imply a loss of income that would also influence their well-being. This can be mitigated if an assurance system (usually public) compensates that loss of income with a subsidy.

However, the income gain that causes the subsidy in the sick person is also an opportunity cost for the Public Administrations, since this income could have been devoted to alternative uses. The consideration of the social perspective balances the gain of one part and the opportunity cost of another. More complex considerations can be established (aversion to risk and diminishing marginal utility of income from the point of view of the individual and neutrality on the part of the Public Administrations, consideration of the administrative costs of tax collection and distribution of the

aforementioned transfers) but this would only complicate an already complex issue. As any model or approach is a simplification of reality, we are forced to recognize this point and move forward[3].

The first of the methods, the **human capital approach**, has its roots in the theories of human capital. According to this theory, increases in a person's stock of knowledge or human capital increase their productivity in the labour market, from where they obtain their monetary income, and in the non-market or domestic sphere, where they produce goods that become part of its utility function. To realize their potential gains in productivity, individuals have incentives to invest in education and job training (Becker, 1967; Ben-Porath, 1967; Mincer 1974). The idea of health as a component of the individual's stock of human capital is not new (for example, Becker, 1964 and Fuchs, 1966), however, the first model of health demand was not developed until 1972 by Michael Grossman (Grossman, 1972; Grossman, 2000).

Very briefly, the key element on which this model is based on is the dual nature of the good "health". Health can be treated as a consumer good and as an investment good. As a consumer good, health is desired by itself since health is a necessary condition to be able to develop our habitual activity and enjoy a series of experiences not acquired in the market, as well as goods and services acquired in the market. "Being in good health" thus becomes a necessary condition to achieve or maintain high levels of well-being. On the other hand, health can be considered at the same time an investment good, since it allows to increase the number of healthy days available to a person and thus increase their potential income. Focusing on this second aspect, a negative shock in the health status of an individual could cause undesired effects on paid and unpaid time of patients (and caregivers).

[3] Also the absence of the job can mean an increase in the leisure time of the individual. However, for practical reasons and considering that the enjoyment of leisure time of a person absence from his/her job will be reduced we will not consider this type of effects.

Within the part that we are analysing, labour productivity lost by the patients, the opportunity cost of the lost resource, paid work time, can be approximated to the remuneration that this factor of production receives in the labour market. Therefore, the salary that the worker receives (per hour, monthly, annual) would be the measurement of the lost work time. Employing the salary as a measure of the lost resource is consistent with a classic competitive equilibrium model, with companies seeking to maximize their profit, where firms contract production factors without quantity restrictions to the point where the marginal productivity of the factor is equalized with the cost marginal to endow one more unit of it. Therefore, the wage (marginal cost) would be equal to the productivity of the last hour worked (or the last worker hired by the company)[4]. Nevertheless, it should be stressed that in the applied studies of cost of illness and economic evaluations it is usual not to use individual data but average salaries estimated by official statistics, where adjustments for age and sex are considered, including adjustments for employment rates (Pike & Groose, 2018).

Taking into account this general framework, several considerations must be made. The first is that in a context of perfect labour markets and in the absence of taxes, it is consistent to identify wages as a correct measure of the productivity of the labour factor. However, labour markets are far from be perfect, in the sense of the conditions that are usually assumed by the manuals of economic theory. The absence of perfect competition or, on the other hand, the presence of oligopolistic markets and monopolistic competition is more the norm than the exception in the markets for goods and services. On the other hand, the negotiation of the salary does not usually occur between worker and company with total flexibility in the conditions and times of work contracted and with a balanced bargaining power. In fact, labour institutions (labour legislation, types of hiring, existence of unions, collective bargaining, etc.) are not exogenous elements to the functioning of the labour market but a part inherent to it. Third, profit maximization is not the most realistic scenario for many entities that

[4] It should be noted that, from the perspective of the worker, in competitive markets, the equilibrium wage is equal to the marginal value of free time. In a context of individuals seeking the highest possible satisfaction or well-being, which would depend on free time and consumption, the individual is willing to work until the marginal value of free time equals the salary. Therefore, the opportunity cost of the time worked is the value of the free time that is waived.

perform their activity in the field of public service. Although the cost of producing such services (for example, education or healthcare) is influenced by market forces, it is also not clear that the salary reflects exactly the productivity of the labour factor. Additionally, the existence of direct taxes on income and indirect taxes on sales also modifies the previous results, giving rise to two different wage concepts: the wage cost paid by the company and the net salary received by the worker. A final element to mention, although without exhausting the list, of great importance for the alternative approach that we are going to expose, is the existence of involuntary unemployment, a market imbalance of great relevance, which moves us away from the proposed perfect market framework with the meeting of supply and demand via adjustment of the price (wage).

Even considering the above, the assessment of labour losses according to the approach of human capital has a solid foundation in classical economic theory (Johannesson, 1996; Johannesson and Karlsson, 1997; Liljas, 1999). This does not suppose an optimal method nor free of critics to value the labour productivity lost. However, as with the assumption of the existence of situations of perfect competition, they can be the first step or point of reference to address an estimate of this item.

The second predominant approach is the so-called **friction cost approach**. The main idea of this approach is that the human capital method overestimates productivity losses by not considering the possibility of compensation for lost work time in situations of short-term work absences (either by the sick person himself on reincorporation or by the companions of the same ones), the cancellation or delays of not urgent works or of substitution in situations of permanent losses (after the called “friction period”).

Following Koopmanschap and Rutten´s work (1997), the friction cost (FC) approach indicates that the human capital (HC) approach overestimates the cost of short term sick leave due to (a) the existence of diminishing marginal returns to labour; (b) the loss of production due to short term sick leave can assumed by internal labour reserves; (c) an individual can make up for the loss of production when she/he returns to work; and (d) non urgent jobs can be cancelled. This implies that the absence of the worker due to illness in short-term losses reduces the effective time of work less than proportionally. According to the Koopmanschap and Rutten's work (1997) estimations for The Netherlands, only 80% of the average value of production lost as a result of the disease should be considered.

In this sense, to consider long-term absences, under this approach a worker who is forced to leave permanently his/her job because illness does not cause a loss in productivity for society, as he will be replaced by another worker. The only loss occurs during the period the post remains vacant while a new employee is being sought (Koopmanschap and van Ineveld, 1992; Koopmanschap et al., 1995). So, it is assumed that individuals on sick leave can be replaced by someone who is already employed or by someone who is currently unemployed after a friction period[5].

The calculation of this period of friction is decisive in this approach. The longer and complex it was, the closer the results estimated by this approach would be to those of the human capital method. In contrast, the shorter the period of friction, the greater the discrepancies. Koopmanschap et al (1995) used aggregate data for the Netherlands on the frequency and duration of absences from work, differentiated by educational levels of employees, in order to determine the frequency of friction periods in 1988 and in 1990. Along the two years, these periods are longer for jobs occupied by graduates. The average duration of the friction period was estimated at 2.8 months in 1988 and 3.2 in 1990.

Posed as an alternative model to the human capital method, trying to correct possible overestimations of the previous one, the friction costs approach is not without its critics (Johannesson and Karlsson, 1997). Following the synthesis of Liljas (1999), the FC approach (FCA) "means that one of the fundamental axioms of the theory of the firm is violated, that is: firms only employ labour until the marginal value (produced by the worker) equals the marginal cost of labour. According to economic theory, therefore, the value of loss of production for an absent worker is equal to his or her gross income for that time period". Also, "the case of internal labour reserves is not convincing because of the very same reason. If the marginal cost for these workers exceeds their marginal value to the firm, they would, according to economic theory, not be employed". If an individual is able to make up for

[5] If the person was previously employed, the initial vacancy would create a chain of vacancies each with their own friction period (for more details, see Van den Hout WB, 2010)

the loss of production when she/he returns to work that would probably mean that the individual would either have to work 'faster' which would reduce her/his utility of being at work, or work overtime, which would reduce his or her leisure time. In addition, cancelled jobs, although non-urgent, will reduce the production of the firm.

For long term absences (permanent sick leave and premature mortality), the FC approach assumes that all long term vacancies can be filled immediately (after a friction period) with previously unemployed individuals while in the human capital approach the existence of an almost perfectly competitive labour market is assumed, in the friction cost approach there are no search problems in the labour market and the supply of employment automatically adjusts to the demand, in quantities and training. Likewise, if this was the case, "it should be possible to solve the problems of unemployment in society by reducing the number of hours worked by employed workers and having unemployed workers work these hours instead". Unfortunately, this does not seem to be the case. Therefore, and although some researchers have made proposals to try to shorten the differences in results derived from both methods (Targoutzidis, 2018), the truth is that there are great differences in the methodological approaches and the hypotheses proposed by both approaches.

Also, in the case of friction costs approach, Kigozi et al. (2016) performed a systematic review to identify economic evaluation and cost of illness studies published in English that have estimated productivity costs using the friction cost approach (period 1996-2013). The authors tried to answer two research questions: "(1) To what extent has the friction cost approach been used to estimate productivity costs in economic evaluation? and (2) How consistent are the methods for valuing productivity costs using the friction cost approach?" They identified 46 studies from 12 countries. 28 studies (61%) were from the Netherlands. A 76% of the studies reported the length of friction period used, but only 35% stating explicitly the source of the estimated friction period. Only 9 studies (20%) reported the elasticity correction factor used. Of these, 7 studies employ a value of elasticity 0.8, originally estimated for the Netherlands (Koopmanschap et al., 1995).

Given the period of time analysed, the low number of studies identified, in spite of including both cost of illness studies and economic evaluations, and considering that most of the articles were from Netherlands, it is not risky to state that the friction costs approach is not widely applied beyond the

country of the authors who proposed it. Kigozi et al. (2016) argue that the difficulty in estimating key parameters for the development of models outside the Netherlands may be one of the reasons for its lack of expansion. While this idea is true, it should also be noted that the elasticity of substitution, where it has been expressly mentioned, maintains the same value as originally estimated by the authors who developed the friction cost method (Koopmanschap et al., 1995). This is a weakness since the value of elasticity and the period of friction estimated for long-term losses should vary with the economic cycle and would not have to be the same in 2002 or in 2012 with respect to the estimated value at the end of the 1980s/beginning of the 90s of the last century.

It should be noted that as has been observed in several studies (Hutubessy et al., 1999; Lofland et al., 2001; Marcotte and Wilcox-Gok 2001; Oliva et al., 2005; Lensberg et al., 2013), the two approaches produce very different results, with lower values in the friction costs method. Pike & Grosse (2018), in a recent systematic review, identified cost of illness studies published during 1995–2017 that used the FCA, with or without comparison to the HCA, and to compare FCA and HCA estimates from those studies that used both approaches. The authors pointed that only 5–8% of all COI studies "included both medical and productivity costs, utilized the FCA, either alone or jointly with the HCA". The vast part of these studies (51 of 80) came from countries that have officially recommended the use of the FCA (Canada, Germany, and, specially, in the Netherlands). The FCA results in "smaller productivity loss estimates than the HCA, although the differential varied widely across studies". On the 38 selected studies that used both methods, in 3 of them, the results estimated by the HCA are less than twice compared with those estimated by the FCA. In contrast, in 9 others, the ratio is 19 times higher or even more. This variability can be explained, to some extent, by the different ways in which each method was applied (for instance, the duration of the friction period considered, which varies in the studies analyzed between 6 weeks and 6 months) but, essentially, they are mainly due to the concepts included (only short-term sick leave or also premature mortality and long-term sick leave).

The authors concluded that human capital approach is the predominant method used to estimate productivity costs in cost-of-illness (COI) studies - friction cost approach is present in an estimated 5–8% of COI studies- and verified that estimates of the economic burden of chronic conditions are much lower when the FCA is used. However, the variability depends on how the two approaches are implemented. They point out that "appears to be little standardization in the use of these methods

among the observed studies". Also, there is clear geographic differences in the use of the FCA with great concentration in three countries[6].

A recent European project tries to develop cross-European recommendations for the identification, measurement and valuation of resource use and lost productivity in economic evaluations using a Delphi procedure (van Lier et al., 2018). There is a high degree of consensus in recommending the social perspective as a reference for economic evaluations in a European context (88% agreement). Thereby, lost productivity costs, including absenteeism (100% agreement) and presenteeism (83% agreement) should be included in any economic evaluation conducted from a societal perspective. However, according to the panellist, lost productivity costs due to absenteeism from unpaid labour (see section 3.2.) should not be included (27% agreement for the inclusion). In the case of absenteeism from paid work, the panel preferred friction costs (73% agreement). The panel warns that "it should be taken into account that the length of the friction period depends on the local economic situation and that friction periods are not available for most European countries. Therefore, countries should try to determine the friction period for their country or, when this is not feasible, perform a sensitivity analysis in which productivity losses are valued using the human capital approach." On the other hand, on the calculation of the labour losses derived from presenteeism or those associated with premature mortality, the panel does not state which approach should be applied.

3.1.1 Other relevant factors

3.1.1.1 Presenteeism

One of the biggest challenges that the assessment of paid time needs to address is the consideration of those situations in which, without being absent from work, the productivity of the worker is reduced to a greater or lesser extent. When the evaluation of productivity loss is related to a sick leave in the workplace, the identification of this time can be quick and easy. It is usual that workers or firms report this situation to the public or private insurer. In the case of absenteeism, the worker does not attend work for some hours or for a short time (a few days) but there is not an administrative record that

[6] This information will be expanded in section 5.

confirms his/her non-attendance. Thus, in sick leave or in absenteeism situations, the information can be easily recorded retrospectively or when the study design was prospective, the researchers could include specific questions and obtain the number of days/hours lost due to an illness or an injury.

However, the case of presenteeism is different. The worker remains at her/his job. The health problem might reduce their productivity, but it is not clear to what extent this happens, given that it is impossible to directly observe individual productivity, within the framework of applied economic evaluations (Pauly et al., 2008). In recent years, a significant number of instruments have been developed to try to measure and assess changes in labour productivity associated with health states. The table 3.2. collects the main instruments identified by Tang (2015) and offers a short description of the main available techniques within the productivity domains assessed by each tool.

Most of these instruments have been developed by USA researches (close to the 60% of methods for identifying the time lost due to illness including the time dedicated to unpaid activities). There are two methods available for determining the time lost on specific health conditions (such as common cold, flu, diabetes or depression): the 'Work and Health Interview' offers the possibility of up to 22 health conditions or health-related problems and the 'Work Productivity Short Inventory' included not only worker health-related condition, but it includes four conditions about the care of relatives. On the other hand, the 'Work Productivity and Activity Impairment Questionnaire' (WPAI) does not include specific illness-related questions in the tool, but it is possible to adapt it for specific health conditions by referring to the health-related problem in the survey questions.

Other issues such as the inclusion of the 'multiplier effects' (see next subsection) or the effects on 'unpaid tasks' (see next section) are only included in two and six, respectively, of the twelve tools included in the Table 3.2. The validity and reliability of these tools were moderate to good in most cases, but some questionnaires also have few studies where their psychometric properties have been reviewed.

In any case, it should be noted that the empirical studies carried out stress the high heterogeneity between the results obtained from the application of different instruments (Meerding et al., 2005; Zhang et al., 2010). Although nowadays the Work Productivity and Activity Impairment Questionnaire is becoming the most used instrument, we cannot identify a gold standard in the identification and measurement of absenteeism and presenteeism, which strongly conditions the comparability between the results of different studies (Zhang et al., 2011; Krol et al., 2013). Issues such as the most appropriate recall period to apply in the case of absenteeism and in the case of presenteeism (Zhang et al. (2011) proposes a recall period of 3 months in questions related to absenteeism and a week for questions related to absenteeism) and the direct comparison between instruments are still far from being solved.

These conclusions are shared by Kigozy et al (2017) in the systematic review carried out on the estimation and inclusion of presenteeism costs in applied economic evaluations. They reviewed a total of 28 studies, most of them COI studies (only 3 were cost-effectiveness analysis). The most frequent conditions identified were obesity, rheumatoid arthritis, migraine and ankylosing spondylitis. Nine instruments measuring presenteeism were identified. The most commonly used questionnaires were the Work Productivity and Activity Impairment (6/28), the Work Limitations Questionnaire (5/28) and the Work and Health Interview (3/28). All studies with one unique exception used salary-based conversion based on human capital approach. None of the studies identified included aspects of compensation mechanisms or multiplier effects. Presenteeism costs represented a relevant part of total costs (52% on average), being greater than absenteeism costs. The proportion of presenteeism costs was higher in rheumatoid arthritis, backpain and insomnia conditions. The authors discussed that (1) "…losses from reduced productivity at work are rarely included in cost-effectiveness or cost-utility analyses, although presenteeism has been associated with significant costs" and "There is limited literature on typical economic evaluations incorporating presenteeism costs and consequently their impact on overall cost-effectiveness results"; (2) "Further assessment of the studies revealed a lack of consensus on the most appropriate instruments and approaches for measuring and valuing presenteeism"; (3) "…the exclusion of this cost category in economic evaluations is likely to result in biased societal decision making".

Table 3.2 Work productivity tools for estimating the productivity cost due the time lost by workers.

Name	Denomination	Country	Specific/General	AB	PR	CM	DY	UP	Frequency of use*
Health and Labor Questionnaire	HLQ	The Netherlands	G	x	x			x	+++
Health and Work Productivity Questionnaire	HPQ	USA	G	x	x				+
Health-Related Productivity Questionnaire Diary	HRPQ-D	USA	G	x	x			x	-
Productivity and Disease Questionnaire	PRODISQ	The Netherlands	G	x	x	x	x		-
Quantity and Quality Method	QQ	The Netherlands	G		x				-
Stanford Presenteeism Scale 13	SPS-13	USA	G	x	x				+++
Valuation of Lost Productivity Questionnaire	VOLP	Canada	G	x	x	x	x	x	-
Work Limitations Questionnaire	WLQ	USA	G		x				++
Work Productivity and Activity Impairment Questionnaire	WPAI	USA	G/S	x	x			x	+++++

Name	Denomination	Country	Specific/General	AB	PR	CM	DY	UP	Frequency of use*
Work Productivity Short Inventory	WPSI	USA	S	x	x				+
iMTA Productivity Cost Questionnaire	iPCQ	The Netherlands	G	x	x			x	-

Source: own elaboration with data from Tang, K (2015). AB=Absenteeism; PR=Presentisms; CM=compensation mechanisms; DY= Work-team dynamics contemplate along the instrument; UP=unpaid task included. * The frequency of use for each instrument is based on a scoping review up to April 2019 and the findings obtained by K. Tang in the review study published in Pharmacoeconomics journal. The most plus symbol indicates the most usage in the literature. A minus symbol indicate that there is only one reference where the instrument was described/applied.

3.1.1.2 Compensating mechanisms and multiplier effects

The estimation of labour losses in the two traditional approaches (human capital and friction costs methods) incurs several questionable elements. In addition to the starting discrepancies of both approaches, in the case of the human capital method, a linear translation of the reduction of available input (labour) to output, via the worker's marginal productivity, may be a consideration too restrictive. In the case of the friction cost method, the presence of compensatory mechanisms in the absence of short term is at the heart of the approach (Jacob-Tacken et al., 2005). However, it is not common to consider that the absence of a worker can cause losses above their marginal productivity considered individually, in form of a multiplier effect, in firms and entities where teamwork is common (Pauly et al., 2002; Nicholson et al., 2006).

Therefore, we could define the multiplier effect as the additional costs that result from the absence of a worker through the negative externalities that it causes in his work team. On the other hand, a compensating mechanism would be the adjustment in the loss of productivity that is smoothed or compensated postponing deadline tasks until the reincorporation of sick worker without economic consequences, by the performance of other workers or by a more intensive use of other available productive factors, provided that this involves a reduced or insignificant cost for the entity[7] .

While in the case of presenteeism, the debate is articulated in how to identify its presence and in the identification of the most appropriate measurement and assessment techniques, in the case of compensatory mechanisms and multiplier effects, the empirical evidence is much scarcer.

An interesting study is that of Jacob-Tacken et al (2005). They obtained data from 153 pharmaceutical company employees and 763 patients in paid employment with different health chronic problems (dyspepsia, psoriasis, chronic fatigue syndrome, low back pain and rheumatoid arthritis). Specific

[7] Note that, in case of using more productive resources such as overtime of other workers or a more intensive use of capital goods with an added cost, this compensatory mechanism would have a cost for the company or entity that could be as high or greater than the marginal productivity of the sick worker.

questionnaires were used to determine the percentage of responses that indicated compensating mechanisms implying productivity costs. The authors noted that "where respondents reported that their absence was compensated during normal hours (by colleagues) or was not compensated at all, we assumed that there were no productivity costs. This assumption enabled us to put a lower bound on the estimate of productivity costs. Where respondents reported that extra hours (either undertaken by colleagues or additional employees hired specifically to fill in) were required to compensate for their absence, we assumed that compensation led to productivity costs. Thus, productivity costs were only calculated where extra effort was necessary to compensate for the absence of an employee".

The results showed that for absences of just one day, productivity costs were relevant in only 17–19% of cases and for absences of two weeks or longer, productivity costs were relevant in 35–39% of cases. Authors employed an additional analysis to determine the agreement between employees and supervisors regarding compensating mechanisms. The percentage of concordance was high on whether compensation covers productivity costs in short term sick leaves. There was much less agreement on longer sick leaves and on specific compensating mechanisms. These results and conclusions are in line with previous articles of Severens et al (1998) and Brower et al. (2002).

Pauly et al. (2002) defined three necessary conditions for the consequences of work losses to be greater than the wage (for the multiplier effect): (i) the employer must be unable to find a replacement worker who is a perfect substitute (in terms of productivity) for the absent worker at the same compensation cost as the absent worker[8]; (ii) production must occur in a teamwork, that is, a production process where the input of any one member affects the productivity of other members and the output cannot be attributed to any single worker; (and iii) there must be "time sensitivity" to firm-level demand, in the sense that price or revenue will fall if part of the output is lost or postponed.

[8] If a manager can find a perfect substitute at the same wage, the cost of the leave would be the wage of the absent worker and the value of the multiplier would be equal to one.

Four years later, some authors of the previous article published an interesting paper adding empirical support to their theories (Nicholson et al., 2006). They used data from a survey of 800 managers in 12 industries, aiming to test the hypothesis that "the cost associated with missed work varies across jobs according to the ease with which a manager can find a perfect replacement for the absent worker, the extent to which the worker functions as part of a team, and the time sensitivity of the worker's output". Thus, they estimate wage multipliers for 35 different jobs. The median multiplier is 1.28, with a wide range depending on the type of job, ranging from the value 1 (absence of multiplier effect in fast food cook and waiter, restaurant and bar) and the value 4.47 (construction engineer) (results for 3-day cost of absence multiplier). In general terms, higher level of qualification is associated with higher multiplier values.

Krol et al. (2012) analysed, simultaneously, multiplier and compensation effects in a randomized trial of 187 Dutch citizens in the framework of a cost-effectiveness analysis of reimbursement for smoking cessation treatment. Productivity costs were calculated applying the friction cost approach. The authors showed that "over half of the respondents stated that their absenteeism was compensated during normal working hours by themselves or colleagues. Only counting productivity costs not compensated in regular working hours reduced the traditional estimate by 57%. Correcting for multiplier effects increased regular estimates by a quarter. Combining both impacts decreased traditional estimates by 29%". The authors concluded that a relevant part of lost production is compensated in normal hours.

Although this is a work of undoubted scientific merit, its results should be taken with caution. As the authors point out "… compensation mechanisms were based on self-reporting data among employees who had experienced the absenteeism themselves. In some cases, employers or colleagues may have better insight in how work was compensated during the employees' absenteeism". "…the multiplier effects applied were extracted from previous research (Nicholson et al., 2006). In half of the cases we needed to apply the median multiplier of 1.28 presented in the paper by Nicholson et al. (2006) because the professions of our respondents did not match the professions presented in their empirical

work. Moreover, the original multipliers were collected in the United States and therefore may not be directly transferable to the Dutch occupational situation".

In this sense, it is interesting to compare the results and conclusions of the previous study with those from Strömberg et al. (2017). The aim of this study was "to propose wage multipliers that can be used to estimate the costs of productivity loss for employers in economic evaluations, using detailed information from managers." The final study sample included a panel of 758 managers from different occupational sectors. Based on assumed scenarios of a period of absenteeism due to sickness, presenteeism and work environment–related problem episodes, and specified job characteristics, managers assessed their impact on group productivity and cost. The estimated mean wage multiplier was 1.97 for absenteeism, 1.70 for acute presenteeism, 1.54 for chronic presenteeism, and 1.72 for other problems related to the work environment. The authors concluded that the use of wages to value the cost of lost productivity resulting from absenteeism, presenteeism, and work environment–related problems underestimates the real costs for firms/entities from the employer's perspective

Therefore, although they are not directly comparable studies, it is possible to think that the point of view of the employers and the employees can condition the results of labour losses adjusted for compensatory effects and multipliers. Likewise, it seems that the quantitative effect of the compensating and multiplying mechanisms will differ depending on the occupation sector, the job position, specific characteristics of the firm or public entity, as well as other more general context elements of each country. Therefore, the estimation of these effects, as happened with the periods of friction, should be calculated for each job and specific situation.

In sum, in Krol et al (2012) words "…research indicates that both multiplier effects and compensation mechanisms are important to consider in the area of productivity cost research" "*How* to exactly consider compensation mechanisms and multiplier effects concurrently in future research remains uncertain."

3.1.1.3 Early retirement

The estimation of early retirement due to a disease poses a significant challenge in estimating labour productivity losses. Thus, it is very complicated, not to say outside the scope of the usual research, to identify a causal relationship between the presence of one or several diseases and the premature retirement of the labour market. Note also that the regulations of each country regarding social security can be very influential when studying this circumstance, since in some countries the labour transition from a health shock can lead to temporary or permanent sick leave while in others the probability of transitioning to an early retirement is greater (García-Gómez, 2011)

In the literature, the most common features identified are: (1) the presence of early retirement in estimating productivity losses is much lower than the presence of absenteeism or sick leave; (2) the estimations of premature retirements are made using the retirement age of the general population; (3) for the diseases where this phenomenon has been studied, the estimated losses are large.

For example, Cooksey et al. (2017) analyzed data of 570 participants in an ankylosing spondylitis cohort study. They estimated work productivity losses using the human capital approach. The cost components included early retirement, absenteeism, presenteeism and unpaid work by carers. For this purpose, the authors used the Work Limitation Questionnaire (WLQ) and the Work Productivity and Activity Impairment (WPAI). The retirement gap is defined as the difference in years between the usual age of retirement and the actual age at which the patients retired. They observed that, on average, these patients "retired 9.5 years earlier than the general population and 10.2 years earlier than the usual retirement age for their specific occupation". Early retirement was associated with functional impairment and lower quality of life.

Marcellusi et al (2016) carried out a probabilistic prevalence cost of illness model, based on a systematic review conducted to determine both the epidemiological and economic data, to calculate the economic burden associated with Diabetes Mellitus in Italy. The study considered direct medical costs and labour productivity losses (absenteeism and early retirement). The authors pointed out that "for the costs resulting from early retirement, an average gross income at retirement was used,

multiplied by the probability of early retirement of the diabetic population". This probability is based in a Danish study (Sorensen et al., 2009), in 17.38 %. Human capital method was used and early retirement costs were a substantial part of the total costs. The model estimated that the total expenditure for the treatment and care of diabetes mellitus (DM) amounted to €20,200 million. Approximately, 53 % of this total expenditure is due to labour productivity losses. Early retirement costs were estimated in €9,060 million.

Laires et al (2016) used "individual level data from the national, cross-sectional, population based EpiReumaPt study where 10,661 inhabitants were randomly surveyed in order to capture and characterize all cases of rheumatic diseases within a representative sample of the Portuguese population". Early retirement due to rare diseases (RD) was assessed through participants' self-reporting ('Did you retire due to RD?'). Then, the authors applied population attributable fractions (PAF) to adjusting the previous estimation ("PAF were calculated as the resulting proportional change in the probability of early retirement due to RD (using logistic multivariable models explaining retirement) after a counterfactual exercise where the presence of RD is artificially eliminated from the sample"). Human capital approach was used for the estimation of productivity costs. The main results showed that estimated annual productivity losses due to premature retirement attributed to RD was €910 million (€1625 per self-reported RD patient and €13,592 per early retiree due to RD). It was estimated a mean global cost of €117,502 per early retiree due to RD from each one's actual age of retirement until the 65 years official age of retirement. Once the PAF methodology was applied, labour productivity losses were reduced by approximately 16% (€761 million and €1359 per self-reported RD patient). The figures estimated represent approximately 0.5% of the national Portuguese gross domestic product (GDP) in 2013.

This figure is close to the Australian study that estimated that arthritis caused an annual estimated loss of approximately 0.7% of GDP due to early retirement. Such Australian study (Schofield et al., 2013) used a microsimulation model, Health& WealthMOD (Schofield et al., 2011), to analyse the impact that arthritis has on labour force participation, personal income and wealth, and government revenue and expenditure amongst Australians aged 45 to 64 years. The authors noted that "to estimate savings and income for each person to the age of 65 years, respondents were assumed to

continue earning at the same level, with an adjustment to increase earnings in line with long term average earnings growth rate less inflation (the real earnings growth rate)".

As can be seen, there is a high degree of heterogeneity in the different approaches used to estimate the labour losses associated with early retirement. Possibly, the difficulty in accessing good sources of information and the methodological difficulty inherent in associating an early retirement with a specific disease are starting elements to be considered. However, the lack of methodological consensus norms also explains the scarce presence of this cost item in cost of illness studies and in the economic evaluations of health care technologies. Finally, it should be noted that the studies identified used the human capital approach as the main method to valuate premature retirement costs, which is consistent with the studies reviewed in the previous sections.

3.1.1.4 Quality Adjusted Life Years (QALYs) instead of monetary valuation of time?

An alternative to be considered in the valuation of time is to renounce its estimation in monetary units and try to include the effects that illnesses and injuries cause over the habitual use of time in other types of units. This was the proposal of the US Panel on Cost-Effectiveness in Health in mid-1990's (Gold et al., 1996). Basically, the Panel warned of the risk of double counting that could involve considering the change in the use of time in the numerator of the cost effectiveness ratio, while, in the denominator, health measures based on preferences such as QALY could be collecting this same effect. As Krol et al. (2013) pointed out "they moreover indicated that respondents in health state valuations underlying QALY calculations would consider the effects on productivity and income when valuing health states, unless explicitly instructed otherwise. This implies that any additional monetary valuation of the impacts on productivity would be double-counting." The conclusion is that the effect of illnesses and injuries on productivity should be valued through a preference-based measure of health (as QALY is).

The Panel's proposal received criticism very soon (Brower el at., 1997; Johannesson and Meltzer, 1998). The problem is that it is not so clear that QALYs or other preferred based measure of health reflect the influence of work loss, and, thus, productivity, resulting in a double counting. In other

words, the Panel's proposal is a criticism of the monetary valuation of time that must be considered but whose validity must be demonstrated empirically.

There are not really many studies that have tried to answer the question of whether people, when assessing changes in health status, implicitly include changes in income derived from labour productivity losses or changes in leisure time. Tilling et al. (2010) reviewed seven studies published up to that time. These studies vary significantly in their design and implementation. The authors point out that the reviewed works do not allow to reach a clear conclusion. Although there is a non-negligible part of the participants in these studies who assess changes in income associated with changes in health status, being this proportion very variable among studies, this does not seem to affect the assessments they make of these health states.

A more recent study carried out by Shiroiwa et al. (2013) tried to determine the influence of income reduction on utility scores, obtaining utility scores of eight health states in a sample of 6,551 respondents with three instruction types: a) no instructions; b) instructed to consider income reduction; and c) instructed not to consider income reduction (compensated). Respondents were randomly sampled from the on-line panel and asked to evaluate 1 of 24 patterns by both standard gamble and time trade-off methods. They main results indicate that even without being instructed about income reduction, many respondents spontaneously assumed that income was lost. The percentage is higher when considering more severe health states. Compared with the ''no instruction'' scenario, utility scores did not change significantly in scenarios (b) and (c) in comparison with scenario (a). The differences in utility scores between scenario (a) and (c) were less than 0.05. The authors concluded that, according to these results, the impact of double counting is negligible.

In fact, the accumulated empirical literature, although not very abundant, is sufficient to question the proposal made by the Panel. Thus, in the recent update of its recommendations, the Second Panel on Cost-Effectiveness in Health and Medicine substantially modifies its recommendations on this point, thus remaining: "In a departure from the original panel, the Second Panel observes that, in general, effects on productivity are unlikely to have been captured by most preference-based measures, and

that evidence is not definitive that the effects of morbidity on leisure are necessarily reflected in the utility scores or quality-of-life weights." "Therefore, it is recommended that the productivity consequences related to changes in health status need to be reflected in the numerator of cost-effectiveness ratios for reference case analyses conducted under the societal perspective, while recognizing the possibility that the uncertainty about how productivity and the effects of morbidity on leisure activities are captured in preference-based measures could lead to double counting. Research recommendations are made to develop improved quality-of-life weights that would avoid such double counting" (Sanders et al., 2016).

3.2 Valuation of the non-remunerated time of the person affected by an illness or injury (the patient)

Although the analysis of informal care and the assessment of caregivers' time, both paid and unpaid, has gained greater interest in recent years in the field of economic evaluation of health interventions, it is striking the scant attention paid to the assessment of the time of unpaid care of patients (Krol et al., 2013).

Two categories of unpaid time can be distinguished: unpaid productive time, that is, time spent on unpaid labour such as household work, and leisure time. In the first case, the most usual assessment is made by defining a shadow price based on the cost of replacing unpaid work time with that of a professional houseworker. However, it would also be worth valuing unpaid work time based on its opportunity cost, which can be approximated by the value of leisure time.

This would lead us to consider the value of leisure time. Following the work by Posnett & Jan (1996), it would be possible to make an approximation to the value of leisure time in relation to its opportunity cost. In this sense, the value of leisure could be established based on the hourly wage that is waived to enjoy one more hour of leisure. However, to this initial approach, several nuances can be considered.

(i) If a person obtains some degree of pleasure (utility) from his/her work, the

opportunity cost of one hour less of leisure will be less than the wage received. More specifically, the value of one hour of leisure will be equal to the hourly wage minus the utility that a work hour reports to the individual.

(ii) If there is involuntary unemployment, as it is the case, in the majority if not in all of the countries, the value of leisure can diverge from the wage.

In this way:

a. If the person considered has a paid employment, the wage will be equal to the leisure value if the utility associated to the work is equal to zero. If the utility associated to the work is positive, the value of leisure time will be greater than the wage. If the utility associated with the work is negative, the value of leisure time will be less than the wage.

b. If the person considered is involuntary unemployed and if the utility associated to the work is equal to zero, the wage will be higher than the valuation of leisure time. If the utility associated with the work is positive, the leisure value can be higher or lower than the wage (depending on the intensity of the utility generated by the work). On the other hand, if the utility associated to the work is negative, the leisure value will be lower than the wage.

c. If the person is voluntary unemployed and if the utility associated to the work was equal to zero, the estimated wage (the one that would be earned in case of being employed) would be greater than the leisure time value. If the utility associated with the work was positive, the valuation of leisure time would be higher than the estimated wage. And, if the estimated utility associated to the work was negative, the value of the leisure time can be higher or lower than the wage that would be received (depending on the intensity of the disutility that the work would hypothetically generate).

Therefore, as it can be seen, although the wage received in the labour market is a first approximation to the assessment of leisure time, there are different situations that make estimating the opportunity cost of leisure a complex task. To the variations in the wages by age, gender, education, experience or innate abilities, we would add the difficulty of revealing the utility or disutility that the work generates in the person considered. A closer estimate to the true opportunity cost should also consider that (dis)utility is related to the type of work performed by an individual.

Thus, for the same person, a job can lead to a certain degree of usefulness while another different job can turn into disutility. Likewise, there are other elements of unobservable heterogeneity that complicate the use of salaries observed as reserve salaries for persons with similar observable characteristics. Actually, Posnett and Jan (1996), aware of the complexity of the effort, mentioned studies carried out in the field of transportation economics to indicate that the estimated leisure values tend to range between 25-75% of the salary received.

In any case, assuming that there are certain margins of error, this does not imply that we should give up trying to value unpaid time, given that it is a valuable input from the perspective of society. However, it also implies that greater efforts must be made to try to incorporate these elements in economic evaluations and that these efforts must also be transferred in order to achieve the greatest possible methodological clarity in order to make the studies comparable and reproducible.

The recommendations by Posnett and Jan (1996) are that the opportunity cost of unpaid time of those people with an employment should be estimated using the wage received, although it can be assumed that there may be deviations from the real value of time. In the case of unemployed people, the average wage of people with similar characteristics could be used as a proxy measure. Likewise, in the case of unpaid productive time such as domestic activities, the market wage of a household employee would be a reasonable proxy as a measure of the opportunity cost.

Another element that should be highlighted is the fact that techniques applied to value the remunerated time can be used to also value the non-remunerated time. In fact, Pike & Groose (2018) (quoting Tranmer et al., 2005) mention that “US analysts have generally included the imputed value

of household production by individuals of both sexes when valuing premature mortality. In contrast, researchers outside the USA often incorrectly equate the HCA with market production, i.e., paid work". On the other hand, "although the FCA does not explicitly consider the value of household production, the seminal FCA studies do suggest estimates of indirect costs should also estimate the imputed value of nonmarket production using data from time-use surveys and patient questionnaires". In fact, many of the studied included in the analysis of Pike & Groose (2018) included estimates of non-market production (majority reported as part of human capital approach estimations).

An interesting overview of the instruments available to measure lost unpaid labour was carried out by Krol and Brower (2015). After revising the references to valuation of unpaid work in 3 health economic textbooks and 28 health economic guidelines, the authors identified five instruments which include questions about unpaid labour: the Migraine Disability Assessment instrument (MIDAS); the Work Productivity and Activity Impairment (the WPAI_GH); the Health and labor Questionnaire (the HLQ); the Valuation of Lost productivity questionnaire (the VOLP); and the iMTA Productivity Cost Questionnaire (the iPCQ). Three of them are suitable for use in economic evaluations. According to the authors, "cost estimates of lost unpaid work based on the HLQ and the VOLP are likely to be lower than the estimates based on the iPCQ, since the former only value the replaced activities while the iPCQ values both replaced and nonreplaced unpaid productivity losses." The article is complemented with the review of the place of unpaid labour in applied economic evaluations in the area of rheumatoid arthritis. The authors conclude that textbooks and guidelines offer little guidance for estimating the value of unpaid labour.

A recently published work used contingent valuation techniques to estimate monetary values of unpaid work and leisure time in a sample of 316 citizens of the Netherlands (Verbooy et al., 2018). They estimated that the Willingness to Accept (WTA) values for trade-off of work and unpaid work and for trade-off of work and leisure time were €15.83 and €15.86 on average, respectively. The mean Willingness to Pay (WTP) values for leisure time vs. unpaid work was €9.37. The truncated values, that is, without considering the values equal to zero, refer us to WTA averages that amount to € 17.84 and € 17.46 and the value of the WTP goes up to € 11.01. In fact, an interesting result of the study is

that, as predicted by the theory, the responses of people who have a paid employment have higher values than those people without a paid employment. On the other hand, the difference between WTA and WTP for trade off work and leisure time was €7.74 on average (€13.88 for truncated values). Another interesting point is that "WTA and WTP values for unpaid work and leisure time observed in this study were quite similar to the value often linked to the value of unpaid work in evaluation studies: the wage of housekeeper, which was valued at approximately €14 in the Netherlands at the time of the study"

Finally, it should be mentioned that in the cited article of van Lier et al. (2018) (section 3.1), the panellist agreed that lost productivity costs due to absenteeism from unpaid labour should not be included in economic evaluations (27% agreement for the inclusion). The main argument not to include these costs was "the lack of standardized methods to value unpaid labour, leading to unreliable cost estimates and a risk of double counting. But, "However, in some populations this may be an important cost category (e.g. elderly people). Therefore, further research is needed to develop appropriate methods to validly assess costs due to decreased productivity in unpaid work."

4. Valuation of the time of the caregivers[9]

Informal care is a heterogeneous service, composed of various specific tasks of help, either to cover needs related to the basic activities of daily life (eating, drinking, grooming, dressing, ...) or instrumental activities (making food , shopping, visit to health care professional, perform domestic tasks,...) of a person with limited autonomy. Usually informal care is provided by one or more members of the social environment of the person who needs such care, mainly the couple or immediate family members.

Due to its nature, its definition and delimitation is not unequivocal, differing significantly between different authors, studies and countries and where cultural, historical and social elements that surround the study will be of great importance. Informal care implies absence of a regulated daily or weekly schedule or planned holidays. They do not usually receive any remuneration for their services although there can exist specific benefits, training and support programmes for carers in some countries. In sum, its most distinctive features are the non-professional character of caregiving and the affective relationship between the person being cared for and the caregiver(s).

Several different techniques are applied in the literature so that the value of informal care can be expressed in monetary terms and therefore, the cost related to informal caregiving could be included in the economic evaluations when societal perspective is considered (van den Berg et al., 2005; van den Berg et al., 2006).

Generally, the existing methods are divided into three different categories; revealed preference methods, stated preference methods and others. The difference between revealed and stated preference is mainly explained by the fact that the former uses responder's preferences for nonmarket goods while the first uses real-life decision data, that is, the preferences are taken from

[9] Although this report focuses on the assessment of the time of people affected by an illness or injury and the people who care for them, a very important aspect prior to the assessment of informal care time is its measurement. In Appendix 1 there are some notes on the most common techniques for measuring informal care time.

informal caregivers' decisions or from close substitutes in the market. Additionally, while revealed preference methods could mask individual differences in the value that caregivers give to their time and ignore the value of the relationship between both, stated preference methods try to estimate how much money the carers would need to be compensated to provide an additional hour of care in specific situations or how much money the carers would be willingness to pay to alleviate an hour of care in specific situation. Furthermore, another difference between these two groups is that stated preference methods consider income-compensated demand curves while the revealed one takes into account uncompensated demand curves (Van den Berg et al., 2004).

More precisely, within these three group we can distinguish different techniques. Thus, within revealed preference methods, we can find two different approaches; the proxy good and opportunity cost methods. Within stated preference methods, we have contingent valuation method and conjoint analysis. And within others, we can apply health-related quality of life and well-being (see table 1). In the following section, all these techniques are discussed into detail.

Table 4.1 Valuation methods for informal care

Revealed preference methods	Stated preference methods	Others
Proxy good method Opportunity cost method	Contingent valuation Conjoint analysis	Well-being Health-related quality of life

Source: own elaboration from Van den Berg et al., 2004.

4.1 Revealed preferences methods

4.1.1 Proxy good method

This is a revealed preference method which values caregiving time spent considering a close substitute at the labour market. In other words, this technique values the care provided taking into account how

much it would cost if informal caregivers would disappear and, consequently, they had to be replaced at the labour market by a close substitute. Thereby, the caregiving time is valued at the wage rate of such market substitute considered, assuming that informal care and professional care are perfect substitutes. However, this might not be the case as individuals may show a clear preference for one type of care (professional or informal), which is the one they finally choose. The reasons of the preferences include the price of professional care, the quality of the professional care, the availability of professional care (waiting lists), and a feeling of obligation to provide the care themselves. However, this market substitutive might vary depending on the tasks performed and valued. For instance, tasks related to housework are valued by a wage of a housekeeper. Likewise, personal care tasks such as helping to bathing, eating, clothing, etc., are valued by a wage of a nurse assistant professional, and finally, practical support tasks are usually distinguished.

In general, the use of such technique is highly applied because of its easiness. In fact, in more than 27% of the cost of illness studies apply such technique when evaluating informal care (Oliva-Moreno et al., 2017)[10]. However, it has several disadvantages that should be mentioned. Firstly, this technique assumes that informal care (the care provided by non-professionals) is a perfect substitute for formal care (care provided by professionals). That means that both types of care have the same quality and efficiency, and, consequently, it does not relate the value of care to the level of education or skills of the caregiver. Moreover, it does not take into account such (dis)utility generated by caregiving to both care`s recipient and caregiver, as both might (not enjoy) enjoy the care received or provided. Finally, it could be quite difficult to establish what is meant by normal household tasks and which tasks are performed as informal caregiving time foregone. Nevertheless, even though there is a consensus of how tasks should be valued when the proxy good method is applied, the heterogeneity of the shadow prices used in such techniques has been tested (Oliva-Moreno et al., 2017).

[10] See section 6- The inclusion of social costs in the applied economic evaluations: a review- for more information in the field of economic evaluation of health care interventions.

4.1.2 Opportunity cost method

This technique is also part of the revealed preference methods as it values the informal caregiving time provided taking into account the benefits forgone by the carer due to the tasks provided. On other words, this method values the best alternatives that caregivers had to resign in order to provide the care. In general, the sacrificed activities (that is, benefits forgone) include paid work time, unpaid work time (such as housekeeping or voluntary work), and leisure time. Thus, the shadow price applied in such technique depends on the type of forgone activity. For instance, for valuing paid work time, it is usually applied the gross hourly wage of the caregivers, except when the caregivers are not in the labour market because they are retired or are dedicated to housework tasks. In these cases, the sacrificed activities are only those related to unpaid work and leisure time. In these cases, the shadow price applied to value the unpaid and leisure time in the opportunity cost method is commonly the wage of a housekeeper for housework tasks and an adapted gross hourly wage for leisure time. Nevertheless, the heterogeneity and arbitrariness in its application is highly discussed in the literature.

An advantage of such technique is the fact that even though it is necessary to distinguish between paid, unpaid and leisure time, it is not required to distinguish between different informal care tasks (as occurs in the proxy good method explained above). However, the application of such technique leads to an issue that should be mentioned. The opportunity cost method values the time depending on the wage of caregivers, meaning that the value of informal care is related to the occupational position of the caregiver. In this sense, there is a great debate on whether it is appropriate that the time performed by highly educated caregivers worth more than the time performed by non-educated cares. Other aspect worth to mention is related to the time horizon, especially when the period of time is quite long, it may be difficult for caregivers to know the time sacrificed due to the caregiving provided. Moreover, as it happens with the proxy good method, informal caregiving leads to different utilities, due to differences in the valuation for the first and for the last hours or between different care tasks. Consequently, it is debatable whether such utilities should be incorporated in economic evaluations. Furthermore, opportunity cost is a technique which takes into account just the valuation of sacrificed activities instead of considering the full impact of caregiving on the caregivers (such as problems, burden, satisfaction, etc.). Then, as occurs in most of the techniques, it could be quite difficult to establish what normal household tasks are and which tasks are performed as informal

caregiving time foregone. In general, opportunity cost method is the most frequently used technique, applied in almost 60% of the cost of illness studies when evaluating informal care (Oliva-Moreno et al., 2017[11]).

4.2 Stated preferences methods

4.2.1 Contingent valuation

This technique is the most commonly used stated preference method. This approach consists in evaluating the time of caregiving taking into consideration the caregivers' well-being in a money metric, with compensation variation and equivalent variation, or what is the same, looking at the willingness to pay (WTP) and willingness to accept (WTA) for a hypothetical caregiving situation. In fact, WTP consists in estimating how much the responders are willing to pay at maximum in order to reduce one hour of caregiving. Likewise, WTA consists in estimating how much the responders are willing to accept (to be compensated) at minimum in order to increase in one extra hour of care. Both, WTP and WTA seems to be commonly used in evolution of informal care when stated preference method is applied. However, WTA technique and questions related to minimum compensation for a required additional hour of care appears to be a more appropriate approach in evaluating informal care since, in such field, it is the most common perspective asking for increasing caregiving and sacrificed time on other different activities (van Exel et al., 2006). The feasibility of such technique has been tested by van den Berg et al. (2005). When proposing an economic model of informal care, they consider the perspectives of informal caregivers and the patient in order to estimate the economic value of unpaid caregiving. Authors also tested that WTP depends positively on wealth and negatively on own health status, remaining ambiguous the effect that other`s health status has.

An important aspect to highlight is the fact that WTP and WTA can be highly different depending on the type of time considered (Verbooy et al., 2018). Thus, when applying these instruments in valuating

[11] See section 6- The inclusion of social costs in the applied economic evaluations: a review- for more information in the field of economic evaluation of health care interventions.

informal care, it should be considered whether the time spent by caregivers is paid work, unpaid work, leisure time or sleep time. Thereby, the average WTA value for an additional hour of unpaid work reaches 15.83€ (9.37€ WTP) while the WTA for an extra hour of leisure time is around 15.86€ (9.56€ for WTP), with influencing factors such as income, level of education, age and household composition considered.

Another useful complement way of valuating unpaid care through contingent valuation is by means of what is called "a well-being valuation method". This estimates the compensation of the variation needed to maintain the well-being (measured through a self-reported subjective happiness question) after caregivers increase an additional hour of caregiving (van den Berg and Ferrer-i-Carbonell, 2007). More precisely, the monetary valuation considers the income that allows individuals to maintain their original well-being after providing an additional hour of care, estimating the compensating variation. Thus, the conclusions proved that it is extremely important to distinguish whether or not the caregivers and the caregiver's recipient are relatives, as for those who are family members, the care causes a larger loss of utility on caregivers in comparison with those who are not, mainly explained by the emotional involvement when caring for a close relative. In this regard, the monetary value when applying the well-being valuations is around 7-10€/h, quite close to the market price of professional home care.

The application of such techniques does not lack of limitations. Firstly, the main bias found in such techniques are what is called protest zeros and strategic answering. Protest zeros are those situations in which the responders designate that their WTA (or WTP) for reducing (increasing) an hour of caregiving is zero euros, not because they reckon that the value of caregiving is equal to zero, but because they consider that the access to informal caregiving should not be conditioned by the payment capacity of individuals, and, consequently, care should be provided in any case. Strategic bias is that situation in which, under a contingent valuation method, the responders surveyed give a value far from what they really think (overestimating or underestimating consciously the value of the services), since they consider that their answer might influence the probability of access to caregiving. Secondly, another problem related to these methods is that economist do not often agree with the central axioms (revealed preference) as they propose that what should be considered is the real

behaviour (revealed preferences) instead of the intention of respondents (stated preferences). And, finally, the problem of double counting may be present in the application of such techniques, due to, unlike what happens with revealed preference methods, the caregivers might consider the health status of their relative when evaluating the time provided.

Regarding its value, the recent literature reveals that the WTA in the evaluation of informal care varies depending on the task performed (personal care and housework tasks) (Koopmanschap et al., 2008). Another interesting topic of research is the identification of differences or similarities in the assessment of the time of informal care between caregivers and people in care (Garrido-García et al., 2015). In case there were no deep differences, thus it would be feasible to derive a monetary valuation for informal care from the preferences of non-carers. However, research in this field is still incipient and it is too early to reach any solid conclusions. However, it can be pointed out from the accumulated research that caregivers' WTA seems to be sensitive to some factors like the real-life circumstances, such as health-related quality of life, income, gender, being housewife or house-husband and burden supported (measured though intensity of care).

4.2.2 Conjoint analysis

Conjoint analysis (CA) or Choice experiments is a stated preference method, which sets multi-attribute alternatives, and value an hour of caregiving in an indirect manner. More precisely, responders are required to rate different hypothetical informal care situations (called vignettes), with different characteristics (called attributes) to reveal their preferences. In this sense, through ranking, rating, discrete choice or best-worst scaling the attributes (such as an hourly wage rate received form informal care or a certain tax refund from Government for caring), it is possible to obtain a monetary valuation (Koopmanschap et al., 2008).

A common hypothetical scenario in the field of informal care is rating different scenarios considering three different attributes: type of informal care task, number of caregiving hours and monetary

compensation per hour worked (van den Berg et al., 2005). The main justification that it is used to apply this technique is the fact that the costs that should be incorporated in economic evaluations are marginal instead of average ones. Therefore, the marginal costs of switching, for instance, from providing 7 hours of care per week to 8 hours are 8€, while the marginal costs of switching from providing 7 hours of care per week to 9 are 18€. Moreover, informal care needs extra compensation of 13.43€ per hour to switch from housework tasks to personal ones.

In general, CA enables to capture the informal caregivers' preferences in an accurate way, due to the heterogeneous commodity of informal caregiving (van den Berg et al., 2008). In this way, van den Berg et al. (2008) designed a questionnaire in which caregivers rated (being "10" the best imaginable and "1" the worst imaginable scenario) four different hypothetical informal caregiving situations which entails different combinations of care hours, care task and monetary compensation. Thus, caregivers had to compare their own informal care situations with the four hypothetical situations and the ratings were associated with factors related to caregivers' own real-life situation, such as subjective burden, caring for a person who is waiting for professional care and whether or not the carers and carers' recipient live together.

In general, CA has several advantages in comparison with the other methods aforementioned. Firstly, caregivers are not directly asked to provide the amount of money that they are willing to pay (or accept) as it entails a trade-off between different scenarios related to care. In fact, information related to both caregivers' preferences and caregivers' recipient preferences are collected (van den Berg et al., 2005). Secondly, caregivers evaluate different scenarios and it captures in a more accurate way the heterogeneity of the nature commodity of informal care. However, one problem derived from the application of such technique might be considering several attributes simultaneously as it is possible to obtain the preferences of responders for more than one potential scenario. And, as previously mentioned, double counting can be also present as responders may take into account the preferences of the care recipient. However, in this sense some authors recently have tried to partially amended this issue estimating, thought discrete choice technique, the willingness to accept values for an hour of informal caregiving taking into consideration positive (such as fulfilment from caring and receiving support) and negative impacts of caregiving (such as mental, health and financial problems suffer by

carers). Thus, they estimated a WTA for an additional hour of caring of 14.57€, allowing the inclusion of a broader spillover-effects of informal caregiving without the risk of double-counting (Hoefman et al., 2018).

4.3 Others (value in non-monetary terms)

Apart from the previous techniques, there are other different methods to measure the impact of informal care in non-monetary terms. As previously mentioned, provision of informal care might lead to support heavy burden in terms of mental, physical or professional problems on the caregiver as well as a higher mortality risk (Koopmanchschap et al., 2008). Therefore, it could be quite relevant to incorporate the effect of an intervention on the health status of caregivers in economic evaluations. In this sense, such effect can be measured through both health-related quality of life (HRQoL) or though well-being of the caregivers.

A way to value HRQoL, and therefore, to incorporate in economic evaluations is though quality-adjusted life years (QALYs) by the use of EQ-5D, SF-6D and HUI3, as they are the measures more commonly used in cost-effectiveness/cost-utility analyses (CEA/CUA). Regarding well-being, apart from the monetary techniques mentioned above (contingent valuation and conjoint analysis), there are other ways to measure overall well-being directly, thought self-reported well-being questions or thought the CarerQol instrument. In both cases, a complete monetary valuation of informal care, that is, all the costs and benefits derived from caregiving, is captured. Once the health effect is measured through this way, both HRQoL and well-being can be translated, changing from nonmonetary outcomes to money outcomes so that they can be included in CEA/CUA (Lachaine et al., 2003; Brower et al., 2006). However, the problem comes when the changes in HRQoL of the caregivers have to be combined with the changes in HRQoL of the care's recipient.

Another issue to be considered in this field is the causality, that is, whether the strain of informal care leads to an effect in HRQoL or well-being, or contrary, it is a poorer HRQoL/well-being what results

from becoming a caregiver. That aspect should be taken into account within the use of longitudinal database as well as controlled trials.

4.4. Main differences across techniques

As it has been described above, there are different techniques in order to estimate the value of informal caregiving. Although all of them have the same goal (accounting the care provided by family, and therefore, incorporating it in economic evaluations), the methodological aspects as well as the ways in which time is measured by each approach heavily differ (see table 4.2).

In brief, even though the applications of the different techniques to value informal care are well-known, it has been proved that there is no consensus on how costs associated with informal caregiving should be included in economic evaluations (Goodrich et al., 2012). In fact, the heterogeneity in the application of these methods, not only for costs but also for outcomes, causes unpredictable impacts which might change the conclusions and recommendations about whether or not the intervention should be funded. In fact, the evidence shows that the monetary value associated to informal care varies significantly depending on the technique used. Thereby, the annual average cost of per informal caregiver in Spain could reach 50,158€ using proxy good method, to 23,064€ estimating the WTA, and 24,114€ applying opportunity cost (Oliva-Moreno et al., 2015).

Regarding WTP and WTA, although both techniques are part of the same method (contingent valuation), there are differences in the value of them when estimating the cost of informal care, being 8.60€/h for WTP and 10.52€/ for WTA (Van den Berg et al., 2005). These figures differ from those obtained using well-being valuation method, in which the unit cost to value caregiving reaches 9.31€ (van den Berg and Ferrer-i-Carbonell, 2007), and 12.36€ considering a conjoint analysis technique (van den Berg et al., 2008). Furthermore, the well-being valuation entails lower monetary values in comparison with opportunity cost methods or even with proxy ones (van den Berg & Ferrer-i-Carbonell, 2007). Concretely, applying the same sample, while opportunity cost technique reports a value ranging from 17.34€/h to 10.64€/h, using well-being technique these figures reach 7-10€/h and

13.51-12.19€/h with proxy good. These results show that potential benefits ignored in the market are more important than the potential ignored costs.

Table 4.2. Information needed to estimate monetary valuation of informal care

Technique	Measurement of time	Hour of caregiving valuation
Proxy 53age method	Household activities	Tariff market substitute household
	Personal care activities	Tariff market substitute nurse
	Practical support activities	Tariff market substitute
Opportunity cost method	Paid work	Gross personal income caregiver
	Unpaid work	Housekeeper wage
	Leisure time	Adapted gross wage
Contingent valuation	WTP/WTA	Hypothetical experiments
Conjoint analysis	Informal care	Hypothetical experiments
Others (no monetary valuation)	HRQoL caregiver	Tariff to calculate QALY
	Well-being caregiver	CarerQol

Source: own elaboration from adapted Hoefman et al., 2013.

Thus, while methods such as well-being valuation, contingent valuation or conjoint analysis take into account all the costs and benefits of providing informal care, proxy good method and opportunity cost do not, creating great differences in the monetary value of careering, depending on the method used. These differences can partially be explained by the fact that informal care may derive in a positive utility (Van den Berg and Ferrer-i-Carbonell, 2007), and this fact is reflected only when contingent

valuation as well as conjoint analysis and well-being methods are applied. Therefore, so that costs associated with informal care could be incorporated in economic evaluations in an appropriate way, as suggested in the literature (Goodrich et al., 2012; Krol et al., 2015), it might be convenient to combine different valuation methods. Thereby, complementing the opportunity cost or proxy good method with HRQoL or well-being measurement may achieve a wider about the real effect of informal caregiving (Van den Berg et al., 2004).

5. The inclusion of social costs in the methodological guides of economic evaluation of different countries

As it has been highlighted, all relevant costs and benefits derived from health care technologies should be considered when economic evaluations of interventions are performed (Goodrich et al., 2012). Although some authors defend that to ignore the social perspective could bias health policies, as costs falling outside the healthcare budget would be disregarded (Johannesson et al., 2009), there seems not to be an agreement across general guidelines on which and how perspective should be applied in economic evaluations.

Already at an early date, a review of national economic evaluation (EE) guidelines by Hjelmgren et al. (2001), identified a lack of consensus on the key aspects of EE, such as the choice of the perspective of the analysis, and costs that should be included in the analysis. Similarly, a review by Jacobs et al (2005) reported large variation among national guidelines in recommendations on costing and valuation. Knies et al. (2010) focused on recommendations in different countries on the study perspective and methods for valuing lost productivity and revealed ongoing differences regarding the inclusion of the societal perspective and, among guidelines advocating this perspective, how to value loss of productivity.

Furthermore, the study by Bracco and Krol (2013) reviewed EE in European submission guidelines and showed a large variation among these guidelines in terms of recommendations regarding costs to be included and methods related to cost calculations. A similar study conducted by the EUnetHTA Joint Action et al. (2016) compared existing methodological guidelines for the EE in countries that have organizations involved in the EUnetHTA project. The study revealed that these guidelines varied extensively in terms of recommendations regarding the choice of the perspective of the analysis. Van Lier et al. (2018) reviewed differences between country-specific guidelines for EE. The study provides consensus-based cross-European recommendations on how to measure and value resource use and lost productivity in EE. More recently, Zhao et al. (2018) reviewed similarities and differences of

pharmacoeconomic guidelines and the issues that varied most in the guidelines were the recommended costs to be included and methods related to indirect cost calculations.

This section presents a comparison of EE guidelines on social costs. By analysing similarities and differences among a total of 27 EE guidelines included, we identified their individual characteristics to provide a way for researchers and experts in the EE to access the present methodological development of the EE in social costs. Methodological issues that substantially varied among the guidelines were mainly those that presented controversy or no consensus regarding an appropriate method. The section is intended to provide a preliminary understanding of these issues, and to enable EE specialists to focus more on them to contribute to the next phase of EE guideline development.

We have conducted a comprehensive overview and comparison of EE guidelines on social costs. The objective of this section was to update and add to previous similar research. We examined differences and similarities among guidelines to highlight the current state of EE guidelines on social costs, as well as methodological issues that are still contested or developed. By conducting this analysis, we hope to contribute to the further development of EE guidelines on social costs.

Relevant guidelines were obtained by performing a literature search in Medline (PubMed) up to March, 2019. Additionally, the websites of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), the primarily ISPOR's 'Pharmacoeconomic Guidelines database was searched.

Information from guidelines was summarized into Table 5.1. The guidelines' content was tabulated on the following topics: the type of economic evaluation, the perspective of the analysis, information on the direct and non-direct/social costs, if any, included in the economic evaluation and which method should be used for the quantification of social costs.

Table 5.1. Overview of country-specific recommendations regarding type of economic evaluation, perspective of the analysis, identification of costs (direct and productivity losses) and methods for calculating productivity costs

Country	Year	Type of economic evaluation	Perspective of the analysis	Direct costs	Productivity losses	Methods for cost valuation	Reference
Australia	2016	CUA is recommended	Health care payer and a supplementary analysis can be provided using a broader societal perspective	Health care resource costs including those incurred by the patient, and the public or private health care provider	Supplementary analyses in society's production may be appropriate	Opportunity costs. HCA is preferred	Pharmaceutical Benefits Advisory Committee (PBAC). Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (version 5.0). Australian Government – Department of Health 2016.
Austria	2006	CEA, CUA, CMA; Choice must be justified	Apart from the societal perspective, other perspectives (e.g. health care system, social	Direct costs include direct medical and direct non-medical costs	Productivity losses resulting from illness and premature death.	Opportunity costs. HCA preferred; use of FCA must be justified	Walter E, Zehetmayr S. Guidelines zur gesundheitso¨konomisce n Evaluation Konsenspapier [Guidelines for health-economic evaluations in

Country	Year	Type of economic evaluation	Perspective of the analysis	Direct costs	Productivity losses	Methods for cost valuation	Reference
			insurance, ...) are possible				Austria]. Wien. Med. Wochenschr. 156(23–24), 628–632 (2006).
Baltic States (Estonia, Latvia, Lithuania)	2002	CEA, CUA, CMA; Choice must be justified	Mainly health care payer perspective. If relevant, societal	All direct costs inside Healthcare system. Nonmedical costs; e.g., social services, patient travel, other costs to the patient or family	Indirect costs should be reported separately	Methods for calculating productivity costs not specified	Behmane, D., Lambot, K., Irs, A., Steikunas, N.: Baltic guideline for economic evaluation of pharmaceuticals (pharmacoeconomic analysis) (2002). https://www.ispor.org/PEguidelines/source/Baltic-PE-guideline.pdf
Belgium	2015	CEA, CUA; Choice must be justified	Health care payer (government + patients). Societal may reported as a separate analysis	Direct healthcare costs. Nonmedical costs may be presented separately if considered important	Productivity losses and indirect healthcare costs may be presented in a separate analysis	Opportunity costs. HCA and FCA must be justified	Cleemput I, Neyt M, Van de Sande S, Thiry N. Belgian guidelines for economic evaluations and budget impact analyses: second edition. December 2015

Country	Year	Type of economic evaluation	Perspective of the analysis	Direct costs	Productivity losses	Methods for cost valuation	Reference
Canada	2017	CEA, CUA; choice must be justified	The perspective should be that of the publicly funded health care payer. Societal perspective if it is in the interest of the decision-makers	All direct healthcare costs, based on the perspective of the publicly funded health care payer	When a broader societal perspective is of interest to the decision-maker, the impact of the intervention on time lost from paid and unpaid work by both patients and informal caregivers as a result of illness	Opportunity costs. FCA is recommended	Guidelines for the economic evaluation of health technologies: Canada. 4th ed. Ottawa: CADTH; 2017 Mar.
Czech Republic	2017	CEA, CUA, CMA; choice must be justified	Health care payers perspective	All relevant direct costs covered from health insurance firms perspective (medical and non-medical) to the disease should be identified			Cost-effectiveness Guidelines. State Institute for Drug Control (May 2017) (http://www.sukl.eu/)

Country	Year	Type of economic evaluation	Perspective of the analysis	Direct costs	Productivity losses	Methods for cost valuation	Reference
Croatia	2011	CEA, CUA; choice must be justified	Public payer. Societal perspective may be presented in addition	Direct cost relevant to Croatian Institute for Health Insurance	Where measurable and relevant, indirect costs and cost falling outside of Croatian Institute for Health Insurance should be reported separately	Methods for calculating productivity costs are not specified	Agency for Quality and Accreditation in Health Care, Department for Development, Research and Health Technology Assessment: The Croatian guideline for health technology assessment process and reporting. Agency for Quality and Accreditation in Health Care, Zagreb (2011)
Denmark	2008	CEA, CUA, CMA, CBA; choice must be justified	Societal perspective is recommended	All relevant cost: direct, indirect and intangible	Report costs due to production loss separately	Opportunity costs. HCA is recommended over FCA	Kristensen, F.B., Sigmund, H. (eds.): Health technology assessment handbook Copenhagen: Danish Centre for Health Technology Assessment. National Board of Health. 2008

Country	Year	Type of economic evaluation	Perspective of the analysis	Direct costs	Productivity losses	Methods for cost valuation	Reference
England & Wales	2013	CUA	The perspective adopted should be the NHS and personal and social services (PSS)	Costs should relate to resources that are under the control of the NHS and PSS		Opportunity costs.	National Institute for Health and Care Excellence: Guide to the methods of technology appraisal 2013 (2013)
Finland	2017	CEA, CUA, CMA, CBA; choice must be justified	Primarily payer's perspective. If relevant, societal	Irrespective of the payer, all direct health care and comparable social welfare costs	If productivity losses are included in the cost calculation, the results must also be presented	Methods for calculating productivity costs are not specified	Lääkkeiden Hintalautakunta Läkemedelsprisnämden: Preparing a health economic evaluation to be attached to the application for reimbursement status and wholesale price for a medicinal product. Ministry of Social Affairs and Health, Pharmaceuticals Pricing Board. 2017.

Country	Year	Type of economic evaluation	Perspective of the analysis	Direct costs	Productivity losses	Methods for cost valuation	Reference
France	2012	CEA, CUA, CBA, CMA, CCA; choice must be justified	Societal perspective.	Direct medical and nonmedical costs attributable to the disease	Production, productivity and human life losses	Opportunity costs. HCA and FCA	Haute Autorité de Santé: Choices in methods for economic evaluation. Haute Autorité de Santé, Saint-Denis La Plaine (2012)
Germany	2009	CEA, CUA, CBA; choice must be justified	The primary perspective will be the health care payer. Optional perspectives can be social security or societal perspectives	Direct medical costs of resources reimbursed by the SHI or patient copayments. Direct non-medical costs (e.g., transport costs, home help) should be included if pertinent	Loss of productivity due to incapacity for work on the cost side as indirect costs	Opportunity costs. Primarily use HCA, but FCA may also be used	Institute for Quality and Efficiency in Health Care: General methods for the assessment of the relation of benefits to costs. Institute for Quality and Efficiency in Health Care, Cologne (2009)
Hungary	2017	CEA, CUA, CMA, CCA, CBA; choice must be justified	Payer's perspective is recommended in most cases, that can be supplemented	It is recommended to take direct healthcare costs and direct non-healthcare costs into	Calculate productivity costs as gross average salary for working aged patients in	HCA	Professional healthcare guideline on the methodology of health technology assessment. National Institute of

Country	Year	Type of economic evaluation	Perspective of the analysis	Direct costs	Productivity losses	Methods for cost valuation	Reference
			with an analysis conducted from societal perspective	account in cost calculations	base-case analysis.		Pharmacy and Nutrition Volume 67, Issue 1, 2017
Ireland	2018	CUA/CEA/CMA Choice must be justified	The perspective should be the publicly-funded health and social care system. Inclusion of societal perspective must be clearly justified	For the reference case, only direct costs relevant to the publicly-funded health and social care system should be included	May include productivity costs, as well as additional costs that may accrue to other public sector agencies, patients or caregivers	Opportunity costs. Methods for calculating productivity costs are not specified	Guidelines for the Economic Evaluation of Health Technologies in Ireland. 2018
Italy	2001	CEA and CUA	Societal and NHS perspective	Direct medical and nonmedical costs. Unpaid services provided by family members and volunteers	Productivity costs.	Opportunity costs. HCA is recommended	Capri, S., Ceci, A., Terranova, L., Merlo, F., Mantovani, L.: Guidelines for economic evaluations in 63aged: ecommendations from the Italian group of

Country	Year	Type of economic evaluation	Perspective of the analysis	Direct costs	Productivity losses	Methods for cost valuation	Reference
							pharmacoeconomic studies. Drug Inf. J. **35**, 189–201 (2001)
The Netherlands	2016	CUA	Societal perspective	All costs in the healthcare system, patient/family, and other sectors	Productivity losses	Opportunity costs. FCA	Zorginstituut Nederland (ZIN). Guideline for economic evaluations in healthcare | 16 juni 2016
Norway	2012	CUA, CEA, CMA, CBA; Choice must be justified	Societal perspective	Direct costs within and outside the healthcare system, regardless of who pays them	Loss in production	Opportunity costs. HCA and FCA are both acceptable, but choice must be justified	Norwegian Medicines Agency: Guidelines on how to conduct pharmacoeconomic analyses. Norwegian Medicines Agency, Oslo (2012)
Poland	2009	CEA, CUA, CMA; Choice must be justified	Healthcare payer perspective primarily.	Direct medical and nonmedical costs	Loss of productivity caused by illness or	HCA is recommended	Agency for Health Technology Assessment: Guidelines for Conducting health technology assessment (HTA).

Country	Year	Type of economic evaluation	Perspective of the analysis	Direct costs	Productivity losses	Methods for cost valuation	Reference
			Societal perspective must be justified		premature death.		Agency for Health Technology Assessment, Warsaw (2009)
Portugal	1998	CEA, CUA, CMA, CBA; Choice must be justified	Societal perspective	Costs of healthcare provided as a result of the treatment and its consequences, nonmedical expenses, informal nursing and other services	The only indirect costs included should be for employees' lost productivity	Opportunity costs. HCA	Da Silva, E.A., Pinto, C.G., Sampaio, C., Pereira, J.A., Drummond, M., Trindade, R.: Guidelines for economic drug evaluation studies. INFARMED 18, 728–729 (1998)
Russian Federation	2016	CEA, CUA, CMA; Choice must be justified	Healthcare payer and societal perspectives	All direct expenses of the healthcare system and direct nonmedical costs	Loss of productivity	Methods for calculating productivity costs are not specified	Guidelines for conducting a comparative clinical and economic evaluation of drugs (2016); Guidelines for assessing the budget impact in the framework of the Programm of the State Guarantee of Free Medical Care in the

Country	Year	Type of economic evaluation	Perspective of the analysis	Direct costs	Productivity losses	Methods for cost valuation	Reference
							Russian Federation (2016)
Scotland	2017	CUA, CEA, CMA; Choice must be justified	The perspective adopted should be the NHS and social work	Costs of resources under the control of the NHS in Scotland and social work			Guidance to manufacturers for completion of New Product Assessment Form (NPAF). Glasgow, Scotland: Scottish Medicines Consortium (2017).
Slovak Republic	2009	CEA, CUA, CMA; Choice must be justified	Societal and healthcare payer perspective	Direct medical and nonmedical costs	Loss of productivity	HCA	Metodicka´ pomoˆcka k vyhla´sˇke Ministerstva zdravotnı´ctva Slovenskej republiky e`. 343/ 2008 Z. z. o podrobnostiach farmakoekonomicke´ho rozboru lieku [Guideline to the Decree of the Ministry of Health of the Slovak Republic no. 343/2008 Z. z.: the details of pharmacoeconomic

Country	Year	Type of economic evaluation	Perspective of the analysis	Direct costs	Productivity losses	Methods for cost valuation	Reference
							analysis of drugs]. Ministerstvo zdravotnı´ctva Slovenskej republiky [Slovak Republic Ministry of Health] (2009).
Slovenia	2013	CEA, CUA, CMA; Choice must be justified	Health insurance and societal perspectives	Direct health costs for all future years			Rules on Classification of Medicines on the List, accepted by the Health Insurance Institute of Slovenia on April 26, 2013.
Spain	2010	CEA, CUA, CMA, CBA; Choice must be justified	Societal perspective; Healthcare payer is recommended as complementary	Direct medical and nonmedical costs	Distinguish between labor losses, time loss, and informal care to avoid double-counting such costs	Opportunity costs, replacement costs or declared preference for informal care costs are acceptable.	López-Bastida, J., Oliva, J., Antoñanzas, F., García-Altés, A., Gisbert, R., Mar, J., et al.: Spanish recommendations on economic evaluation of health technologies. Eur. J. Heal Econ. 11, 513–520 (2010)

Country	Year	Type of economic evaluation	Perspective of the analysis	Direct costs	Productivity losses	Methods for cost valuation	Reference
						HCA and FCA are both acceptable	
Sweden	2017	CEA, CUA, CMA CBA; Choice must be justified	Societal perspective	All relevant costs associated to the treatment and illness should be identified, quantified and evaluated	Production loss	HCA	Ändring i Tandvårds- och läkemedelsförmånsverkets allmänna råd (TLVAR 2003:2) om ekonomiska utvärderingar (2017)
Switzerland	2011	CEA, CUA, CMA, CBA; Choice must be justified	Societal and health service perspective	Direct medical and nonmedical costs	Loss of productivity	Methods for calculating productivity costs are not specified	Document Operationalisierung der Begriffe Wirksamkeit, Zweckmässigkeit und Wirtschaftlichkeit; Arbeitspapier vom 21. Juli 2011 21. Juli 2011
USA	2016	CEA and CUA	Payer perspective	Healthcare, social care			AMCP Format Executive Committee members. The AMCP Format for Formulary Submissions (Version 4.0, April 2016).

Country	Year	Type of economic evaluation	Perspective of the analysis	Direct costs	Productivity losses	Methods for cost valuation	Reference
							http://www.amcp.org/FormatV4/.

Source: Own elaboration. CUA = Cost utility analysis, CEA = Cost effectiveness analysis, CMA = Cost minimisation analysis, CBA = Cost benefit analysis, CCA = Cost consequences analysis. HCA = Human capital approach, FCA = Friction cost approach

Despite some EE guidelines recommended a healthcare payer perspective (see Table 5.1), most of them also accepted the inclusion of a societal perspective as an additional analysis. Generally speaking, current national EE guidelines identified similar resources to include in direct costs: primarily direct medical and nonmedical costs arising as a result of the proposed treatment and its consequences, though there was less consensus on how to value productivity losses. Guidelines that requested the societal perspective universally included productivity losses but varied in how specific they were regarding inclusion of both absenteeism and decreased productivity while at work, or economic losses due to premature death.

According to our results, various countries all over Europe, Australia, Canada and USA produced numerous EE guidelines. Some of these were updated every few years such as the guidelines of Australia, Belgium, Canada, Czech Republic, Finland, Hungary, Ireland, The Netherlands, Scotland, Sweden, and the United States of America. However, some guidelines have never been updated since they were produced such as the guideline of Portugal. Therefore, EE guidelines should be reviewed periodically to ensure that they keep pace with methodological developments and changing environments. Many countries produced compulsory EE guidelines for use prior to reimbursement submissions. However, some guidelines remain voluntary.

The choice of the perspective is vital, because it provides a basis for the measurement of costs. Although the societal perspective was often recommended in the literature since it is comparatively ideal in theory (because it takes all relevant consequences into account at a broader scope). Table 5.2 shows that, although the healthcare payer/provider was the perspective most commonly recommended in 8 out of the 27 economic evaluation guidelines included in our review, 6 guidelines recommended the application of a societal perspective. Even though a societal perspective is the ideal in theory because it takes all relevant costs into account at a broader scope, it is very difficult to implement. In addition, we found 5 guidelines recommending both the societal and health care perspective and 8 guidelines recommended a main perspective but considered the inclusion of other perspectives. For example, Spain recommended the application of the societal perspective, although accepted the healthcare perspective as complementary. On the contrary, in Finland, the main

perspective was the one from the healthcare payer, but admitted the use of a societal perspective, if relevant.

There remained little agreement on methods for valuing productivity losses, indicating no movement towards standardization since the guideline versions reviewed by Knies et al. (2010). Bracco et al. (2013) suggested that the reason behind the lack of consensus on which perspective to be applied might be that the target audience of formalized guidelines more likely cared about costs that they must bear than those falling outside their responsibility. Although recommended costs to be included depend on the choice of the perspective, some remarkable differences exist among the guidelines. Several guidelines did not detail which costs should be included, instead briefly describing all relevant costs related to the perspective. Even in those guidelines that recommended the same perspective, the included costs differed. For example, from the societal perspective, some guidelines recommended direct medical and nonmedical costs as well as productivity losses, while others stated that direct costs and productivity losses should be included without specifying more details.

In addition, Bracco et al. (2013) indicated that there is little agreement on the methods for lost productivity evaluation. We agree with their conclusion, as our results showed that the measurement of lost productivity basically involves two methods: the HCA and FCA methods. Ten guidelines recommended the HCA and 5 guidelines recommended both HCA and FCA, as Table 5.2 shows. Some guidelines did not recommend FCA because they considered them to be challenging for data collection, due to requiring far more empirical work before they can be applied. In general, both methods have flaws as discussed in the previous section and can only be used to evaluate lost productivity of paid labour. For unpaid work or leisure time, limited guidelines exist. From a health care perspective, some guidelines only included direct health care costs, while some mentioned additional costs.

Table 5.2. Summary of the country-specific recommendations regarding economic evaluations' perspective and methods from the 27 guidelines identified

	N	%
Perspective		
Healthcare payer / provider	8	29.63%
Societal	6	22.22%
Both	5	18.52%
Supplementary analysis to include any additional perspective	8	29.63%
Costs to be included		
Only direct healthcare costs	10	37.04%
Direct healthcare costs and indirect costs	14	51.85%
Inclusion of indirect costs should be justified or included only if relevant	3	11.11%
Specific recommendation to include productivity losses	20	74.07%
*Method to value productivity losses**		
Human capital approach	10	58.82%
Friction cost approach	2	11.76%
Both methods	5	29.41%

* The percentage for the method to value productivity losses is calculated over the 17 EE guidelines that do mention to include productivity losses (14 direct healthcare costs and indirect costs + 3 inclusion of social costs justified or if relevant)

6. The inclusion of social costs in applied economic evaluations: a review

To illustrate the practical application of time evaluation in economic evaluations of health interventions, we have performed a review focusing two research questions: i) To what extent social costs are included in economic evaluations and ii) How are productivity losses and informal care costs valued in economic evaluations? In order to do this, a systematic review of economic evaluations of certain diseases (Alzheimer´s disease and stroke due to their great burden on patients (Feigin et al., 2017; Collaborators GD, 2019); diabetes mellitus, due to its high prevalence (WHO, 2016); and rare diseases as, despite being much less prevalent, they pose a great burden on the society (Angelis et al., 2015)) was carried out for the period 2000-2018.

6.1 Methods

A review of published full economic evaluations was conducted to explore how social costs were included in economic evaluations, if they were, under the following inclusion criteria: (1) being an original economic evaluation of any technology or intervention related to any of the diseases listed in the previous section; (2) incorporated costs related to productivity losses or informal care costs or both; (3) health outcomes should include, at least, Quality-Adjusted Life Years (QALYs); (4) healthcare provider and societal perspective results should be provided separately; and (5) were written in English.

6.1.1 Search strategy

We performed several systematic reviews, one for each disease or group of diseases in case of Rare Diseases, of economic evaluations including social costs, using two different literature databases: Medline (PubMed) and the Cost-Effectiveness Analysis (CEA) Registry from the TUFTS Medical Center. In case of the Medline search, the following terms were used: (“Costs and Cost Analysis” OR “cost-effectiveness” OR “cost-utility” OR “cost-benefit” OR “economic evaluation” OR “economic analysis” OR “QALY” OR “quality-adjusted life years”) AND (the specific disease for each performed search). We used both formal keywords (MeSH terms) and natural keywords in tittle or abstract. We only kept those economic evaluations in which QALYs were measured at least as they are the standard

outcomes that make easier the comparison between EE. In case of Alzheimer Disease, the following terms were used: “Alzheimer Disease”, “Alzheimer´s Disease” or “dementia”. When using the last term, only those papers that specifically stated that most of the subjects had Alzheimer or that used data from Alzheimer´s Disease Organizations or datasets were included. A similar approach was followed for stroke, using the terms “stroke” or “cerebrovascular disease” but, in case of the latter, including only the economic evaluations that specifically showed that most of the patients had stroke. In rare disease review we used the indications for the active substances considered as orphan drugs by the European Medicines Agency. In some cases when the active substance had more than one indication, we reviewed the disease along the Orphanet database, available elsewhere. On the other hand, the CEA Registry contains more than 7,200 cost-utility analyses on a wide range of diseases published from the late 1970s onwards. All references are fully reviewed by two reviewers and only papers that contain an original economic evaluation with the health effects being measured in terms of QALYs are included in the registry (Thorat et al., 2012).

6.1.2 Study selection

After the removal of duplicates, the study selection was carried out in two stages. In the first stage, relevant studies were identified after reading their titles and abstracts. Full texts for all selected articles were then obtained for the second stage of the review, and studies were excluded if they were not an original economic evaluation using QALYs as an outcome, if they did not include social costs (productivity losses or informal care or both) or if they did not separate perspectives (healthcare provider, when only direct healthcare costs are considered, and societal perspective, where all costs are included).

6.1.3 Data extraction and analysis

After revising the abstracts of all articles that satisfied the inclusion criteria, the following information was collected: authors, year of publication and journal, type of analysis carried out (cost-utility or cost-effectiveness and cost-utility), country, the type of intervention assessed in the economic evaluation (drugs, non-pharmaceutical therapy (health education), diagnostic or screening device or a medical procedure), the perspective applied, which costs were included in the economic evaluation, method

to measure social costs, source of information and unit costs applied. Microsoft excel was used to summarize the results from the systematic literature review.

6.2 Results

6.2.1 Study selection

As Figure 6.1 shows, 15,516 records were identified from both searches, Medline and CEA Registry, after removing duplicates (n = 890). After reading the title and abstract, 1,229 full-texts were reviewed and 1,138 were excluded due to different reasons. It is noteworthy that 968 full cost-utility analyses were identified, 180 of them (18.60%) included social costs, but only 91 separated both perspectives (healthcare provider and societal ones). Hence, those 91 studies were included in this review since they were full economic evaluations, using QALYs as the main outcome, including social costs and with differentiated healthcare provider and societal perspectives results.

6.2.2 Characteristics of the revised studies

The characteristics of the 91 studies that are included in this review are presented in Tables A2.1 and A2.2 (see Appendix 2). With respect to social costs, overall, informal care costs were included in thirty-seven studies (40.66%), productivity losses in forty-five studies (49.45%) and nine studies considered both types of social costs (9.89%).

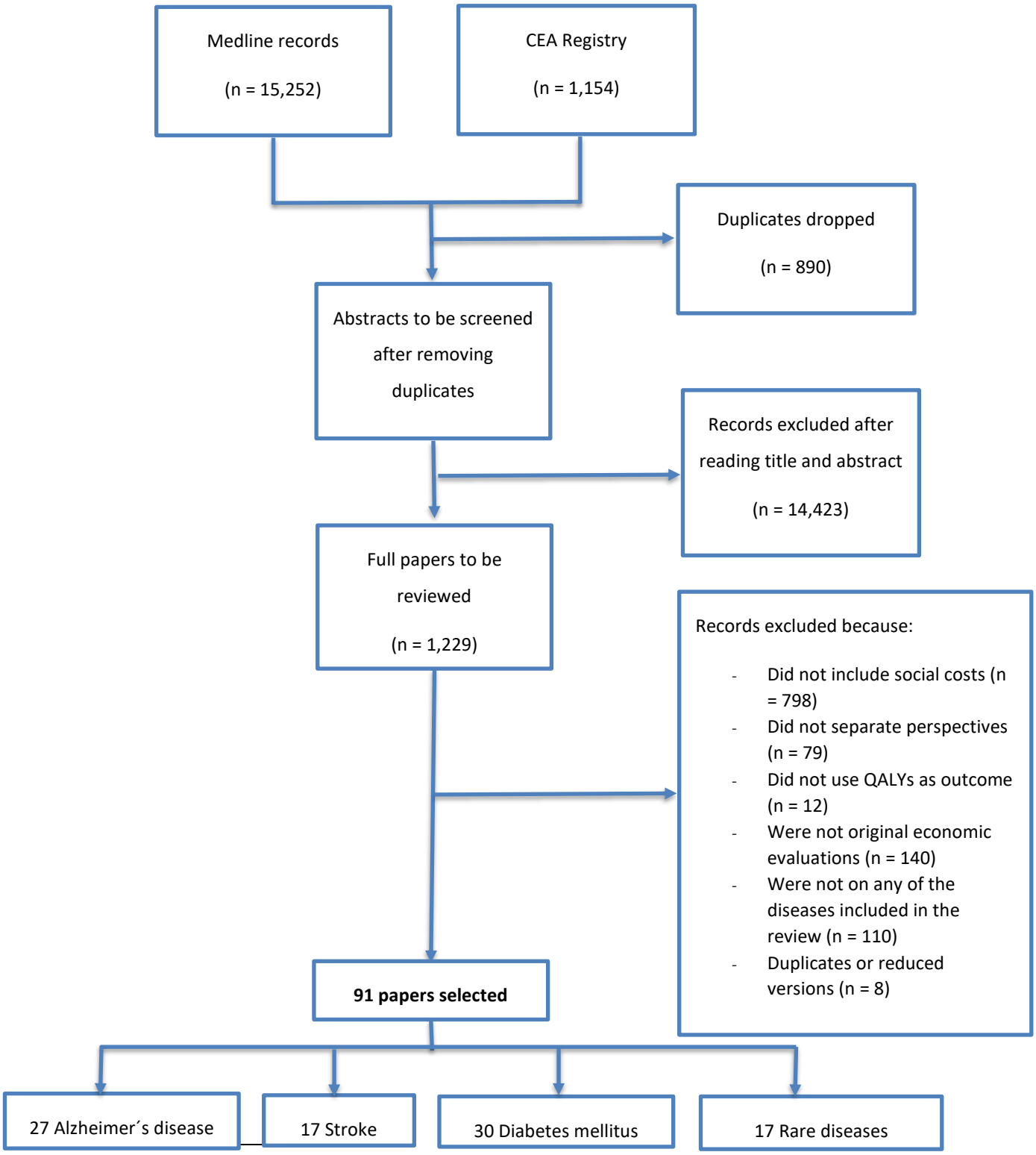
When analysing the inclusion of social costs by disease, in case of Alzheimer´s disease, only one study included productivity losses in addition to informal care costs (Lamb et al., 2018). All the economic evaluations in Alzheimer´s diseases included informal care costs (n = 27). When looking at rare diseases, productivity losses were estimated in 76.5% of the studies (n = 13), informal care costs were included in two other studies (Risebrough et al., 2008; Kanters et al., 2014) and both types of social costs in another two studies (Teerawattananon et al., 2007; Landfeldt et al., 2017). In case of stroke, productivity losses were included in eight studies, as well as informal care costs. Only one study included both social costs when evaluating an intervention for stroke (van Eeden et al., 2015). Productivity losses were the most common social costs in diabetes mellitus economic evaluations (80% of the studies, n = 24). Informal care costs were included only in one study (Greeley et al., 2011),

whereas five studies considered both types of social costs (Rosen et al., 2005; Huang et al., 2010; Patel et al., 2011; Brown et al., 2015; Slangen et al., 2017).

Most of the studies were performed in the United States (n = 22) and in the United Kingdom (n = 19). Then, eleven more studies were carried out in Sweden (Almbrand et al., 2000; Jönsson et al., 2005; Lindgren et al., 2007; Ghatnekar et al., 2010; Kasteng et al., 2011; Valentine et al., 2011; Svensson et al., 2012; Kiadaliri et al., 2014; Steen-Carlsson and Persson, 2014; Borg et al., 2016; Steen-Carlsson et al., 2017); eight in the Netherlands (Wolfs et al., 2009; Rombach et al., 2013; Kanters et al., 2014; Tsiachristas et al., 2014; van Dussen et al., 2014; van Eeden et al., 2015; Roze et al., 2016; Slangen et al., 2017); six in Spain (Mar et al., 2005; López-Bastida et al., 2009; González-Juanatey et al., 2012; Barón-Esquivias et al., 2015; Hornberger et al., 2015; Parody et al., 2015); three in France (Touchon et al., 2014; Roze et al., 2016; Hornberger et al., 2017), Norway (Gulbrandsen et al., 2001; Rive et al., 2012; Huetson et al., 2015) and Canada (Risebrough et al., 2008; Lachaine et al., 2011; Haig et al., 2016); two in Denmark (Sogaard et al., 2014; Roze et al., 2017), Switzerland (Valentine et al., 2011; Pfeil et al., 2012), Germany (Hartz et al., 2012; Diel et al., 2015) and Thailand (Teerawattananon et al., 2007; Kulpeng et al., 2014); and one in Taiwan (Fuh and Wang, 2008), China (Sheng et al., 2017), Korea (Park et al., 2016), Brazil (Araúo et al., 2010), Iran (Farshchi et al., 2016), Singapore (Nguyen et al., 2016) and Finland (Kolu et al., 2016). One study, however, was based on a multinational setting using data from Belgium, France, Germany, Italy and Spain (Gschwend et al., 2009).

Most of the interventions assessed were pharmaceutical interventions, followed by non-pharmacological therapy, such as health education interventions, and diagnostic procedures. Although the main bulk of the studies (n = 64) were only a cost-utility analysis, 27 additionally incorporated a cost-effectiveness analysis. Most of the combined cost-utility and cost-effectiveness analyses were performed when analysing rare diseases. When looking at the year of publication, most of the studies were published between years 2010 to 2014 (n = 39) and 2015 to 2018 (n = 30). Twelve more papers were published between 2005 and 2009, and 10 papers before 2005.

Figure 6.1. Flowchart of searching and selection of papers[12]



[12] We considered that it was not necessary to assess whether there was any study selection in the included studies.

6.2.3 Methods for estimating productivity costs

As Tables A2.1 and A2.2. (see Appendix 2) show, out of the 91 studies included in this review, the human capital approach method was used in thirty-two analyses, whereas the friction cost method was applied in only two studies (Tsiachristas et al., 2014; Slangen et al., 2017). In case of Slangen et al. (2017), the authors do not provide information of the unit cost applied, neither the length of the friction period nor any adjustment made. They do state that production losses are limited to the period needed to replace a sick worker (the friction period itself).

The source of information comes from Dutch national official registers, such as the Dutch governmental manual for health care cost analysis (Z N, 2015). This lack of detail makes it difficult to compare the calculations used by the studies from different countries. However, in case of the work carried out by Tsiachristas et al. (2014), authors provide the readers with mean hourly wages by age and gender, which range from 11.19€ per hour if age lies between 15 to 19 years old to 45.67€ per hour if 55 to 60 years old in case of males. Those differences are narrower for women, with the minimum being at 10.16€ per hour and the maximum at 34.21€. Authors also inform about the length of the friction cost period (160 days) and a correction for the elasticity of labour time (0.8). Instead of using national official registers, the data comes from published literature (Tan et al., 2012).

In case of using the human capital approach, in most of the cases the source of information was national official registers: for example, the National Bureau of Statistics of China, the United States, the United Kingdom, France, Korea; Statistics Denmark, Finland or Sweden; and the United States compensation or income distribution survey or the different editions from the Dutch costing manual for health care research. However, some authors also used data from other studies, such as specific data from the United Kingdom (Landfeldt et al., 2016) or from Germany (Diel et al., 2014). Five studies used gender specific wages (Valentine et al., 2011a, 2011b; Roze et al., 2016, 2017; Lamb et al., 2018), three analyses included national wages by age group (Valentine et al., 2011; Kiadaliri et al., 2014; Steen-Carlsson and Persson, 2014), and one study used gender and age-adjusted gross wage (Miners et al., 2002). The remaining studies used national hourly, monthly or yearly average income.

When looking at costs between studies and countries, the highest cost per hour of productivity loss, in euros, was found in two studies performed in The Netherlands, at 34.79€ per hour (Rombach et al.,

2013; van Dussen et al., 2014), whereas the lowest estimate is provided in a German study (Diel et al., 2015), at 10.71€ per hour. In case of using US dollars, the lowest value per hour was 11.03$ in the United States (Slejko et al., 2010), while the highest wage per hour was found in a Swedish study, at 92.42$ per hour (Svensson et al., 2012).

Apart from the human capital approach and the friction cost method, two studies used different methods (Kasteng et al., 2011; Borg et al., 2016). There were eighteen works that, despite stating they did include productivity losses, the authors did not provide any information on the method used to value productivity costs.

6.2.4 Methods for estimating informal care costs

Twenty-three studies used the opportunity cost method to value informal care costs, over the ninety-one papers selected in this review, whereas the replacement cost method was applied in three studies Weycker et al., 2007; van Eeden et al., 2015; Michaud et al., 2018) and both methods were used in five analyses (Patel et al., 2004; Fuh et al., 2008; Romeo et al., 2013; Orgeta et al., 2015; Knapp et al., 2017). In fifteen studies where the authors stated that they did include informal care costs, they did not mention which method was used to value informal caregiving time (Tables 1, 2 and 4).

For those using both methods, there was one paper which did not give information on the unit cost, but did explain that, in case of the opportunity cost method, the authors applied the national Taiwanese average wage per hour, whereas in the replacement cost method, the hourly pay of a professional caregiver was selected (Fuh et al., 2008). The other four studies, which were all performed in the United Kingdom (Patel et al., 2004; Romeo et al., 2013; Orgeta et al., 2015; Knapp et al., 2017), showed that unit cost per hour was indeed higher when using the replacement cost method, compared to the opportunity cost method.

Hourly unit costs ranged from 4.17£ (Patel et al., 2004) to 16.9£ (Knapp et al., 2017) in case of the application of the opportunity cost method, but those differences were larger when using the replacement cost method: 12.54£ (Patel et al., 2004)to 41.6£ (Knapp et al., 2017). These four British studies used the national hourly minimum wage to value informal caregiving time in case of the

opportunity cost method, while a homecare worker hourly wage was applied is the replacement cost method was used. One study did not report the source (Orgeta et al., 2015), whereas the other three used data from published literature (McDaid, 2001; Curtis, 2010, 2014).

In those studies that used the replacement cost method, the authors did not provide the unit cost applied, although they did state that the hourly wage rate for home health aides/professional care attendants (Weycker et al., 2007; Michaud et al., 2018) or the hourly wage of professional caregivers (van Eeden et al., 2015). Whereas the one on stroke did not detail the source of information (van Eeden et al., 2015) the other two studies, which were both on Alzheimer´s disease and from the United States, used the same source of information (Leon et al., 1998).

When using the opportunity cost method, the source of information was divided between published literature and national official registers, such as the National Bureau of Statistics of the United States, the United Kingdom or Canada; the United States revenue and customs survey or the annual survey of hours and earnings, as well as the Dutch costing manual for health care research. Nine studies applied the national minimum wage (Patel et al., 2004; Getsios et al., 2010, 2012; Lachaine et al., 2011; Nagy et al., 2011; Guo et al., 2012; Romeo et al., 2013; D'Amico et al., 2015; Orgeta et al., 2015; Knapp et al., 2017), three analyses used the hourly wage of paid housekeepers (López-Bastida et al., 2009; Wolfs et al., 2009; Kanters et al., 2014), one study applied the hourly earnings of a district nurse (Hornberger et al., 2017), and another one used the median national hourly earnings (Doan et al., 2013). Moreover, one analysis used gender-specific data (Lamb et al., 2018) and another study used gender and age-adjusted matched wages (Sogaard et al., 2014).

When looking at hourly costs between studies, diseases and countries, the highest unit cost per hour of informal care, in euros, was found in a French Alzheimer´s disease study (Hornberger et al., 2017), at 42.92€ per hour, whereas the lowest estimate was given by a German study (Hartz et al., 2012), also in Alzheimer, at 3.45€ per hour. In case of using Great Britain pounds (GBP), the lowest value per hour was 4.10£ (Nagy et al., 2011), while the highest wage per hour was found at 36.74£ per hour (Lamb et al., 2018), both of them were in Alzheimer.

Table 6.1. Summary results of the 91 studies selected from the search strategy

	Total (N = 91)	Studies including productivity losses (N = 45, 49.45%)		Studies including informal care costs (N = 37, 40.66%)		Studies including both social costs (N = 9; 9.89%)	
	N (%)	N	%	N	%	N	%
Productivity losses	54 (59.34%)						
The method is described	42 (77.78%)	36	80%			6	66.66%
… If described							
Human capital approach	37 (88.10%)	32	88.88%			5	83.33%
Friction cost method	3 (7.14%)	2	5.56%			1	16.67%
Both	0 (0%)	0	0%			0	0%
Other methods	2 (4.76%)	2	5.56%			0	0%
The unit cost (wage/hour, wage/month, wage/year) is provided	26 (48.15%)	22	48.89%			4	44.44%
The information source is stated	30 (55.56%)	25	55.56%			5	55.56%
… If stated							
National official registers	22 (73.33%)	19	76%			3	60%
Literature	4 (13.33%)	3	12%			1	20%
Authors´ elaboration/collection	4 (13.33%)	3	12%			1	20%
Informal care costs	46 (50.55%)						

	Total (N = 91)	Studies including productivity losses (N = 45, 49.45%)		Studies including informal care costs (N = 37, 40.66%)		Studies including both social costs (N = 9; 9.89%)	
	N (%)	**N**	**%**	**N**	**%**	**N**	**%**
The method is described	31 (67.39%)			26	70.27%	5	55.56%
… If described							
Opportunity cost method	23 (74.19%)			19	73.08%	4	80%
Replacement cost method	3 (9.68%)			2	7.69%	1	20%
Contingent valuation	0 (0%)			0	0%	0	0%
More than one method	5 (16.13%)			5	19.23%	0	0%
Other methods	0 (0%)			0	0%	0	0%
The unit cost (value/hour or value/month) is provided	27 (58.70%)			23	62.16%	4	44.44%
The information source is stated	26 (56.52%)			22	59.46%	4	44.44%
… If stated							
National official registers	9 (34.62%)			7	31.82%	2	50%
Literature	15 (57.69%)			14	63.64%	1	25%
Authors´ elaboration/collection	2 (7.69%)			1	4.55%	1	25%

6.3 Some comments

The current review has identified 91 papers that included social costs (productivity losses, informal care or both) in the economic evaluation of interventions targeted at four diseases (Alzheimer´s disease, rare diseases, stroke and diabetes mellitus) during the period 2000-2018. Overall, informal care costs were included in thirty-seven economic evaluations (40.66%), productivity losses in forty-five studies (49.45%) and nine articles considered both types of social costs (9.89%).

In case of Alzheimer´s disease, only one study included productivity losses in addition to informal care costs (Lamb et al., 2018) and the remaining twenty-six studies only included informal care costs. When looking at rare diseases, productivity losses were estimated in thirteen, out of 17 studies, informal care costs were included in two other studies (Risebrough et al., 2008; Kanters et al., 2014) and both types of social costs in another two studies (Teerawattananon et al., 2007; Landfeldt et al., 2017). In case of stroke, productivity losses were included in eight studies, and informal care costs were considered in another eight articles. Only one study included both social costs when evaluating an intervention for stroke (van Eeden et al., 2015). Contrary to Alzheimer´s disease, productivity losses were the most common social costs in diabetes mellitus economic evaluations (80% of the studies), while informal care costs were included only in one study (Greeley et al., 2011), and five studies considered both types of social costs (Rosen et al., 2005; Huang et al., 2010; Patel et al., 2011; Brown et al., 2015; Slangen et al., 2017). These results would confirm the role that informal care plays on some chronic diseases that pose a vast burden on individual´s autonomy, as it is the case for Alzheimer´s disease or stroke (Hoefman and Brouwer, 2013; Oliva-Moreno et al., 2017). The main role of informal care in Alzheimer and stroke is substituted by the relevance that productivity losses seem to play in case of rare diseases and diabetes mellitus.

Out of the 54 studies including productivity losses, the human capital approach method was applied in thirty-two analyses, and the friction cost approach was applied in only two studies (Tsiachristas et

al., 2014; Slangen et al., 2017). Actually, only one of the two papers using the friction cost method (Tsiachristas et al., 2014) provided with full details on i) the unit cost per hour for different age and gender-groups; ii) the length of the friction period, which was established at 160 days per year; and iii) a correction for the elasticity of labour time, set at 0.8. It should be highlighted that both works using the friction cost method were performed in the Dutch setting, following the recommendations in the Dutch governmental manual for health care cost analysis (Z N, 2015). Actually, the friction cost method was developed by Dutch health economists who were not in favour of using the human capital approach, as it could lead to an overestimation of costs from a societal perspective (Koopmanschap et al., 1995; Brouwer and Koopmanschap, 2005; Kigozi et al., 2016).

A recent review indeed confirmed that smaller productivity cost estimates were obtained when using the friction cost approach (Pike and Grosse, 2018), compared to the human capital method, but the relative magnitudes widely varied. Moreover, the friction cost method limits productivity losses to the actual friction period, which is the time to replace the sick individual by other worker, and, hence, the friction costs refer to the reduction of productivity during the friction period as well as the costs related to hiring a new employee (Pike and Grosse, 2018). Therefore, the information needed to estimate productivity losses according to the friction method requires much more detailed data (beginning and length of the friction period, the costs of hiring replacement workers and some measure to correct for medium-term macro-economic effects), which does not occur when applying the human capital approach. However, even if the advantages of using the friction cost approach have been clearly established (Koopmanschap et al., 1995; Krol et al., 2013; Kigozi et al., 2016), the number of economic evaluations applying the friction cost method is very limited. Our review in fact identified only two studies using the friction cost method, compared to another thirty-two articles that used the human capital approach (Tsiachristas et al., 2014; Slangen et al., 2017). This finding would be in line with a review that found that, over 138 full cost-of-illness studies, only 12 of them (8%) reported productivity cost estimates using the friction cost approach only. It is true that they also found 35 studies that used both methods, of which twenty-six reported comparable estimates between both approaches and concluded that estimates calculated via the human capital approach were larger than the ones obtained when using the friction cost method. Moreover, we also found that eighteen authors did not clearly state the method used to value productivity losses, which enhances improvements in the reporting of productivity loss valuing methods.

Within the sixty economic evaluations including informal care costs, twenty-three studies used the opportunity cost method, the replacement cost method was applied in three studies (Weycker et al., 2007; van Eeden et al., 2015; Michaud et al., 2018) and both methods were used in five analyses (Patel et al., 2004; Fuh and Wang, 2008; Romeo et al., 2013; Orgeta et al., 2015; Knapp et al., 2017). These results would be consistent with the findings from a recent systematic review on the valuation of informal care in cost-of-illness studies (Oliva-Moreno et al., 2017), which concluded that the opportunity cost method (60% of the studies) and the replacement cost approach (26%) were the most commonly used methods to value informal care time. However, there are another valuation methods which have not been found in any of the identified studies of our review, such as the contingent valuation method, but have been highly valued in the existing literature. For example, van der Berg et al. (2005) used the contingent valuation method to value informal care, finding small differences in the willingness to pay of both informal care givers and receivers. However, the gap became larger when looking at the willingness to accept between both groups. Those differences in the willingness to accept might reflect individual (relationship between the caregiver and the care receiver) and caregiving (type of tasks performed) characteristics (De Meijer et al., 2010) or might mirror the burden that informal caregiving poses on caregivers, which might be controlled in economic evaluations by the consideration of caregivers´ utility (Hoefman et al., 2014).

Moreover, more novel valuation methods can serve as a complement to the most commonly used methods to value informal caregiving time, as some authors have already suggested for the particular case of well-being valuation method (van den Berg and Ferrer-i-Carbonell). Furthermore, we also identified five studies that applied both valuation approaches, the opportunity and the replacement cost methods (Patel et al., 2004; Fuh and Wang, 2008; Romeo et al., 2013; Orgeta et al., 2015; Knapp et al., 2017), four of them in Alzheimer´s disease and one of them in stroke. The authors concluded that higher estimates were obtained when using the replacement cost method than the opportunity costs approach, maybe due to the fact that higher unit costs were applied in case of the former valuation method. However, some authors have already suggested that those differences in the final results might point to the amount of time devoted to informal care (van den Berg et al., 2006), rather than the valuation applied in each method. Such studies including both valuation techniques are very

useful since they allow for a more straightforward comparison in terms of methodological issues, but also to consider an interval of the economic impact that a particular disease might have on the society.

As observed in productivity losses estimates, we identified twelve studies that did not report the method used to value informal care, although the authors did incorporate informal care costs in their economic evaluation estimations. Moreover, the non-reporting of unit costs when using the replacement cost method alone also deserves mention. Both issues highlight the need for good quality reporting of informal care valuation methods in economic evaluation.

This review has led to several conclusions. First of all, there seems to be a pattern in terms of social costs included in the economic evaluation of interventions at particular diseases. For example, informal care costs were much more prevalent in Alzheimer´s disease economic evaluations, as all of the studies selected actually included them. On the other hand, productivity losses were reported in twenty-nine of the thirty studies included for diabetes mellitus. This finding could be related to i) the mean age of people affected by each disease, with the Alzheimer´s disease age being higher than the diabetes mellitus age; and ii) the type and complexity of needs that each disease poses on their sufferers (Organization WH, 2016; Collaborators GD, 2019) (24, 26). Secondly, valuation methods of social costs do not seem to follow any agreement and, for example, in case of productivity losses and the use of the friction costing approach, there are no studies outside the Netherlands using this method, which could perhaps be related to the lack of country-specific parameters and guidelines for the application of the different valuation methods available. The human capital approach was used in thirty-two of the economic evaluations incorporating productivity losses, whereas the friction cost method was found only twice. Moreover, although more methods are available for valuing informal care, only the opportunity and the replacement cost methods have been found in the selected studies in this review, being the former much more used than the latter. Thirdly, there seems to be space for improvement in terms of completeness of information on how to value productivity losses and informal care in economic evaluations. As it has been aforementioned, from the 54 studies including productivity losses, one third did not explicitly state the method used to value productivity losses. This figure decreased to 20% (12 out of 60) in case of including informal care costs.

The current review also has some strengths and limitations. It assesses original economic evaluation studies using QALYs as outcome from two different databases (Medline and the CEA Registry) that incorporate a societal perspective into their analysis and results can be differentiated when using a healthcare provider/payer perspective and a societal perspective. Although care has been taken to include all relevant studies in the literature, some economic evaluations may have been missed in our search strategy. For example, cost-effectiveness that do not incorporate a cost-utility analysis as well will have been dropped from this review. Moreover, our review focused on the inclusion of productivity losses and informal care costs as a societal perspective in economic evaluations. However, other non-monetary costs that informal caregivers have to face (mental and physical health problems related to the care provided, support when carrying out their own care tasks) (Hoefman et al., 2014) and other monetary costs that actually might be related to informal caregiving (Hanly et al., 2013; Hoefman et al., 2014) have not been considered in this review.

Due to the increasing burden of chronic conditions worldwide (Yach et al., 2004; Riley et al., 2015), this review on economic evaluations at four different diseases (Alzheimer´s disease, rare diseases, stroke and diabetes mellitus) provides with some figures on how social costs are included and valued. In order to make results more comparable between and across diseases and regions, data and guidelines on the valuation of social costs for specific country settings contexts are needed in order to provide with reliable estimates on the economic burden that some diseases pose on the society. Moreover, more attention needs to be given to the reporting of social costs, as it has been shown in this review that data in terms of methodological issues is still sometimes lacking.

7. Concluding remarks

The valuation of social costs has experienced great methodological developments in recent years, being especially remarkable the accuracy of time identification and valuation tools, for both patients and informal caregivers. Nonetheless, along the revised sections of this document, it has been highlighted that research efforts in this field of interest need to be increased in the coming years in order to improve the bulk of existing scientific evidence.

A general comment, very present in the literature reviewed, and that affects practically all of the methods 88agedorn, is that the choice of method to be applied on numerous occasions is conditioned by the available data. Conversely, the advance in techniques and the response to several of the debates raised in this field involve the improvement of the available data. Therefore, to advance in the assessment of the social costs associated with diseases and injuries, a general strategy should be established to improve the sources of data in the previous phases of identification and measurement of social resources.

- Concerning the valuation of paid time, the debate about whether the human capital approach or the friction cost method is preferred is still far from being over. The most important theoretical debates surged in the 90s. Since then, there has been no advance towards a synthesis of both methods, nor has a new method surged that overtakes the previous discrepancies between the two methods. In any case, there is enough applied research to affirm that the application of one method or another leads to very different results.

  In the applied literature of cost of illness studies and EEHT, the human capital approach is clearly the main method used. One of the reasons behind, but not the only one, is its greater simplicity in terms of application, whereas the friction costs method requires an adaptation to country-specific characteristics and an update to each stage of the economic cycle, which makes its implementation more complicated.

- There is a growing body of evidence regarding the relevance of presenteeism in the time valuation of paid time. However, there is no tool which can be named as a gold standard to determine the productivity loss associated with suffering from an illness or injury and to remain at work. Such lack of instruments endangers the comparability between studies and, hence, it implies that research focused on this issue must continue in the successive years.

- In the field of early retirement, the available research in estimating productivity losses is scarcer than the presence of absenteeism or sick leave. For the diseases where this phenomenon has been studied, the estimated losses are large but there is a high degree of heterogeneity in the different approaches used to estimate the labour losses.

- The existing literature about compensating mechanisms and multiplier effects points that both can be of great relevance in the estimation of labour productivity loss due to an illness or an injury. Still, the literature up to date is very scarce and more researches is needed, in more countries and where both employers and employees' points of view are considered, due to possible divergences.

- The debate on whether the economic evaluation of patients' time in terms of QALYs or any other health status indicator based on patients' preferences could entail a double-counting effect has been mitigated by the empirical results derived from recent studies, which conclude that the risk of double-counting seems to be negligible. However, it is not a closed topic at all, since the existing literature is not very plentiful and more empirical researches will be necessary to end with the discussion.

- While there is indeed a considerable amount of applied literature in the valuation of paid time, the assessment of unpaid time is very limited, as well as its inclusion in economic evaluation guidelines in different countries.

- In the case of the methods of valuation of informal caregiving time, although the different available methods can also lead to results within a wide range of variation, there has not been such an intense debate about their suitability as occurs in the case of labour productivity loss. That might be explained by the fact that each method adds a different complementary information, and hence, each of them value the caregiving time considering different frameworks. Nevertheless, in the applied literature of cost of illness studies and EEHT, the opportunity cost method is the prevailing approach.

- The systematic review of EE guidelines has permitted to identify areas of agreements and disagreements by comparing EE guidelines on social costs. Some of these discrepancies are due to the recommended perspective in those guidelines (in some cases, the financer perspective; in others, the societal perspective; and in others, both perspectives).

  - When the valuation of paid time exists, there are countries that opt for the human capital approach, while others choose the friction costs method, and there are some others that do not even mention the method to be applied. In general, there are no instructions about how to deal with the valuation of presenteeism and the consideration of compensating mechanisms and multiplier effects. There are not considerations on the valuation of patients´ unpaid time either.
  - In those cases where the informal caregiving time is explicitly stated, there are no advices on which time valuation method is preferable.
  - It can be summarized that methodological issues still remain unclear in terms of general agreement and require further investigation.

- In the applied literature review, we revised 1,229 full papers, from which 980 were economic evaluations assessing a healthcare intervention in any of the four diseases of interest. Although 798 out of the 980 EE were excluded because social costs were not included, 170 (more than 17%) did include productivity losses or informal care costs or both. Moreover, when looking at the results in some particular diseases showed that the proportion of studies including productivity losses or informal care costs did not differ substantially, but the proportion of analyses including both types of social costs was quite low (less than 10%). However, when looking at each disease in particular, wider differences in terms of which social costs were included were reported.
    - In case of the method used to valuate productivity losses, the human capital approach was the preferred one, being used in more than 70% of the studies included in this review. The use of friction costs approach is very concentrated in few countries, pointing towards the aforementioned differences between countries in economic evaluation guidelines. A similar figure (around 70%) was also shown for the application of the opportunity cost method to assess informal caregiving time, which is also in line whit what other researchers have found in the applied literature of cost of illness studies.

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References (1)

- Almbrand B, Johannesson M, Sjostrand B, Malmberg K, Ryden L. Cost-effectiveness of intense insulin treatment after acute myocardial infarction in patients with diabetes mellitus; results from the DIGAMI study. Eur Heart J. 2000;21(9):733-9.
- Angelis A, Tordrup D, Kanavos P. Socio-economic burden of rare diseases: A systematic review of cost of illness evidence. Health Policy. 2015;119(7):964-79.
- Araújo DV, Martins SCO, Passos RBF, Teich V. Analysis of the cost-effectiveness of thrombolysis with alteplase in stroke. Arg Bras Cardiol. 2010;95(1):12-20.
- Barón Esquivias G, Escolar Albaladejo G, Zamorano JL, Betegón Nicolás L, Canal Fontcuberta C, de Salas-Cansado M, et al. Cost-effectiveness Analysis Comparing Apixaban and Acenocoumarol in the Prevention of Stroke in Patients With Nonvalvular Atrial Fibrillation in Spain. Revista Española de Cardiología (English Edition). 2015;68(8):680-90.
- Becker GS (1964). Human Capital. Chicago: Columbia University Press.
- Ben-Porath, Y. The production of human capital and the life cycle of earnings. Journal of Political Economy 1967; 75(4): 352-365
- Biasutti M, Dufour N, Ferroud C, al. e. Cost-effectiveness of magnetic resonance imaging with a new contrast agent for the early diagnosis of Alzheimer's disease. PloS One. 2012;7.
- Borg S, Nahi H, Hansson M, Lee D, Elvidge J, Persson U. Cost effectiveness of pomalidomide in patients with relapsed and refractory multiple myeloma in Sweden. Acta Oncol. 2016;55(5):554-60.
- Bracco A, Krol M. Economic evaluations in European reimbursement submission guidelines: current status and comparisons. Expert Rev Pharmacoecon Outcomes Res. 2013; 13: 579-95.
- Brouwer, W.B., Koopmanschap, M.A., Rutten, F.F.: Productivity costs measurement through quality of life? A response to the recommendation of the Washington Panel. Health Econ. 1997; 6(3), 253–259
- Brouwer WBFK, M.A.; Rutten, F.F.H. Productivity costs in cost-effectiveness analysis numerator or denominator: a further discussion. Health Economics. 1997; 6:511 – 4
- Brouwer WBF, Exel NJA, Koopmanschap MA, Rutten FFH. Productivity costs before and after absence from work; as important as common? Health Policy 2002; 61: 173–187.
- Brouwer WBF, Exel JA, Baltussen RMPM, Rutten FFH. A dollar is a dollar-or is it? Value Health.

2006;9(5):341–7.

- Brouwer WBF, Koopmanschap, M.A. The friction-cost method : replacement for nothing and leisure for free? . Pharmacoeconomics. 2005;23(2):105-11.
- Brouwer WB, van Exel NJ, van Gorp B, Redekop WK. The CarerQol instrument: a new instrument to measure care-related quality of life of informal caregivers for use in economic evaluations. Qual Life Res. 2006 Aug;15(6):1005-21.
- Brown GC, Brown MM, Turpcu A, Rajput Y. The Cost-Effectiveness of Ranibizumab for the Treatment of Diabetic Macular Edema. Ophthalmology. 2015;122(7):1416-25.
- Claxton K, Walker S, Palmer S, Sculpher M. Appropriate perspectives for health care decisions (CHE research paper no. 54). Centre for Health Economics; 2010.
- Coduras A, Rabasa I, Frank A, al. e. Prospective One-Year Cost-of-Illness Study in a Cohort of Patients with Dementia of Alzheimer's Disease Type in Spain: The ECO Study. J Alzheimers Dis. 2010;19:601-15.
- Collaborators GD. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;18(1):88-106.
- Collins D, Lapsley H, Brochu S, et al. International guidelines for the estimation of the avoidable costs of substance abuse. Ottawa (Canada): Office of Research and Surveillance. International Steering Committee on Estimating Avoidable Costs of Substance Abuse. Drug Strategy and Controlled Substances Programme. Healthy Environments and Consumer Safety Branch. Health Canada; 2006.
- Cooksey R, Husain MJ, Brophy S, Davies H, Rahman MA, Atkinson MD, et al. The Cost of Ankylosing Spondylitis in the UK Using Linked Routine and Patient-Reported Survey Data. PloS ONE 2015; 10(7): e0126105.
- Costa N, Ferlicoq L, Derumeaux-Burel H, Rapp T, Garnault V, Gillette-Guyonnet S, et al. Comparison of informal care time and costs in different age-related dementias: a review. Biomed Res Int. 2013; 2013:852368.
- Culyer, Anthony J (2018) Cost, context and decisions in Health Economics and cost-effectiveness analysis. Discussion Paper. CHE Research Paper. Centre for Health Economics, University of York , York, UK.
- Curtis L. Unit Costs of Health and Social Care 2014. University of Kent: PSSRU. 2014.

- Curtis L. Unit Costs of Health and Social Care. University of Kent: PSSRU. 2010.
- D'Amico F, Rehill A, Knapp M, Aguirre E, Donovan H, Hoare Z, et al. Maintenance cognitive stimulation therapy: an economic evaluation within a randomized controlled trial. Journal of the American Medical Directors Association. 2015;16(1):63-70.
- Davidson RL, L.A. Is the societal approach wide enough to include relatives? Incorporating relatives´ costs and effects in a cost-effectiveness analysis. Appl Health Econ Health Policy. 2010;8(1):25-35.
- De Meijer C, Brouwer W, Koopmanschap M, van den Berg B, van Exel J. The value of informal care—a further investigation of the feasibility of contingent valuation in informal caregivers. Health Econ. 2010;19(7):755–71. Health Economics. 2010;19(7):755-71.
- Demaerschalk BM, Switzer JA, Xie F, Fan L, Villa KF, Wu EQ. Cost utility of hub-and-spoke telestroke networks from societal perspective. Am J Manag Care. 2013;19(12):976-85.
- Diel R, Hittel N, Schaberg T. Cost effectiveness of treating multi-drug resistant tuberculosis by adding Deltyba to background regimens in Germany. Respir Med. 2015;109(5):632-41.
- Diel R, Nienhaus A, Lampenius N, Rüsch-Gerdes S, Richter E. Cost of multi drug resistance tuberculosis in Germany. Resp Med. 2014;108.
- Doan QV, Gillard P, Brashear A, Halperin M, Hayward E, Varon S, et al. Cost-effectiveness of onabotulinumtoxinA for the treatment of wrist and hand disability due to upper-limb post-stroke spasticity in Scotland. Eur J Neurol. 2013;20(5):773-80.
- Eddy DM, Kahn R, Schlessinger L. Clinical outcomes and cost-effectiveness of strategies for managing people at high risk for diabetes. Ann Intern Med. 2005;143(4):251-64.
- EUnetHTA Joint Action, Work Package, Subgroup, Heintz E et al. Is There a European View on Health Economic Evaluations? Results from a Synopsis of Methodological Guidelines Used in the EUnetHTA Partner Countries. Pharmacoeconomics. 2016; 34: 59-76.
- Farshchi A, Aghili R, Oskuee M, Rashed M, Noshad S, Kebriaeezadeh A, et al. Biphasic insulin Aspart 30 vs. NPH plus regular human insulin in type 2 diabetes patients; a cost-effectiveness study. BMC Endocr Disord. 2016;16(1):35.
- Feigin VL, Norrving B, Mensah GA. Global Burden of Stroke. Circ Res. 2017;120(3):439-48.
- Forster A, Dickerson J, Young J, Patel A, Kalra L, Nixon J, et al. A structured training programme for caregivers of inpatients after stroke (TRACS): a cluster randomised controlled trial and cost-effectiveness analysis. The Lancet. 2013;382(9910):2069-76.

- Forster A, Young J, Chapman K, Nixon J, Patel A, Holloway I, et al. Cluster Randomized Controlled Trial: Clinical and Cost-Effectiveness of a System of Longer-Term Stroke Care. Stroke. 2015;46(8):2212-9.
- Fuchs VR. Economics, values and health care reform. The American Economic Review 1966; 86(1): 1-24
- Fuh JL, Wang SJ. Cost-effectiveness analysis of donepezil for mild to moderate Alzheimer's disease in Taiwan. International journal of geriatric psychiatry. 2008;23(1):73-8.
- García-Gómez P. Institutions, health shocks and labour market outcomes across Europe. Journal of health economics 2011; 30 (1), 200-213
- Garrido-García S, Sánchez-Martínez FI, Abellán-Perpiñán JM, van Exel J. Monetary valuation of informal care base don carers´ and noncarers´ preferences. Value in Health 2015; 18(6): 832-840
- Getsios D, Blume S, Ishak KJ, Maclaine G, Hernandez L. An economic evaluation of early assessment for Alzheimer's disease in the United Kingdom. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2012;8(1):22-30.
- Getsios D, Blume S, Ishak KJ, Maclaine GD. Cost effectiveness of donepezil in the treatment of mild to moderate Alzheimer's disease: a UK evaluation using discrete-event simulation. PharmacoEconomics. 2010;28(5):411-27.
- Ghatnekar O, Hjalte F, Taylor M. Cost-effectiveness of dasatinib versus high-dose imatinib in patients with Chronic Myeloid Leukemia (CML), resistant to standard dose imatinib–a Swedish model application. Acta Oncol. 2010;49(6):851-8.
- Gibson MJH, A. Valuing the invaluable a new look at the economic value of family caregiving. Issue Brief (Public Policy Inst (Am Assoc Retired Pers)). 2007;IB82:1 – 12.
- Gold M, Siegel J, Russell L, Weinstein M. Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996.
- González-Juanatey JR, Álvarez-Sabin J, Lobos JM, Martínez-Rubio A, Reverter JC, Oyagüez I, et al. Cost-effectiveness of Dabigatran for Stroke Prevention in Non-valvular Atrial Fibrillation in Spain. Revista Española de Cardiología (English Edition). 2012;65(10):901-10.
- Goodrich K, Kaambwa B, Al-Janabi H. The inclusion of informal care in applied economic evaluation: a review. Value in Health 2012; 15(6): 975-981
- Greeley SAW, John PM, Winn AN, Ornelas J, Lipton RB, Philipson LH, et al. The Cost-Effectiveness of Personalized Genetic Medicine: The case of genetic testing in neonatal diabetes.

Diabetes Care. 2011;34(3):622-7.

- Grossman M (2000) The Human Capital Model of the Demand for Health. In AJ. Culyer and JP Newhouse (eds.). Handbook of Health Economics, Amsterdam: North-Holland-Springer-Verlag.
- Grossman, M (1972). The Demand for Health: A Theoretical and Empirical Investigation. New York: Columbia University Press.
- Group TDPPR. Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. Diabetes Care. 2003;26(9):2518-23.
- Gschwend MH, Aagren M, Valentine WJ. Cost-effectiveness of insulin detemir compared with neutral protamine Hagedorn insulin in patients with type 1 diabetes using a basal-bolus regimen in five European countries. J Med Econ. 2009;12(2):114-23.
- Gulbrandsen N, Wisløff F, Nord E, Lenhoff S, Hjorth M, Westin J, et al. Cost-utility analysis of high-dose melphalan with autologous blood stem cell support vs. melphalan plus prednisone in patients younger than 60 years with multiple myeloma. Eur J Haematol. 2001;66:328-36.
- Guo S, Getsios D, Hernandez L, Cho K, Lawler E, Altincatal A, et al. Florbetaben PET in the Early Diagnosis of Alzheimer's Disease: A Discrete Event Simulation to Explore Its Potential Value and Key Data Gaps. International journal of Alzheimer's disease. 2012.
- Haig J, Barbeau M, Ferreira A. Cost-effectiveness of ranibizumab in the treatment of visual impairment due to diabetic macular edema. J Med Econ. 2016;19(7):663-71.
- Hanly P, Ceilleachair AO, Skally M, O'Leary E, Kapur K, Fitzpatrick P, et al. How much does it cost to care for survivors of colorectal cancer? Caregiver's time, travel and out-of-pocket costs. Support Care Cancer. 2013.
- Hartz S, Getsios D, Tao S, Blume S, Maclaine G. Evaluating the cost effectiveness of donepezil in the treatment of Alzheimer's disease in Germany using discrete event simulation. BMC neurology. 2012;12:2.
- Harwood H, Fountain D, Livermore G. The economic costs of alcohol and drug abuse in the United States 1992. Report prepared for the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism. Rockville, MD (US): National Institutes of Health. Department of Health and Human Services; 1998. NIH Publication No. 98-4327.
- Herman WH, Ackermann RT, Brandle M, Engelgau MM, Hamman RF, Hicks K, et al. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with

impaired glucose tolerance. Ann Intern Med. 2005;142(5):323-32.

- Hidalgo A, Oliva J, González A, Aranda I. Cuidados informales asociados a la limitación de la autonomía en supervivientes a accidentes cerebrovasculares. Gac Sanit. 2011;25(Espec Congr 1):1-2.
- Hjelmgren J, Berggren F, Andersson F. Health Economic Guidelines—Similarities, Differences and Some Implications. Value Health. 2001; 4: 225-50.
- Hoefman RJ, van Exel J, Brouwer W. How to include informal care in economic evaluations. Pharmacoeconomics. 2013; 31(12):1105-19
- Hoefman RJ, van Exel J, Rose JM, van de Wetering EJ, Brouwer WB. A discrete choice experiment to obtain a tariff for valuing informal care situations measured with the CarerQol instrument. Med Decis Making. 2014;34(1):84-96.
- Hoefman RJ, van Exel J, Brouwer WBF. The Monetary Value of Informal Care: Obtaining Pure Time Valuations Using a Discrete Choice Experiment. Pharmacoeconomics. 2018; 37(4): 531-540
- Hoerger TJ, Hicks KA, Sorensen SW, Herman WH, Ratner RE, Ackermann RT, et al. Cost-effectiveness of screening for pre-diabetes among overweight and obese U.S. adults. Diabetes Care. 2007;30(11):2874-9.
- Hornberger J, Bae J, Watson I, Johnston J, Happich M. Clinical and cost implications of amyloid beta detection with amyloid beta positron emission tomography imaging in early Alzheimer's disease – the case of florbetapir. Current medical research and opinion. 2017;33(4):675-85.
- Hornberger J, Michalopoulos S, Dai M, Andrade P, Dilla T, Happich M. Cost-Effectiveness of Florbetapir-PET in Alzheimer's Disease: A Spanish Societal Perspective. The journal of mental health policy and economics. 2015;18(2):63-73.
- Huang ES, O'Grady M, Basu A, Winn A, John P, Lee J, et al. The cost-effectiveness of continuous glucose monitoring in type 1 diabetes. Diabetes Care. 2010;33(6):1269-74.
- Huetson P, Palmer JL, Levorsen A, Fournier M, Germe M, McLeod E. Cost-effectiveness of once daily GLP-1 receptor agonist lixisenatide compared to bolus insulin both in combination with basal insulin for the treatment of patients with type 2 diabetes in Norway. J Med Econ. 2015;18(8):573-85.
- Hutubessy RC, van Tulder MW, Vondeling H, Bouter LM. Indirect costs of back pain in The Netherlands: a comparison of the human capital method with the friction cost method. Pain 1999; 80:201–207.
- Hux MJ, O'Brien BJ, Iskedjian M, al. e. Relation between severity of Alzheimer's disease and

costs of caring. CMAJ. 1998;159(5):457-65.

- Jacob-Tacken, K. H., Koopmanschap, M. A., Meerding, W. J., & Severens, J. L.. Correcting for compensating mechanisms related to productivity costs in
  - economic evaluations of health care programmes. Health Economics, 2005; 14(5), 435-443.
- Jacobs P, Ohinmaa A, Brady B. Providing systematic guidance in pharmacoeconomic guidelines for 99agedorn99 costs. Pharmacoeconomics 2005; 23(2), 143–153.
- Jiménez-Martín S, Oliva J, Vilaplana Prieto C. Sanidad y dependencia, matrimonio o divorcio: atención sanitaria y servicios sociales. ¿una cuestión de integración o sólo de coordinación? Madrid: Círculo de la Sanidad; 2011 , Available at: http://wwwcirculodelasanidadcom/documentos/sanidadydependenciapdf. 2011.
- Johannesson M, Jönsson B, Borgquist L. Willingness to pay for antihypertensive therapy: results of a Swedish pilot study. Journal of Health Economics. 1991;10:461-74.
- Johannesson M, Jönsson B, Jönsson L, Kobelt G, Zethraeus N. Why should economic evaluations of medical innovations have a societal perspective? OHE briefing. 2009;51:1–32
- Johannesson M. The willingness to pay for health changes, the human-capital approach and the external costs. Health Policy. 1996;36:231 – 44
- Johannesson, M and Karlsson, G The friction cost method: A comment. Journal of Health Economics, 1997; 16: 249-255.
- Johannesson M. Avoiding Double-Counting in pharmacoeconomic studies. Pharmacoeconomics. 1997;11(5):385 – 8.
- Johannesson, M and Meltzer D. Some reflections on cost-effectiveness analysis. Health Economics, 1998; 7: 1-7.
- Jönsson B, Carides GW, Burke TA, Dasbach ÈJ, Lindholm LH, Dahlöf B. Cost effectiveness of losartan in patients with hypertension and LVH: An economic evaluation for Sweden of the LIFE trial. J Hypertens. 2005;23:1425-31.
- Jönsson B. Ten arguments for a societal perspective in the economic evaluation of medical innovations. Eur J Health Econ. 2009;10(4):357–9.
- Kanters TA, Hoogenboom-Plug I, Rutten-Van Mölken MPMH, Redekop W, van der Ploeg AT, Hakkaart L. Cost-effectiveness of enzyme replacement therapy with alglucosidase alfa in classic-infantile patients with Pompe disease. Orphanet J Rare Dis. 2014;9.

- Kasteng F, Eriksson J, Sennfalt K, Lindgren P. Metabolic effects and cost-effectiveness of aripiprazole versus olanzapine in schizophrenia and bipolar disorder. Acta Psychiatr Scand. 2011;124(3):214-25.
- Kiadaliri AA, Gerdtham UG, Eliasson B, Carlsson KS. Cost-utility analysis of glucagon-like Peptide-1 agonists compared with dipeptidyl peptidase-4 inhibitors or neutral protamine 100agedorn Basal insulin as add-on to metformin in type 2 diabetes in 100agedo. Diabetes Ther. 2014;5(2):591-607.
- Kigozi J, Jowett S, Lewis M, Barton P, Coast J. Estimating productivity costs using the friction cost approach in practice: a systematic review. Eur J Health Econ. 2016;17(1):31-44.
- Kigozi J, Jowett S, Lewis M, Barton P, Coast J. The Estimation and Inclusion of Presenteeism Costs in Applied Economic Evaluation: A Systematic Review. Value Health. 2017 Mar;20(3):496-506.
- Kirbach S, Simpson K, Nietert PJ, Mintzer J. A markov model of the cost effectiveness of olanzapine treatment for agitation and psychosis in Alzheimer's disease. Clinical drug investigation. 2008;28(5):291-303.
- Knapp M, King D, Romeo R, Adams J, Baldwin A, Ballard C, et al. Cost-effectiveness of donepezil and memantine in moderate to severe Alzheimer's disease (the DOMINO-AD trial). International journal of geriatric psychiatry. 2017;32(12):1205-16.
- Knies S, Severens JL, Ament AJ, Evers SM. The transferability of valuing lost productivity across jurisdictions. Differences between national pharmacoeconomic guidelines. Value Health 2010; 13(5), 519–527
- Kolu P, Raitanen J, Puhkala J, Tuominen P, Husu P, Luoto R. Effectiveness and Cost-Effectiveness of a Cluster-Randomized Prenatal Lifestyle Counseling Trial: A Seven-Year Follow-Up. PloS One. 2016;11(12):e0167759.
- Koopmanschap MA, Rutten FFH. A practical guide for calculating indirect costs of disease. Pharmacoeconomics 1997; 10 (5): 460-6
- Koopmanschap MA, Rutten FH, van Ineveld BM, van Roijen L. The friction cost method for measuring indirect cost of disease. J Health Econ 1995; 14:171-189 .
- Koopmanschap MA, van Ineveld BM. Towards a new approach for estimating indirect costs of disease. Soc Sci Med, 1992; 34:1005-1010.

- Koopmanschap MA; van den Berg, B.; Brouwer, W.B.F. An overview of methods and applications to value informal care in economic evaluations of healthcare. Pharmacoeconomics. 2008;26(4):269 – 80
- Krol, M., et al. Productivity cost calculations in health economic evaluations: correcting for compensation mechanisms and multiplier effects. Soc. Sci. Med. 2012: 75(11), 1981–1988.
- Krol M, Brouwer W. Unpaid work in health economic evaluations. Soc Sci Med. 2015 Nov;144:127-37
- Krol M, Brouwer W, Rutten F. Productivity costs in economic evaluations: past, present, future. Pharmacoeconomics. 2013; 31: 537-4.
- Krol M, Brouwer W. How to estimate productivity costs in economic evaluations. Pharmacoeconomics. 2014;32(4):335–44.
- Krol M, Papenburg K, van Exel J. Does including informal care in economic evaluations matter? A systematic review of inclusion and impact of informal care in cost-effectiveness studies. Pharmacoeconomics 2015; 33(2): 123-135
- Kulpeng W, Sompitak S, Jootar S, Chansung K, Teerawattananon Y. Cost-utility analysis of dasatinib and nilotinib in patients with chronic myeloid leukemia refractory to first-line treatment with imatinib in Thailand. Clin Ther. 2014;36(4):534-43.
- Kuo S, Bryce CL, Zgibor JC, Wolf DL, Roberts MS, Smith KJ. Cost-effectiveness of implementing the chronic care model for diabetes care in a military population. J Diabetes Sci Technol. 2011;5(3):501-13.
- Lachaine J, Beauchemin C, Legault M, Bineau S. Economic evaluation of the impact of memantine on time to nursing home admission in the treatment of Alzheimer disease. Canadian journal of psychiatry Revue 101agedorn101101 de psychiatrie. 2011;56(10):596-604.
- Laires, P. A., Gouveia, M., Canhao, H., & Branco, J. C.. The economic impact of early retirement attributed to rheumatic diseases: results from a nationwide population-based epidemiologic study. Public Health 2016; 140, 151-162.
- Lamb SE, Mistry D, Alleyne S, Atherton N, Brown D, Copsey B, et al. Aerobic and strength training exercise programme for cognitive impairment in people with mild to moderate dementia: the DAPA RCT. Health technology assessment (Winchester, England). 2018;22(28):1-202.
- Landfeldt E, Alfredsson L, Straub V, Lochmuller H, Bushby K, Lindgren P. Economic Evaluation

in Duchenne Muscular Dystrophy: Model Frameworks for Cost-Effectiveness Analysis. Pharmacoeconomics. 2017;35(2):249-58.

- Landfeldt E, Lindgren P, Bell CF, Guglieri M, Straub V, Lochmüller H, et al. Quantifying the burden of caregiving in Duchenne muscular dystrophy. J Neurol 2016;263(5):906-15.
- Lensberg BR, Drummond MF, Danchenko N, Despiégel N, François C. Challenges in measuring and valuing productivity costs, and their relevance in mood disorders. Clinicoecon Outcomes Res. 2013; 18 (5):565-73.
- Leon J, Cheng C-K, Neumann PJ. Alzheimer's disease care: costs and potential savings. Health Aff. 1998;17(6):206-16.
- Liljas B. How to calculate indirect costs in economic evaluation. Pharmacoeconomics, 1998; 13:1-7.
- Lindgren P, Lindström J, Tuomilehto J, Uusitupa M, Peltonen M, Jönsson B, et al. Lifestyle intervention to prevent diabetes in men and women with impaired glucose tolerance is cost-effective. Int J Technol Assess Health Care. 2007;23(2):177-83.
- Lofland JH, Lock lear JC, Frick KD. Different approaches to valuing the lost productivity of patients with migraine. Pharmacoeconomics, 2001; 19:917–925.
- Lopez-Bastida J, Hart W, Garcia-Perez L, Linertova R. Cost-effectiveness of donepezil in the treatment of mild or moderate Alzheimer's disease. Journal of Alzheimer's disease : JAD. 2009;16(2):399-407.
- Lopez-Bastida J, Serrano-Aguilar P, Perestelo-Perez L, Oliva-Moreno J. Social-economic costs and quality of life of Alzheimer disease in the Canary Islands, Spain. Neurology. 2006;67(12):2186-91.
- Luan FL, Kommareddi M, Ojo AO. Universal prophylaxis is cost effective in cytomegalovirus serology-positive kidney transplant patients. Transplantation. 2011;91(2):237-44.
- Luan FL, Stuckey LJ, Park JM, Kaul D, Cibrik D, Ojo A. Six-month prophylaxis is cost effective in transplant patients at high risk for cytomegalovirus infection. J Am Soc Nephrol. 2009;20(11):2449-58.
- Mar J, Begiristain JM, Arrazola A. Cost-effectiveness analysis of thrombolytic treatment for stroke. Cerebrovasc Dis. 2005;20(3):193-200.
- Marcellusi, A., Viti, R., Mecozzi, A., & Mennini, F. S. The direct and indirect cost of diabetes in Italy: a prevalence probabilistic approach. Eur J Health Econ 2016; 17(2), 139-147.
- Marcotte DE, Wilcox-Gok V. Estimating the employment and earnings costs of mental illness: recent developments in the United States. Soc Sci Med., 2001; 53:21–27.

- Maud A, Vazquez G, Nyman JA, Lakshminarayan K, Anderson C, Qureshi AI. Cost-effectiveness analysis of protected carotid artery stent placement versus endarterectomy in high-risk patients. J Endovasc Ther. 2010;17:224-9.
- McDaid D. Estimating the costs of informal care for people with Alzheimer's disease: methodological and practical challenges. Int J Geriatr Psychiatry. 2001;16:400-5.
- McMahon PM, Araki SS, Neumann PJ, Harris GJ, Gazelle GS. Cost-effectiveness of functional imaging tests in the diagnosis of Alzheimer disease. Radiology. 2000;217(1):58-68.
- Meerding WJ, Ijzelenberg W, Koopmanschap MA, Severens JL, Burdorf A. Health problems lead to considerable productivity loss at work among workers with high physical load jobs. J Clin Epidemiol. 2005;58(5):517–23.
- Michaud TL, Kane RL, McCarten JR, Gaugler JE, Nyman JA, Kuntz KM. Using Cerebrospinal Fluid Biomarker Testing to Target Treatment to Patients with Mild Cognitive Impairment: A Cost-Effectiveness Analysis. PharmacoEconomics – open. 2018;2(3):309-23.
- Mincer J. Schooling, Experience, and Earnings. Human Behavior & Social Institutions, Columbia University Press 1974.
- Miners AH, Lee CA, Sabin CA, Tolley KH. Cost-utility analysis of primary prophylaxis versus treatment on-demand for individuals with severe haemophilia. Pharmacoeconomics. 2002;20(11):759-74.
- Nagy B, Brennan A, Brandtmuller A, Thomas SK, Sullivan SD, Akehurst R. Assessing the cost-effectiveness of the rivastigmine transdermal patch for Alzheimer's disease in the UK using MMSE- and ADL-based models. International journal of geriatric psychiatry. 2011;26(5):483-94.
- Nguyen HV, Tan GS, Tapp RJ, Mital S, Ting DS, Wong HT, et al. Cost-effectiveness of a National Telemedicine Diabetic Retinopathy Screening Program in Singapore. Ophthalmology. 2016;123(12):2571-80.
- Nicholson S, Pauly MV, Polsky D, Sharda C, Szrek H, Berger ML. Measuring the effects of work loss on productivity with team production. Health Econ. 2006;15(2):111–23.
- OECD, Eurostat andWorld Health Organization (2017), A System of Health Accounts 2011: Revised edition, OECD Publishing, Paris.
- Oliva J, Lobo F, Lopez-Bastida J, Zozaya N, Romay R: Indirect costs of cervical and breast cancer in Spain. Eur. J. Health Econ. 2005; 6, 309–313.

- Oliva-Moreno J, Peña-Longobardo LM, Vilaplana-Prieto, C. An estimation of the value of informal care provided to dependent people in Spain. Applied Health Economics and Health Policy 2015; 13(2): 223-231
- Oliva-Moreno J, Trapero-Bertran M, Peña-Longobardo LM, Del Pozo-Rubio R. The Valuation of Informal Care in Cost-of-Illness Studies: A Systematic Review. Pharmacoeconomics. 2017;35(3):331-45.
- Oostenbrink JB, Bouwmans CAM, Koopmanschap MA, Rutten FFH. Manual for Costing Studies, Methods and Standard Unit Costs for Economic Evaluations in Health Care. Amstelveen, the Netherlands: College voor Zorgverzekeringen. 2004.
- Orgeta V, Leung P, Yates L, Kang S, Hoare Z, Henderson C, et al. Individual cognitive stimulation therapy for dementia: a clinical effectiveness and cost-effectiveness pragmatic, multicentre, randomised controlled trial. Health technology assessment (Winchester, England). 2015;19(64):1-108.
- Park HY, Ku HM, Sohn HS, Seo HS, Yung Lee H, Hwa Lim K, et al. Cost-effectiveness of Bedaquiline for the Treatment of Multidrug-resistant Tuberculosis in the Republic of Korea. Clin Ther. 2016;38(3):655-67 e1-2.
- Parody E, Pedraza S, Garcia-Gil MM, Crespo C, Serena J, Davalos A. Cost-Utility Analysis of Magnetic Resonance Imaging Management of Patients with Acute Ischemic Stroke in a Spanish Hospital. Neurol Ther. 2015;4(1):25-37.
- Patel A, Knapp M, Perez I, Evans A, Kalra L. Alternative strategies for stroke care: cost-effectiveness and cost-utility analyses from a prospective randomized controlled trial. Stroke. 2004;35(1):196-203.
- Patel A, Maissi E, Chang HC, Rodrigues I, Smith M, Thomas S, et al. Motivational enhancement therapy with and without cognitive behaviour therapy for Type 1 diabetes: economic evaluation from a randomized controlled trial. Diabet Med. 2011;28(4):470-9.
- Pauly, M. V., Nicholson, S., Xu, J., Polsky, D., Danzon, P. M., Murray, J. F., et al. A general model of the impact of absenteeism on employers and employees. Health Economics 2002; 11(3), 221-231.
- Pauly MV, Nicholson S, Polsky D, Berger ML, Sharda C. Valuing reductions in on-the-job illness: 'presenteeism' from managerial and economic perspectives. Health Econ. 2008;17(4):469–85.
- Pfeil AM, Kressig RW, Szucs TD. Alzheimer's dementia: budget impact and cost-utility analysis of a combination treatment of a cholinesterase inhibitor and memantine in Switzerland. Swiss medical weekly. 2012;142:w13676.

- Pike J, Grosse SD. Friction Cost Estimates of Productivity Costs in Cost-of-Illness Studies in Comparison with Human Capital Estimates: A Review. Appl Health Econ Health Policy. 2018
- Posnett J, Jan S. Indirect cost in economic evaluation: The opportunity cost of unpaid inputs. Health Economics 1996; 5(1): 13-23
- Ramjerdi F, Rand L, Saetermo IA, Saelensminde K. The Norwegian Value of Time Study, Part 1. TÖI-report 379 Institute of Transport Economics: Oslo. 1997.
- Riley L, Guthold R, Cowan M, Savin S, Bhatti L, Armstrong T, et al. The World Health Organization STEPwise Approach to Noncommunicable Disease Risk-Factor Surveillance: Methods, Challenges, and Opportunities. Am J Public Health. 2015;106:74-8.
- Risebrough N, Oh P, Blanchette V, Curtin J, Hitzler J, Feldman BM. Cost-utility analysis of Canadian tailored prophylaxis, primary prophylaxis and on-demand therapy in young children with severe haemophilia A. Haemophilia. 2008;14(4):743-52.
- Rive B, Aarsland D, Grishchenko M, Cochran J, Lamure M, Toumi M. Cost-effectiveness of memantine in moderate and severe Alzheimer's disease in Norway. International journal of geriatric psychiatry. 2012;27(6):573-82.
- Rombach SM, Hollak CEM, Linthorst GE. Cost-effectiveness of enzyme replacement therapy for Fabry disease. Orphanet J Rare Dis. 2013;8.
- Romeo R, Knapp M, Hellier J, Dewey M, Ballard C, Baldwin R, et al. Cost-effectiveness analyses for mirtazapine and sertraline in dementia: randomised controlled trial. The British journal of psychiatry : the journal of mental science. 2013;202:121-8.
- Rosen AB, Hamel MB, Weinstein MC, Cutler DM, Fendrick AM, Vijan S. Cost-effectiveness of full medicare coverage of angiotensin-converting enzyme inhibitors for beneficiaries with diabetes. Ann Intern Med. 2005;143(2):89-99.
- Roze S, de Portu S, Smith-Palmer J, Delbaere A, Valentine W, Ridderstrale M. Cost-effectiveness of sensor-augmented pump therapy versus standard insulin pump therapy in patients with type 1 diabetes in Denmark. Diabetes Res Clin Pract. 2017;128:6-14.
- Roze S, Duteil E, Smith-Palmer J, de Portu S, Valentine W, de Brouwer BF, et al. Cost-effectiveness of continuous subcutaneous insulin infusion in people with type 2 diabetes in the Netherlands. J Med Econ. 2016;19(8):742-9.
- Roze S, Smith-Palmer J, Valentine W, Payet V, de Portu S, Papo N, et al. Cost-Effectiveness of Sensor-Augmented Pump Therapy with Low Glucose Suspend Versus Standard Insulin Pump Therapy

in Two Different Patient Populations with Type 1 Diabetes in France. Diabetes Technol Ther. 2016;18(2):75-84.

- Roze S, Smith-Palmer J, Valentine WJ, Cook M, Jethwa M, de Portu S, et al. Long-term health economic benefits of sensor-augmented pump therapy vs continuous subcutaneous insulin infusion alone in type 1 diabetes: a U.K. perspective. J Med Econ. 2016;19(3):236-42.
- Saint-Laurent Thibault C, Ozer Stillman I, Chen S, Getsios D, Proskorovsky I, Hernandez L, et al. Cost-utility analysis of memantine extended release added to cholinesterase inhibitors compared to cholinesterase inhibitor monotherapy for the treatment of moderate-to-severe dementia of the Alzheimer's type in the US. Journal of medical economics. 2015;18(11):930-43.
- Salata BM, Hutton DW, Levine DA, Froehlich JB, Barnes GD. Cost-Effectiveness of Dabigatran (150 mg Twice Daily) and Warfarin in Patients >/= 65 Years With Nonvalvular Atrial Fibrillation. Am J Cardiol. 2016;117(1):54-60.
- Sanders GD, Neumann PJ, Basu A et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. JAMA. 2016 Sep 13;316(10):1093-103.
- Schofield DJ, Shrestha RN, Percival R, Passey ME, Callander EJ, Kelly SJ. The personal and national costs of lost labour force participation due to arthritis: an economic study. BMC Public Health 2013;13:188.
- Schofield D, Shrestha R, Callander E, Percival R, Kelly S, Passey M, Fletcher S: Modelling the cost of ill health in Health&WealthMOD (Version II): lost labour force participation, income and taxation, and the impact of disease prevention. Int J Microsimulation 2011, 4(3):32–36.
- Severens JL, Laheij RJF, Jansen JBMJ, van de Lisdonk EH, Verbeek ALM. Estimating the cost of lost production in dyspepsia. Aliment Pharmacol Therap 1998; 12: 919–923.
- Sheng G, Chen S, Dong C, Zhang R, Miao M, Wu D, et al. Societal implications of medical insurance coverage for imatinib as first-line treatment of chronic myeloid leukemia in China: a cost-effectiveness analysis. J Med Econ. 2017;20(4):371-81.
- Shiroiwa T, Fukuda T, Ikeda S, Shimozuma K. QALY and productivity loss: empirical evidence for "double counting." Value Health. 2013;16(4):581-587.
- Siegel JET, G.W.; Russell, L.B.; Luce, B.R.; Weinstein, M.C., Gold, M.R.; and the members of the Panel on Cost Effectiveness in Health and Medicine. Guidelines for pharmacoeconomic studies. Recommendations from the panel on cost effectiveness in health and medicine. Panel on cost

Effectiveness in Health and Medicine. Pharmacoeconomics. 1997;11(2):159 – 68.

- Slangen R, Faber CG, Schaper NC, Joosten EA, van Dongen RT, Kessels AG, et al. A Trial-Based Economic Evaluation Comparing Spinal Cord Stimulation With Best Medical Treatment in Painful Diabetic Peripheral Neuropathy. J Pain. 2017;18(4):405-14.
- Slejko JF, Page RL, 2nd, Sullivan PW. Cost-effectiveness of statin therapy for vascular event prevention in adults with elevated C-reactive protein: implications of JUPITER. Curr Med Res Opin. 2010;26(10):2485-97.
- Sogaard R, Sorensen J, Waldorff FB, Eckermann A, Buss DV, Phung KT, et al. Early psychosocial intervention in Alzheimer's disease: cost utility evaluation alongside the Danish Alzheimer's Intervention Study (DAISY). BMJ open. 2014;4(1):e004105.
- Sorensen, J.: Attributable costs of complications among people with diabetes. In Centre for Applied Health. Services Research and Technology Assessment. Syddansk universitet (2009)
- Steen Carlsson K, Andsberg G, Petersson J, Norrving B. Long-term cost-effectiveness of thrombectomy for acute ischaemic stroke in real life: An analysis based on data from the Swedish Stroke Register (Riksstroke). Int J Stroke. 2017;12(8):802-14.
- Steen Carlsson K, Persson U. Cost-effectiveness of add-on treatments to metformin in a Swedish setting: liraglutide vs sulphonylurea or sitagplitin. J Med Econ. 2014;17(9):658-69.
- Strömberg C, Aboagye E, Hagberg J, Bergström G, Lohela-Karlsson M. Estimating the Effect and Economic Impact of Absenteeism, Presenteeism, and Work Environment-Related Problems on Reductions in Productivity from a Managerial Perspective. Value Health. 2017 Sep;20(8):1058-1064.
- Svensson J, Ghatnekar O, Lindgren A, Lindvall O, Norrving B, Persson U, et al. Societal value of stem cell therapy in stroke–a 107agedorn107 study. Cerebrovasc Dis. 2012;33(6):532-9.
- Tan SS, Bouwmans CA, Rutten FF, Hakkaart-van Roijen L. Update of the Dutch manual for costing in economic evaluations. Int J Technol Assess Health Care. 2012;28(2):152-8.
- Targoutzidis A. Some adjustments to the human capital and the friction cost methods. Eur J Health Econ. 2018 Dec;19(9):1225-1228.
- Teerawattananon K, Iewsakul S, Yenjitr C, Ausayakhun S, Yenjitr W, Mugford M, et al. Economic Evaluation of Treatment Administration Strategies of Ganciclovir for Cytomegalovirus Retinitis in HIV/AIDS Patients in Thailand. PharmacoEconomics. 2007;25(5):413-28.
- Teipel SJ, Ewers M, Reisig V, Schweikert B, Hampel H, Happich M. Longterm cost-effectiveness of donepezil for the treatment of Alzheimer's disease. Eur Arch Psychiatry Clin Neurosci.

2007;257(6):330-6.

- Thorat T, Cangelosi M, Neumann PJ. Skills of the trade: the Tufts Cost-Effectiveness Analysis (CEA) Registry. J Benefit-Cost Analysis. 2012;3:1-9.
- Tilling C, Krol M, Tsuchiya A, et al. In or out? Income losses in health state valuations: a review. Value Health 2010; 13: 298–305.
- Tong T, Thokala P, McMillan B, Ghosh R, Brazier J. Cost effectiveness of using cognitive screening tests for detecting dementia and mild cognitive impairment in primary care. International journal of geriatric psychiatry. 2017;32(12):1392-400.
- Touchon J, Lachaine J, Beauchemin C, Granghaud A, Rive B, Bineau S. The impact of memantine in combination with acetylcholinesterase inhibitors on admission of patients with Alzheimer's disease to nursing homes: cost-effectiveness analysis in France. The European journal of health economics : HEPAC : health economics in prevention and care. 2014;15(8):791-800.
- Tranmer JE, Guerriere DN, Ungar WJ, Coyte PC. Valuing patient and caregiver time: a review of the literature. Pharmacoeconomics. 2005;23(5):449–59.
- Tsiachristas A, Cramm JM, Nieboer AP, Rutten-van Mölken MPMH. Changes in costs and effects after the implementation of disease management programs in the Netherlands. Cost Eff Resour Alloc. 2014;12.
- Valentine WJ, Aagren M, Haglund M, Ericsson A, Gschwend MH. Evaluation of the long-term cost-effectiveness of insulin detemir compared with neutral protamine 108agedorn insulin in patients with type 1 diabetes using a basal-bolus regimen in Sweden. Scand J Public Health. 2011;39(1):79-87.
- Valentine WJ, Palmer AJ, Erny-Albrecht KM, Ray JA, Cobden D, Foos V, et al. Cost-effectiveness of basal insulin from a US health system perspective_comparative analyses of detemir, glargine, and NPH. Adv Ther. 2006;23(2):191-207.
- Valentine WJ, Palmer AJ, Lammert M, Langer J, Brandle M. Evaluating the long-term cost-effectiveness of liraglutide versus exenatide BID in patients with type 2 diabetes who fail to improve with oral antidiabetic agents. Clin Ther. 2011;33(11):1698-712.
- van den Berg B, Bleichrodt H, Eeckhoudt L. The economic value of informal care: a study of informal caregivers' and patients' willingness to pay and willingness to accept for informal care. Health Econ. 2005;14(4):363–76. Health Economics. 2005;14(4):363-76.

- van den Berg B, Brouwer W, Koopmanschap M. Economic valuation of informal care: An overview of methods and applications. Eur J Health Econ., 2004; 5: 36-45.
- van den Berg B, Brouwer W, van Exel J, Koopmanschap M, van den Bos GA, Rutten F. Economic valuation of informal care: lessons from the application of the opportunity costs and proxy good methods. Soc Sci Med. 2006;62(4):835-45.
- van den Berg B, Brouwer W, van Exel J, Koopmanschap M. Economic valuation of informal care: the contingent valuation method applied to informal caregiving. Health Economics 2005; 14(2): 169-183
- van den Berg B, Ferrer-I-Carbonell A. Monetary valuation of informal care: the well-being valuation method. Health Economics. 2007;16(11):1227-44.
- Van den Hout WB. The value of productivity: human-capital versus friction-cost method. Ann Rheum Dis. 2010; 69 (Suppl 1): i89–91.
- van Dussen L, Biegstraaten M, Hollak CEM, Dijkgraaf MGW. Cost-effectiveness of enzyme replacement therapy for type 1 Gaucher disease. Orphanet J Rare Dis. 2014;9.
- van Eeden M, Kootker JA, Evers SM, van Heugten CM, Geurts AC, van Mastrigt GA. An economic evaluation of an augmented cognitive behavioural intervention vs. computerized cognitive training for post-stroke depressive symptoms. BMC Neurol. 2015;15:266.
- van Exel J, Brouwer W, van den Berg B, Koopmanschap M. With a little help from an anchor: Discussion and evidence of anchoring effects in contingent valuation. Journal of Behavioral and Experimental Economics 2006; 35(5): 836-853
- van Lier et al. Consensus-based cross-European recommendations for the identification, measurement and valuation of costs in health economic evaluations: a European Delphi study. Eur J Health Econ. 2018 Sep;19(7):993-1008.
- Verbooy K, Hoefman R, van Exel J, Brouwer W. Time is money: Investigating the value of leisure time and unpaid work. Value in Health 2018; 21(12): 1428-1436
- Weycker D, Taneja C, Edelsberg J, Erder MH, Schmitt FA, Setyawan J, et al. Cost-effectiveness of memantine in moderate-to-severe Alzheimer's disease patients receiving donepezil. Current medical research and opinion. 2007;23(5):1187-97.
- Wilson EC, Shulgina L, Cahn AP, Chilvers ER, Parfrey H, Clark AB, et al. Treating idiopathic

pulmonary fibrosis with the addition of co-trimoxazole: an economic evaluation alongside a randomised controlled trial. Pharmacoeconomics. 2014;32(1):87-99.

- Wolfs CA, Dirksen CD, Kessels A, Severens JL, Verhey FR. Economic evaluation of an integrated diagnostic approach for psychogeriatric patients: results of a randomized controlled trial. Archives of general psychiatry. 2009;66(3):313-23.
- Woods RT, Bruce E, Edwards RT, Elvish R, Hoare Z, Hounsome B, et al. REMCARE: reminiscence groups for people with dementia and their family caregivers – effectiveness and cost-effectiveness pragmatic multicentre randomised trial. Health technology assessment (Winchester, England). 2012;16(48):v-xv, 1-116.
- World Health Organization. Global report on diabetes. WHO Library Cataloguing-in-Publication Data, France. 2016.
- Yach D, Hawkes C, Gould L, al. e. The Global Burden of Chronic Diseases: Overcoming Impediments to Prevention and Control. JAMA. 2004;291(21):2616-22.
- Z N. Guideline for conducting economic evaluations in health care [in Dutch]. Diemen, ZiNL. 2015.
- Zhang W, Gignac MA, Beaton D, Tang K, Anis AH, Canadian Arthritis Network Work Productivity Group. Productivity loss due to presenteeism among patients with arthritis: estimates from 4 instruments. J Rheumatol. 2010;37(9):1805–14.
- Zhang W, Bansback N, Anis AH. Measuring and valuing productivity loss due to poor health: a critical review. Soc Sci Med. 2011;72(2):185–92
- Zhao Y, Feng HM, Qu J, Luo X, Ma WJ, Tian JH. A systematic review of pharmacoeconomic guidelines. J Med Econ. 2018 Jan;21(1):85-96.

References (2): Economic evaluation guidelines

- Agency for Health Technology Assessment: Guidelines for Conducting health technology assessment (HTA). Agency for Health Technology Assessment, Warsaw (2009).
- Agency for Quality and Accreditation in Health Care, Department for Development, Research and Health Technology Assessment: The Croatian guideline for health technology assessment process and reporting. Agency for Quality and Accreditation in Health Care, Zagreb (2011)
- AMCP Format Executive Committee members. The AMCP Format for Formulary Submissions (Version 4.0, April 2016). http://www.amcp.org/FormatV4/.
- Ändring i Tandvårds- och läkemedelsförmånsverkets allmänna råd (TLVAR 2003:2) om ekonomiska utvärderingar (2017).
- Behmane, D., Lambot, K., Irs, A., Steikunas, N.: Baltic guideline for economic evaluation of pharmaceuticals (pharmacoeconomic analysis) (2002). ttps://www.ispor.org/PEguidelines/source/Baltic-PE-guideline.pdf
- Capri, S., Ceci, A., Terranova, L., Merlo, F., Mantovani, L.: Guidelines for economic evaluations in italy: recommendations from the Italian group of pharmacoeconomic studies. Drug Inf. J. **35**, 189–201 (2001).
- Cleemput I, Neyt M, Van de Sande S, Thiry N. Belgian guidelines for economic evaluations and budget impact analyses: second edition. December 2015
- Cost-effectiveness Guidelines. State Institute for Drug Control (May 2017) (http://www.sukl.eu/)
- Da Silva, E.A., Pinto, C.G., Sampaio, C., Pereira, J.A., Drummond, M., Trindade, R.: Guidelines for economic drug evaluation studies. INFARMED **18**, 728–729 (1998).
- Document Operationalisierung der Begriffe Wirksamkeit, Zweckmässigkeit und Wirtschaftlichkeit; Arbeitspapier vom 21. Juli 2011 21. Juli 2011.
- Guidance to manufacturers for completion of New Product Assessment Form (NPAF). Glasgow, Scotland: Scottish Medicines Consortium (2017).
- Guidelines for conducting a comparative clinical and economic evaluation of drugs (2016); Guidelines for assessing the budget impact in the framework of the Programm of the State Guarantee of Free Medical Care in the Russian Federation (2016).
- Guidelines for the Economic Evaluation of Health Technologies in Ireland. 2018

- Guidelines for the economic evaluation of health technologies: Canada. 4th ed. Ottawa: CADTH; 2017 Mar.
- Haute Autorité de Santé: Choices in methods for economic evaluation. Haute Autorité de Santé, Saint-Denis La Plaine (2012)
- Institute for Quality and Efficiency in Health Care: General methods for the assessment of the relation of benefits to costs. Institute for Quality and Efficiency in Health Care, Cologne (2009)
- Kristensen, F.B., Sigmund, H. (eds.): Health technology assessment handbook Copenhagen: Danish Centre for Health Technology Assessment. National Board of Health. 2008.
- Lääkkeiden Hintalautakunta Läkemedelsprisnämden: Preparing a health economic evaluation to be attached to the application for reimbursement status and wholesale price for a medicinal product. Ministry of Social Affairs and Health, Pharmaceuticals Pricing Board. 2017.
- López-Bastida, J., Oliva, J., Antoñanzas, F., García-Altés, A., Gisbert, R., Mar, J., et al.: Spanish recommendations on economic evaluation of health technologies. Eur. J. Heal Econ. 11, 513–20.(2010).
- Metodicka´ pomoˆcka k vyhla´sˇke Ministerstva zdravotnı´ctva Slovenskej republiky e`. 343/ 2008 Z. z. o podrobnostiach farmakoekonomicke ´ho rozboru lieku [Guideline to the Decree of the Ministry of Health of the Slovak Republic no. 343/2008 Z. z.: the details of pharmacoeconomic analysis of drugs]. Ministerstvo zdravotnı´ctva Slovenskej republiky [Slovak Republic Ministry of Health] (2009).
- National Institute for Health and Care Excellence: Guide to the methods of technology appraisal 2013.
- Norwegian Medicines Agency: Guidelines on how to conduct pharmacoeconomic analyses. Norwegian Medicines Agency, Oslo (2012).
- Pharmaceutical Benefits Advisory Committee (PBAC). Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (version 5.0). Australian Government – Department of Health 2016.
- Professional healthcare guideline on the methodology of health technology assessment. National Institute of Pharmacy and Nutrition Volume 67, Issue 1, 2017
- Rules on Classification of Medicines on the List, accepted by the Health Insurance Institute of Slovenia on April 26, 2013.
- Walter E, Zehetmayr S. Guidelines zur gesundheitso¨konomischen Evaluation Konsenspapier [Guidelines for health-economic evaluations in Austria]. Wien. Med. Wochenschr. 156(23–24), 628–

632 (2006).

- Zorginstituut Nederland (ZIN). Guideline for economic evaluations in healthcare | 16 juni 2016.

Appendix 1: Measurement of informal caregiving

One of the relevant issues to be considered before evaluating costs associated with informal care is the way in which the caregiving time is collected. There are three main methods to acquire the information related to caregiving: the recall method, the daily method and the direct questions.

In the **daily method**, considered the gold standard way of measuring unpaid caregiving, caregivers are asked to report the time spend in doing all the tasks provided during a specified period of time. More precisely, a daily way of asking for time spent in informal caregiving during a typical 24-h period was developed by van den Berg & Spauwen (2006). Here, informal care tasks are divided into: (i) support activities of daily living (ADL) such as eating, drinking, personal care, moving around in the house and out of house; (ii) support with instrumental activities of daily living (IADL) such as making trips, healthcare contacts, organising help, aids, house adaptations or taking care of financial matters; (iii) housework such as preparation of food and drinks, cleaning the house, washing, ironing and sewing, shopping and maintenance work; and (iv) several general categories such as sleeping, paid work and unpaid work. The questions are collected several times a day, for instance, during breakfast, lunch, dinner, between breakfast and lunch, between lunch and dinner, and before going to bed. However, due to its procedure, one of the main disadvantages of this method is the fact that it does not only require a lot of time and effort but also it is highly costly, and it is not always feasible

Regarding **recall method**, it provides retrospective information on how much time caregivers spent on a list of tasks during the previous day or week as a whole. In fact, the recall questionnaire focuses on the same tasks as the diary. However, comparing these different methods, the time collected through the diary method tends to be lower in comparison with those obtained from the recall method, especially in tasks related to housework (van den Berg et al., 2004), making the recall method more likely to overestimate the time spent on caregiving and seems to be unstable over time. However, if one assumes that caregivers are able to separate the usual tasks from the tasks provided due the demand of the disabled person, the recall method is a valid instrument to collect unpaid time of care in comparison with the diary (van den Berg & Spauwen, 2006). Finally, as mentioned before, even though the daily method allows collecting complete and detailed information on caregiving, it is very time-consuming method and, consequently, it might generate bias.

Another different way of collecting unpaid care is those proposed by Homan in which time is measured in an aggregated way instead of in the disaggregated ways as occurs with the previous methods mentioned above (Homan, 1988). More precisely, this method considers just one question related to the aggregated time spent in caring concerning just a certain task, rather than many different questions. For instance, a question could be: "how many hours do you spend in household tasks?" In this way, the issue related to double accounting is solved.

An issue to highlight when collecting caregiving time is what is called *"joint production"*. This is defined as carrying out more than one activitiy simultaneously by one person and it is not possible to distinguish whether these activities are done because of carer or because of leisure. An example of that case is when a caregiver supervises a person with limitations at the same time that she/he watches TV or when a caregiver cooks, not only for the person who is cared for but for all the family. Linked to this issue, another very common problem is the overestimation of caregiving hours, especially in recall method, as many caregivers tend to declare caring 24 hours per day for 365 days annually, because they cannot distinguish between care tasks and leisure (joint production). In that cases, researchers often use a restriction of 16 hours per day of caring, considering, at least, 8 hours for rest (Oliva-Moreno et al., 2017).

There are several instruments to measure the time spent by family in providing care (all of them follow the recall method); the Caregiver Activity Time Survey (CATS), the Caregivers Activity Survey (CAS) and the Resource Utilization in Dementia (RUD) (Clipp & Moore, 1995; Davis et al., 1997; and Wimo et al., 2002). However, they also lead to the same concerns as mentioned above when measuring hours of informal care. Nevertheless, a recent paper designed a standardized questionnaire for measurement, valuation and estimation of costs of informal care (Landfeldt et al., 2019), trying to solve some of these issues. The questionnaire is called "Caregivers Indirect and Informal care Cost Assessment Questionnaire (CIIQ)", which contains 13 questions related to caregiver working situation as well as the provision of family care. In fact, not only unpaid care is measured but also paid informal care is collected in this questionnaire. Particularly, it calculates the total number of hours of unpaid care, in which a minimum number of rest of six hours daily is considered for eating, sleeping and toileting. In

brief, the novelty of such questionnaire is the fact that it collects information on working week annually and number of weeks of annual leave, including paid vacations and public holidays to perform a more accurate estimation of the valuation of informal care in terms of forgone activities due to care by caregivers. However, it has some bias recoded such as only one caregiver is interview or not possibility to separate normal task from the caregiving tasks.

In brief, it is well-known that there is a high heterogeneity in the methodological aspects related to measure the unpaid caregiving. In fact, more than 53% of all cost of illness studies have not revealed the measurement methods applied when incorporating informal care cost, about 27% used recall method, 15% used direct questions and more than 4% used other unspecified ones. This leads to a huge difference in the estimation of informal caregiving hours across studies, which ranges from 10 to 120 weekly hours in diseases such as dementia (Oliva-Moreno et al., 2017).

References Appendix 1

- Clipp EC, Moore MJ. Caregiver time use: an outcome measure in clinical trial research on Alzheimer's disease. Clin Pharmacol Ther. 1995; 58(2):228-36.
- Davis KL, Marin DB, Kane R, Patrick D, Peskind ER, Raskind MA, Puder KL. The Caregiver Activity Survey (CAS): development and validation of a new measure for caregivers of persons with Alzheimer's disease. International Journal of Geriatric Psychiatry 1998; 12(10): 978-988.
- Homan ME. The Allocation of Time and Money in One-Earner and Two Earner Families; An EconomicAnalysis. Erasmus University Rotterdam: Rotterdam, 1988
- Landfeldt E, Zethraeus N, Lindgren P. Standardized Questionnaire for the Measurement, Valuation, and Estimation of Costs of Informal Care Based on the Opportunity Cost and Proxy Good Method. Applied Health Economics and Health Policy 2019; 17(1): 15-24
- Oliva-Moreno J, Trapero-Bertran M, Peña-Longobardo LM, Del Pozo-Rubio R. The Valuation of Informal Care in Cost-of-Illness Studies: A Systematic Review. Pharmacoeconomics. 2017;35(3):331-45.
- van den Berg B, Brouwer W, Koopmanschap M. Economic valuation of informal care: An overview of methods and applications. Eur J Health Econ., 2004; 5: 36-45.
- van den Berg B, Spauwen P. Measurement of informal care: an empirical study into the valid measurement of time spent on informal caregiving. Health Economics 2006; 15(5): 447-460
- Wimo A, von Strauss E, Nordberg G, Sassi F, Johansson L. Time spent on informal and formal care giving for persons with dementia in Sweden. Health Policy. 2002; 61(3):255-68.

Appendix 2

Table A2.1: List of economic evaluations including social costs (productivity losses, informal care costs or both) by disease and year of publication

Authors & publication year	Country	Disease	Type of Economic Evaluation	Intervention type	Productivity losses included		Informal care costs included	
					Yes / No	*Method*	*Yes / No*	*Method*
ALZHEIMER´S DISEASE								
Michaud et al. (2018)	United States	Alzheimer´s Disease	CUA	Diagnostic / screening	No	-	Yes	Replacement cost method
Lamb et al. (2018)	United Kingdom	Alzheimer´s Disease	CUA	Non-pharmacological therapy	Yes	Human capital approach	Yes	Opportunity cost method
Hornberger et al. (2017)	France	Alzheimer´s Disease	CUA	Diagnostic / screening	No	-	Yes	Opportunity cost method
Tong et al. (2017)	United Kingdom	Alzheimer´s Disease	CUA	Diagnostic / screening	No	-	Yes	Not available
Knapp et al. (2017)	United Kingdom	Alzheimer´s Disease	CUA	Pharmaceutical	No	-	Yes	Opportunity cost and

Authors & publication year	Country	Disease	Type of Economic Evaluation	Intervention type	Productivity losses included		Informal care costs included	
					Yes / No	*Method*	*Yes / No*	*Method*
								replacement cost method
Hornberger et al. (2015)	Spain	Alzheimer´s Disease	CUA	Diagnostic	No	-	Yes	Opportunity cost method
Saint-Laurent et al. (2015)	United States	Alzheimer´s Disease	CUA	Pharmaceutical	No	-	Yes	Not available
D´Amico et al. (2015)	United Kingdom	Alzheimer´s Disease	CUA/CEA	Medical procedure	No	-	Yes	Opportunity cost method
Orgeta et al. (2015)	United Kingdom	Alzheimer´s Disease	CUA	Non-pharmacological therapy	No	-	Yes	Opportunity cost and replacement cost method
Touchon et al. (2014)	France	Alzheimer´s Disease	CUA	Pharmaceutical	No	-	Yes	Not available
Sogaard et al. (2014)	Denmark	Alzheimer´s Disease	CUA	Non-pharmacological therapy	No	-	Yes	Opportunity cost method

Authors & publication year	Country	Disease	Type of Economic Evaluation	Intervention type	Productivity losses included		Informal care costs included	
					Yes / No	*Method*	*Yes / No*	*Method*
Romeo et al. (2013)	United Kingdom	Alzheimer´s Disease	CUA/CEA	Pharmaceutical	No	-	Yes	Opportunity cost and replacement cost method
Pfeil et al. (2012)	Switzerland	Alzheimer´s Disease	CUA	Pharmaceutical	No	-	Yes	Not available
Hartz et al. (2012)	Germany	Alzheimer´s Disease	CUA	Pharmaceutical	No	-	Yes	Opportunity cost mehtod
Rive et al. (2012)	Norway	Alzheimer´s Disease	CUA	Pharmaceutical	No	-	Yes	Opportunity cost method
Getsios et al. (2012)	United Kingdom	Alzheimer´s Disease	CUA	Pharmaceutical	No	-	Yes	Opportunity cost method
Guo et al. (2012)	United States	Alzheimer´s Disease	CUA	Diagnostic / screening	No	-	Yes	Opportunity cost method
Woods et al. (2012)	United Kingdom	Alzheimer´s disease	CUA/CEA	Non-pharmacological therapy	No	-	Yes	Not available

Authors & publication year	Country	Disease	Type of Economic Evaluation	Intervention type	Productivity losses included		Informal care costs included	
					Yes / No	*Method*	*Yes / No*	*Method*
Lachaine et al. (2011)	Canada	Alzheimer´s Disease	CUA	Pharmaceutical	No	-	Yes	Opportunity cost method
Nagy et al. (2011)	United Kingdom	Alzheimer´s Disease	CUA	Pharmaceutical	No	-	Yes	Opportunity cost method
Getsios et al. (2010)	United Kingdom	Alzheimer´s Disease	CUA	Pharmaceutical	No	-	Yes	Opportunity cost method
López-Bastida et al. (2009)	Spain	Alzheimer´s Disease	CUA	Pharmaceutical	No	-	Yes	Opportunity cost method
Wolfs et al. (2009)	The Netherlands	Alzheimer´s Disease	CUA	Diagnostic	No	-	Yes	Opportunity cost method
Fuh et al. (2008)	Taiwan	Alzheimer´s Disease	CUA	Pharmaceutical	No	-	Yes	Opportunity cost and replacement method
Kirbach et al. (2008)	United States	Alzheimer´s Disease	CUA	Pharmaceutical	No	-	Yes	Not available

Authors & publication year	Country	Disease	Type of Economic Evaluation	Intervention type	Productivity losses included		Informal care costs included	
					Yes / No	*Method*	*Yes / No*	*Method*
Weycker et al. (2007)	United States	Alzheimer´s Disease	CUA	Pharmaceutical	No	-	Yes	Replacement cost method
McMahon et al. (2000)	United States	Alzheimer´s Disease	CUA	Diagnostic / screening	No	-	Yes	Opportunity cost method
RARE DISEASES								
Sheng et al. (2017)	China	Chronic myeloid leukemia	CUA/CEA	Care delivery	Yes	Human capital approach	No	-
Landfeldt et al. (2017)	United Kingdom	Duchenne Muscular dystrophy	CUA	Diagnostic	Yes	Human capital approach	Yes	Opportunity cost method
Borg et al. (2016)	Sweden	Multiple Myeloma	CUA/CEA	Pharmaceutical	Yes	Net production minus consumption during the patient´s remaining life	No	-

Authors & publication year	Country	Disease	Type of Economic Evaluation	Intervention type	Productivity losses included		Informal care costs included	
					Yes / No	*Method*	*Yes / No*	*Method*
Park et al., (2016)	Korea	Multidrug-resistant tuberculosis	CUA	Pharmaceutical	Yes	Human capital approach	No	-
Diel et al (2015)	Germany	Tuberculosis	CUA/CEA	Pharmaceutical	Yes	Human capital approach	No	-
van Dussen et al. (2014)	The Netherlands	Type 1 Gaucher disease	CUA	Pharmaceutical	Yes	Human capital approach	No	-
Kanters et al. (2014)	The Netherlands	Pompe disease	CUA/CEA	Pharmaceutical	No	-	Yes	Opportunity cost method
Kulpeng et al. (2014)	Thailand	Chronic Myeloid Leukemia	CUA/CEA	Pharmaceutical	Yes	Not available	No	-
Wilson et al. (2014)	United Kingdom	Idiopathic pulmonary fibrosis	CUA/CEA	Pharmaceutical	Yes	Human capital approach	No	-

Authors & publication year	Country	Disease	Type of Economic Evaluation	Intervention type	Productivity losses included		Informal care costs included	
					Yes / No	*Method*	*Yes / No*	*Method*
Rombach et al. (2013)	The Netherlands	Fabry-Anderson disease	CUA/CEA	Pharmaceutical	Yes	Human capital approach	No	-
Luan et al. (2011)	United States	Cytomegalovirus, Kidney Transplant	CUA/CEA	Pharmaceutical	Yes	Human capital approach	No	-
Ghatnekar et al. (2010)	Sweden	Chronic Myeloid Leukemia	CUA/CEA	Pharmaceutical	Yes	Human capital approach	No	-
Luan et al. (2009)	United States	Cytomegalovirus, Kidney Transplant	CUA/CEA	Pharmaceutical	Yes	Human capital approach	No	-
Risebrough et al. (2008)	Canada	Haemophilia	CUA	Pharmaceutical	No	-	Yes	Opportunity cost method
Teerawattananon et al. (2007)	Thailand	Cytomegalovirus retinitis HIV/AIDS	CUA	Pharmaceutical	Yes	Human capital approach	Yes	Opportunity cost method
Miners et al. (2002)	United Kingdom	Haemophilia	CUA	Care delivery / Pharmaceutical	Yes	Human capital approach	No	-

Authors & publication year	Country	Disease	Type of Economic Evaluation	Intervention type	Productivity losses included		Informal care costs included	
					Yes / No	*Method*	*Yes / No*	*Method*
Gulbrandsen et al. (2001)	Norway	Multiple Myeloma	CUA	Pharmaceutical	Yes	Human capital approach	No	-
STROKE								
Steen Carlsson et al. (2017)	Sweden	Acute ischemic stroke	CUA/CEA	Surgical	Yes	Not available	No	-
Salata et al. (2016)	United States	Atrial fibrillation	CUA	Pharmaceutical	Yes	Human capital approach	No	-
Van Eeden et al. (2015)	The Netherlands	Stroke	CUA/CEA	Health education or behaviour	Yes	Human capital approach	Yes	Replacement cost method
Parody et al. (2015)	Spain	Stroke	CUA	Medical procedure	Yes	Not available	No	-
Foster et al. (2015)	United Kingdom	Stroke	CUA	Care delivery	No	-	Yes	Not available
Barón Esquivias et al. (2014)	Spain	Stroke	CUA/CEA	Pharmaceutical	No	-	Yes	Not available

Authors & publication year	Country	Disease	Type of Economic Evaluation	Intervention type	Productivity losses included		Informal care costs included	
					Yes / No	*Method*	*Yes / No*	*Method*
Doan et al. (2013)	United Kingdom	Upper limb post-stroke spasticity	CUA	Pharmaceutical	No	-	Yes	Opportunity cost method
Demaerschalk et al. (2013)	United States	Stroke	CUA	Care delivery	No	-	Yes	Opportunity cost method
Forster et al. (2013)	United Kingdom	Stroke	CUA	Care delivery	No	-	Yes	Not available
González-Juanatey et al. (2012)	Spain	Stroke & atrial firbrillation	CUA	Pharmaceutical	No	-	Yes	Opportunity cost method
Svensson et al. (2012)	Sweden	Stroke	CUA/CEA	Medical procedure	Yes	Human capital approach	No	-
Araújo et al. (2010)	Brazil	Stroke	CUA	Pharmaceutical	Yes	Human capital approach	No	-
Slejko et al. (2010)	United States	Cardiovascular diseases	CUA	Pharmaceutical	Yes	Human capital approach	No	-
Maud et al. (2010)	United States	Carotid stenosis	CUA	Medical procedure	Yes	Not available	No	-

Authors & publication year	Country	Disease	Type of Economic Evaluation	Intervention type	Productivity losses included		Informal care costs included	
					Yes / No	*Method*	*Yes / No*	*Method*
Mar et al. (2005)	Spain	Stroke	CUA	Medical procedure / pharmacological	No	-	Yes	Not available
Jönsson et al. (2005)	Sweden	Stroke	CUA	Pharmaceutical	Yes	Not available	No	-
Patel et al. (2004)	United Kingdom	Stroke	CUA	Care delivery	No	-	Yes	Opportunity and replacement cost method
DIABETES MELLITUS								
Roze et al. (2017)	Denmark	Diabetes mellitus type 1	CUA	Medical device	Yes	Human capital approach	No	-
Slangen et al. (2017)	The Netherlands	Diabetes mellitus type 2	CUA	Surgical	Yes	Friction cost method	Yes	Opportunity cost method
Farshchi et al. (2016)	Iran	Diabetes mellitus type 2	CUA	Pharmaceutical	Yes	Not available	No	-

Authors & publication year	Country	Disease	Type of Economic Evaluation	Intervention type	Productivity losses included		Informal care costs included	
					Yes / No	*Method*	*Yes / No*	*Method*
Nguyen et al. (2016)	Singapore	Diabetes mellitus type 2	CUA	Screening	Yes	Not available	No	-
Kolu et al. (2016)	Finland	Diabetes mellitus type 2	CUA	Health education intervention	Yes	Human capital approach	No	-
Roze et al. (2016)	United Kingdom	Diabetes mellitus type 1	CUA	Medical device, pharmaceutical	Yes	Human capital approach	No	-
Roze et al. (2016)	France	Diabetes mellitus type 1	CUA	Medical device, pharmaceutical	Yes	Human capital approach	No	-
Haig et al. (2016)	Canada	Diabetes mellitus type 1 or type 2	CUA	Medical procedure, pharmaceutical	Yes	Not available	No	-
Roze et al. (2016)	The Netherlands	Diabetes mellitus type 1	CUA	Pharmaceutical	Yes	Not available	No	-
Huetson et al. (2015)	Norway	Diabetes mellitus type 2	CUA	Pharmaceutical	Yes	Human capital approach	No	-

Authors & publication year	Country	Disease	Type of Economic Evaluation	Intervention type	Productivity losses included		Informal care costs included	
					Yes / No	*Method*	*Yes / No*	*Method*
Brown et al. (2015)	United States	Diabetes mellitus type 1 or type 2	CUA	Pharmaceutical	Yes	Human capital approach	Yes	Not available
Steen and Persson (2014)	Sweden	Diabetes mellitus type 2	CUA	Pharmaceutical	Yes	Human capital approach	No	-
Kiadaliri et al. (2014)	Sweden	Diabetes mellitus type 2	CUA / CEA	Pharmaceutical	Yes	Human capital approach	No	-
Tsiachristas et al. (2014)	The Netherlands	Diabetes mellitus type 2	CUA	Management program intervention	Yes	Friction cost method	No	-
Valentine et al. (2011)	Switzerland	Diabetes mellitus type 2	CUA/CEA	Pharmaceutical	Yes	Human capital approach	No	-
Kasteng et al. (2011)	Sweden	Diabetes mellitus type 1 or type 2	CUA	Pharmaceutical	Yes	Days lost from work multiplied by the average national gross income plus	No	-

Authors & publication year	Country	Disease	Type of Economic Evaluation	Intervention type	Productivity losses included		Informal care costs included	
					Yes / No	*Method*	*Yes / No*	*Method*
						employer contributions		
Kuo et al. (2011)	United States	Diabetes mellitus type 1 or type 2	CUA	Care delivery	Yes	Human capital approach	No	-
Patel et al. (2011)	United Kingdom	Diabetes mellitus type 1	CUA/CEA	Health education or behaviour	Yes	Not available	Yes	Not available
Greeley et al. (2011)	United States	Diabetes mellitus type 1	CUA	Screening	No	-	Yes	Not available
Valentine et al. (2011)	Sweden	Diabetes mellitus type 1	CUA/CEA	Pharmaceutical	Yes	Human capital approach	No	-
Huang et al. (2010)	United States	Diabetes mellitus type 1	CUA	Diagnostic – Medical device	Yes	Not available	Yes	Not available
Gschwend et al. (2009)	Belgium, France, Germany, Italy and Spain	Diabetes mellitus type 1	CUA	Pharmaceutical	Yes	Human capital approach	No	-

Authors & publication year	Country	Disease	Type of Economic Evaluation	Intervention type	Productivity losses included		Informal care costs included	
					Yes / No	*Method*	*Yes / No*	*Method*
Lindgren et al. (2007)	Sweden	Diabetes mellitus type 2	CUA/CEA	Health education or behaviour	Yes	Not available	No	-
Hoerger et al. (2007)	United States	Pre-diabetes	CUA/CEA	Diagnostic – Health education or behaviour	Yes	Not available	No	-
Valentine et al. (2006)	United States	Diabetes mellitus	CUA/CEA	Pharmaceutical	Yes	Not available	No	-
Herman et al. (2005)	United States	Diabetes mellitus type 2	CUA	Health education intervention – pharmaceutical	Yes	Not available	No	-
Rosen et al. (2005)	United States	Diabetes melitus	CUA/CEA	Pharmaceutical	Yes	Not available	Yes	Not available
Eddy et al. (2005)	United States	Diabetes melitus	CUA	Health education or behaviour	Yes	Not available	No	-

Authors & publication year	Country	Disease	Type of Economic Evaluation	Intervention type	Productivity losses included		Informal care costs included	
					Yes / No	*Method*	*Yes / No*	*Method*
The Diabetes Prevention Program Research Group (2003)	United States	Diabetes mellitus type 2	CUA	Pharmaceutical – Health education or behaviour	Yes	Not available	No	-
Almbrand et al. (2000)	Sweden	Diabetes melitus type 1 or type 2	CUA/CEA	Pharmaceutical	Yes	Human capital approach	No	-

CUA: Cost-Utility Analysis; CEA: Cost-Effectiveness Analysis

Table A2.2: List of economic evaluations including productivity losses using the human capital approach or the friction cost method or others.

Authors & publication year	Country	Disease	Human capital approach			Friction cost method			Others
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*	
Lamb et al. (2018)	United Kingdom	Alzheimer´s Disease	36.74£ per hour	National official registers (ONS)	Gender-specific median earnings data by occupational classifications				
Sheng et al. (2017)	China	Chronic myeloid leukemia	Not available	National official registers (National Bureau of Statistics of China)	Average salary income by age-group				
Landfeldt et al. (2017)	United Kingdom	Duchenne Muscular dystrophy	92,495£ per year	Landfeldt et al. (2016)	Production losses				

Authors & publication year	Country	Disease	Human capital approach			Friction cost method			Others
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*	
					due to absenteeism and impaired productivity while working				
Roze et al. (2017)	Denmark	Diabetes mellitus type 1	DKK 615,965.56 per year for males and DKK 422,627.56 per year for females	National official registers (Statistics Denmark)	Average male and female annual salaries. Average age at first income was 26 years old and average age of retirement at 65 years old				

Authors & publication year	Country	Disease	Human capital approach			Friction cost method			Others
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*	
Slangen et al. (2017)	The Netherlands	Diabetes mellitus type 2				Not available	National official registers (ZiNL: Dutch governmental manual for health care cost analysis, 2015) (86)	Production losses are confined to the period needed to replace a sick worker	
Kolu et al. (2016)	Finland	Diabetes mellitus type 2	4,365.53€ per month	National official registers (Statistics Finland)	Women's average national monthly salary scales multiplied by 1.3 to encompass related expenses.				

Authors & publication year	Country	Disease	Human capital approach			Friction cost method			Others
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*	
Roze et al. (2016)	United Kingdom	Diabetes mellitus type 1	Not available	Not available	Average annual salaries for the UK				
Roze et al. (2016)	France	Diabetes mellitus type 1	56,032€ for males and 45,198.82€ for females per year	National official registers (Institut National de la Statistique et des Études Économiques: Écart de Salaires Mensuels Nets Entre les Hommes et les Femmes en 2012)	Average male and female annual salaries. Average age at first income was 26 years old and average age of retirement at 65 years old				

Authors & publication year	Country	Disease	Human capital approach			Friction cost method			Others
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*	
Salata et al. (2016)	United States	Atrial fibrillation	28.14$ per hour	National official registers (June 2006 National Compensation Survey)	National average wage				
Borg et al. (2016)	Sweden	Multiple Myeloma							Net production minus consumption during the patient´s remaining life (Ekman, 2002)
Park et al. (2016)	Korea	Multidrug-resistant tuberculosis	23,735.21 Korean wons	National official registers (Korean Statistical	As a parameter entered to the model, the mean hourly wage was				

Authors & publication year	Country	Disease	Human capital approach			Friction cost method			Others
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*	
				Information Service)	multiplied by mean labour time in a monthly cycle and by employment -population ratio				
Van Eeden et al. (2015)	The Netherlands	Stroke	Not available	Not available	Calculated by multiplying the number of sick days by the costs of labour, corrected for different age categories				

Authors & publication year	Country	Disease	Human capital approach			Friction cost method			Others
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*	
Diel et al (2015)	Germany	Tuberculosis	10.71€ per hour	Literature (Diel et al., 2014)					
Huetson et al. (2015)	Norway	Diabetes mellitus type 2	Not available	Not available	Time off work per complicatio n and event experienced				
Brown et al. (2015)	United States	Diabetes mellitus type 1 or type 2	41,361.10$ per year	National official registers (Bureau of Labour Statistics. B-2: Average Hours and Earnings of Production and Nonsupervisory Employees	Considering decreases in employment for diabetics and employment rates for people aged 63 years old				

Authors & publication year	Country	Disease	Human capital approach			Friction cost method			Others
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*	
				on Private Nonfarm Payrolls by Major Industry Sector, 1966 to Date. U.S. Census Bureau Economics and Statistics Administration)					
van Dussen et al. (2014)	The Netherlands	Type 1 Gaucher disease	34.79€ per hour	National data (Dutch costing manual 2010 for health care research)	Sick leave and (permanent) work disability				
Wilson et al. (2014)	United Kingdom	Idiopathic pulmonary fibrosis	16.59£ per hour	National official registers (ONS					

Authors & publication year	Country	Disease	Human capital approach			Friction cost method			Others
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*	
				and Annual Survey of Hours and Earnings (ASHE) 2012)					
Kiadaliri et al. (2014)	Sweden	Diabetes mellitus type 2	6,753.73SEKs if age 0-19 years old; 363,832.58SEKs if age 20-34; 557,796.18SEKs if age 35-49; 496,306.66SEKs if age 50-64; 22,352.88SEKs if age 65-74; 2,536.17SEKs if age 75-84; 414.31SEKs if age ≥ 85	National official registers (Statistics Sweden)	Age-specific expected annual salary adjusted for hours worked and labour force participation				

Authors & publication year	Country	Disease	Human capital approach			Friction cost method			Others
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*	
Tsiachristas et al. (2014)	The Netherlands	Diabetes mellitus type 2				**Males**: 11.19€ per hour if age 15-19 years old; 20.58€ if age 20-24; 28.05€ if age 25-29; 34.38€ if age 30-35; 39.46€ if age 35-40; 42.53€ if age 40-45; 44.44€ if age 45-50; 45.30€ if age 50-55; 45.67€ if age 55-60; 45.38€ if age 60-65 **Females**: 10.16€ per hour if age 15-19 years old; 19.92€ if age	Literature (Tan et al., 2012)	The friction cost period was determined at 23 weeks (160 days). The productivity costs per hour is reflected by the gross added value of the labour that a worker would have produced,	

Authors & publication year	Country	Disease	Human capital approach			Friction cost method			Others
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*	
						20-24; 27.39€ if age 25-29; 31.94€ if age 30-35; 33.92€ if age 35-40; 33.70€ if age 40-45; 33.53€ if age 45-50; 33.92€ if age 50-55; 34.21€ if age 55-60; 33.25€ if age 60-65		including a correction for the elasticity of labour time (0.8)	
Steen and Persson (2014)	Sweden	Diabetes mellitus type 2	6,753.73SEKs if age 0-19 years old; 363,832.58SEKs if age 20-34; 557,796.18SEKs if age 35-49; 496,306.66SE	National official registers (Statistics Sweden)	Age-specific expected annual salary adjusted for hours worked and labour				

Authors & publication year	Country	Disease	Human capital approach			Friction cost method			Others
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*	
			Ks if age 50-64; 22,352.88SEKs if age 65-74; 2,536.17SEKs if age 75-84; 414.31SEKs if age ≥ 85		force participation				
Rombach et al. (2013)	The Netherlands	Fabry-Anderson disease	34.79€ per hour	National data (Dutch costing manual 2010 for health care research)	Sick leave and (permanent) work disability				
Svensson et al. (2012)	Sweden	Stroke	92.42$ per hour		Mean full-time employment (35 hours of work per week) wage of Sweden including pay roll				

Authors & publication year	Country	Disease	Human capital approach			Friction cost method			Others
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*	
					taxes. Adjustments for part-time employment and unemployment were made to represent the actual mean income of a person in the workforce.				
Luan et al. (2011)	United States	Cytomegalovirus, Kidney Transplant	277.34 and 776.56$ per year	Authors´ assumption	5 and 10 working days were lost for patients				

Authors & publication year	Country	Disease	Human capital approach			Friction cost method			Others
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*	
					with CMV disease without and with a hospital admission, respectively				
Valentine et al. (2011)	Switzerland	Diabetes mellitus type 2	Not available	Not available	Average annual salaries for men and women of working age in each country				
Kasteng et al. (2011)	Sweden	Diabetes mellitus type 1 or type 2							Days lost from work multiplied by the average national gross income

Authors & publication year	Country	Disease	Human capital approach			Friction cost method			Others
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*	
									plus employer contributions
Kuo et al. (2011)	United States	Diabetes mellitus type 1 or type 2	Not available	National official registers (U.S. Department of Labour; Bureau of Labour Statistics)	Average hourly wage of a U.S. nonfarm production worker				
Valentine et al. (2011)	Sweden	Diabetes mellitus type 1	165,470.93SEKs for males and 137,996.51SEKs for females	National official registers (Statistics Sweden)	Gender-specific annual salaries for individuals between the ages of 18 and 65 years old				

Authors & publication year	Country	Disease	Human capital approach			Friction cost method			Others
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*	
Ghatnekar et al. (2010)	Sweden	Chronic Myeloid Leukemia	1,992.94€ per month	National official registers (Income Distribution Survey 2003)	Average monthly salary for individuals aged 45–64 years including pay-roll taxes of 41%				
Araújo et al. (2010)	Brazil	Stroke	12,605.39 R$ per month for productivity loss; 3,000.53 R$ per month for early retirement	National official registers (Instituto Brasileiro de Geografia e Estatística.IBGE, Pesquisa mensal de emprego: estimativas do mês de julho de 2007)	Loss of productivity and early retirement. Mean annual income and rate of unemployment for productivity loss; 12 minimum				

Authors & publication year	Country	Disease	Human capital approach			Friction cost method			Others
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*	
					wages for early retirement				
Slejko et al. (2010)	United States	Stroke	11.03$ per hour	National official registers (Current Population Survey of the Bureau of Labour Statistics, 2008)	Average wages for adults over 55 years				
Luan et al. (2009)	United States	Cytomegalovirus, Kidney Transplant	277.34 and 776.56$ per year	Authors´ assumption	5 and 10 working days were lost for patients with CMV disease without and with a				

Authors & publication year	Country	Disease	Human capital approach			Friction cost method			Others
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*	
					hospital admission, respectively				
Gschwend et al. (2009)	Belgium, France, Germany, Italy and Spain	Diabetes mellitus type 1	Not available	Not available					
Teerawattananon et al. (2007)	Thailand	Cytomegalovirus retinitis HIV/AIDS	60.95 Thai bats per hour	Structured questionnaire interviews					
Miners et al. (2002)	United Kingdom	Haemophilia	433.33 – 866.67£ per week	National official registers (Office for National Statistics: New earnings survey, 1998)	Weekly average UK gender and age-adjusted gross wage rate				

Authors & publication year	Country	Disease	Human capital approach			Friction cost method			Others
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*	
Gulbrandsen et al. (2001)	Norway	Multiple Myeloma	1,110.55 NOKs per day	Literature (Bank, personal communicatio n)					
Almbrand et al. (2000)	Sweden	Diabetes melitus type 1 or type 2	115,396.63€ per year	National official registers (Statistics Sweden)	Average value of labour production of a Swedish worker				

Unit costs updated to 2017 prices using the Consumer Price Index available in OECD Data.

Table A2.3: List of economic evaluations including informal care costs using the opportunity cost or the replacement cost method or others.

Authors & publication year	Country	Disease	Opportunity cost method			Replacement cost method		
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*
Michaud et al. (2018)	United States	Alzheimer´s Disease				Not available	Literature (Leon et al., 1998)	Hourly wage rate for home-health aides/personal care attendants
Lamb et al. (2018)	United Kingdom	Alzheimer´s Disease	36.74£ per hour	National official registers (ONS)	Gender-specific median earnings data by occupational classifications			
Hornberger et al. (2017)	France	Alzheimer´s Disease	42.92€ per hour	Literature (Biasutti et al., 2012)	Hourly rate for a district			

Authors & publication year	Country	Disease	Opportunity cost method			Replacement cost method		
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*
					nurse in France			
Knapp et al. (2017)	United Kingdom	Alzheimer´s Disease	16.9£ per hour	Literature (Curtis et al., 2014)	Hourly minimum wage	41.6£ per hour	Literature (Curtis et al., 2014)	Home care worker hourly wage
Landfeldt et al. (2017)	United Kingdom	Duchenne Muscular dystrophy	Valued at 35% of the country-specific national mean gross wage	Literature (Johannesson et al., 1991; United States Department of Transportation, 2011)	Unpaid informal care was quantified as the number of hours of leisure time devoted to informal care			
Slangen et al. (2017)	The Netherlands	Diabetes mellitus type 2	7.44€ per hour	National data (Dutch governmental manual for				

Authors & publication year	Country	Disease	Opportunity cost method			Replacement cost method		
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*
				health care cost analysis.)				
Hornberger et al. (2015)	Spain	Alzheimer´s Disease	16.56€ per hour	Literature (Coduras et al., 2010)				
D´Amico et al. (2015)	United Kingdom	Alzheimer´s Disease	4.11£ per hour	Not available	UK national minimum wage			
Orgeta et al. (2015)	United Kingdom	Alzheimer´s Disease	6£ per hour	Not available	UK national minimum wage	19£ per hour	Not available	UK minimum wage of a home care professional
Van Eeden et al. (2015)	The Netherlands	Stroke				Not available	Not available	Hourly wage rates of professional caregivers
Sogaard et al. (2014)	Denmark	Alzheimer´s Disease	Not available	Not available	National age-matched			

Authors & publication year	Country	Disease	Opportunity cost method			Replacement cost method		
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*
					and gender-matched net and gross wages			
Kanters et al. (2014)	The Netherlands	Pompe disease	15.09€ per hour	Literature (Oostenbrink et al., 2004)	Wage rate of a paid housekeeper			
Romeo et al. (2013)	United Kingdom	Alzheimer´s Disease	8.84£ per hour	Literature (Curtis et al., 2010)	Hourly minimum wage	21.84£ per hour	Literature (Curtis et al., 2010)	Home care worker hourly wage
Doan et al. (2013)	United Kingdom	Upper limb post-stroke spasticity	7.91£ per hour	National official registers (UK 2009 Annual Survey of Hours and Earnings)	Median hourly earnings			
Demaerschalk et al. (2013)	United States	Stroke	15.50$ per hour	National official				

Authors & publication year	Country	Disease	Opportunity cost method			Replacement cost method		
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*
				registers (Bureau of labour statistics)				
Hartz et al. (2012)	Germany	Alzheimer´s Disease	3.45€ per hour	Literature (Teipel et al., 2007)				
Rive et al. (2012)	Norway	Alzheimer´s Disease	33.50€ (lost production) and 5.21€ (lost leisure time) per hour	Literature (Ramjerdi et al., 1997) and official registers (OECD, 2009)	Mean hourly earnings of employees in industry and revealed preference approach			
Getsios et al. (2012)	United Kingdom	Alzheimer´s Disease	5.74£ per hour	National official registers (HMRevenue and Customs)	UK national minimum wage			

Authors & publication year	Country	Disease	Opportunity cost method			Replacement cost method		
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*
Guo et al., (2012)	United States	Alzheimer´s Disease	4.89$ per hour	National official registers (US Department of Labour)	US federal minimum wage			
González-Juanatey et al. (2012)	Spain	Stroke & atrial firbrillation	11.70€ per hour	Literature (Hidalgo et al., 2011; Jiménez-Martín et al., 2011)				
Lachaine et al. (2011)	Canada	Alzheimer´s Disease	6.98 CAN$ and 16.21 CAN$ per hour	Literature (Hux et al., 1998)	Ontario minimum wage and average industrial aggregate wage			

Authors & publication year	Country	Disease	Opportunity cost method			Replacement cost method		
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*
Nagy et al. (2011)	United Kingdom	Alzheimer´s Disease	4.10£ per hour	Not available	UK national minimum wage			
Getsios et al. (2010)	United Kingdom	Alzheimer´s Disease	5.74£ per hour	National official registers (HMRevenue and Customs)	UK national minimum wage			
López-Bastida et al. (2009)	Spain	Alzheimer´s Disease	6.73€ per hour	Literature (López-Bastida et al., 2006)	Cost per hour of the gross wage for a domestic cleaner			
Wolfs et al. (2009)	The Netherlands	Alzheimer´s Disease	6.97€ per hour	Literature (Oostenbrink et al., 2004)	Wage rate of a paid housekeeper			

Authors & publication year	Country	Disease	Opportunity cost method			Replacement cost method		
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*
Fuh et al. (2008)	Taiwan	Alzheimer´s Disease	Not available	Not available	Average wage per hour	Not available	Not available	Hourly pay of a professional caregiver
Risebrough et al. (2008)	Canada	Haemophilia	12.39 CAN$	National official registers (Statistics Canada)				
Weycker et al. (2007)	United States	Alzheimer´s Disease				Not available	Literature (Leon et al., 1998)	Hourly wage rate for home-health aides/personal care attendants
Teerawattananon et al. (2007)	Thailand	Cytomegalovirus retinitis HIV/AIDS	64.09 Thai Bats	Structured questionnaire interviews				

Authors & publication year	Country	Disease	Opportunity cost method			Replacement cost method		
			Unit cost	*Source*	*Others*	*Unit cost*	*Source*	*Others*
Patel et al. (2004)	United Kingdom	Stroke	4.17£ per hour	Literature (McDaid, 2001)	UK minimum wage rate	12.54£ per hour	Literature (McDaid, 2001)	Unit cost of a social services home help worker
McMahon et al. (2000)	United States	Alzheimer´s Disease	17.56$ per hour	National official registers (US Bureau of Labour Statistics)				

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