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Cost Effectiveness Analysis with the RIVM Chronic Disease Model

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Rapport in het kort

Kosten effectiviteit analyse met het RIVM Chronische Ziekten Model

De medische kosten van álle ziekten die kunnen optreden in gewonnen levensjaren dienen te worden meegenomen in kosten effectiviteit analyses als ook de effecten van de medische zorg voor álle ziekten in gewonnen levensjaren worden meegenomen. In kosten effectiviteit analyses van primaire preventie worden vaak alleen de medische kosten van direct gerelateerde ziekten meegenomen. Bij kosten effectiviteit analyses van stoppen met roken interventies worden bijvoorbeeld wél de besparingen dankzij de vermeden kosten van longkanker meegenomen maar niet de medische kosten van een heupfractuur die iemand kan oplopen in zijn extra levensjaren. Dit is niet consistent als de winst in levensjaren dankzij de behandeling van de heupfractuur wel wordt meegenomen in de kosten effectiviteit analyse.

Eén van de toepassingen van het RIVM Chronische Ziekten Model (CZM) is het schatten van de kosten effectiviteit van interventies gericht op het verbeteren van de volksgezondheid in Nederland. De centrale vraagstelling van dit rapport is hoe we in kosten effectiviteit analyses met het CZM omgaan met de medische kosten en gezondheidseffecten van ziekten die zijn opgelopen in extra levensjaren. Met het CZM is het mogelijk om de medische kosten in gewonnen levensjaren in kosten effectiviteit analyses mee te nemen. Op basis van inzichten uit de recente economische literatuur concluderen wij dat de medische kosten van álle ziekten die kunnen optreden in extra levensjaren dienen te worden meegenomen als de effecten van de medische zorg in gewonnen levensjaren niet zijn te scheiden van de effecten van de interventie.

Trefwoorden: kosten effectiviteit analyse; modellering; chronische ziekten; sterftetafel; kwaliteit van leven; kosten van ziekten

Abstract

Cost Effectiveness Analysis with the RIVM Chronic Disease Model

Support of decision makers in health care priority setting is one of the objectives of cost effectiveness analysis. Cost effectiveness analysis presents the costs and effects of an intervention compared to an alternative in cost effectiveness ratios. The denominator of the ratio measures the health gain from the intervention and the numerator measures the costs of obtaining that health gain.

The objective was to develop a methodology to be used with economic evaluations conducted with the RIVM Chronic Disease Model (CDM). Using the CDM to compute health effects and costs ensures that the same model is used for all different economic evaluations, which improves their comparability. The current report describes how cost effectiveness ratios are computed with the CDM. Special attention is paid to the selection and estimation of the costs and effects to be included during years of life gained.

A cost effectiveness module was written to be attached to the RIVM Chronic Disease Model (CDM). To decide what costs and effects to include, a distinction was made between diseases causally related and diseases indirectly related to the intervention. Given this distinction the approach from Nyman (Health Economics 2004) was followed: all costs that directly produce the utility measured in the denominator have to be included in the numerator of the cost effectiveness ratio. To estimate the impact of indirectly related diseases on quality of life we use data from the Dutch Burden of Disease study. Data from the Costs of Illness study in the Netherlands were used to estimate the impact of an intervention on total health care costs.

We argue that for comparison of different interventions with the RIVM CDM, one should include the costs and effects of both causally related and indirectly related diseases, since it seems impossible to isolate the precise effects of an intervention.

Keywords: cost effectiveness analysis; modelling; chronic diseases; life table; quality of life; costs of illness

Preface

In the MAP-SOR project ‘Priority setting in chronic diseases: methodology for budget allocation’ the aim is to develop a methodology to support optimal allocation of the health care budget with respect to chronic diseases that enables one to compare the costs and consequences (health effects) of primary prevention with secondary and tertiary prevention. To enable this, the first step in the development of the budget allocation problem is to make sure that different interventions can be compared in terms of costs and consequences. To develop a method to consistently deal with health effects and costs we have developed a cost effectiveness module (implemented in a Mathematica package) to be used in conjunction with the RIVM Chronic Disease Model (CDM). By using this module in combination with the CDM to compute health effects and costs it can be ensured that the same methodology and the same type of costs and effects are taken into account for all different interventions that are compared. The module was designed to allow for different choices about what costs and effects to include in the cost effectiveness analysis. For instance, whether or not to include the consequences of so called unrelated medical care in life years gained (i.e. the costs of care for dementia and the effects of dementia on quality of life in the evaluation of smoking cessation interventions). In this report the conceptual model and model equations behind the cost effectiveness module in the CDM are presented. We would like to thank Guus de Hollander and Johan Polder for helpful comments on draft versions of this report.

Contents

Summary

Background
In cost effectiveness analysis costs and effects of a program or intervention and at least one alternative are calculated and presented in a so-called cost effectiveness ratio. In the denominator of this ratio the health gain due to the intervention is being measured. The numerator measures the costs of obtaining that health gain. In the MAP-SOR project 'Priority setting in chronic diseases: methodology for budget allocation' the aim is to develop a methodology to support optimal allocation of the health care budget with respect to chronic diseases that enables one to compare the costs and effects of primary prevention with secondary and tertiary prevention. To enable this, the first step in the development of the budget allocation problem is to make sure that different interventions can be compared in terms of costs and effects.

Objective
The goal of the present study is to develop a methodology to be used with economic evaluations conducted with the RIVM Chronic Disease Model (CDM). The CDM is a multistate transition model that links prevalence of risk factors to the incidence of 28 chronic diseases. The model allows to compute effects on life years gained and quality of life, taking account of co-morbidity. Using the CDM to compute health effects and costs ensures that the same model is used for all different interventions, which improves their comparability. The current report describes how cost effectiveness ratios are computed alongside the CDM. Thereby, the focus on the selection and estimation of the costs and effects to be included during years of life gained.

Methods
A cost effectiveness module was written to be attached to the RIVM Chronic Disease Model (CDM). In order to decide what costs and effects are taken into account we will first make a distinction between diseases causally related and diseases indirect related to the intervention. Given this distinction we follow the approach recently set out by Nyman in Health Economics to determine which costs and (effects) to include in the economic evaluation: all costs that directly produce the utility measured in the denominator have to be included in the numerator of the cost effectiveness ratio. To estimate the impact of indirect related diseases on the quality of life we use data from the Dutch Burden of Disease study. Data from the Costs of Illness study in the Netherlands is used to estimate the impact of an intervention on total health care costs.

Results
Following the Nyman approach we distinguish three different cost effectiveness ratios: 1) all health effects are ascribed to the interventions while costs of indirect related diseases are excluded; 2) only the minimum gain in QALYs and life years that can be attributed to the interventions are included while costs of indirect related diseases are excluded; 3) all health effects ànd costs of all diseases are included.

Conclusions
We argue that if one wants to compare different interventions in within the RIVM CDM, the third ratio is the best, since it seems impossible to isolate the precise effects of an intervention. Only taking into account the medical costs of causally related diseases results in a too optimistic view of the impact of an intervention on future health care costs.

1. Introduction

In the MAP-SOR project ‘Priority setting in chronic diseases: methodology for budget allocation’ the aim is to develop a methodology to support optimal allocation of the health care budget with respect to chronic diseases that enables one to compare the costs and consequences (health effects) of primary prevention with secondary and tertiary prevention. To enable this, the first step is to make sure that different interventions can be compared in terms of costs and consequences. Therefore, we have developed a cost effectiveness module (implemented in a Mathematica package) to be used in conjunction with the RIVM Chronic Disease Model (CDM). Cost effectiveness analysis (CEA) is an analytic tool in which costs and effects of a program or intervention and at least one alternative are calculated and presented in a ratio of incremental costs to incremental effects. It compares the costs and effects of a program or intervention to at least one alternative (comparator). Results are usually presented in a ratio of incremental costs to incremental effects. The lower this ratio, the more cost effective it is to implement the investigated intervention. That is, the more health effects are obtained for given expenditures. Some interventions turn out to be dominant, because they are less costly and, at the same time, generate more health effects than their comparator. Other interventions result in better health but at additional costs.

In this report the conceptual model and model equations behind the cost effectiveness module in the CDM are presented. The module was designed to allow for different choices about what costs and effects to include in the cost effectiveness analysis. Special attention is paid whether or not to include the consequences of so called unrelated medical care in life years gained (i.e. the costs of care for dementia and the effects of dementia on quality of life in the evaluation of smoking cessation interventions). The main advantage of using the CDM for economic evaluations is that it enables one to compare interventions aimed at different diseases and/or risk factors within a common framework which makes comparison easier [1]. Furthermore, the inclusion of the CEA computations as a module to the CDM allows for a wide range of sensitivity analyses, for instance on the rate of discount, the intervention costs, or the effectiveness of the intervention.

In section 2 the conceptual model is laid out, and the background for different choices about costs and effects is given. Section 3 discusses the data sources used in the CEA module and explains the model equations implemented in Mathematica. Finally, section 4 contains a discussion.

2. Conceptual model

2.1 Cost Effectiveness Analysis

2.1.1 Introduction

Cost effectiveness analysis (CEA) has been developed as a tool to inform policy makers about the costs and effects of medical interventions to support their decisions on the optimal allocation of health care resources. If more and more cost effectiveness results become available, ideally they could be ranked in a so-called 'league table', which makes it possible to compare interventions in their cost effectiveness. Furthermore, the information gathered in a CEA combined with an objective function and a budget constraint enables one to construct budget allocation models However, differences in perspectives, data sources and adopted methodologies make it difficult to construct such 'league tables' and develop budget allocation models because the cost effectiveness ratios are not well comparable. In the following subsection several factors that determine the type and range of costs and effects included in a cost effectiveness analysis are discussed. Special attention is given to an important methodological controversy in CEA: the inclusion of medical costs in life years gained.

2.1.2 Costs and effects included in a CEA

Before an economic evaluation is defined it must be exactly specified what costs and effects to include in the analysis. The first step in this process is to determine the perspective from which an economic evaluation is conducted. The *perspective* refers to the point of view from which costs and effects are considered: for instance the patient's, societal or health care perspective. It determines what costs and effects are included and how they are valued. For instance, patient travel costs count as a cost from the patient's and societal perspective, while they may not be counted from the health care perspective. The choice of perspective often depends on the research question or is prescribed by methodological guidelines [2].

Given the perspective the next step is to determine which effects one wants to include in the analysis. Ideally, one wants to include all effects that are influenced by the intervention under investigation. For instance, considering an intervention to support smoking cessation. This affects the number of smokers, hence the sale of cigarettes, hence the profits of the tobacco industry, the number of employees in this industry, etc. Suppose that one wants to include all these effects, then the problems arise if one tries to make all these effects comparable. In cost benefit analysis all effects that are possibly altered by the intervention are included and valued in monetary terms. Main reasons for the development of cost effectiveness analysis in health care were the theoretical objections against and practical problems involved in valuing lives and disease states. Therefore, in cost effectiveness analyses of health care interventions it is common practice to include only the health related effects which are often valued in life years or quality adjusted life years (QALYs) gained.[1] Given the effect measure that is chosen the next step is to determine what costs to include. Besides the already mentioned perspective this largely depends on the interpretation of the effect measure which forms the basis of a lot

[1] In some cost effectiveness analysis other effect measures as life years or QALys gained are chosen. However, we will focus on these two effect measures since these two are also used in cost effectiveness analysis conducted with the CDM.

of methodological controversies. One of these methodological issues is whether or not to include costs of so-called unrelated medical care.

In economic literature a distinction is made between related/direct and unrelated/indirect medical costs. Related medical costs are those costs that are directly associated with an intervention such as the costs of the intervention (e.g. costs of a smoking cessation program or costs of a new type of cancer therapy) and medical costs that are directly influenced by the intervention (e.g. the costs of lung cancer or the medical costs of cancer treatment after the therapy). Unrelated medical costs are medical costs that are incurred because an intervention successfully extends a patients life. For instance, if a smoking intervention successfully extends a former smokers life and he or she gets dementia, the costs of dementia are called unrelated medical costs. Classic textbooks such as Drummond and Gold et al mention the fact that it would be logical to include unrelated medical costs if all the credit in life extension is assigned to the smoking intervention [3, 4]. However, current practice in most CEA is that, mostly for pragmatic reasons, only medical costs of so-called related diseases are taken into account while costs of other diseases are not taken into account. For instance, in a CEA of a new heart transplant surgery procedure one only takes into account the medical costs of heart disease and not of dementia. As already pointed out by Meltzer [5] the distinction between related and unrelated diseases is not unambiguous and differs from that of related and unrelated medical care: even though heart disease is related to the intervention, the costs for heart disease in life years gained can be termed costs of unrelated medical care, since they would not incurred if the intervention did not extend a patients life.

The decision whether to include indirect medical costs has largely been taken place within the context of economic welfare theory. Focus in this discussion was if one should take into account unrelated medical care if one wants to maximize social welfare. Garber and Phelps [6] formulate a rather restrictive model of lifetime health utility maximisation and come to the conclusion that including unrelated medical costs does not alter the ranking of different interventions. Meltzer developed a less restrictive model and comes to the conclusion that taking into account unrelated medical care can alter the ranking of different interventions, but states that if one wants to maximize social welfare, defined as maximizing QALYs, one should also include non-medical costs and expenditures. This led to the conclusion that interventions that favour the young and rich are systematically more cost effective than those that favour the old and poor.

In a recent article by Nyman [7] new criteria for the inclusion of costs and effects in CEA were proposed. With regard to the inclusion of unrelated medical costs he proposes the following criterion: ‘all costs that directly produce the utility measured in the denominator have to be included in the numerator of the cost effectiveness ratio’. Thus if life years are (at least part) gained due to unrelated medical care, the costs thereof should be included. However, consumption costs should be excluded since their utility is not measured in the denominator. Nyman’s interpretation of a QALY differs from that of Meltzer: Meltzer interprets QALYs as utilities that capture more than only health related quality of life, while Nyman interprets QALYs as a measure that only captures health related quality of life.

2.2 Cost effectiveness analysis in the RIVM Chronic Disease Model (CDM)

2.2.1 Introduction

The RIVM Chronic Disease Model (CDM) has been developed as a tool to describe the morbidity and mortality effects of autonomous changes of and interventions on chronic disease risk factors taking into account integrative aspects [8]. The model contains several risk factors including cholesterol, systolic blood pressure, smoking, activity level, and Body Mass Index. It models 28 chronic diseases: cardiovascular diseases, distinguishing acute myocardial infarction, other coronary heart disease, stroke, and chronic heart failure, COPD, asthma, diabetes mellitus, dementia, osteoarthritis, dorsopathy, osteoperosis and 15 different forms of cancer. The model is structured in such a way that new diseases and risk factors can be relatively easily added. The mathematical model structure is called a multi-state transition model and is based on the life table method. The model states defined are the risk factor classes and disease states. State transitions are possible due to changes between classes for any risk factor, incidence, remission and progress for any disease, and mortality. The model describes the life course of cohorts in terms of changes between risk factor classes and changes between disease states over the simulation time period. Risk factors and diseases are linked through relative risks on disease incidence. That is, incidence rates for each risk factor class are found as relative risks times baseline incidence.
The main model parameters are:

- the initial population numbers;
- initial class prevalence rates and transition rates for all risk factors;
- initial prevalence, incidence, remission and progress rates for all diseases and;
- relative risk values specified by risk factor and chronic disease.

All model parameters and variables are specified by gender and age. The time step used for modelling is 1 year. The main model outcome variables are incidence, prevalence and mortality numbers specified by disease, and integrative measures such as total and quality-adjusted life years. Examples of the integrative aspects of the model are the joint effects of combined risk levels, different causes of morbidity and mortality being distinguished, the effects of mortality selection and the statistical modelling of dependent competing risks.

2.2.2 Defining scenarios

One of the applications of the CDM is to estimate and compare the cost effectiveness of interventions aimed at improving the level of public health of the Dutch population. Interventions can be life style interventions that affect the level of public health through their effect on risk factors such as smoking, but can also be targeted at specific diseases.

Estimating the cost effectiveness of an intervention with the CDM is done by comparing the costs and effects of an intervention scenario with a so-called current practice scenario. The basic formula for calculating a cost effectiveness ratio (CER) can be denoted as:

(1) $CER = (C_{s1} - C_{s2}) / (E_{s1} - E_{s2})$

CER *Cost Effectiveness Ratio*
s *scenario index*

s1 *current practice scenario*
s2 *intervention scenario*
E_s *total health Effects (Life Years or Quality Adjusted Life Year's) scenario s*
C_s *total Costs scenario s*

In the intervention scenario some parameters of the models are adjusted to reflect the effects of the intervention. In the current practice scenario the parameters of the CDM are not altered and can be interpreted as the scenario with a continuation of current health care policy. For instance, in a smoking cessation intervention, stop rates of smokers can be increased in the CDM [9]. This will decrease the number of smokers which causes a decrease in the incidence, and thus also the prevalence of smoking related diseases.

2.2.3 Costs and effects

The CDM allows to find health effects in terms of disease prevalences and incidences, life years (section 3.3) and in QALYs (section 3.4). Our study population is naturally defined by the possibilities of the CDM. It models the entire Dutch population, following the life course of birth cohorts over time. Health care costs in the CDM will be linked to the prevalence of diseases (see section 3.2). Intervention costs may be linked either to the size of the population, to the number of users of the intervention or be modelled as a fixed cost. The total costs and health effects of a scenario are the sum of the discounted costs and effects of all years (i.e. net present value):

(2) $$C_s = \sum_{t=1}^{t} 1 \Big/ (1 + r_c)^{t-1} * c_{s,t}$$

r_c *discount rate for costs*
$c_{s,t}$ *total health care costs scenario s time t*

(3) $$E_s = \sum_{t=1}^{t} 1 \Big/ (1 + r_e)^{t-1} * e_{s,t}$$

r_e *discount rate for effects*
$e_{s,t}$ *total health effects scenario s time t*

In previous CEA studies with the CDM the health care perspective was chosen and only costs incurred by the health care system were included. This means that for instance the costs of informal care or productivity losses were not included. In this report also, we will only describe how to take into account costs and effects from a health care perspective. This does not mean that the CDM is unsuitable for CEA from a societal perspective but it allows us to focus on what costs of medical care should be included. The general methodology as described in this report can also be applied if one adopts a societal perspective.

Given the perspective and the study intervention it is obvious, what part of the intervention costs should be taken into account. If a smoking cessation requires a smoker to take time off from work the costs thereof are not taken into account in a CEA from a health care perspective. However, some choices to include costs or not are not that obvious. For instance, if we model an intervention that successfully lowers the prevalence of lung cancer should we also take into account the costs of for instance dementia? The CDM explicitly deals with competing risks and substitute mortality and morbidity and a decrease in the prevalence of a

(smoking-related) disease like lung cancer might cause an increase in the prevalence of another (not smoking-related) disease i.e. dementia. In other words, the CDM offers the opportunity to take into account substitute health care costs and effects. This feature of the CDM implies that different choices for taking into account health effects and costs are possible. In order to decide what costs and effects are taken into account we will first make a distinction between diseases causally related and diseases indirect related to the intervention (2.2.4). Given this distinction we follow the approach recently set out by Nyman in Health Economics to determine which costs and (effects) to include in the economic evaluation [7].

2.2.4 Causally related and indirect related diseases

To develop a method to consistently deal with direct and indirect health costs and effects within the CDM we classify the diseases modelled in the CDM in *causally related diseases* and *indirect related diseases*. A disease is *causally related* to the intervention if the intervention influences its incidence *rate* and/or prevalence *rate.*[2] For disease specific interventions modelled in the CDM, the diseases at which the interventions are targeted are causally related diseases. Thus if an intervention decreases the incidence of lung cancer, lung cancer of course is causally related to the intervention. For risk factor interventions a disease is causally related if it has a relative risk greater than one. Thus, lung cancer is causally related to a smoking cessation intervention. This principle also holds for intermediate diseases which increase the incidence on another disease. An example of an intermediate disease is diabetes: diabetes increases the risk of coronary heart disease which implies that coronary heart disease is causally related to a diabetes prevention intervention. All diseases which incidence and/or prevalence rate is not directly influenced or through the effects on risk factors is what we call not causally related to the intervention. However, the fact that the prevalence rate and incidence rate of these not causally related diseases are unaffected by the intervention does not mean that the incidence and or prevalence in absolute numbers are unaffected by the intervention. If an intervention successfully extends a patients life, an increase in the incidence and prevalence of the not causally related diseases may occur. Thus, effects on these diseases are always indirect in that they only occur because the intervention extends the patient's life. Therefore, we will term not causally related diseases *indirect related* diseases. Figure 1 displays this principle.

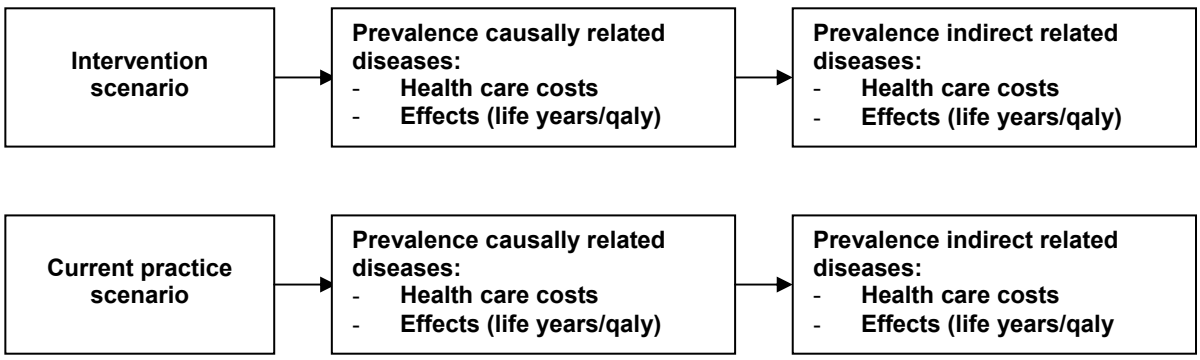

Figure 1: Conceptual model of economic evaluations

[2] If a disease has more than one state it is causally related to the intervention if the prevalence and/or prevalence rate of at least one disease state is influenced by the intervention.

To avoid confusion it should be noted that the concept of causally and indirect related diseases is different from the concept of substitute morbidity and mortality [10]. A disease can be causally related to the intervention and at the same time also be a substitute disease for another causally related disease. For instance, AMI can be a substitute disease for lung cancer but both are causally related to a smoking intervention.

2.2.5 Estimating cost effectiveness ratios

Effects and costs in the CDM depend on the disease prevalence and mortality projections of the CDM. However, it is the question exactly what health care costs and effects can be attributed to the intervention. Should we include only costs and effects of related or indirect related diseases or a combination of both? For instance, if a successful heart transplantation results in an increase in life expectancy, can we attribute all the gain in life years to that heart transplantation? It could be the case, that that person received additional treatment for substitute diseases indirect related to the intervention, for instance treatment of lung cancer that would not have been necessary had the person died from the previous severe heart disease. If that is the case, how can we separate the effects from the two different treatments?

To determine which costs and consequences to include in the economic evaluation we followed the approach recently set out by Nyman in Health Economics [7]. All costs that directly produce the utility measured in the denominator have to be included in the numerator of the cost effectiveness ratio. By using this as the underlying principle for the conceptual model, and following figure 1, we distinguish three different methods to calculate the cost effectiveness ratio with the CDM:

- Method 1: in the denominator the gain in effects (life years or QALYs gained) of both causally related and indirect related diseases is taken into account, while only the difference in health care costs of causally related diseases is included in the numerator. This method is not consistent with the Nyman principle but follows Dutch guidelines for pharmacooeconomic research [2] and has been practiced in CDM cost effectiveness analyses so far [9]. This can be denoted as:

$$(4)\ CER1 = \frac{\sum_{t=1}^{t} 1/(1+r_c)^{t-1} * (cr_{s1,t} + ci_{s1,t} - cr_{s2,t} - ci_{s2,t})}{\sum_{t=1}^{t} 1/(1+r_e)^{t-1} * (er_{s1,t} + eu_{s1,t} - er_{s2,t} - eu_{s2,t})}$$

  CER1 *Cost Effectiveness Ratio using method 1*
  $ci_{s,t}$ *intervention costs scenario s at time t*
  $cr_{s,t}$ *health care costs of causally related diseases scenario s at time t*
  $er_{s,t}$ *health effects of causally related diseases scenario s at time t*
  $eu_{s,t}$ *health effects of indirect related diseases scenario s at time t*

  Since only medical costs of causally related diseases are taken into account, this ratio does not capture the full impact of the intervention on total health care costs. Implicitly it is assumed that all health effects are ascribed to the intervention.

- Method 2: only the minimum gain in QALYs and life years that can be attributed to the intervention are included (indirect related diseases are not taken into account) while health care costs of indirect related diseases were excluded. This means that in the

denominator the gain in effects due to the causally related diseases is taken into account, and only the difference in health care costs of causally related diseases is included in the numerator:

$$(5)\ CER2 = \frac{\sum_{t=1}^{t} 1/(1+r_c)^{t-1} * (cr_{s1,t} + ci_{s1,t} - cr_{s2,t} - ci_{s2,t})}{\sum_{t=1}^{t} 1/(1+r_e)^{t-1} * (er_{s1,t} - er_{s2,t})}$$

CER2 Cost Effectiveness Ratio using method 2

This approach is consistent with the Nyman principle but may be difficult to estimate.

- Method 3: all health effects ànd all health care costs are included. This means that in the denominator the gain in effects of both causally related and indirect related diseases is taken into account, and both the difference in health care costs of causally related and indirect related diseases is included in the numerator. This approach is also consistent with the Nyman principle:

$$(6)\ CER3 = \frac{\sum_{t=1}^{t} 1/(1+r_c)^{t-1} * (cr_{s1,t} + cu_{s1,t} + ci_{s1,t} - cr_{s2,t} - ci_{s2,t} - cu_{s2,t})}{\sum_{t=1}^{t} 1/(1+r_e)^{t-1} * (er_{s1,t} + eu_{s1,t} - er_{s2,t} - eu_{s2,t})}$$

CER3 Cost Effectiveness Ratio using method 3
$cu_{s,t}$ health care costs of indirect related diseases scenario s at time t

In the following section we will discuss how we can estimate the costs and effects of causally related and indirect related diseases with the CDM. After that, we will discuss how to estimate and interpret the different methods for calculating cost effectiveness ratios.

3. Mathematical model and data sources

3.1 Introduction

In the previous chapter the conceptual model was discussed. A distinction was made between causally related and indirect related diseases and three different methods for estimating cost effectiveness ratios were distinguished. With the CDM the future prevalence of 28 chronic diseases that cover about 20% of the health care costs in the Netherlands in 1999. The diseases causally related to an intervention modelled with the CDM must be one or more of these 28 diseases. However, to get a better understanding of the effects of an intervention on all indirect related diseases and therefore on total health care costs and total health effects of the Dutch populations we have to take into account more than only the 28 diseases modelled in the CDM.

The following sections contain a description of the model equations that are implemented in Mathematica to estimate cost effectiveness ratios and it is explained how the impact of so-called indirect related diseases is estimated.

3.2 Estimating disease costs

To estimate the health care costs of causally and indirect related diseases data of the Costs of Illness (COI) in the Netherlands study are used [11]. In that study the total direct health care costs in the Netherlands of 1999 are uniquely attributed to a disease or disease category specified by gender and age classes. To assign the COI data on total costs per disease to individual patients we assume that the total costs attributed to diseases in that study can also be attributed to individual patients. To estimate the age and sex specific costs per disease per year per year per patient the total costs per disease are divided by the number of patient years lived as estimated with the CDM. This approach is the same as used by Barendregt et al in their study on the health care costs of smoking [12]. In CDM Technical Report no.5 it is described how costs per patient per disease per year were estimated [13]. To estimate the costs per disease per year per disease per patient the total costs per disease are divided by the number of patient years lived as estimated with the CDM. For some diseases age sex specific costs were estimated. For other diseases only an average for both sexes and all age classes is used. Given the estimated costs per patient per disease per year we can write the total health care costs of causally related diseases in a year as a function of disease prevalences:[3]

$$(7)\ cr_{s,t} = pop_{s,t} * \sum_{1}^{rd} p_{rd,t} * cp_{rd}$$

$cr_{s,t}$	*health care costs of causally related diseases scenario s at time t*
cp_{rd}	*costs per year per patient for causally related disease rd*
$p_{rd,s,t}$	*prevalence rate of causally related disease d scenario s at time t*
$pop_{s,t}$	*population scenario s at time t*
t	*time (years)*

[3] All parameters in the CDM are age and sex specific. For notational simplicity we will omit age and sex indices.

Since the COI study is a top down study in which health care costs are uniquely attributed to diseases we assume that health care costs for patients with more than one CDM disease equals the sum of the disease costs for these individual diseases.

We did not estimate the costs per individual indirect related disease per person per year. Since we assume the prevalence rates of indirect related diseases constant we estimated the average health care costs of *all* indirect related diseases. To estimate the costs of all indirect related diseases we first estimate the age and sex specific average health care costs per person:

$$(8)\ ac = \sum_{d} tc_{d,1999} \Big/ pop_{1999}$$

ac	*average health care costs per person*
$tc_{d,1999}$	*total health care costs for disease d in 1999*
pop_{1999}	*population size the Netherlands 1999*

To estimate the health care costs of all indirect related diseases per person first the average costs of the related diseases per person per disease are computed:

$$(9)\ cn_{rd} = tc_{rd,1999} / pop_{1999}$$

$cn_{rd,}$ *average costs per year per person for related disease d*

Given the average costs per person the next step in estimating the costs of indirect related disease is to subtract the average costs of related diseases per person from the average total health care costs per person. To obtain to total health care costs of indirect related diseases in a year we multiply by the population size:

$$(10)\ cu_{s,t} = pop_{s,t} * (ac - \sum_{1}^{rd} cn_{rd})$$

$cu_{s,t}$	*health care costs of all indirect related diseases scenario s at time t*
$ac_{s,t}$	*average health care costs per person*

We assume that all persons alive on average incur the average the average health care cost per year (specified by age and gender) that is corrected for the causally related diseases. People who have one of the causally related diseases also incur these costs, due to co-morbidities, and thus the difference in health care costs between scenario's depends on the difference in the prevalence of intervention related diseases and on the difference in population numbers.

3.3 Estimating life years

Life years gained is a measure of health outcome which counts the difference in life expectancy with and without the intervention. This measure only takes account of reductions in mortality. We can estimate the number of life years lived in a period by assuming that all

births and deaths take place at the end of a period. In this case the life years equals the population size at the beginning of that year:

$$(11)\ ly_{s,t} = pop_{s,t}$$

$ly_{s,t}$ *life years lived in year t scenario s*

If we want to estimate the gain in life years that can be attributed to the intervention and do not want to take into account the gain in life years that might be due to treatment of indirect related medical care, we have to make assumptions. One way is to assume that all the gain in years lived with one or more of the indirect related disease can be ascribed to the medical care for those diseases. The number of life years that would have been lived without receiving medical care for indirect related diseases can then be denoted as:

$$(12)\ lyr_{s,t} = pop_t * \prod_{ud}(1 - p_{ud})$$

$lyr_{s,t}$	*life years lived with no disease or one of the related diseases*
ud	*index for indirect related diseases*
p_{ud}	*prevalence rate of indirect related disease ud*

An alternative interpretation of equation (12) is the amount of life years lived by the total population in full health or with one or more of the causally related diseases. In this case we will interpret the probability of having not one of the indirect related diseases as the expected value an individual lives in full health or with one the causally related diseases (expressed as fraction per year). The expected value is then interpreted as the fraction of a year lived in full health or with one of the causally related diseases.

3.4 Costs per life year gained

Given the previous sections we can now estimate the costs per life year gained using the three different methods:

$$(13)\ CLY1 = \frac{\sum_{t=1}^{t} 1/(1+r)^{t-1} * (cr_{s1,t} + ci_{s1,t} - cr_{s2,t} - ci_{s2,t})}{\sum_{t=1}^{t} 1/(1+r)^{t-1} * (ly_{s1,t} - ly_{s2,t})}$$

$$(14)\ CLY2 = \frac{\sum_{t=1}^{t} 1/(1+r)^{t-1} * (cr_{s1,t} + ci_{s1,t} - cr_{s2,t} - ci_{s2,t})}{\sum_{t=1}^{t} 1/(1+r)^{t-1} * (lyr_{s1,t} - lyr_{s2,t})}$$

$$(15)\ CLY3 = \frac{\sum_{t=1}^{t} 1/(1+r)^{t-1} * (cr_{s1,t} + cu_{s1,t} + ci_{s1,t} - cr_{s2,t} - cu_{s2,t} - ci_{s2,t})}{\sum_{t=1}^{t} 1/(1+r)^{t-1} * (ly_{s1,t} - ly_{s2,t})}$$

CLY1 Cost per Life Year gained method 1
CLY2 Cost per Life Year gained method 2
CLY3 Cost per Life Year gained method 3

The estimate of the costs per life year gained is by definition the lowest using method 1. Using method 2 only the gain in life years of the population that has no indirect related disease is attributed to the intervention. Since the prevalence rates of indirect related diseases are assumed constant the difference in life years without indirect related diseases can be interpreted as the minimum gain in life years that can be attributed to the intervention. However, the costs per life year gained as computed using method 2 should be interpreted with, since we cannot exactly separate the effects of an intervention and those of unrelated medical care. The cost per life year using method 1 is an optimistic estimate of the true effects of the intervention, since it ignores health care costs of indirect related diseases. We argue that if one wants to compare different interventions with the RIVM CDM, the costs per life year gained using method 3 should be used, since it seems impossible to isolate the precise effects of an intervention. Furthermore, the third method is consistent in including all costs in the numerator and all effects in the denominator.

3.5 Estimating quality adjusted life years (QALYs)

The CDM is not only used to compare scenarios not only in terms of mortality but also in terms of morbidity. Two metrics that are often used to combine morbidity and mortality are quality adjusted life years (QALYs) and Disability Adjusted Life Years (DALYs). QALYs and DALYs have in common that they use a 'weight' to correct for a health state that is less perfect. This weight is either called a disability weight (using DALYs) or a quality weight (using QALYs). A chronic disease with a severe impact on quality of life could have a disability weight of 0.9 on a scale of 0 (perfect health state) to 1 (death). Correspondingly, this disease would be valued with a quality weight of 0.1 on a scale of 0 (death) to 1 (perfect health state). QALYs aggregate the actual health quality over time, DALYs aggregate the loss of health compared to perfect health. In the CDM we use DALY weights instead of QALY weight to calculate the health quality of time for several reasons:

- Daly weights are more easily available for more diseases;
- the same methodology is used to derive Daly weights for all diseases so the ranking is more consistent;
- the use of DALY weights is common within the RIVM to calculate burden of disease.

To estimate the effects on quality of life of diseases that are not explicitly modelled in the CDM we will use the Dutch Burden of Disease study [14] and assume that the prevalence rates, specified by age and sex, stay fixed over time. It is assumed that the incidence and prevalence rates of indirect related diseases, specified by age and sex, stay constant over time. Since population numbers can differ between scenario's this means that the prevalence in absolute numbers of these diseases can differ between scenarios. We use Dutch Daly weights [15] to calculate the quality of life and for CDM diseases for which there are not Dutch DALY weights we use we use international DALY weights [16].

To calculate the number of QALYs lived by the population we first estimate the mean quality of life in the population and then multiply this by the population numbers. Assessing the mean quality of life in population can be problematic for two reasons. The first one is that in the marginal model version of the CDM that we do not know exactly the amount of co-

morbidity and thus we have to estimate the estimate the amount of co-morbidity (see Appendix 1). The second reason is that there are more methods to weigh those co-morbid states:

- additive method: if a person has more than one disease his quality of life equals one minus the sum of the disability weights for those diseases;
- proportional method: the decrease in quality of life equals the product of the individual quality of life weights for those diseases (defined as 1 minus the disability weights);
- worst disease method: decrease in the quality of life equals the decrease in the quality of life of the disease with the highest disability weight.

Appendix 1 describes how to estimate the amount of co-morbidity in the marginal model version of the CDM. In the joint model version we do not need the estimate the amount of co-morbidity and the prevalence of co-morbid states is produced as output of the model. The general formula for calculating the amount of QALYs in a year if we take into account all diseases is:

$$(16)\ q_{s,t} = pop_{s,t} * mq_{ad,s,t}$$

$q_{s,t}$ *number of QALYs in scenario s time t*
mq_{ad} *mean quality of life in the population taking into account causally related and indirect related diseases*

If we want to estimate the amount of QALYs and do not want to take into account the QALYs that might be due to treatment of indirect related medical care, we make the same assumption as in section 3.3. The number QALYs that would have been lived without receiving medical care for indirect related diseases can then be denoted as:

$$(17)\ qr_{s,t} = pop_{s,t} * \prod_{ud}(1 - p_{ud,t}) * mq_{rd,s,t}$$

$qr_{s,t}$ *number of QALYs lived with no disease or one of the related diseases in scenario s time t*
$mq_{rd,s,t}$ *mean quality of life taking into account only causally related diseases*

3.6 Costs per QALY gained

The costs per QALY gained using the three different methods can be denoted as:

$$(18)\ CQ1 = \frac{\sum_{t=1}^{t} 1/(1+r)^{t-1} * (cr_{s1,t} + ci_{s1,t} - cr_{s2,t} - ci_{s2,t})}{\sum_{t=1}^{t} 1/(1+r)^{t-1} * (q_{s1,t} - q_{s2,t})}$$

$$(19)\ CQ2 = \frac{\sum_{t=1}^{t} 1/(1+r)^{t-1} * (cr_{s1,t} + ci_{s1,t} - cr_{s2,t} - ci_{s2,t})}{\sum_{t=1}^{t} 1/(1+r)^{t-1} * (qr_{s1,t} - qr_{s2,t})}$$

$$(20)\ CQ3 \quad = \frac{\sum_{t=1}^{t} 1/(1+r)^{t-1} * (cr_{s1,t} + cu_{s1,t} + ci_{s1,t} - cr_{s2,t} - cu_{s2,t} - ci_{s2,t})}{\sum_{t=1}^{t} 1/(1+r)^{t-1} * (q_{s1,t} - q_{s2,t})}$$

CQ1 Cost per QALY gained method 1
CQ2 Cost per QALY gained method 2
CQ3 Cost per QALY gained method 3

Analogue to the costs per life year gained the costs per QALY gained are lowest using method 1.

4. Discussion

In this report the conceptual model and model equations implemented in the cost effectiveness module in the CDM are presented. The focus thereby was on developing a methodology to consistently deal with direct and indirect medical costs and direct and indirect health effects. Other important methodological choices such as the choice of discount rate were not addressed in this report.

In order to decide what costs and effects are taken into account we make a distinction between diseases causally related and diseases indirect related to the intervention. Given this distinction we follow the approach recently set out by Nyman in Health Economics to determine which costs and (effects) to include in the economic evaluation: all costs that directly produce the utility measured in the denominator have to be included in the numerator of the cost effectiveness ratio. Following the Nyman approach we distinguish three different cost effectiveness ratios: 1) all health effects are ascribed to the interventions while costs of indirect related diseases are excluded; 2) only the minimum gain in QALYs and life years that can be attributed to the interventions are included while costs of indirect related diseases are excluded; 3) all health effects ànd costs of all diseases are included.

To estimate the impact of indirect related diseases on the quality of life we use data from the Dutch Burden of Disease study. Three methods to calculate the quality of life in case of co-morbidity based on the quality of life values of each of the diseases are introduced. In future research we hope to investigate how these methods compare with self reported generic measures of population health. Data from the Costs of Illness 1999 study in the Netherlands is used to estimate the impact of an intervention on total health care costs. It is assumed that the total costs attributed to diseases in that study can also be attributed to individual patients and that costs only are a function of age and gender. A next step might be to also distinguish patient costs per incident case, prevalent cases and costs in the last year before death.

We argue that if one wants to compare different interventions in within the RIVM CDM, the third ratio is the best, since it seems impossible to isolate the precise effects of an intervention. This approach is consistent in including all costs in the numerator and all effects in the denominator. The Dutch guidelines for pharmacoeconomic research prescribe that only the costs of related diseases should be taken into account. In practice this means that in our terminology only medical costs of causally related diseases are taken into account (method 1). In our opinion this method systematically biases the results of cost effectiveness analysis since health care costs of indirect related diseases are not taken into account. Furthermore, not taking into account costs of indirect related diseases also favours interventions that prolong life compared to interventions that increase the quality of life.

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Appendix 1: Estimating the average quality of life using the RIVM Chronic Disease Model

In the following subsections different methods are explained how to calculate population mean quality of life values taking into account co-morbidity and population heterogeneity. We introduce three methods to calculate the quality of life in case of co-morbidity based on the quality of life values of each of the diseases. First we apply these methods to calculate the population mean values in a homogenous population, i.e. with the co-morbidity prevalence rates being equal to the product of the marginal disease prevalence rates. Then we apply these methods for a heterogeneous population, i.e. with co-morbidity resulting from joint epidemiological risk factors. In the following subsections the subscript *d* is used as an index for diseases. This can be either read as *rd* if we take into account only the causally related diseases or as *ad* if both causally and indirect related diseases are taken into account.

Additive decrease of Quality of life

If a person has/suffers more than one disease his quality of life equals one minus the sum of the sum of DALY weights for those diseases. For instance, if a person has disease 1 and 2 his quality of life equals: $(1\text{-}DALY_1\text{-}DALY_2)$. When using this method one must acknowledge that theoretically there is no minimal quality of life anymore since individual Daly weight may add up to more than one. This method, in fact, is the same as calculating the quality of life without taking into account co-morbidity and just adding up the burden of all diseases.

$$q = (1\text{-}p_1)(1\text{-}p_2) + (1-p_2)\,p_1\,(1\text{-}DALY_1) + (1-p_1)\,p_2\,(1\text{-}DALY_2) + p_1\,p_2\,(1-DALY_1-DALY_2)$$

$$= 1\text{-}p_1\,DALY_1 - p_2\,DALY_2 \text{ etc.}$$

$$= 1 - \Sigma_d\, p_d\, DALY_d$$

$DALY_d$ *DALY weight of disease d*

Proportional decrease quality of life

The decrease in the quality of life is proportional. For someone who has disease 1 and 2 his quality of life equals: $(1\text{-}DALY_1)\,(1\text{-}DALY_2)$. If there are only 2 diseases the mean quality of life in the population equals:

$$q = (1\text{-}p_1)(1\text{-}p_2) + (1-p_2)\,p_1\,(1\text{-}DALY_1) + (1-p_1)\,p_2\,(1\text{-}DALY_2) + p_1\,p_2\,(1\text{-}DALY_1\,(1\text{-}DALY_2)$$

$$= (1-p_1\,DALY_1)\,(1-p_2\,DALY_2) \text{ etc.}$$

$$= \Pi_d\,((1\text{-}p_d) + p_d\,(1\text{-}DALY_d)) = \Pi_d\,(1 - p_d\,DALY_d)$$

Quality of life equals the quality of life of worst disease

Assuming that the diseases are ordered in terms of Daly weights, e.g.. $DALY_1 \geq DALY_2 \geq DALY_3$ ……$DALY_n$. So someone who has disease 1 and 2 his quality of life equals: $(1\text{-}DALY_1)$ since disease 1 is worse than 2. The fraction of the population that gets the weight of disease *d* equals the prevalence rate of disease *d* minus the fraction of the population that has disease *d* but also a disease with a higher DALY weight. We can write this principle for three diseases:

$$P_1 = p_1$$
$$P_2 = p_2 * (1 - p_1)$$
$$P_3 = p_3 * (1 - (p_1 + p_2 - p_1 * p_2))$$

$P_1 = p_1$

$P_2 = (1 - P_1) p_2$

$P_3 = (1 - P_1 - P_2) p_3$ etc.

P_d fraction of the population for which disease *d* is the worst disease

Using this we can define a recursive definition of the prevalence rate Pd:

$$P_d = \begin{cases} p_d & \text{if } d = 1 \\ p_d (1 - \sum_{d=1}^{d-1} P_d) & \text{else} \end{cases}$$

The mean quality of life can then be written as:

$$q = 1 - \sum_{d=1}^{n} P_d DALY_d$$

Accounting for heterogeneity in the population

We can account for heterogeneity in the population by estimating the prevalence rates of diseases within risk factor classes using relative risks:

$$RM^{(1)}_{d,i} = RR^{(1)}_{d,i} / (\Sigma_i p^{(1)}_i * RR^{(1)}_{d,i})$$
$$p_d(i) = RM^{(1)}_{d,i} * p_d$$

i	*index for different classes of risk factor 1*
$p^{(1)}(i)$	risk factor 1 class prevalence rates
$RR^{(1)}_{d,i}$	*relative risk for risk factor 1 class i for having disease d compared to class i=1*
$RM^{(1)}_{d,i}$	*mean risk multiplier for risk factor 1 class i for disease d*

Then the population co-morbidity rate of two diseases 1 and 2 is:

$$\Sigma_i \, RM^{(1)}_{1,i} \, RM^{(1)}_{2,I} \, p_{d1} \, p_{d2}$$

Using this formula we can calculate the quality of life value in a heterogeneous population assuming additive decrease, proportional decrease, and the worst disease respectively.

Additive decrease

$$\begin{aligned} q \quad &= \Sigma_i \, p^{(1)}(i) * \\ &\quad \{ (1-p_1(i)) (1- p_2(i)) + (1 - p_2(i)) \, p_1(i) (1- DALY_1) + \\ &\quad (1 - p_1(i)) \, p_2(i) (1- DALY_2) + p_1(i) \, p_2(i) (1 - DALY_1 - DALY_2) \} \\ &= 1 - \Sigma_i \, p^{(1)}(i) \, \{ p_1(i) \, DALY_1 - \Sigma_i \, p_2(i) \, DALY_2 \} \\ &= 1 - p_1 \, DALY_1 - p_2 \, DALY_2 \end{aligned}$$

Thus the additive decrease is equal for homogeneous and heterogeneous populations.

Proportional decrease

$$\begin{aligned} q \quad &= \Sigma_i \, p^{(1)}(i) * \\ &\quad \{ (1-p_1(i)) (1- p_2(i)) + (1 - p_2(i)) \, p_1(i) (1 - DALY_1) + \\ &\quad (1 - p_1(i)) p_2(i) (1- DALY_2) + p_1(i) p_2(i) (1 - DALY_1) (1 - DALY_2) \} \\ &= \Sigma_i \, p^{(1)}_i \, \{ (1 - p_1(i) \, DALY_1) (1 - p_2(i) \, DALY_2) \} \\ &= 1 - p_1 \, DALY_1 + p_2 \, DALY_2 + \Sigma_i \, p^{(1)}(i) \, RM^{(1)}_{1,i} \, RM^{(1)}_{2,i} \, p_1 \, p_2 DALY_1 \, DALY_2 \\ &= (1 - p_1 \, DALY_1) (1 - p_2 \, DALY_2) + \\ &\quad (\Sigma_i \, p^{(1)}(i) \, RM^{(1)}_{1,i} \, RM^{(1)}_{2,i} - 1) \, p_1 \, p_2 \, DALY_1 \, DALY_2 \end{aligned}$$

Thus in case of proportional decrease the population mean value increases taking into account population heterogeneity.

Worst disease

$$\begin{aligned} q \quad &= \Sigma_i \, p^{(1)}(i) * \\ &\quad \{ 1 - p_1(i) \, DALY_1 - (1 - p_1(i) \, p_2(i) \, DALY_2 \} \\ &= 1 - p_1 \, DALY_1 - (1 - p_1) \, p_2 \, DALY_2 + \end{aligned}$$

$$(\Sigma_i \, p^{(1)}(i) \, RM^{(1)}_{1,i} \, RM^{(1)}_{2,i} - 1) \, p_1 \, p_2 \, DALY_2$$

Likewise, in case of worst disease effects the population mean value increases taking into account population heterogeneity.

We conclude that the three methods result in different population quality of life values since the calculated quality of life values in co-morbidity states are different. Taking into account population heterogeneity resulting in extra co-morbidity through joint epidemiological risk factors does not the result for the additive decrease method, but it does affect the other methods. The changes are proportional to the change of the calculated co-morbidity prevalence rates.