Appendix B6. Methodology for WP6 – development of the cost effectiveness module

Data Collection

The academic literature was searched for the different diseases, in combination with the EConDA countries. We looked for publications which contained information on costs and/or quality of life. No limitation in the search year was defined. The reference list of the found literature was also searched for any grey literature that may come up. Searches were performed in an ad hoc manner several times during the run of the EConDA project, in order to see whether new literature had been published.

Contact persons in each EConDA country were approached via email and telephone. They were asked for any sources of information on costs and/or quality of life that could have been missed or would not be openly available. Local partners could be used to gain access to unpublished information, or information published in a language other than English or Dutch.

Results from the consensus

In WP 4 ("Form a consensus on methodology for measuring cost-effectiveness of interventions for chronic diseases") several issues were discussed on who best to perform cost-effectiveness research within the EConDA project. It was felt that this consensus should be leading for the way WP6 was performed. For the purpose of WP 6, the conclusions of the consensus can be summarized as follows.

There are several options available for economic evaluations. The consensus was that the Cost-Effectiveness Analysis (CEA) is the most useful method for EConDA. In a CEA, the difference in costs between two interventions is divided by the difference in health outcomes. The resulting proportion is called the Incremental Cost-Effectiveness Ration (ICER) and can be compared to a societal Willingness-to-pay (WTP), often called the threshold (1), which is the "price" a society is willing to pay for an extra unit of health "output". Cost-minimization was considered too limited and cost-benefit analysis (CBA) not practical given the inherent need to translate health directly into money. In order to do this, an explicit

threshold value for the willingness-to-pay for health outcomes is a necessity in a CBA, whereas highly controversial. Such a threshold value will therefore not be determined by EConDA, as this was deemed a political decision. EConDA will simply state the outcomes in terms of an ICER, which the model user, such as a decision maker, may interpret as "cost-effective" or "not cost-effective", depending on his/her conceived threshold.

Furthermore, economic parameters such as discounting rates were considered best taken country-specific. A good source for this are published country-specific guidelines for health-economic or pharmaco-economic research. An overview can be found on the website of the International Society of Pharmacoeconomics and Outcomes Research or ISPOR.(2)

In order to estimate the costs of interventions and disease, the preferred method was considered to use tariffs, or the actual costs if available. Expert opinions and average costs (from the literature) were deemed acceptable.

Also, health outcomes should be measured using an existing framework of quality of life (QoL) measurement, such as the quality-adjusted life years (QALY). Otherwise there is a risk of incomparability with other cost-effectiveness studies. Additionally, excluding QoL might penalise patients, who may not experience an increase in life expectancy, but whose quality of life may be significantly improved by a treatment. Also, it was considered fair that extended survival be weighted with QoL measurements. Still, in reporting it was considered important to separate QALYs gained through both extended survival and increased QoL.

A societal perspective was preferred, with the direct and indirect costs presented separately. In the country-specific guidelines, Finland (3), The Netherlands (4) and Portugal (5)state a preference for a societal perspective. In the UK (guidelines for England/Wales (6)), a health care payer perspective is the norm, as is the case in Poland.(7) In the latter case, including a societal perspective is advised in scenario analysis. In Lithuania (guidelines for the Baltic states (8)), the perspective should be the health care system, but a societal perspective can be taken "if relevant". Finally, no guidelines have been published for Bulgaria and Greece.

This shows that although the consensus was that a societal perspective should be taken in EConDA, this view is not necessarily always taken by local decision makers. Therefore, it was important that direct health-care costs and indirect non-health care costs (productivity losses) are presented separately.

A preference was stated to use the friction cost methodology (FC), over the human capital (HC) methodology, although FC is only stated in the guidelines for The Netherlands.(4) The difference between the two approaches is that in the HC approach, the patient's perspective is taken. This approach counts any hour not worked as lost. The FC approach takes the employer's perspective, and only counts as lost, those hours not worked until another employee takes over.(9,10)

Although EConDA will not present a threshold, we here list the thresholds, as they would hold according to the WHO CHOICE (World Health Organisation - Cost effectiveness and strategic planning) model. This model proposed a threshold of 3 times the GDP per capita and it can be used to compare/interpret outcomes of the EConDA model.

- Bulgaria: лв 33.000 / QALY
- Finland: € 90.000 / QALY
- Greece: € 59.000 / QALY
- Lithuania: € 58.000 / QALY
- Netherlands: € 106.000 / QALY
- Poland: zł 225.000 / QALY
- Portugal: € 62.000 / QALY
- UK: £ 73.000 / QALY

A final note on comparing the outcomes of a cost-effectiveness study between countries is warranted. There is a strong tendency, which was also voiced during the consensus meeting, to compare outcomes between countries. This is often based on the epidemiological starting point of most researchers. Populations are often largely comparable and differences between countries can be explained by (often) only a few parameters. However, cost-effectiveness outcomes are the result of many country-specific parameters.(11) Outcomes are therefore only of use in the countries themselves. It is also because of that, that opposite to registration processes of drugs, reimbursement procedures inclusive CE are not centralized at an EU-level and likely will not be soon either.

1.1. Types of Interventions

Any type of intervention can be implemented into the EConDA model. As example interventions within the EConDA project, four different types of interventions have been implemented. First, smoking cessation has been implemented. The aim of this intervention is to reduce the number of smokers and thus the number of smoking related diseases.

Secondly, taxes on sugar sweetened beverages (SSBs) are implemented in the model. The idea is that a higher price, through a price elasticity, will drop the demand for SSBs. These will be replaced by more healthy alternatives, which will then in turn lead to a lower BMI.

A multicomponent lifestyle intervention (MCLI) is a programme that aims to reduce a person's energy intake and help them to be more physically active by changing their behaviour. To be considered multicomponent, the programme must include diet, physical activity and behavioural therapy (for example, counselling sessions).(12) Behavioural techniques most commonly used are goal setting and review of goals (behaviour and outcome), action planning, barrier identification and problem solving, self-monitoring of behaviour, feedback on performance, instruction on how to perform behaviour and planning social support and social change.(13)

Thirdly, screening was analysed, again a different type of intervention. In the EConDA model, screening for albuminuria was implemented as the prototype here. Albuminuria is a risk factor for end stage renal disease (ESRD), independent of the traditional measure of kidney function, the estimated glomerular filtration rate (eGFR). (14) Raised albuminuria is also associated with cardiovascular disease (CVD), even after adjustment for traditional cardiovascular risk factors and eGFR.(15,16) The adjusted risk of cardiovascular mortality is more than doubled at the upper end of the microalbuminuria category (30–299 mg/g), compared with the risk in individuals with normal albuminuria.(15-17) Elevated albumin is preferably assessed by the urinary albumin-to-creatinine ratio.(18) The idea of screening for albuminuria is that patients with elevated levels of urinary albumin will then be treated earlier than if they would wait before having presented themselves to their GP with lower eGFR and potential complaints. It has been shown that reducing albuminuria using pharmaceuticals, may reduce the incidence of CVD and renal adverse outcomes such as type 2 diabetes (T2DM) and hypertension, even in the general, otherwise

healthy population.(19-25) By treating these patients, renal disease, ESRD and CVD may potentially be delayed or even prevented. Population based screening for albuminuria is therefore a potentially cost-effective way of preventing CKD, ESRD and CVD.(26)

Finally, a direct intervention to treat one of the diseases has also been implemented. Much time has been used to prepare the implementation of roflumilast in the EConDA model. Roflumilast has been on the market for some time, but is not reimbursed at this time in The Netherlands, despite a relatively low ICER.(27) In the UK, NICE recommends roflumilast for people with severe COPD only if they are taking part in a research study (clinical trial) that is investigating using roflumilast at the same time as a bronchodilator (a type of inhaled drug), also despite a relatively low ICER.(28,29) Roflumilast is targeted as an add-on to current treatment, for COPD patients with severe or very-severe COPD. Based on Dutch data, annual treatment or roflumilast would cost € 604 (30), while the yearly costs would be € 294 lower, due to a 20% reduction in the number of exacerbations.(31) Roflumilast would have the effect of reducing the probability of going from the severe to the very severe stage, with a risk ratio of 0.861.(27)

Since roflumilast is a simple add-on to the current treatment, it was deemed a perfect candidate for implementation in the ECoNDA model. However, it became clear in a late stage of the project that the EConDA model will not have a distinction between the severe and very severe stages. This made it difficult to implement roflumilast. In order to illustrate how EConDA can be used to model interventions, a hypothetical drug is implemented based on roflumilast, but also targeted at moderate COPD.

2. Results

Obviously, for CE-analysis good cost data are required. Necessary cost data was lacking for many countries, and many diseases. Searches in the literature did not yield usable sources, and several efforts have been made to secure grey literature from local EConDA partners. This did not yield more information, except a promise at a late stage for local Bulgarian data.

The European Cardiovascular Disease Statistics 2012 was one specific source that allowed the calculation of both direct and indirect costs for all countries, for CHD, stroke and hypertension.(32) This publication provided health care costs for cardiovascular disease (CVD), coronary heart disease (CHD) and

cerebrovascular diseases, on a population level. It was primarily used to estimate the proportion between the direct health-care and the indirect non-health care costs (production losses due to mortality and morbidity and informal care). The proportion for CHD was used for CHD, cerebrovascular disease was used for stroke and CVD was used for hypertension.

Another fruitful source of country-specific information was the Diabetes Atlas, 6th edition from the International Diabetes Federation (IDF).(33) The atlas contains a country summary table, including the mean diabetes-related healthcare expenditures per person with diabetes. It did not provide an estimate of the indirect non-health care costs.

The Netherlands had the most country-specific information available, followed by the United Kingdom. Dutch estimates were used as proxies for the other countries when data were lacking, using the necessary economic parameters to translate costs from one country to another (see 3.6). We start with the results from The Netherlands, followed by the estimates from the United Kingdom. We then provide an overview of the other EConDA countries.

2.1. Costs in The Netherlands

Direct health care costs used in EConDA for The Netherlands can be found in Table 1. Direct health-care costs per population year (i.e. costs for the entire population in a country during a single year) for CHD and stroke were given by the European Cardiovascular Disease Statistics 2012.(32) Direct health care costs per patient year for CHD hypertension and stroke were provided by the Dutch Costs of Illness ("Kosten van Ziekten") study.(34)

Costs of COPD by stage was provided by a Dutch study outlining the societal costs of asthma, COPD and respiratory allergy, per population year and per patient year.(35,36) The direct health care costs per patient year are provided for different age groups, however not by severity of disease. Using the proportion between the disease stage specific costs in the UK, from Flack et al. and the direct stage for all patients, a cost per patient in The Netherlands is calculated.(37)

End-stage renal disease (ESRD) costs were provided by Boersma et al.(26) No costs for the treatment of non-ESRD CKD was found. Instead, expert opinion of resource use was provided by Dr. Susan van

Logteren (nephrologist at the University Medical Center Groningen). Based on these expert opinions, the "National Transmural Agreement on Chronic Kidney Damage" from the Dutch GP Society (38) and the "Dutch Guideline for Cost Research, Methods and Prices for Economic Evaluations in Health Care" (39), estimates were made for the different stages of CKD

Next to the IDF Diabetes Atlas, a country-specific Dutch study was found.(33,40) Both estimates for direct costs strongly diverged. In order to remain consistent over all countries, it was decided that the estimate provided by the IDF Diabetes Atlas will be used. (33) The study by Van der Heijden et al. was be used to calculate indirect costs (see next paragraph).(40)

No costs for the treatment of impaired glucose tolerance (IGT) was found. Expert opinion was provided by a GP with a special focus on diabetes in Hardenberg (Hans van Hateren). Based on an official 10-year risk table for cardio-vascular risks (41) and the "Dutch Guideline for Cost Research, Methods and Prices for Economic Evaluations in Health Care" (39), an estimate was calculated for IGT (Table 1). IGT in The Netherlands is only treated in the first line. A distinction between patients with and without further risk factors was taken into account, with IGT without any further risk factors yielding a yearly cost of € 50,39, and IGT with extra risk factors € 116,41. These extra risk factors are:

- Male smokers >50 with systolic blood pressure (SBP) > 140 mmHg and/or low density lipoprotein (LDL) > 2.5 mmol/l;
- All males >55 with SBP > 140 mmHg and/or LDL > 2.5 mmol/l;
- All female smokers >65 with SBP > 140 mmHg and/or LDL > 2.5 mmol/l ;
- All smokers aged >65; and
- All patients aged >70.

For the calculation of costs drugs by expert opinion, the Dutch website "Medicijnkosten" [Drug costs] (30) was used for drug prices, as well as the "Farmacotherapeutisch Kompas" [Pharmacotherapeutic Compass] (42) which provides information on the dosage of drugs. Finally, costs of other resource use such as doctor's visits, were provided by the "Guideline for Cost Research, Methods and Prices for Economic Evaluations in Health Care". (39)

Table 1 Direct disease costs for The Netherlands used in EConDA.

Direct costs	Cost per population year (x 1 mln)	Cost per patient year	Source
	(in €)		
CHD	1,735.4	3,632	(32,34)
CKD			
Stage 1		159	Expert opinion
Stage 2		159	Expert opinion
Stage 3		238	Expert opinion
Stage 4		310	Expert opinion
Stage 5		310	Expert opinion
ESRD		79,846	(26)
COPD	437.4		(35-37)
Mild		636	(35-37)
Moderate		1,491	(35-37)
Severe		4,887	(35-37)
Hypertension		193	(34)
Stroke	1,489.3	27,326	(32,34)
Type 2 Diabetes Mellitus (T2DM)		5,230	(33)
Impaired Glucose Tolerance (IGT)			
No extra risk factors		83	Expert opinion
With extra risk factors		83	Expert opinion

Estimates of the indirect (non-health care) costs can be found in Table 2. Costs per population year for CHD and stroke are provided by the European Cardiovascular Disease Statistics 2012.(32) The direct costs per patient year from the Dutch Costs of Illness ("Kosten van Ziekten") study (34) are multiplied by the proportion between direct and indirect costs from the European Cardiovascular Disease Statistics 2012, to estimate indirect costs per patient year for CHD, stroke and hypertension. As mentioned before, the proportion for CHD was used for CHD, cerebrovascular disease was used for stroke and CVD was used for hypertension.

Indirect costs for COPD, both from the human capital and friction cost perspectives, were available from Suijkerbuijk et al.(35,36) An average was calculated over the two age groups provided in the study, namely patients 40-49 and patients 50-64 years old. The study by Suijkerbuijk et al. provided estimates both estimated using both the Human Capital (HC) and Friction Cost (FC) methodologies (see 2.2). Although the consensus was that there was a preference for the FC method, and the Dutch guidelines state that the FC method is preferred (4), estimates for COPD in The Netherlands were the only ones found using the FC methodology. In order to remain consistent for all diseases, it was decided that we would use the HC approach for all diseases, and thus also for COPD, in The Netherlands.

The proportion between the indirect and direct costs for diabetes in a study provided by Van der Heijden et al, was multiplied with the direct cost estimate, to calculate the indirect costs for T2DM.(33,40)

No information was found for the Indirect costs for CKD and IGT. The indirect costs for IGT were assumed to be equal to 0, since it is unlikely that a person will lose productivity because of this illness directly. Loss of productivity will likely occur either at the onset of T2DM, or due to co-morbidities such as CHD and hypertension. Calculating indirect costs will therefore likely lead to double counting of indirect costs. The indirect costs for CKD was taken equal to CHD, since these diseases were deemed "most similar".

Table 2 Indirect disease costs for The Netherlands used in EConDA.

Indirect costs	Cost per population year (x 1 mln)	Cost per patient year	Source
	(in €)		
CHD	2,147.7	4,495	(32,34)
CKD		4,495	Assumption
COPD		6,396	(35,36)
Hypertension		172	(32,34)
Stroke	1,071.6	19,662	(32,34)
Type 2 Diabetes Mellitus (T2DM)		2,651	(33,40)
Impaired Glucose Tolerance (IGT)		0	Assumption

2.2. Costs in the United Kingdom

For the United Kingdom, country-specific data on direct health care costs was found for CHD and COPD, based on a report Flack et al.(37) Country-specific costs for stroke come from a study by Youman et al.(43) The IDF Diabetes Atlas provided a country-specific estimate for T2DM. For the other diseases, Dutch proxies are used. The costs can be found in Table 3.

Table 3 Direct disease costs for the United Kingdom used in EConDA.

Direct costs	Cost per population year (x 1 mln)	Cost per patient year	Source
	(in £)		
CHD	2,024.4	1,521	(32,37)
CKD			
Stage 1		134	NL proxy
Stage 2		134	NL proxy
Stage 3		201	NL proxy
Stage 4		261	NL proxy
Stage 5		261	NL proxy
ESRD		67,183	NL proxy
COPD			
Mild		639	(37)
Moderate		1,498	(37)
Severe		4,911	(37)
Hypertension		162	NL proxy
Stroke	1,979.0	2,541	(32,43)
Type 2 Diabetes Mellitus (T2DM)		2,857	(33)
Impaired Glucose Tolerance (IGT)		70	NL proxy

Country-specific indirect costs for the UK were found for CHD, stroke and COPD.(32,37,43,44) Indirect costs for COPD were calculated from the estimate of direct costs for COPD from Flack et al. (37) and the proportion between direct and indirect costs from the study by Britton et al.(44) Estimates for CHD and stroke were made using the direct estimates and the proportion between direct and indirect costs on per population year.(32) An estimate for the indirect costs of hypertension was calculated using the Dutch proxy estimate for direct costs for hypertension and the proportion between direct and indirect costs for CVD.(32) The Dutch estimate for indirect costs for T2DM is used as a proxy for the United Kingdom. The assumptions for CKD and IGT are the same as for The Netherlands. For an overview see Table 4.

Table 4 Indirect disease costs for the United Kingdom used in EConDA.

Indirect costs	Cost per population year (x 1 mln)	Cost per patient year	Source
	(in £)		
CHD	5,483.5	4,121	(32,37)
CKD		4,121	Assumption
COPD		548	(37,44)
Hypertension		252	(32), NL proxy
Stroke	1,979.0	10,053	(32,43)
Type 2 Diabetes Mellitus (T2DM)		1,448	NL proxy
Impaired Glucose Tolerance (IGT)		0	Assumption

2.3. Costs in other EConDA countries

Country specific estimates were available for the other countries in EConDA, for the direct health care costs per patient year for diabetes.(33) The European Cardiovascular Disease Statistics 2012 provided country specific estimates for the direct and indirect costs for CHD and stroke per population year.(32) No other country-specific estimates were found and the Dutch data was used as a proxy. As mentioned before, during the EconDA workshop performed in Sofia, Bulgaria, country-specific data for Bulgaria was promised, and this is in the process of being validated. If this data is usable, this will significantly improve the usefulness of the model for Bulgarian decision makers.

Indirect cost estimates for hypertension, stroke and CHD per patient year were based on the Dutch estimates for direct costs, but using the country-specific proportion between direct and indirect costs from the European Cardiovascular Disease Statistics 2012.(32) Indirect costs for COPD was based on the direct estimate for Dutch COPD patients, in order to stay consistent with the proxy country used for the other diseases. However, the proportion between direct and indirect costs was used from the available UK source.(44)

Table 5 Direct disease costs for Bulgaria, Finland, Greece, Lithuania, Poland and Portugal in EConDA.

Direct costs	Bulgaria		Finland		Greece		Lithuania		Poland		Portugal		Source
	Cost/ pop yr (x 1 m ln)	Cost/ pat yr	Cost/ pop yr (x 1 m ln)	Cost/ pat yr	Cost/ pop yr (x 1 m ln)	Cost/ pat yr	Cost/ pop yr (x 1 m ln)	Cost/ pat yr	Cost/ pop yr (x 1 m ln)	Cost/ pat yr	Cost/ pop yr (x 1 m ln)	Cost/ pat yr	
	(in лв)		(in €)		(in €)		(in €)		(in Zł)		(in €)		
CHD	120.3	5,767	448.8	3,961	632.0	2,874	64.1	2,995	4,462.1	7,874	207.4	2,682	(32), NL proxy
CKD													
Stage 1		242		179		124		132		350		118	NL proxy
Stage 2		242		179		124		132		350		118	NL proxy
Stage 3		363		268		186		199		525		177	NL proxy
Stage 4		472		349		241		258		683		230	NL proxy
Stage 5		472		349		241		258		683		230	NL proxy
ESRD		121,567		89,900		62,156		66,527		175,933		59,160	NL proxy
COPD	901.4	2,209	561.6	1,517	418.8	1,196	463.7	1,147	1,133.1	3,016	370.8	1,027	NL proxy
Mild		1,065		731		577		553		1,454		495	NL proxy
Moderate		2,497		1,715		1,352		1,296		3,408		1,161	NL proxy
Severe		8,186		5,622		4,432		4,250		11,175		3,807	NL proxy
Hypertension		306		229		131		159		418		108	NL proxy
Stroke	97.2	43,395	821.1	29,805	609.2	21,624	39.3	22,532	2,654.0	59,244	167.8	20,181	(32), NL proxy
Type 2 Diabetes Mellitus (T2DM)		901		3,922		1,773		827		3,357		1,515	(33)
Impaired Glucose Tolerance (IGT)		127		94		65		65		184		62	NL proxy

Table 6 Indirect disease costs for Bulgaria, Finland, Greece, Lithuania, Poland and Portugal used in EConDA.

Direct costs	Bulgaria		Finland		Greece		Lithuania		Poland		Portugal		Source
	Cost/ pop yr (x 1 m ln)	Cost/ pat yr	Cost/ pop yr (x 1 m ln)	Cost/ pat yr	Cost/ pop yr (x 1 m ln)	Cost/ pat yr	Cost/ pop yr (x 1 m ln)	Cost/ pat yr	Cost/ pop yr (x 1 m ln)	Cost/ pat yr	Cost/ pop yr (x 1 m ln)	Cost/ pat yr	
	(in лв)		(in €)		(in €)		(in €)		(in Zł)		(in €)		
CHD	299.9	14,374	312.0	2,753	1,040.1	4,730	166.0	7,750	9,308.2	16,425	496.4	6,421	(32), NL proxy
CKD	□	14,374	□	2,753	□	4,730	□	7,750	□	16,425	□	6,421	Assumption
COPD	□	10,712	□	7,357	□	6,986	□	5,562	□	14,624	□	4,982	NL/UK proxy
Hypertension	□	444	□	110	□	100	□	253	□	513	□	147	(32), NL proxy
Stroke	205.6	91,777	318,4	11,558	477,0	16,934	66,1	37,848	4,841.0	108,062	386,.2	46,431	(32), NL proxy
Type 2 Diabetes Mellitus (T2DM)	□	457	□	1,988	□	899	□	419	□	1,702	□	768	NL proxy
Impaired Glucose Tolerance (IGT)	0	0	0	0	0	0	0	0	0	0	0	0	Assumption

Table 7 Utility scores in order to calculate quality adjusted life years (QALY) used in EConDA.

Utility values	BU	FI	GR	LT	NL	PL	PT	UK	Source
Healthy persons	1	1	1	1	1	1	1	1	Assumption
CHD	0,71	0,71	0,71	0,71	0,71	0,71	0,71	0,76	(11)
CKD	0,89	0,89	0,89	0,89	0,89	0,89	0,89	0,89	(45)
Stage 1	0,94	0,94	0,94	0,94	0,94	0,94	0,94	0,94	(45)
Stage 2	0,92	0,92	0,92	0,92	0,92	0,92	0,92	0,92	(45)
Stage 3	0,88	0,88	0,88	0,88	0,88	0,88	0,88	0,88	(45)
Stage 4	0,84	0,84	0,84	0,84	0,84	0,84	0,84	0,84	(45)
Stage 5	0,80	0,80	0,80	0,80	0,80	0,80	0,80	0,80	(45)
ESRD	0,66	0,66	0,66	0,66	0,66	0,66	0,66	0,66	(45)
COPD	0,69	0,69	0,69	0,69	0,69	0,69	0,69	0,73	(11,46)
Mild	0,83	0,83	0,83	0,83	0,83	0,83	0,83	0,83	(47)
Moderate	0,79	0,79	0,79	0,79	0,79	0,79	0,79	0,79	(47)
Severe	0,7	0,7	0,7	0,7	0,7	0,7	0,7	0,7	(47)
Hypertension	0,72	0,72	0,72	0,72	0,72	0,72	0,72	0,72	(46)
Stroke	0,54	0,54	0,54	0,72	0,54	0,72	0,54	0,74	(11,48)
Type 2 Diabetes Mellitus (T2DM)	0,66	0,66	0,66	0,66	0,66	0,66	0,66	0,66	(46)
Impaired Glucose Tolerance (IGT)	1	1	1	1	1	1	1	1	Assumption

2.4. Quality of life

In order to translate the number of life years, that come from the epidemiological model, to quality adjusted life years (QALYs), utility scores are necessary. Country specific estimates were found for several diseases/country combinations.

Country specific estimates of CHD and stroke was found for the UK and The Netherlands (Table 11).(11) A multi-country average of five countries, including Lithuania and Poland, was found as an estimate for stroke in those two countries.(48) For the other EConDA countries, in line with the way costs were treated, the Dutch proxy was used. Quality of life estimates for CKD was only found for Japan. This estimate has been used for all EConDA countries.(45)

A study by Sullivan et al., contains a catalogue of EQ-5D, an often used measure of quality of life, for several diseases in the UK.(46) From this catalogue, we used the utility estimate for COPD (ICD-9: 496), hypertension (ICD-9: 401) and T2DM (ICD-9: 250). No better estimates for other countries were found for hypertension or T2DM, for which the UK proxy was used. There was a country-specific estimate for COPD in The Netherlands, which was also used as a proxy for the other EConDA countries.

In addition to the single state COPD estimate, a multi-stage overview of quality of life in different COPD stages was also found.(47) The utility weight for the severe COPD group was calculated by taking the average of the utility weight values of stages 3 and 4. The estimate of the mild COPD stage, which was not investigated in the Rutten-van Mölken study, the utility weight for this stage was based on two other studies, from China and Korea. (49,50)

It was assumed that patients with a comorbidity, will receive the quality of life estimate of the lowest of the diseases that patients suffers from. Further assumptions were that the quality of life of people without any diseases, or with only IGT, was 1.

2.5. Interventions

Smoking cessation

SSB Taxes

Partner countries were asked to submit information on multicomponent lifestyle interventions (MCLI) that were active or had been tested in their countries. Very little information was retrieved in this way. This was probably due to very few MCLI programmes being rolled out at national or regional level in EConDA countries. Therefore research studies which investigated the effect of MCLI on body weight in adults carried out in EConDa countries were also retrieved. Studies investigating six different interventions were identified for the UK, one each for Greece, Finland and Portugal and two for the Netherlands. For the UK, an intervention delivered by the NHS was selected. For Netherlands, the intervention with best weight loss results was selected. The characteristics of interventions selected per country, including their costs and effect on weight loss are summarised in Table 8.

For Lithuania, Poland and Bulgaria, the Greek intervention will be used in the absence of country specific information. The assumption was made that a similar intervention delivered in these countries would have a similar effect on weight loss and would cost the same. The model will use country specific information on the effect of MCLI on weight loss (Table 8). The impact of rolling out the country specific MCLI at national level on population body weight and associated future disease burden to 2050 was modelled.

Two intervention scenarios are modelled with the following assumptions:

1. MCLI participants regain the lost weight over 5 years and return to their baseline weight as is suggested by two large reviews. (51,52)
2. MCLI participants keep the lost weight off over time.

Further assumptions for both scenarios above are:

1. 12% of obese persons take up a MCLI when offered it by their General Practitioner or Family Doctor.(12)
2. 87% of those who start a MCLI complete it.(12)
3. Only obese individuals (BMI≥30) will be offered a MCLI as it has been previously shown that interventions achieving weight loss of a similar magnitude to interventions in Table 8 having a more beneficial cost-effective ratio in more obese individuals. (53)
4. Individuals taking up the MCLI will be selected at random from the entire population distribution of obesity.

Table 8 Selected multicomponent lifestyle interventions for EConDA countries.

Country	Intervention	% reduction BMI/weight	% regain BMI	Cost of intervention	Length of follow up
Greece	Group sessions targeting diet and PA ((54)	2.11% statistically significant reduction in BMI (-1.6 kg) (from mean 28.4 to 27.8 in intervention gp at month 3)	N/A	175 Euros (Pers. comm. Moschonis G, 2015)	3 months
UK	Size down- NHS group-based weight loss programme (55)	2.5kg reduction (imputed analysis) 3.7kg reduction in complete cases analysis @ 12 months follow up (from BMI 33.77 to 33.03; 0.67 BMI unit reduction in a year in imputed analysis)	0.56 kg/year average of studies *	£91.87 per participant (see above)	12 months
Finland	Finnish intervention (56)	4.3kg reduction at 12 months (BMI change -1.6 units), 3.5kg reduction at 3 year follow up	0.56 kg/year average of studies *	N/A	3 years
Netherlands	Dutch intervention (57,58)	2.25 kg reduction at 12 months; -1.1 units BMI change(in imputed analysis), 3.1 kg reduction in complete cases analysis. At 24 months, 1.8 kg reduction (imputed) 2.4 kg (complete cases)	N/A	N/A	24 months
Portugal	Self determination theory (59)	5.49 kg reduction (in imputed analysis), 6.03 kg reduction in complete cases analysis.	N/A	110 Euros (Pers comm Ana Rito 2015)	12 months

Screening for albuminuria has been implemented in the EConDA model following the guidelines used in the Prevention of REnal and Vascular ENdstage Disease (PREVEND) study.(60) A vial of morning urine from the screened population is send by mail to a central lab for measurement of the urinary albumin concentration (UAC). If it is elevated, meaning a measurement of greater than or equal to 30 mg/L UAC, a confirmatory test is executed primary care level. This confirmatory test consists of two 24 hr urine samples, which are tested for urinary albumin excretion (UAE). The impact of screening once in the general population at national level, on associated future disease burden to 2050 was modelled.

Patients confirmed with an elevated UAC are given annual treatment with angiotensin-converting-enzyme inhibitor (ACEi). Costs were based on the cost-effectiveness study by Boersma et al. and include drug costs, an annual prescription fee for the pharmacist and primary care costs.(26) Costs for the screening program as used in the EConDA project can be found in Table 9.

The effect of measurements is implemented as a risk ratio (RR) on the transition probabilities due to treatment. The RR to go from the "30-299" to ">300" albuminuria state is 0,45, and the RR to go to a worse eGFR state is 0.673.(61,62)

As a direct intervention, a hypothetical intervention is modelled, based on the treatment option of Roflumilast. This hypothetical option will reduce the number of exacerbations, leading to a lower cost of disease, and will slow the progression from Moderate to Severe COPD. The cohort is assumed to the hypothetical treatment as an add-on to their present treatment options, for the rest of their life. The RR of going from the Moderate to Severe disease stage is 0.90, based on one off improvement of lung function of 46 mL, an average patient of 1.70 metres (men) or 1.65 (women), where the average maximum lung function in litres (FEV1 – forced expired volume in 1 second) of the patients is calculated using the following function(63)

FEV1{litres} = 4.30*height{metres} - 0.029*age{years} - 2.49.

FEV1{litres} = 3.95*height{metres}-0.025*age{years}-2.60.

For this calculation we used an age of 65. It was assumed in this RR calculation that the cohort exists of an equal amount of men and women.

The one-off improvement in lung function may also lead to patients going to a better disease stage. For patients in the Stage III, assuming a uniform distribution over de disease stage, an improvement of 2.41%pt means that 2.41/20 = 12.1% will go to Stage II. We further assume that the lung function increase does not lead to GOLD stage I (i.e. best case is that patients are now at 80% FEV1% pred). Finally, it was assumed that the increase is persistent.

The EConDA model was used to calculate the price of this hypothetical intervention for different levels of a WTP threshold. This so called threshold analysis is performed for 1/3, 2/3, 3/3 and 4/3 of the WHO CHOICE threshold. The cost of disease is reduced by € 176 per patient per year in The Netherlands for Severe patients and by € 134 per patient per year for Moderate patients.

Table 9 Intervention costs for albuminuria screening used in EConDA.(26)

Intervention costs	BU	FI	GR	LT	NL	PL	PT	UK
	(in лв)	(in €)	(in €)	(in €)	(in €)	(in Zł)	(in €)	(in £)
Cost of screening								
Prescreening for UAC[a]	15	9	6	4	8	17	6	6
Confirmatory test for UAE[a]	129	74	51	35	66	146	49	56
Annual costs of treatment								
Treatment with ACEi[a]	170	98	68	46	87	192	64	73
Prescription fee pharmacist	56	32	22	15	29	63	21	24
Primary care costs	157	91	63	42	80	177	60	68

a UAC = Urinary Albumin Screening, UAE = Urinary Albumin Excretion, ACEi = angiotensin-converting-enzyme inhibitor

Table 10 Reduction of costs due to a decrease in exacerbations, used in EConDA.

	BU	FI	GR	LT	NL	PL	PT	UK
	(in лв)	(in €)	(in €)	(in €)	(in €)	(in Zł)	(in €)	(in £)
In patients with								
Moderate COPD	262	151	104	70	134	295	99	83
Severe COPD	344	198	137	92	176	387	130	110

2.6. Economic parameters

The cost year used in EConDA is 2013. In order to translate future costs and health outcomes to the year 2013, discount rates are used (Table 11). As mentioned, the sources of the discount rates are country-specific health-economic and pharmacoeconomic guidelines.(2) In most countries, the same discount rate is used for both health outcomes and costs. Both The Netherlands and Poland use differential discounting, with a lower discount rate for the health outcomes than for the costs.(64) No health-economic of pharmaco-economic guidelines have been published for Bulgaria or Greece. The discount rate of 3% for both health outcomes and costs is therefore based on recent three publications, all from Greece which all used 3%.(65-67)

All costs and prices that are used in EConDA, are also translated to the year 2013. This is done using the Harmonised Index of Cunsumer Prices (HICP) (Table 12). The HICP is a consumer price index which is compiled according to a methodology that has been harmonised across all EU countries.

Table 11 Discount rates used in EConDA.

	Health outcomes	Costs	Source
Bulgaria	3.0%		(65-67)
Greece	3.0%		(65-67)
Finland	3.0%		(3)
Lithuania	3.0%		(8)
Netherlands	1.5%	4.0%	(4)
Poland	5.0%	3.5%	(7)
Portugal	5.0%		(5)
United Kingdom	3.5%		(6)

Table 12 **Harmonised Index of Consumer Prices (HICP) used in EConDA.**(68)

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Bulgaria	76,41	82,03	86,80	88,84	94,30	100,00	107,42	115,55	129,36	132,56	136,58	141,22	144,59	145,14
Finland	84,50	86,80	88,50	89,70	89,80	90,50	91,70	93,10	96,80	98,30	100,00	103,30	106,60	109,00
Greece	71,50	74,10	77,00	79,70	82,10	85,00	87,80	90,40	94,20	95,50	100,00	103,10	104,20	103,30
Lithuania	95,53	97,01	97,34	96,29	97,41	100,00	103,79	109,83	122,01	127,09	128,60	133,90	138,14	139,75
Netherlands	80,90	85,10	88,40	90,30	91,60	93,00	94,50	96,00	98,10	99,10	100,00	102,50	105,40	108,10
Poland	75,60	79,60	81,20	81,80	84,70	86,50	87,60	89,90	93,70	97,40	100,00	103,90	107,70	108,60
Portugal	78,50	82,00	85,00	87,80	90,00	91,90	94,70	97,00	99,50	98,60	100,00	103,60	106,40	106,90
United Kingdom	43,15	58,02	71,09	81,94	91,68	100,00	106,61	111,84	120,69	127,43	135,16	143,03	147,86	152,59

Table 13 **Annual exchange rates against the US$ used in EConDA.**[a,b]

	Currency	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013*
Bulgaria	Лв	-	-	-	1.700	1.574	1.575	1.560	1.429	1.337	1.406	1.478	1.407	1.523	1.473
Finland	€	1.085	1.117	1.061	0.885	0.805	0.805	0.797	0.73	0.684	0.72	0.755	0.719	0.778	0.753
Greece	€	1.085	1.117	1.061	0.885	0.805	0.805	0.797	0.73	0.684	0.72	0.755	0.719	0.778	0.753
Lithuania	Lt[c]	4.003	4.000	3.671	3.058	2.776	2.780	2.752	2.523	2.360	2.482	2.610	2.483	2.689	2.600
Netherlands	€	1.085	1.117	1.061	0.885	0.805	0.805	0.797	0.73	0.684	0.72	0.755	0.719	0.778	0.753
Poland	Zł	4.346	4.097	4.082	3.888	3.651	3.234	3.103	2.765	2.41	3.119	3.015	2.962	3.252	3.161
Portugal	€	1.085	1.117	1.061	0.885	0.805	0.805	0.797	0.73	0.684	0.72	0.755	0.719	0.778	0.753
United Kingdom	£	0.661	0.694	0.667	0.612	0.546	0.55	0.543	0.5	0.546	0.641	0.647	0.624	0.631	0.640

a All exchange rates based on official exchange rates from (68), except for the exchange rates of Bulgaria, Lithuania and 2013 all countries (69).

b The exchange rates for the Euro countries are necessarily the same.
c Lithuania uses the Euro from Jan 1, 2015. Lithuanian prices where therefore transformed to Euros using the fixed exchange rate of 3.4528 Lt per euro.

Table 14 Purchasing Power Parities (PPPs) used in EConDA.(68)

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013*
Bulgaria[a]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Finland	0.994	1.01	1	1.01	0.976	0.977	0.949	0.941	0.918	0.9	0.911	0.907	0.925	0.93
Greece	0.677	0.67	0.66	0.689	0.696	0.714	0.698	0.719	0.701	0.695	0.702	0.693	0.684	0.643
Lithuania[a]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Netherlands	0.892	0.905	0.902	0.927	0.909	0.896	0.867	0.858	0.842	0.838	0.849	0.832	0.842	0.826
Poland	1.84	1.86	1.83	1.84	1.86	1.87	1.84	1.84	1.86	1.86	1.82	1.82	1.85	1.82
Portugal	0.699	0.705	0.708	0.706	0.716	0.684	0.661	0.66	0.649	0.631	0.632	0.628	0.617	0.612
United Kingdom	0.635	0.626	0.628	0.641	0.633	0.636	0.626	0.646	0.651	0.653	0.691	0.698	0.703	0.695

a No PPPs available for Bulgaria and Lithuania. Proxies were used.

Country estimates of prices and costs are listed in the local currency. That means that for all countries, except for Bulgaria, Poland and the United Kingdom, Euros are used. Bulgaria uses the Bulgarian Lev (лв). Poland uses Polish Zloty (Zł). Prices in the United Kingdom are given in British Pounds (£). If country-specific estimates are available, but they are listed in a different currency, the prices are transferred using exchange rates (Table 13).

If no country-specific estimates are available, using exchange rates is not necessary, since these do not explicitly take the difference in price level into account. For this, Purchasing power parities (PPPs) were used to convert the prices of one country to another (Table 14). PPPs are the rates of currency conversion that equalise the purchasing power of different currencies by eliminating the differences in price levels between countries. In their simplest form, PPPs are simply price relatives which show the ratio of the prices in national currencies of the same good or service in different countries.

Since no PPPs are available for Bulgaria and Lithuania, the prices are translated to other country currencies using the PPPs of Greece, which in turn are then translated to Bulgarian and Lithuanian currencies using existing exchange rates (Table 12).

As an example of how the HICP, exchange rates and PPPs have been applied in EConDA, we estimate the direct health care costs per patient year of hypertension in Lithuania (Table 5). The Dutch Cost of Illness study estimates the costs for hypertension in The Netherlands at € 182.90.(34) The cost year for this study was 2011. Using the PPPs in 2011 (Table 14), we transfer the costs at the Dutch price level, to the costs at the Greek price level:

<Cost> * <PPP new> / <PPP old>

= € 182.90*0.693/0.832 = € 152

Next, these costs are immediately transferred to Lithuanian Litas, the currency at that time, using the official exchange rate (Table 13):

<Cost> * <exchange rate against US$ new> / < exchange rate against US$ old>

= € 152*2.483/0.719 = Lt 526

These costs are now in the cost year 2011, and need to be inflated to the cost year 2013. This is done by using the HICP (Table 12):

<Cost> *<HICP new> / <HICP old> = Lt 526 * 139.75 / 133.90 = Lt 549

Since Lithuania uses the Euro, the official exchange rate against the Euro (3.4528 Litas for a Euro) is then applied:

<Cost> / 3.4528 = Lt 549 / 3.4528 = € 159

3. Discussion

Possible overlap between direct and indirect costs between diseases. All estimates are from that one disease, but co-morbidities are not taken into account. The co-morbidities for T2DM include time for the treatment of diabetes foot and problems with your eyes which are not covered with the CHD model, and I can imagine that you feel bad enough to have to stay home at the later stages for CKD due to your nephropathy directly, but this is also usual at a later age. (And thus after the retirement age.)

Stroke costs UK £2,541, which is much lower than in other countries. Local source. Possible mistake in Flack, therefore Youman as source.

In all countries tried to contact several people. Reactions from EConDA partners in Portugal, but unfortunately unable to provide better estimates. Reactions from Finland, but they were also unable to obtain economic data. No reactions from other countries, despite several tries to contact local experts, over several different means. This may be partly due to the general unavailability of data, but also due to researchers holding on to the data they have. In this case, the researchers may not see the added advantage of sharing the data. During the workshops, in which it could be made clear what the advantage is of country-specific data, many researchers have indicated they would now search for better data. There has for example been a direct promise from partners in Bulgaria to provide estimates for direct costs as soon as possible.

A recent trial has been undertaken in The Netherlands, called Trial ISRCTN41209683, “Effectiveness of a protocol-based lifestyle program to prevent type 2 diabetes”.(70) The setup of the trial indicates that a large amount of information is collected on patients with a status equivalent to the EConDA disease IGT. Although the trial has official finished, no further publication other than the trial protocol has been published. Personal communication with the primary investigator Dr. Hesselink indicates that economic data has indeed been collected, but has not been analysed and, at this time, they are not expecting to analyse it.

Both examples, Bulgarian data that may be available but that was not provided to the WP6 investigators, and a Dutch trial that has collected but not analysed economic data, indicate that more information is likely to be available than was found in unpublished form. This suggests that a fertile avenue of further investigation would be to streamline the gathering of available data. This would have to take into account the politics of data ownership, but also the local differences in financing of studies. A uniform data architecture is of great value to the individual countries, as it will make tools like EConDA more usable, but also to the European community at large.

In paragraph 2.2, we have seen that the consensus meeting decided that the friction cost (FC) method was preferred for the calculation for the indirect costs. However, we have also seen that the Dutch guidelines are the only guidelines that use this methodology.(4) The guidelines for the other EConDA countries, insofar as that they are available, prefer the use of the human capital (HC) approach. As a recap, the HC approach takes the patient's perspective and counts any hour not worked as lost. The FC approach takes the employer's perspective, and only counts those hours as lost, that are not worked until another employee takes over.(9,10)

Despite the consensus, it was decided to use the HC approach in EConDA. This was primarily due to the availability of data. Since the FC method is only mentioned in the Dutch guidelines, it comes as no surprise that any estimates using a FC methodology comes from a Dutch publication. The study by Suijkerbuijk et al. provided estimates for lost work due to COPD in the FC methodology (see 3.1).(35,36) No other estimates using the FC methodology were found. Therefore, it was decided, in order to remain consistent for all diseases, that we would use the HC approach for all diseases and all countries.

In line with this, the European Cardiovascular Disease Statistics 2012 (32) states that it uses the HC approach to the valuing of lost productivity. However, in a chapter describing the methodology of the study, it is stated that the friction cost method was used for premature morbidity costs.(71) The friction period, the period of an employee's absence from work due to illness before he or she is replaced by another worker, is estimated to be 90 days in Europe. This is corroborated with a publication by the same research group, using the same methodology, but on a different set of diseases.(72) This inconsistency is not explored in the report, or in the paper. PM: Have sent two emails to Dr Leal – no response yet.

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