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Standardizing the Inclusion of Indirect Medical Costs in Economic Evaluations

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Abstract

A shortcoming of many economic evaluations is that they do not include all medical costs in life-years gained (also termed indirect medical costs). One of the reasons for this is the practical difficulties in the estimation of these costs. While some methods have been proposed to estimate indirect medical costs in a standardized manner, these methods fail to take into account that not all costs in life-years gained can be estimated in such a way. Costs in life-years gained caused by diseases related to the intervention are difficult to estimate in a standardized manner and should always be explicitly modelled. However, costs of all other (unrelated) diseases in life-years gained can be estimated in such a way.

We propose a conceptual model of how to estimate costs of unrelated diseases in life-years gained in a standardized manner. Furthermore, we describe how we estimated the parameters of this conceptual model using various data sources and studies conducted in the Netherlands. Results of the estimates are embedded in a software package called 'Practical Application to Include future Disease costs' (PAID 1.0). PAID 1.0 is available as a Microsoft® Excel tool (available as Supplemental Digital Content via a link in this article) and enables researchers to 'switch off' those disease categories that were already included in their own analysis and to estimate future healthcare costs of all other diseases for incorporation in their economic evaluations.

We assumed that total healthcare expenditure can be explained by age, sex and time to death, while the relationship between costs and these three variables differs per disease. To estimate values for age- and sex-specific per capita health expenditure per disease and healthcare provider stratified by time to death we used Dutch cost-of-illness (COI) data for the year 2005 as a backbone. The COI data consisted of age- and sex-specific per capita health expenditure

uniquely attributed to 107 disease categories and eight healthcare provider categories. Since the Dutch COI figures do not distinguish between costs of those who die at a certain age (decedents) and those who survive that age (survivors), we decomposed average per capita expenditure into parts that are attributable to decedents and survivors, respectively, using other data sources.

Life-saving (or death-postponing) interventions induce medical consumption in so-called life-years gained (LYG). This medical consumption in LYG has also been labelled as 'indirect' medical costs and in the theoretical economic literature a further distinction has been made between related and unrelated medical costs in LYG.^[1] Subsequently, there has been discussion as to whether all of this medical consumption in LYG (related and unrelated) should be included in economic evaluations.^[1-8] In practice, as prescribed in (pharmacoeconomic) guidelines,^[9,10] many economic evaluations do take into account those costs in LYG that are related to the intervention under evaluation, while ignoring other medical costs altogether. However, the costs that are termed 'related' and therefore included, in practice do not necessarily adhere to the definitions of 'related' and 'unrelated' employed in the theoretical literature.^[11]

In the practice of economic evaluations, related costs are usually defined on the level of diseases, and only the costs occurring in LYG of diseases to which the intervention is targeted are taken into account. For instance, in an economic evaluation of statins for the prevention of cardiovascular disease, usually all costs of future cardiovascular disease are included and costs of all other diseases in LYG are excluded. In an evaluation of a colorectal cancer screening programme, only the future (averted) costs of colorectal cancer are included. However, if these interventions result in gains in life expectancy, it is likely that costs for other diseases, besides the diseases to which the intervention is targeted, will occur, so that the cost effectiveness might change.^[4,12-15] Theoretically, the distinction between related and unrelated has nothing to do with diseases, and costs are only unrelated if they, conditional on reaching a certain age, are independent of the intervention.^[1] In the above-mentioned examples on cardiovas-

cular disease and colorectal cancer, some of these disease-specific costs may be theoretically called related while others are not. Furthermore, costs of other diseases, which are not included in the economic evaluation, may also be partly related.

Besides the lack of consensus regarding the theoretical appropriateness of including future medical costs, we think that an important reason why many guidelines still do not advocate the inclusion of all future medical costs is the lack of practical tools to facilitate their inclusion. Since economic evaluations of life-saving (preventive and curative) interventions are conducted in a variety of settings, including those of new (and often expensive) drugs, a standardized way to account for medical costs in LYG is of great importance. However, the question then becomes 'how can we standardize the inclusion of indirect medical costs?'. The simplest way to include indirect medical costs in a standardized way is to multiply age-specific per capita medical consumption with the LYG in an economic evaluation. For example, if an intervention causes a person to die at his/her 80th birthday instead of his/her 79th, the indirect medical costs are then estimated by simply taking the average per capita health expenditure of a 79-year-old person.

However, adding age-specific average per capita health consumption has been shown to result in biased estimates of the apparent costs of ageing. Zweifel et al.^[16] were the first to conclude, using longitudinal Swiss sick fund data, that healthcare expenditure depend on time to death, rather than time since birth (age). Higher average healthcare costs at a higher age are caused mainly by the fact that elderly people die, with associated high healthcare utilization in the period just before dying. The role of proximity to death (also known as the 'red-herring' hypothesis) has been

confirmed in other studies.^[17-20] Further research revealed that the strength of the proximity to death effect differed starkly between healthcare providers^[20,21] and between different diseases.^[22] Wong et al.^[22] found that the time-to-death effect was strongest for the most lethal diseases such as lung cancer, septicemia, heart failure and renal failure. The diseases where the time-to-death effect could not be found had a non-life-threatening nature, and were either chronic or only had planned non-urgent inpatient treatment.

Gandjour and Lauterbach^[23] were the first to link the 'red herring' literature to the practice of economic evaluations. By modelling total per capita health expenditure conditional on age and proximity to death they demonstrated that cost-effectiveness analyses overestimate the incremental cost-effectiveness ratio (ICER) of preventive interventions if they do not explicitly model the high costs of the last year of life, as these costs are only postponed by prevention. Although Gandjour and Lauterbach^[23] showed that adding age-specific per capita costs without accounting for the high expenditure near death results in overestimates of medical costs in LYG. Their approach also has its limitations since it cannot be combined with most economic evaluations in practice. This holds because costs of related diseases are already included in most economic evaluations, and therefore it is incorrect to add *all* medical costs in LYG to the ICER, even when corrected for the costs in the last year of life.^[11] Clearly, only the costs of all other (unrelated) diseases should be included. One solution to this problem may be to *not* model the costs of related diseases in cases of life-saving interventions. Then, the approach proposed by Gandjour and Lauterbach^[23] could be considered appropriate.

However, simply adding per capita costs stratified by age and proximity to death ignores cost differences between diseases as well as the fact that some of these per capita costs will indeed significantly change as a result of the intervention. A successful weight loss intervention will change the per capita expenditure on diabetes and cardiovascular disease. However, it will probably not alter the expenditure on dementia, for instance. A colorectal cancer screening prevention will

probably influence future spending on colorectal cancer (and possibly also other types of cancer) but will not influence future spending on all other diseases. Therefore, while it is impossible to standardize the inclusion of indirect medical costs for all diseases and for all interventions, it might be possible to standardize inclusion of the indirect medical costs of *all other* diseases besides the diseases to which the intervention is targeted. This would make ICER estimates more precise as well as improve the comparability of results of different economic evaluations.

We describe a methodology that can be used to include costs of unrelated diseases during LYG in a standardized manner in economic evaluations. This methodology has been implemented in a toolkit designed to facilitate inclusion of indirect medical costs in economic evaluations in practice in the Netherlands: the 'Practical Application to Include future Disease costs' (PAID 1.0) [available as Supplemental Digital Content 1, <http://links.adisonline.com/PCZ/A95>. Important: be sure to enable the macros embedded in PAID 1.0. If these are disabled, PAID 1.0 does not function properly; please also download the manual (Supplemental Digital Content 2) from <http://links.adisonline.com/PCZ/A96>]. This tool enables researchers to incorporate indirect medical costs in their economic evaluation in a tailor-made fashion. Depending on the diseases for which costs are already included in the basic economic evaluation, future costs of all other diseases can be added using PAID 1.0, in combination with the survivor curves from the basic economic evaluation. This article highlights the methodology underlying PAID 1.0. In the following section, we explain the conceptual model and the data sources and methodology used to estimate the parameters of the conceptual model behind PAID 1.0. In the results section, we present the estimated model parameters embedded in PAID 1.0.

1. Methodology Underlying the 'Practical Application to Include future Disease costs' (PAID 1.0) Model

Suppose someone conducts an economic evaluation of a stroke care intervention resulting in a

substantial increase in life expectancy. The costs of stroke have already been estimated in this study as they are expected to change due to the intervention. An important question in that context obviously is *how* the costs of all other diseases should then be estimated?

1.1 Conceptual Framework

If the goal is to develop a general framework to estimate the costs of all diseases not directly related to an intervention, it is convenient to start by breaking total healthcare expenditure down by diseases. Conceptually, lifetime healthcare costs are then the sum of disease-specific expenditure one incurs throughout life. Since disease-specific expenditure is strongly determined by age and time to death,^[22] individual lifetime healthcare costs can be estimated using equation 1:

$$lhc(g) = \sum_a^{n-1} \sum_i sc_i(a, g) + \sum_i dc_i(n, g) \quad (\text{Eq. 1})$$

where $lhc(g)$ = lifetime healthcare costs for an individual of sex g ; a = age in years; n = age at death; dc = decedent costs (per capita healthcare costs in the last year of life); sc = survivor costs (per capita healthcare costs in all other years); and i = index for diseases.

Equation 1 simply states that individual healthcare expenditure are the sum of per capita disease-specific expenditure in the last year of life and 'other' years, and can be thought of as lifetime health expenditure if the current health expenditure pattern would remain constant. Now suppose an intervention that increases life expectancy influences the health expenditure for Z , a set of related diseases. The costs of all other diseases can then be simply estimated by summing over the remaining disease categories (equation 2):

$$\sum_a^{n-1} \sum_{i \notin Z} sc_i(a, g) + \sum_{i \notin Z} dc_i(n, g) \quad (\text{Eq. 2})$$

where Z = the set of related diseases.

By first breaking down lifetime healthcare expenditure into disease components, it is simple to exclude costs of certain diseases to avoid double counting of costs and to model the costs of those

diseases for which treatment patterns are expected to change separately.

The toolkit PAID 1.0 contains estimates of age- and sex-specific costs for a range of diseases stratified by last year of life and other years as in equation 1. PAID 1.0 is available as a Microsoft® Excel tool (see the Supplemental Digital Content 1) and enables researchers to select the diseases whose costs are already modelled and therefore should be excluded to calculate per capita costs for all other diseases as in equation 2. The costs of all other diseases as estimated with PAID 1.0 can then be combined with the survivor curves of the intervention and comparator under study to estimate differences in costs of unrelated diseases. The number of survivors in the scenarios can be multiplied with survivor costs of unrelated diseases estimated by PAID 1.0 and the number of deaths in both scenarios can be multiplied by the decedent costs of unrelated diseases estimated by PAID 1.0 (see the PAID 1.0 user manual available as Supplemental Digital Content 2 for more details on how to use PAID 1.0).

1.2 Estimating the Input of PAID 1.0: Disease-Specific Per Capita Health Expenditure Stratified by Last Year of Life and 'Other Years'

To produce consistent estimates of disease-specific per capita costs for decedents (costs per capita in the last year of life) and survivors (costs per capita in all other years) as in equation 1, we combined information from several data sources. As the backbone we used cost-of-illness (COI) data for the Netherlands in 2005.^[24] In that study, the 2005 total direct healthcare costs in different healthcare settings in the Netherlands were uniquely attributed to 107 disease categories (including the remainder category 'not disease related') and eight healthcare provider categories, specified by sex and 21 age classes. Appendix A in the Supplemental Digital Content 3 (<http://links.adisonline.com/PCZ/A97>) displays tables of the health providers (table A1) and diseases (table A2) distinguished in the 2005 COI study. This was a sequel to earlier 1999 and 2003 Dutch COI studies^[25-27] and COI estimates were made using the healthcare cost definitions of the System of

Health Accounts (SHA)^[28] for international comparability. To translate the age categories from the COI data into age-year-specific per capita health expenditure, we interpolated the 21 age classes using cubic splines.

Since the Dutch COI figures do not distinguish between costs of survivors and decedents, the most important step in the estimation of equation 1 was the decomposition of average per capita expenditure into a part that is attributable to those who die at a certain age and a part that is attributable to those who survive that age. This decomposition was accomplished by assuming that average costs in a single year at a particular age is the weighted average of those surviving that year and those dying that particular year (note that all input parameters and model calculations are age and sex specific, but that for notational purposes age and sex indices were omitted) [equation 3]:

$$ac_i = (1 - m) \times sc_i + m \times dc_i \quad (\text{Eq. 3})$$

where ac_i = average per capita healthcare expenditure for disease i ; and m = mortality rate.

Per capita healthcare expenditure for survivors and decedents for a particular disease can then be calculated if we know the mortality rate and the ratio (r_i) between healthcare costs for those dying at a particular age and those surviving that age (equation 4):

$$\begin{aligned} dc_i &= r_i \times sc_i \\ ac_i &= sc_i + (r_i - 1) \times m \times sc_i \\ sc_i &= \frac{ac_i}{1 + (r_i - 1) \times m} \end{aligned} \quad (\text{Eq. 4})$$

To divide the average per capita costs per disease according to the above-specified relationships, we used additional data sources. Mortality rates for 2005 from Statistics Netherlands were employed.^[29] Given mortality rates, the only additional input needed is disease-specific cost ratios of decedents and survivors. However, these were only available for hospital expenditure.^[22] Since, the effect of proximity to death on healthcare expenditure differs strongly per healthcare provider,^[21] we could not use these ratios directly to decompose all disease-specific per capita health expenditure. Therefore, we used these ratios only

to decompose hospital expenditure (equation 5):

$$sc_{i,j=1} = \frac{ac_{i,j=1}}{1 + (r_{i,j=1} - 1) \times m} \quad (\text{Eq. 5})$$

with index j denoting the healthcare provider; $j=1$ refers to the hospital sector.

Wong et al.^[22] estimated disease-specific ratios for 75 diseases categorized using the International Shortlist for Hospital Morbidity Tabulation (ISHMT) format, which is highly compatible with the COI categories, resulting in 71 matches of 107 disease categories, which amounts to 60% of total hospital expenditure in 2005 (table A2 in the Supplemental Digital Content 3 displays the matches of COI categories to the ISHMT categories). For the non-disease-related expenditure (11.7% of total expenditure), we assumed the ratios to equal one and thus, conditional on age and sex, the costs to be equal for survivors and decedents. For the remaining disease categories, we used the age- and sex-specific mode of the 71 matched disease ratios. The mode was estimated by kernel density estimates using average costs per disease as weights.

For other healthcare providers besides hospitals, no empirically estimated disease-specific ratios were available. However, for some major health providers (providers of ambulatory healthcare, drugs and appliances, nursing and residential care) we had access to decedent/survivor ratios for total expenditure in 1999 estimated in previous research using data from insurance claims.^[17] To estimate disease-specific ratios for these three healthcare providers (ambulatory healthcare, drugs and appliances, nursing and residential care), we exponentiated all disease-specific hospital ratios by a constant (equation 6):

$$r_{i,j>1} = r_{i,j=1}^{x_{j>1}} \quad (\text{Eq. 6})$$

where j = index denoting the healthcare provider; $j=1$ implies hospital care; $r_{i,j>1}$ = ratio ([costs decedents]/[costs survivors]) for disease-specific health expenditure of disease i for healthcare provider j other than hospital care; $x_{j>1}$ = scaling constant for healthcare provider j other than hospital care.

Thus, if, for example, the disease-specific hospital ratios for diseases a , b and c equal 4, 9 and 16, respectively, and the scaling factor x for long-term care equals 0.5, the disease-specific ratios

for this healthcare provider would equal 2, 3 and 4, respectively. Equation 6 implies that, for each healthcare provider, the age- and sex-specific distributions of ratios [(disease costs decedents)/(disease costs survivors)] are proportional on the log scale. Suppose we use equation 6 for a given baseline disease (denoted by $i=1$), then this can be rewritten as shown in equation 7:

$$\begin{aligned} r_{i=1,j>1} &= r_{i=1,j=1}^{x_{j>1}} \Rightarrow \\ \log(r_{i=1,j>1}) &= x_{j>1} \log(r_{i=1,j=1}) \Rightarrow \\ x_{j>1} &= \frac{\log(r_{i=1,j>1})}{\log(r_{i=1,j=1})} \end{aligned} \quad (\text{Eq. 7})$$

Since we assume $x_{j>1}$ to be equal for all diseases, we can similarly state that (equation 8):

$$x_{j>1} = \frac{\log(r_{i>1,j>1})}{\log(r_{i>1,j=1})} \quad (\text{Eq. 8})$$

Thus (equation 9):

$$x_{j>1} = \frac{\log(r_{i=1,j>1})}{\log(r_{i=1,j=1})} = \frac{\log(r_{i>1,j>1})}{\log(r_{i>1,j=1})} \text{ for all values of } i \quad (\text{Eq. 9})$$

Equation 9 describes how the effect of proximity to death on healthcare expenditure differs between healthcare sectors. A value of x higher than one implies that, for that health provider, the relationship between time to death and healthcare expenditure is stronger for all diseases than in the hospital sector. A value for x lower than one implies that the relationship is less strong. An alternative way of scaling the ratios would be to multiply all hospital ratios by a constant. However, since some ratios were smaller than one, we chose to scale the hospital ratios on a log scale. This way, we ensured that the relationship between time to death and healthcare expenditure did not change from negative (ratio smaller than one) to positive (ratio greater than one) or *vice versa*. Equation 9 can be rearranged (equation 10) to describe how the proximity to death relationship differs between diseases:

$$\frac{\log(r_{i>1,j>1})}{\log(r_{i=1,j>1})} = \frac{\log(r_{i>1,j=1})}{\log(r_{i=1,j=1})} \text{ for all values of } i \quad (\text{Eq. 10})$$

In the example mentioned above, it is easy to check that $\log(16)/\log(4) = \log(4)/\log(2) = 2$.

To ensure that the sum of disease-specific costs of decedents and survivors match those of total costs in such a way that the ratio for total expenditure in that healthcare sector equals the empirically estimated ratios (denoted $r_{tot,j>1}$),^[17] we exponentiated all disease-specific hospital ratios by the constant x such that the following assumption is not violated (equation 11):

$$r_{tot,j>1} = \frac{\sum_i dc_{i,j>1}}{\sum_i sc_{i,j>1}} = \frac{\sum_i r_{i,j=1}^x \times sc_{i,j>1}}{\sum_i sc_{i,j>1}} \quad (\text{Eq. 11})$$

Combining equation 11 with equation 5, we can calculate total survivor expenditure for healthcare providers other than hospital care using the estimated ratio for total expenditure as a function of mortality rates, average costs per disease for that healthcare provider, disease-specific hospital ratios and the scaling constant (equation 12):

$$\begin{aligned} sc_{tot,j>1} &= \frac{\sum_i ac_{i,j>1}}{1 + (r_{tot,j>1} - 1) \times m} \\ sc_{i,j>1} &= \frac{ac_{i,j>1}}{1 + (r_{i,j=1}^{x_{j>1}} - 1) \times m} \\ sc_{tot,j>1} &= \sum_i sc_{i,j>1} = \sum_i \frac{ac_{i,j>1}}{1 + (r_{i,j=1}^{x_{j>1}} - 1) \times m} \end{aligned} \quad (\text{Eq. 12})$$

Equation 12 now contains only one unknown variable: the scaling factor x . Age-, sex- and healthcare provider-specific values for x were found by numerically minimizing the error, as defined by the distance between total survivor costs calculated using the empirically estimated ratios for total expenditure (denoted $sc_{tot,j>1}$) for these three healthcare providers (ambulatory healthcare, drugs and appliances, nursing and residential care) and the total survivor costs calculated as the sum of the disease-specific survivors costs (equation 13):

$$\left(sc_{tot,j>1} - \sum_i \frac{ac_{i,j>1}}{1 + (r_{i,j=1}^x - 1) \times m} \right)^2 \quad (\text{Eq. 13})$$

For the remaining provider categories (mainly being overhead type healthcare costs, see table A1 in the Supplemental Digital Content 3), it is assumed that costs are equal for decedents and survivors and that costs depend solely on age and sex.

2. Estimated Model Parameters in PAID 1.0

To show the effect of the decomposition of average per capita health expenditure by costs related to those dying and those surviving, figure 1

displays average per capita costs in the last year of life and other years specified by sex and age, stacked for the different healthcare providers (in this figure we have omitted costs for all other healthcare providers [see Table A1 in the Supplemental Digital Content 1 for a complete list] as

Fig. 1. Average annual healthcare expenditure per capita (€, year 2005 values) in the Netherlands by age and sex, for four healthcare providers and stratified by last year of life and other years: (a) men average; (b) women average; (c) men survivors; (d) women survivors; (e) men decedents; and (f) women decedents. GP = providers of ambulatory healthcare; HC = hospitals; LTC = nursing and residential care facilities; Med = retail sale and other providers of medical goods.

Table I. Ratios of (decedent costs)/(survivor costs) for men aged 75 years

Healthcare provider	Ratio for total costs	Scaling factor x	Lung cancer ratio	Stroke ratio	Depression ratio
Hospitals	8.5	NA	121.1	6.3	2.8
Nursing and residential care facilities	7.6	0.90	73.7	5.2	2.5
Providers of ambulatory healthcare	2.2	0.42	7.6	2.2	1.6
Retail sale and other providers of medical goods	2.3	0.46	8.9	2.3	1.6

NA = not applicable.

these depend on age solely and not on time to death). Figures 1a and b display the average per capita health expenditure resulting from interpolating the COI study (summed over all 107 disease categories). Figures 1c–f display the estimates summed over all 107 disease categories that are the result of the decomposition of the COI data into costs of decedents and costs of survivors. Please note that the y-axis of different panels have different scales.

From figure 1 it can be concluded that costs in the last year of life are very high at a very young age and decrease sharply thereafter. The major cause for this decrease is that mortality in the first year of life is often preceded by a period of intensive hospital care, whereas mortality among children, adolescents and especially young adults is mostly caused by (traffic) accidents.^[29] At middle age, costs in the last year of life increase again. Total costs of survivors increase exponentially at old age mainly due to frailty, disability, co-morbidity and subsequent needs for nursing and residential care. Survivor costs in hospital, for GPs and for medicines, do not depend strongly on age, so the

age-related increase in total healthcare expenditure is produced mainly in the long-term care sector. At older age, the share in long-term care costs increases sharply in survivors. Interestingly, absolute cost levels are somewhat higher in women than in men, especially at a higher age. This may be explained to a certain extent by the fact that the nursing and residential care population mainly consists of women.^[24]

Table I displays estimates of some disease-specific ratios for different healthcare providers for men aged 75 years. It can be seen that the relationship between time to death and healthcare expenditure is strongest for the hospital care providers. As a result, the scaling factors estimated needed to calculate disease-specific decedent/survivor ratios are all below one. Furthermore, the disease-specific ratio is highest for lung cancer and lowest for depression.

Table II displays estimates of lifetime health expenditure broken down by healthcare provider. Lifetime healthcare expenditure was estimated by calculating the expected value of equation 1 using mortality rates for 2005 summed over all diseases.

Table II. Estimated lifetime healthcare costs (€, y 2005 values) stratified by last y of life and all other y and healthcare provider

Healthcare provider	Men			Women		
	last y of life	other y	% costs in last y of life ^a	last y of life	other y	% costs in last y of life ^a
Total	30 017	207 979	13 (4)	34 766	279 059	11 (4)
Hospitals	15 571	80 389	16 (3)	13 017	91 452	12 (2)
Nursing and residential care facilities	8 046	20 897	28 (10)	15 373	45 633	25 (11)
Providers of ambulatory healthcare	3 011	44 596	6 (3)	3 020	65 980	4 (3)
Retail sale and other providers of medical goods ^a	2 767	34 872	7 (4)	2 664	45 323	6 (3)
Other healthcare providers	622	27 225	2 (2)	691	30 671	2 (2)

a The numbers between brackets are the percentage of costs in the last y of life if the relationship between proximity to death and healthcare expenditure is ignored and only the cost-of-illness data are used.

Fig. 2. Average annual healthcare expenditure per capita (€, year 2005 values) in the Netherlands by age, stratified by last year of life and other years, for two different disease categories: (a) average circulatory system; (b) average neoplasms; (c) survivors' circulatory system; (d) survivors' neoplasms; (e) decedents' circulatory system; and (f) decedents' neoplasms. GP = providers of ambulatory healthcare; HC = hospitals; LTC = nursing and residential care facilities; Med = retail sale and other providers of medical goods.

To show the importance of including time to death, we compared the percentage of healthcare expenditure consumed in the last year of life with a naive estimate in which we did not make a distinction between costs in the last year of life and other years as derived from the original COI data. Table II makes clear that the share of hospital costs is much higher in the last year of life

than in other years. However, also for long-term care, a large share of lifetime healthcare expenditure is realized in the last year of life (28% for men and 25% for women). It should be noted that although this seems very large, the share that is expected to be spent on long-term care in the last year of life would also be substantial if costs in the last year of life (conditional on age) are the

Table III. Estimated lifetime healthcare costs (€, year 2005 values) stratified by last y of life and other years specified by disease category

Disease category	Men			Women		
	last y of life	other y	% costs in last y of life ^a	last y of life	other y	% costs in last y of life ^a
Total	30 017	207 979	13 (4)	34 766	279 059	11 (4)
Infectious and parasitic disease	535	7 019	7 (3)	454	7 454	6 (2)
Neoplasms	5 091	8 976	36 (5)	3 744	11 562	24 (3)
Endocrine, nutritional and metabolic diseases	805	5 190	13 (4)	1 117	7 261	13 (5)
Diseases of the blood and the blood-forming organs	331	859	28 (6)	340	1 081	24 (6)
Mental and behavioural disorders	6 136	29 522	17 (6)	10 080	47 875	17 (7)
Diseases of the nervous system	1 727	16 094	10 (4)	1 532	20 152	7 (3)
Diseases of the circulatory system	4 822	27 450	15 (5)	5 882	25 456	19 (6)
Diseases of the respiratory system	2 372	10 634	18 (5)	1 499	10 835	12 (4)
Diseases of the digestive system	1 294	19 537	6 (2)	1 183	22 806	5 (2)
Diseases of the genitourinary system	1 209	6 096	17 (6)	1 050	10 540	9 (4)
Pregnancy, childbirth and the puerperium	15	669	2 (0)	47	12 480	0 (0)
Diseases of the skin and subcutaneous tissue	315	3 855	8 (3)	348	4 422	7 (3)
Diseases of the musculoskeletal system and connective tissue	1 189	13 506	8 (3)	2 112	23 292	8 (3)
Congenital malformations	34	1 839	2 (0)	28	1 728	2 (0)
Certain conditions originating in the perinatal period	65	2 781	2 (0)	54	2 484	2 (0)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	2 166	20 914	9 (3)	1 840	27 201	6 (3)
Injury, poison and certain other consequences of external causes	1 061	6 900	13 (5)	2 063	10 304	17 (7)
Not allocated/not disease related	850	26 136	3 (3)	1 396	32 123	4 (4)

a The numbers between brackets are the percentage of costs in the last y of life if the relationship between proximity to death and healthcare expenditure is ignored.

same as in other years (10% for men and 11% for women). Seen this way, it can be concluded that the effect of including proximity to death effect is most pronounced for hospital expenditure.

To focus on the differences in healthcare expenditure patterns between diseases, figure 2 displays a similar graph as figure 1, but now for two different disease categories instead of total expenditure: neoplasms and diseases of the circulatory system. Please note that the y-axes have different scales.

Figure 2 clearly illustrates the differences between disease categories. Per capita expenditure for neoplasms is, on average, lower than for circulatory diseases. However, in the last year of life, per capita health expenditure is much higher for neoplasms. More specifically, the average healthcare expenditure for neoplasms is largely determined by hospital expenditure in the last year of life.

Table III presents estimates of lifetime healthcare costs broken down into costs in the last year

of life and other years for different disease categories. Table III demonstrates, for example, that cancer is a major cost component in the last year of life, but hardly in other years. The same goes for diseases of the blood and blood-forming organs.

3. Discussion

Since economic evaluations of life-saving (preventive) interventions are conducted in a variety of settings, including those of new (and often expensive) drugs, a standardized way to account for indirect medical costs is of great importance. While some methods have been proposed to estimate medical costs in LYG,^[23] these methods do not take into account that, in most economic evaluations, a part of these indirect medical costs have already been covered; namely, those costs related to the disease or intervention that was evaluated. These future costs that are expected to

change as a result of an intervention should always be explicitly modelled and, hence, this is common practice in the majority of economic evaluations. Subsequently, simply adding per capita health expenditure stratified by age and proximity to death will result in double counting of the costs of related diseases.^[11]

We have proposed a methodology to estimate the costs of all other diseases in LYG in a standardized manner that avoids this double counting. Starting from the framework developed by Gandjour and Lauterbach,^[23] we present a methodology to adjust per capita health expenditure stratified by age and proximity to death for the costs of the diseases already included in the main economic evaluation. In this conceptual model, it is assumed that total healthcare expenditure can be explained by age, sex and time to death, while the relationship between costs and these three variables differs per disease. We present estimates of our conceptual model, which are embedded in a toolkit called PAID 1.0, tailored for economic evaluations in the Netherlands. Disease-specific average per capita expenditure from the Dutch COI 2005 study^[24] were decomposed into a part that is attributable to those who die at a certain age and a part that is attributable to those who survive that age. To accomplish this we used estimates of ratios of decedent/survivor costs for disease-specific hospital expenditure and total expenditure for healthcare providers other than hospitals. Our results on the effect of the last year of life with respect to total health expenditure calculated as the sum of disease-specific health expenditure for all healthcare providers are in line with previous research conducted in the Netherlands.^[11]

In our methodology, we accounted for the fact that the relationship between age, sex and proximity to death and per capita costs differs between diseases.^[22] This allows the relationship between time to death and healthcare costs to be altered if the costs of related diseases are excluded.^[11] Consequently, for our methodology it is essential to know what the role of age and proximity to death on disease-specific per capita health expenditure is for each disease. Our conceptual model is similar to the concept of 'other cause'/'back-

ground' mortality, which is often used in simulation models to decompose total mortality rates into a part related to the intervention and a part unrelated to the intervention. To decompose average per capita health expenditure into costs in the last year of life and all other years, we had to make several assumptions. Most importantly, we assumed that the disease-specific ratios estimated in Wong et al.,^[22] based on 60% of hospital expenditure, could be generalized to total hospital expenditure and that the disease-specific ratios could be used to decompose disease-specific costs for some other healthcare providers under some constraints.

Furthermore, the validity of PAID 1.0 crucially depends on the validity of the COI study and the allocation of the health expenditure to disease categories in that study. Another limitation is that we dichotomized proximity to death into two categories. A further version of PAID could be improved by stratifying into more periods. This becomes more important if we consider the timing of health expenditure and the role of discounting therein. We used total healthcare expenditure in the Netherlands from 2005 as a starting point. This implies that age-specific cross-sectional data are interpreted in a longitudinal fashion, as is done when constructing life tables and also in many Markov models. The implicit assumption is that current observed patterns of health expenditure remain constant. Of course, the longer the period modelled, the more problematic this assumption becomes. We do not claim that the parameters included in our conceptual model are the only ones that are needed to estimate indirect medical costs. Technological progress, innovation, changes in morbidity patterns, developments in the labour market and institutional changes may have an impact on future healthcare costs, but have not been included. Although we recognize these limitations, we are convinced that it is better to provide an estimate using all current, albeit imperfect, knowledge than no estimate at all. While the former estimate may be imprecise, the latter is surely wrong.

In economic evaluations, modelling techniques are applied frequently to estimate the effects of life-prolonging interventions on health and

healthcare costs. Usually, in these models, an intermediate effect such as blood pressure, newly detected cases through screening, or short-term survival (as estimated using observational data, an RCT or meta-analyses) is connected to causally related events (most importantly, death) that could not be observed within the trial period of the intervention because the follow-up period is too short. Thus, models are used to reach beyond the time horizon of trials. As a result, costs and effects beyond the observed period have to be estimated from other data sources. In cost-effectiveness studies that capture both health effects and costs of related diseases during added LYG, PAID 1.0 allows the estimation of future healthcare costs, correcting for costs of diseases already included in the basic evaluation, taking into account that the relationship between healthcare expenditure and proximity to death differs per disease and healthcare provider. If costs are included for only a limited follow-up period while, at the same time, health effects are modelled for the whole course of life after the follow-up period, PAID 1.0 can be used for the inclusion of age-specific costs of survivors and decedents.

PAID 1.0 is populated with country-specific (Dutch) data and not immediately transferable for use in other countries. The most important ingredient to construct similar tools for other countries is top-down COI studies, covering all healthcare expenditure, which have already been conducted in a variety of countries.^[30] The relationship between healthcare costs and proximity to death is less well researched for different countries, but we expect this variable to be less susceptible to variation between countries than healthcare expenditure itself.^[31] Therefore, if country-specific information on the influence of time to death on health expenditure is lacking, an option might be to 'borrow' data from other countries, e.g. those presented in this article.

4. Conclusions

We think that the use of PAID 1.0 improves comparability between economic evaluations in the Netherlands and we hope that our proposed methodology may inspire researchers from other

countries to further refine and improve standardized estimation of indirect medical costs.

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