Policy Expensive Medicines

in the Netherlands

from 2006 to 2012

Policy review
and a
Cost-effectiveness Model
in
Colorectal Cancer

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List of Abbreviations

AE	Adverse Event
BSC	Best Supportive Care
CTX	Cetuximab
CT	Chemotherapy
CRC	Colorectal Cancer
CFH	Committee Pharmaceutical Help (Commissie Farmaceutische Hulp)
CE	Cost-Effectiveness
CEAC	Cost-Effectiveness Acceptability Curve
CEA	Cost-Effectiveness Analysis
CUA	Cost-Utility Analysis
DSA	Deterministic Sensitivity Analysis
DBC	Diagnose Treatment Combinations (Diagnose Behandel Combinaties)
CBG	Drug Assessment Board (College ter Beoordeling van Geneesmiddelen)
GVS	Drug-Reimbursement-System (Geneesmiddelen Vergoedingssysteem)
NFU	Dutch Academic Hospital Association (Nederlandse Federatie van Universitair Medische Centra)
NZa	Dutch Care Authority (Nederlandse Zorgautoriteit)
NVZ	Dutch Hospital Association (Nederlandse Vereniging vna Ziekenhuizen)
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
5-FU	Fluorouracil
FOLFIRI	Folinic Acid (leucovorin) - Fluorouracil - Irinotecan combination therapy
FOLFOX	Folinic Acid (leucovorin) - Fluorouracil - Oxaliplatin combination therapy
GDP	Gross Domestic Product
RVZ	Health Care Council (Raad voor Volksgezondheid en Zorg)
CVZ	Health Care Insurance Board (College voor Zorgverzekeringen)
WMG	Health Care Market Regulation Act (Wet Marktordening Gezondheidszorg)
ZVW	Health Insurance Act (Zorgverzekeringswet)
HRQoL	Health-related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
iMTA	Institute for Medical Technology Assessment
ACP	Insured Package Advisory Committee (Advies Commissie Pakket)
KRAS WT	K-RAS Wild-Type
LV	Leucovorin
LY	Life Year
mCRC	Metastatic Colorectal Cancer
MoH	Minister of Health
NICE	National Institute for Clinical Excellence
ORR	Overall Response Rate
OS	Overall Survival
P4P	Pay for Performance agreement
PSA	Probabilistic Sensitivity Analysis
PFS	Progression Free Survival
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomized Controlled Trial
SA	Sensitivity Analysis
T=0	Time = 0 (when a medicine is added to the policy expensive medicines)
T=4	Time = 4 (4 years after addition to the policy expensive medicines)
VOI	Value of Information analysis
VEGF	Vascular Endothelial Growth Factor

Abstract

Spending on expensive medicines in Dutch hospitals was from managed 2006 to 2012 through a policy that listed specific expensive medicines for which extra budget was available. Coverage with evidence development, for the Netherlands a new policy instrument, was implemented for the medicines listed on the policy. In this paper the Dutch policy expensive medicines will be discussed in two parts.

In the first part the policy is described including the history, the intention, the associated procedures and assessment criteria. Also the execution of the policy in practice is discussed. To be added to the policy, and to stay on it after four years, medicines were assessed on therapeutic value, cost or budget impact, real-life use and cost-effectiveness. Although the guidelines ask for a cost-effectiveness estimation, in many cases the initial application for addition to the policy expensive medicines was approved without a well described incremental cost-effectiveness ratio (ICER). This led to uncertainties about the cost-effectiveness (CE) of all four reassessments that were finalized until mid-2013. Nevertheless pragmatic solutions, such as price and risk-sharing arrangements, are being negotiated after the reassessments.

The second part of this paper describes the initial assessment of cetuximab in third-line use in chemotherapy refractory colorectal cancer (CRC) patients, for which no estimation of the ICER was presented. Despite that the application was approved and cetuximab was added to the policy for this indication. To investigate if a robust cost-effectiveness estimation was possible a Markov model was created to estimate the CE of cetuximab in third line metastatic colorectal cancer (mCRC) using data available in the public domain. The model estimates that compared to best supportive care (BSC) the ICER of cetuximab is €191.417/QALY. In a subgroup of patients with KRAS WT genotype for which cetuximab shows better efficacy, the ICER is more favourable: €144.716/QALY. Deterministic sensitivity analyses show that the model is most sensitive to changes in data on survival. Probabilistic sensitivity analyses show that the actual ICERs might be somewhat lower than the primary analysis showed.

The Dutch system of assessment of new expensive medicines has been thorough by taking into account the relevant factors for decision making. However, when implementing coverage with evidence development as a policy instrument it should be clear at the start which data needs to be collected for an effective reassessment after four years. More stringent CE assessment at the start would have been able to prevent uncertainties at the reassessment. This research shows that, at least for cetuximab in third-line mCRC patients, it is possible to give a robust estimation of the cost-effectiveness of a drug, even without the availability of patient level data.

1. Introduction

The Dutch health care system is amongst the most advanced in the world. It is funded by social health insurance and care is provided by private parties. Government involvement in the health care system transitioned since early 1990s from regulation on the supply-side towards government-managed competition. The implementation of the Health Insurance Act (ZVW: Zorgverzekeringswet) in 2006 was the result of many years of preparation. In the new system health insurance companies have a central role. They buy care on behalf of their insured. Citizens 18 years of age and older have to buy a basic benefit package from a private healthcare insurer, who are obliged to enrol everyone that applies. Subsidies to the poorer citizens make the insurance affordable for everyone and a risk equalization fund compensates the healthcare insurers for insured with high risk of high cost. The ZVW is financed via community-rated premiums (45%), income-related contributions (50%) and taxes (5%)The major challenge for the Dutch government is to maintain a balance between adequate but affordable health care for every Dutch citizen (Schut and Rutten 2009; Schut and Van de Ven , 2011; Van de Ven and Schut , 2009). Although the intention of the reform was to improve the conditions for price negotiations between healthcare insurers and care givers and so contain cost of health care cost containment was not seen in the years following the introduction of the ZVW. The Dutch Bureau of Statistics (CBS: Centraal Bureau voor Statistiek) estimated for 2011 that almost 15% of GDP is spent on health care and the trend is that this percentage will be growing in the coming years, especially with no or low economic growth in the Netherlands[1].

One sector in which the government tries to manage spending is the pharmaceutical market, which in 2011 accounted for about 10% of the total spending on health care[2].The pharmaceutical market is complicated mainly because it is unclear who the buyers are. The sellers, namely pharmaceutical companies, sell products that are used by patients that are prescribed by physicians and paid by health insurance companies. Free market mechanisms, which are based on demand and supply, are disturbed in such a market. Demand is not based on the demand of a patient alone but on a physician diagnosing and deciding what treatment to give. Furthermore in economic theory demand depends on the price. In the Dutch pharmaceutical market both the patient and the prescribing physician are hardly aware of the price of a drug and a decision for giving a treatment in general is based on the outcome of the treatment and not on the price, with as a result that drug prices are relatively high compared to other consumer products (Baumol and Blinder 2009; Schut and Varkevisser , 2009).

An important way in which the Dutch government tries to manage spending on pharmaceutical care is by controlling the basic benefit package, the treatments that are reimbursed by the basic health insurance. In and outpatient medicines are handled differently in the Dutch health care system. All outpatient medicines, i.e. medicines sold by pharmacies outside hospitals, that are within the benefit package are listed on a positive list of reimbursed medicines, the Drug-Reimbursement-System (GVS: in Dutch: Geneesmiddelen vergoedingssysteem). Reimbursement of inpatient medicines, i.e. medicines that are given in the hospital, is less controlled by the government than the

[1] CBS Website “Health care spending” (Accessed May 2012): http://statline.cbs.nl/StatWeb/publication/?VW=T&DM=SLNL&PA=71914NED&D1=0-23,37-45&D2=9-l&HD=101210-0925&HDR=G1&STB=T

[2] Nefarma website “Pharmaceutical care spending” (Accessed August 2012): http://www.nefarma.nl/website/feiten-en-cijfers/farmaceutische-zorguitgaven

reimbursement of outpatient medicines. The inpatient medicines, also called specialist medicines, are part of the Diagnose Treatment Combinations (DBC: Diagnose Behandel Combinaties). The DBC-system, introduced in 2005 and updated regularly, is an expense claim system for the hospitals. It includes upfront identified care products based on the needed care of a patient with a certain diagnosis. Included in a DBC is the whole treatment a patient receives including for example physician time, hospital stay, paper work and drug treatment. Although initially prices for DBCs were set by the government to improve the health care markets, nowadays an increasing number of prices of DBCs are freely negotiable between the healthcare insurers and hospitals (De Kam , 2009). The legal basis for reimbursing DBC with the public funds of the basic benefit package lies in the ZVW where it is written that care that holds up to the standard of "established medical and scientific practice" is reimbursed by the basic health insurance (Dutch Health Insurance Act , 2005). It is assumed that specialist care, including specialist pharmaceutical care is up to current treatment standards. In the current Dutch system healthcare insurers are responsible for checking this assumption, and in case of doubt they can ask the Dutch government to assess if this is the case.

Expensive medicines that use a big part of hospital budgets have been a point of discussion in Dutch government since the 1940s (Steenhoek , 2008). In recent years an increasing number of innovative, but expensive medicines became available for specialist hospital care. Clinical trials showed good efficacy but it was not clear if in real life the medicines were going to be as effective, and these trials rarely showed relative efficacy compared to standard treatment in the Netherlands. Furthermore these medicines were consuming a big part of the hospital budgets, leading to inequalities for patients because they were not able to get the best treatment in certain hospitals. Because of the limited budgets hospitals had to choose between treatments to spend the budget on. Furthermore, should a hospital by chance a hospital have a lot of patients needing an expensive medicines the budget of that hospital would run out earlier than in hospitals with less patients on expensive medicines, leading to inequality in patient access to these medicines. (Kuijpers and Toenders, 2006). To keep new innovative medicines available for patients the Dutch government has made efforts to compensate hospitals for these high costs by the introduction of the policy expensive medicines in 2002 (NZa , 2002). In 2006 the policy was updated with a list of specific medicines for which the hospitals could get extra budget additional to their standard budget. A new policy instrument, coverage with evidence development (CED), was associated to the policy: the medicines were put on the list under the condition that the requesting party would perform outcomes research with the drug to improve the evidence on the real life use of the drug and the collect data for cost-effectiveness (CE) research (Kuijpers and Toenders, 2006).

This paper investigates the execution of the policy expensive medicines that was in place from 2006 to 2012 with a focus on the CED and on the cost-effectiveness assessment that is done for the policy using health economic modelling. The paper consists of two parts. In the first part the intention of the policy, the associated procedures, assessment criteria, and involved stakeholders, are described. The first section ends with the description of the policy in practice. In practice it was seen that for the initial CE assessments of medicines, guidelines were followed less stringently than for example for the initial assessment of therapeutic value. Although an estimation of the CE of the medicine was requested, in several cases this was not done sufficiently by the requesting party, and the assessment committee approved the applications with the argument that at the initial assessment there would be not enough (real life) evidence to prove CE of medicines (Kuijpers and Toenders,

2006). An example of an application in which the CE estimation was deemed insufficient by the assessment committee, but was approved, is the application of cetuximab in third line metastatic colorectal cancer (mCRC) (CVZ, 2009). To show how an initial CE estimation could be done using health economic modelling, in the second part of the paper a CE model is described that gives an estimation of the CE of cetuximab compared to best supportive care (BSC) in third line mCRC using publically available data. The results are described and discussed in the light of the policy expensive medicines.

2. Policy expensive medicines

2.1. Methods policy review

For finding the documentation for the review of the policy expensive medicines first the Dutch governmental structure on drug policy had to be investigated. This was done using the official governmental websites[3]. Since the Dutch Health Care Authority (NZa: Nederlandse Zorgautoriteit) and the Health Care Insurance Board (CVZ: College Voor Zorgverzekeringen) are the governmental bodies that are mainly responsible for the execution of the policy first the websites of these bodies were searched for policies and procedural documents related to expensive medicines.

The policy expensive medicines was updated regularly on the NZa website. New NZa policies refer to the preceding policy, so starting with the last version of the policy (NZa , 2011) via backward referencing the policies over the years were traced back to the first one containing the list of medicines for which outcomes research was mandatory in 2006 (NZa , 2006) and to the first policy expensive medicines in 2002 (NZa , 2002). Only these three policies were used in the review of the policy since they include the major changes in the policy as indicated. The policy expensive medicines included alongside the list of medicines a description of the legislative basis of the policy, and a description of the procedure and criteria that should be followed to get a new drug listed on the policy. Over the years the description of the procedure and criteria have been regularly updated and therefore the last policy, BR/CU-2017, will be used as a basis of the policy review (NZa , 2011).

The CVZ website was searched for relevant documents by using the Dutch search term for 'expensive medicines': 'dure geneesmiddelen'. Documents found via this search were read and scanned for relevance for this paper. The CVZ website is organized in such a way that links to relevant documents per subject are collected on one webpage. The webpage that describes outcomes research included links to the main procedural documents used in this paper to describe the policy (Kuijpers and Toenders, 2006; Kuijpers, 2010). These procedural documents refer to other documents of interest, such as guidelines on how to perform research (CVZ, 2006; Delwel, 2008; Hakkaart-van Roijen, et al, 2010) and templates that should be used to create submission dossiers[4]. Other documents that were found and used on the CVZ website include policy review documents (Busschbach and Delwel, 2010; Delwel and Goettsch, 2012; Zwaap, 2009).

Also scientific literature was searched for relevant publications on policy on expensive medicines and/or outcomes research in the Netherlands. A PubMed search with the following search term ("outcomes research" AND policy AND Netherlands) returned 7 articles. When reading the abstracts or full articles 5 articles were ruled out as irrelevant (1 is a duplicate; 2 are irrelevant congress reports; 1 is not on expensive medicines; 1 is a review on costs). This leaves 2 articles that were used in the review (Franken et al. , 2013; Hoebert et al. , 2011). An additional PubMed search with the terms (expensive AND (drug OR drugs) AND policy AND Netherlands) retrieved 24 articles. When reading the abstracts or full articles 20 articles were ruled out (1 is about India; 1 is about USA; 1 is about cannabis; 1 is about animal use ; 2 are not about expensive medicines; 1 is about a model; 13

[3] Websites: CVZ: www.cvz.nl; Dutch government: www.overheid.nl; NZa: www.nza.nl. (All accessed December 2012).

[4] Website CVZ (accessed March 2013): www.cvz.nl.

are before the implementation of mandatory outcomes research in 2006) leaving four articles (Gaultney et al. , 2012; Niezen et al. , 2006; Sandmann et al. , 2013; Steenhoek , 2008).

2.2. Introduction

In the years following the introduction of the policy expensive medicines in 2002 the access to expensive medicines in the Netherlands improved, but a side-effect of the policy was that the money spent on expensive specialist medicines increased with 20-30% over 2002-2005 (Kuijpers and Toenders, 2006). Also the money spent on hospital medicines grew with a much higher rate than the volume of medicines used, indicating that indeed the expensive medicines were causing the higher expenditure of hospitals (Niezen et al. , 2006). To contain the spending in 2006 the policy was updated with a list of specific medicines for which the extra budgeting applied. Extra budget could be negotiated for this limited amount of expensive medicines between the hospitals and the healthcare insurers. To maintain an incentive to prescribe the medicines efficiently only part of the total cost of the medicines would be compensated by the Dutch government. Assessment of medicines was based on a prognosis of the costs, the therapeutic value and cost-effectiveness. Because at market entry the cost effectiveness of these medicines was uncertain the extra financing of the medicines was given under the condition that after initially three but later four years the medicines would be reassessed on the same criteria as at initial assessment. Additional outcomes research in the Netherlands was mandatory so that the real life use of the drug and the CE could be taken into account in the decision making process for keeping the additional financing of the expensive medicines (Kuijpers and Toenders, 2006). In 2012 the policy expensive medicines has been made redundant with the introduction of a new policy that introduced an add-on system (NZa , 2012a). The rest of this chapter will describe and discuss the procedures regarding the policy expensive medicines that was in place from 2006-2012.

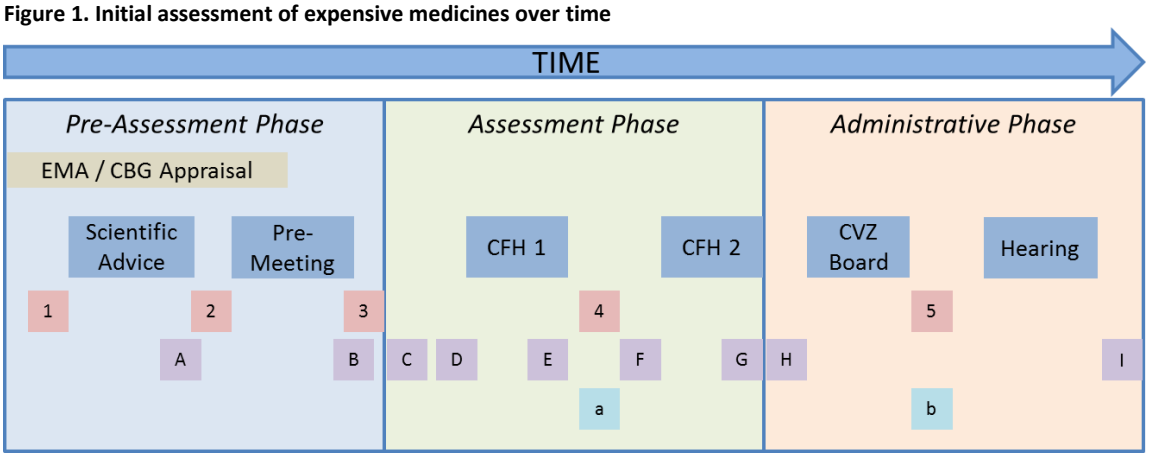
2.3. Procedures

NZa and CVZ created and operationalized procedures through which applications for addition of new medicines to the policy were assessed as visualised in Figure 1. The application for addition of a drug to the policy could only be done by parties as identified by the Health Care Market Regulation Act (WMG; In Dutch: Wet Marktordening Gezondheidszorg)[5] (from here on referred to as 'WMG party'). Next to the requesting WMG party other non-governmental parties of interest that could be involved in the decision making process include scientific- or lobby-groups for physicians, hospitals, patients, healthcare insurers and pharmaceutical companies, and individual drug manufacturers (registration holders for the drug). The decision to add a drug to the policy was made by the NZa based on an advice of the board of the CVZ. They are advised by an independent committee, the Committee Pharmaceutical Help (CFH; Commissie Farmaceutische Hulp), that consists of 22 professionals from several relevant fields[6] (Kuijpers and Toenders, 2006; NZa , 2011) Three phases can be identified in the assessment of expensive medicines: the pre-assessment, assessment and administrative phase (Kuijpers and Toenders, 2006).

[5] Namely individual hospitals, Dutch Hospital Association (NVZ: Nederlandse Vereniging voor Ziekenhuizen); Dutch Federation of Academic Hospitals (NFU: Nederlandse Federatie voor Universitair Medische Centra); Dutch Health Care Insurers (ZN: Zorgverzekeraars Nederland) and the Order of Medical Specialists (OMS: Orde van Medisch Specialisten)

[6] Website CVZ: "Dossiereisen": http://www.cvz.nl/zorgpakket/cfhagenda/commissie/dossiereisen/dossiereisen.html

Figure 1. Initial assessment of expensive medicines over time



Blue boxes: (Possible) meetings; Red boxes (1-5): Requester actions; Purple boxes (A-I): CVZ actions; Turquoise boxes (a-b): Other parties of interest actions.
Indicated actions:
1: Request for scientific advice at CVZ. Include questions to be answered in writing. (tentative)
2: Request for pre-meeting at CVZ. Two weeks before pre-meeting draft dossier should be submitted. (tentative)
3: Final dossier is submitted to CVZ.
4 & a: Respond to draft report after CFH meeting 1 within 7-10 days.
5 & b: Respond to draft letter to NZa from the CBV board.
A: Consult physicians/patients to identify gaps concerning standard treatment.
B: Send minutes pre-meeting within two weeks to requester and other involved parties.
C: Check dossier for completeness and if complete confirm this to the requester.
D: Create draft reports for CFH.
E: Update draft reports after CFH meeting and send for review to involved parties within one week after the CFH meeting.
F: Update draft report with comments involved parties
G: Finalise report and send to involved parties for information.
H: Draft letter of advice for NZa by the chairman of the board of CVZ
I: After tentative CVZ board meeting and hearing with involved parties the chairman of the board of CVZ sends final letter of advice to the NZa.

The pre-assessment phase is meant to answer questions and make sure the dossier reviewed by the CFH is complete and of good quality. There are differences between pre-assessment for T=0 and T=4. At T=0 pre-assessment is tentative, whereas for T=4 pre-assessment is mandatory (Kuijpers and Toenders, 2006; Kuijpers, 2010). At T=0 the requesting WMG party or other parties with interest can ask the CVZ for scientific advice regarding the setup and execution of the cost effectiveness research. Another tentative meeting that can be requested is the pre-meeting in which the requester, or other parties of interest, discuss with the CVZ the draft dossiers (Delwel, 2008; Kuijpers and Toenders, 2006). At T=4, around three months before the final dossiers are due to be submitted to the CVZ, the WMG party should do a request for continuation of the drug on the policy and a mandatory pre-meeting with CVZ should be requested. At the pre-meeting should be present, next to the WMG party, at least one treating physician who is mandated by the scientific professional group and the drug manufacturer. Furthermore it is advisable that a (principle) investigator of the outcomes research is present at the meeting (Kuijpers, 2010).

The assessment phase is similar during T=0 and T=4. Assessment of the submitted dossiers by the CFH is assisted by CVZ that acts as secretariat. CVZ drafts reports that are discussed at monthly CFH meetings. Prioritization of reports discussed in the monthly CFH meetings is done internally by NZa and CVZ. The CFH drafts an advice to be distributed to involved parties. After the comments from involved parties are returned, CVZ incorporates them. The new drafts are discussed in the next CFH meeting where the CFH decides on a final advice text for the board of CVZ. The CFH assesses the drugs' relative efficacy compared to current standard treatment, the cost, the outcomes research, and cost effectiveness and comes to an advice for the board of CVZ (Kuijpers and Toenders, 2006; Kuijpers, 2010).

Subsequently during the administrative phase the chairman of the board of CVZ decides on a final advice for the Minister of Health (MoH). If the chairman of CVZ expects no discussions in society when the advice is given he can make a final advice without consulting the rest of the board of CVZ. In case of doubts concerning the concept advice, either procedural or administrative, the chairman will discuss the advice with the rest of the board of the CVZ. Furthermore the requesting WMG party and other interested parties can reply to the concept advice. Arguments for questioning can be procedural or policy-based, but not concerning the therapeutic value, cost prognosis or framework for outcomes research of the drug under review. Participation of involved parties is primarily in writing, but the chairman can decide to call a hearing where the parties can orally elucidate on their comments. In cases where the societal consequences of the advice are expected to be large the board of the CVZ can decide to include as an extra step appraisal by the Insured Package Advisory Committee (ACP: Advies Commissie Pakket). The ACP, that consist of experts from several relevant fields, advises the board of the CVZ on the societal consequences of the advice the CVZ gives. When a final decision on the advice was made a letter of advice from the CVZ board and the CFH report attached as annex is sent to the NZa. These documents are also published on the CVZ website (Kuijpers and Toenders, 2006; Kuijpers, 2010).

2.4. Requirements and assessment criteria

The CVZ has published templates for the different dossiers that the requesting WMG party are required to use on its website[7]. The drug for which the request for addition to the policy is done needs to be registered for the specific indication by EMA or CBG. If this is not the case the drug can still be added to the policy in case (1) the incidence of the disease is in less than 1 in 150.000 inhabitants; (2) the effectiveness of the drug in the indication is scientifically substantiated and (3) there is no other registered treatment for the indication in the Netherlands (NZa , 2011). The four main criteria that are assessed are the following and will be described in detail below: (1) Therapeutic value. (2) Cost or budget impact. (3) Real-life use.(4) Cost effectiveness.

2.4.1. Therapeutic value

To be added to the policy a new drug should, when compared to the standard or usual treatment have added therapeutic value, or, in case of equal therapeutic value, the application of the drug has significant benefit to the public health in the Netherlands (NZa , 2011). The CFH defined the therapeutic value of a drug as follows: the combined valuation of all relevant properties of the drug that determine the place of the drug in the treatment algorithm of the disease compared to other available and recommended treatments. Primarily the therapeutic value of a drug depends on the

[7] Website CVZ: www.cvz.nl; accessed March 2013.

balance between effectiveness and adverse events (AEs) compared to this balance of the standard or usual treatment of the disease. The standard or usual treatment can be a drug but also a non-pharmaceutical treatment. Professional guidelines can often guide what usual or standard treatment is. The CFH assesses the therapeutic value of medicines based on six criteria: (1) Efficacy; (2) Effectiveness; (3) Adverse events; (4) Experience; (5) Applicability; and (6) User-friendliness. The *efficacy* is the therapeutic effect of the drug measured by randomized clinical trials (RCT). The *effectiveness* of a drug is measured by more than RCTs only. Also for example real-life data and quality of life (QoL) data are needed to prove the effectiveness of a drug. Effects of *adverse events* that are seen in RCTs and observational research with the assessed medicines are assessed. The *experience* is important for the assessment of a drug since this can show the benefit/risk ratio in real life. Experience can be measured in the number of prescriptions or in patient-years. *Applicability* is of importance when a drug is only applicable for certain groups of patients. For example in certain age-groups or not in pregnant women. And finally *user-friendliness,* this is high when the application of a drug is easy.

2.4.2. Cost or budget impact

Only drugs that are expected to have a significant budget impact at T=0 and indeed have it at T=4 are added to the policy at T=0 and stay on it at T=4. It was decided that total net purchasing cost of the drug in the Netherlands should be at least €2.5 million. In case a drug is already on the policy for a similar indication the cost may be added up. The CFH makes a cost prognosis per patient per year and total costs based on a cost prognosis dossier submitted by the requester. The cost prognosis dossier should be no longer than 8 pages and is calculated with information on the potential number of patients to be treated with the assessed drug (including expected on- and off-label use), the dose of the drug, the treatment duration, and the list-price of the drug. Sources should include if available (peer-reviewed) literature, professional guidelines, real-life data, and estimates from treating physicians (CVZ, a; Kuijpers and Toenders, 2006; NZa , 2011). At T=4 the requester needs to provide data on the actual budget impact that the drug had in the third year after it was added to the policy (Kuijpers, 2010).

2.4.3. Effective application

One of the questions that the outcomes research should answer is if the real-life application of the drug is effective. Is the real-life application of the drug based on the registered indication or are there differences found? Differences between the clinical studies and real-life that might be found could be in for example the treated patient population, off-label use, too little clinical efficacy, or under-treatment because of cost. To be able to answer these questions relevant information should be gathered with the outcomes research, including patient characteristics, relevant drug characteristics, efficacy data and AEs. For the assessment of effective application at T=4 only Dutch data suffice (Delwel, 2008; Kuijpers, 2010).

2.4.4. Cost effectiveness

A second question that should be answered with the gathered outcomes research data is about the cost-effectiveness (CE) of the treatment relative to standard treatment. Although it is not a primary outcome for decision making in the Dutch health care system, CE of a treatment is one of the assessment criteria that is used for decision making. It was assumed that CE assessment at T=0 was too uncertain because of the lack of data, e.g. long-term and real-life data. Therefore the definitive assessment of the CE of the drug was done at T=4. To make sure that after four years enough data

would be available to assess the CE reliably, at T=0 a framework for outcomes research, including an estimation of the CE based on the available data at T=0, had to be prepared by the requester. Also the data gaps had to be described and a framework had to be included how to acquire the necessary data to get a more reliable estimation of the cost effectiveness at the time of reassessment (T=4). The following sections of the outcomes research should be considered in the framework . (1) Literature research for cost effectiveness. (2) The research question. (3) The cost effectiveness estimation at T=0. (4) Description on how the outcomes research is expected to improve the CE estimation at T=4. (5) Feasibility. (6) Preconditions and bottlenecks. (7) Existing and current research. (Kuijpers and Toenders, 2006; NZa , 2011).

Table 1. Summary of guidelines for pharmacoeconomic research in The Netherlands (CVZ, 2006)

#	Topic	Explanation
1	Perspective	Societal perspective is needed
2	Choice of comparator	Standard or usual care
3	Analysis technique	CUA (QoL improvement is important benefit), CEA (if QoL is not important), CMA (in case of no therapeutic added value)
4	Analysis period	Should be long enough to make valid and reliable conclusion on efficacy and safety
5	Cost	Use CVZ guidance for cost-research (Hakkaart-van Roijen, Tan, and Bouwmans 2010)
6	Value QoL and QALYs	In case of CUA QALYs should be presented. Generic QoL measure is not valid.
7	Modelling	A supplementary, transparent, simple but complete model, that is based on previous CE and clinical research
8	Incremental analysis	Incremental differences between investigated treatments should be reported
9	Discounting	Discounting of future cost with 4% and future effect with 1.5%
10	Sensitivity analysis	Deterministic variables: univariate; Stochastic variables in model: probabilistic
11	Expert panel	In case of missing data and expert panel is used to obtain data, the selection of the panel should be disclosed

Abbreviations: CEA – Cost Effectiveness Analysis; CMA – Cost Minimization Analysis; CUA – Cost Utility Analysis; CVZ – College Voor Zorgverzekeringen; QoL – Quality of Life; QALY – Quality Adjusted Life Years

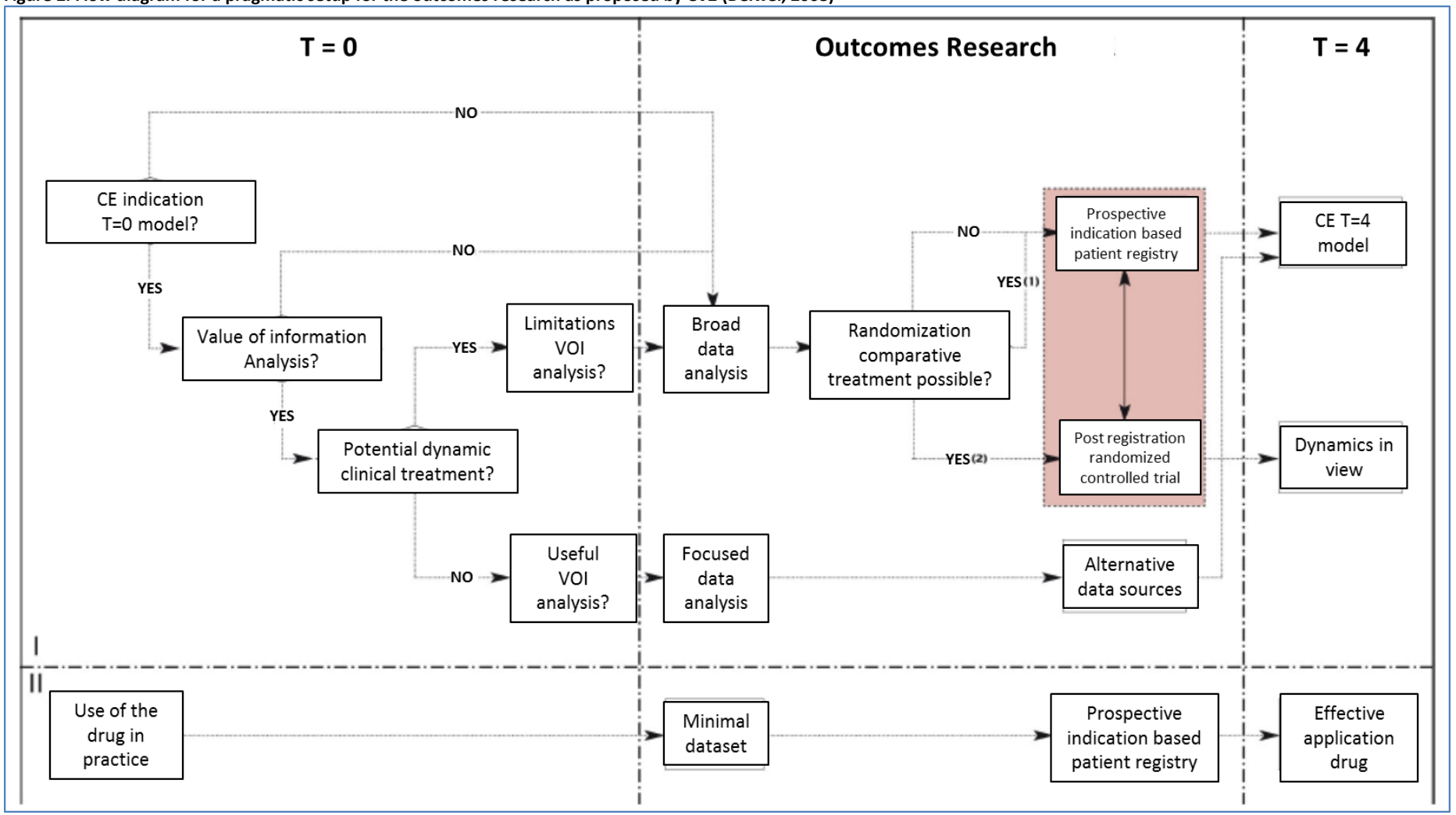
For the CE estimation the applicant should follow the existing guidelines for pharmacoeconomic research (CVZ, 2006). These guidelines include guidance on 11 topics, summarized in Table 1, that should be followed for the creation of a pharmacoeconomic dossier. At T=0 the requesting WMG party was encouraged to model the CE with a health economic model, but only a description of the model to be used at T=4 was sufficient. Requesters were also encouraged to perform a value of information (VOI) analysis on the health economic model to determine additional data needed for optimal decision making based on results of the model. A value of information analysis depends on thresholds for what is cost-effective. Since there are no official thresholds on CE that are accepted by society in the Netherlands, it was advised to use a range of thresholds in the calculation of the analysis. Although the requesting WMG party is responsible for the submission of dossiers at T=0 and T=4 and the setup of the outcomes research, it was deemed important that other parties of interest (for example organisations representing physicians, patients, manufacturers and health economists) were closely involved in the process of outcomes research and dossier development (Delwel, 2008). In the second part of this paper a T=0 economic model will be described in detail.

2.4.5. Outcomes research

The fact that drugs were added to a list temporarily under the condition of data collection was new in Dutch health care policy. To substantiate the term outcomes research in the light of the policy expensive medicines the CVZ set up a working group consisting of experts from the different professional fields. The working group created the guideline document 'Guideline for Outcomes Research' containing practical information concerning the pragmatic collection of data for assessing the CE of the medicines on the policy in real-life practice (Delwel, 2008). The guideline advocates a pragmatic set-up of the outcomes research as can be seen in the flow chart presented in Figure 2. The flowchart, which is published in the guidelines, gives a summary of the guidelines for outcomes research. The chart is divided in two parts: part I describes the possible pathways to follow for obtaining the CE estimation. Part II describes how the effective application of the drug should be investigated.

The guideline outcomes research identifies three possible types of data being collected with the research. To get a reliable CE estimation at T=4 either a broad or a focussed data collection is needed (part I, outcomes research section Figure 2). Broad data collection would be needed in case the CE indication at T=0 is very uncertain because there was no estimation with a model or a VOI analysis was not performed or had limitations. This means that all possible relevant data with respect to cost, clinical information, patient characteristics, and patient reported outcomes are collected. Data collection should in this case preferably be done with a prospective disease specific patient registry, and in some cases this will be a post registration RCT. The choice of research should be done with professionals in the field. In case randomisation or inclusion of treatment arm treated with standard treatment is impossible data for a comparative treatment arm can be included using retrospective chart review. Focussed data collection is possible when CE estimation at T=0 is relatively certain and VOI analyses revealed specific data gaps or points of interest for research. In general setup of post registration RCTs or patient registries is not needed in this case. Alternative data sources like existing patient registries, QoL studies and (international) literature should be sufficient to gather the missing data. For the analysis of effective application a minimal dataset is needed (part II, outcomes research section Figure 2. Minimal dataset data should be Dutch data, preferably collected in a prospective patient registry.

Figure 2. Flow diagram for a pragmatic setup for the outcomes research as proposed by CVZ (Delwel, 2008)



2.5. Policy expensive medicines in practice

From 2006 until 2012 45 T=0 appraisals (on 34 different medicines) have led to the provisionally addition to the policy expensive medicines. The type of pharmaceuticals added to the policy were medicines for oncology, auto-immune diseases, macular degeneration and orphan diseases (CVZ, 2012a). Since the end of 2010 four reassessments have been finalized and published on the CVZ website: omalizumab (asthma), ranibizumab (macular degeneration), alglucosidase alfa (Pompe disease) and agalsidase (Fabry's disease)[8]. The interest of society increased since in 2012 the policy expensive medicines was replaced with an add-on system. A negative decision at T=4 initially resulted in removal from the policy meaning that hospitals would not get additional funding when the medicines were prescribed. After the policy update in 2012 a negative decision by the CVZ resulted in an advice to the minister to remove the treatment from the basic benefit package, which is much more impactful for patients since this implicitly means that the drug would not be available anymore. Therefore the board of CVZ decided that with all four reassessments the ACP appraisal was needed to come to a final advice.

2.5.1. Summary finalized T=4 reassessments

At reassessment it was concluded by the CFH that omalizumab as addition to usual therapy in severe asthma has a therapeutic added value compared to not adding it. However, the CFH concluded that the CE estimation was insufficient and very uncertain because of methodological problems. Furthermore it was clear that, with at least an incremental cost-effectiveness ratio (ICER) of €36.000/QALY, it is uncertain that the drug is cost-effective at all. The ACP advised CVZ to research pragmatic solutions to prevent omalizumab being removed from the basic benefit package. Their argument was that because patients, who can't help that insufficient data are collected over four years to obtain reliable CE data, would suffer most by losing an effective treatment without an equal alternative. After this advice CVZ started negotiating with the manufacturer and several other involved field parties and they came up with a pay-for-performance agreement (P4P). It was agreed that the manufacturer pays for non-successful treatment. This would mean a lower budget impact for the basic benefit package and thus by definition a better ICER. Because of the experimental character of the agreement it was decided to make it temporary. After two years a reassessment would take place to investigate if the P4P agreement led to a more cost effective use of omalizumab, if the P4P should continue with the same conditions, and if P4P agreements in general are good policy instruments to improve CE use of expensive medicines (CVZ, 2012a).

In the case of ranibizumab in macular degeneration CVZ advised to remove ranibizumab from the list of reimbursed medicines. As opposed to the omalizumab case in this case a comparable treatment is available, namely bevacizumab. Interestingly bevacizumab has no label for this indication but is used

[8] On CVZ website (accessed June 2013):
Omalizumab:
http://www.cvz.nl/binaries/live/cvzinternet/hst_content/nl/documenten/rapporten/2012/rpt1207-omalizumab-xolair.pdf;
Ranibizumab: http://www.cvz.nl/binaries/content/documents/cvzinternet/nl/documenten/cfh-rapporten/2012/cfh1201-ranibizumab-lucentis.pdf;
Alglucosidase alfa: http://www.cvz.nl/binaries/live/cvzinternet/hst_content/nl/documenten/cfh-rapporten/2012/cfh1201-alglucosidase-alfa-myozyme.pdf
Agalsidase: http://www.cvz.nl/binaries/live/cvzinternet/hst_content/nl/documenten/cfh-rapporten/2012/cfh1202-agalsidase-replagal-fabrazyme.pdf

off-label abundantly and is thus part of the usual treatment in the Netherlands. When looking at efficacy the CFH concluded that ranibizumab and bevacizumab are equally effective. The CFH could not conclude on the CE because of insufficient information. However, when assuming equal efficacy and a much lower price (by a factor 10) of bevacizumab it seemed clear that bevacizumab is probably more cost effective. The ACP agreed with this and therefore the final advice is to remove ranibizumab from the basic benefit package (CVZ, 2012b).

The reassessment of the medicines used in the orphan diseases Pompe and Fabry's drew quite some media attention in the Netherlands. Draft reports were leaked to the press and publication led to significant protests from society. The leaked draft conclusions, and also the final conclusions, are to remove the medicines from the basic benefit package. This advice was based mainly on the unfavourable CE of the medicines. Depending on the disease and patient population within the disease the ICERs range from €300.000/QALY to €15.000.000 /QALY. However, the ACP advised CVZ that it would be unethical to take away their only treatment and to keep the medicines conditionally reimbursed by public funds. The advice from CVZ to the MoH included to remove the medicines from the basic benefit package but to fund them via a different way with public money. Furthermore transparent guidelines for the use of the medicines should be created. Also price negotiations with the manufacturers should be initiated (CVZ, 2012c).

2.5.2. Pilot studies feasibility outcomes research

After the introduction of the conditional addition to the policy in 2006 and the publication of the outcomes research guidelines in 2008 CVZ asked the Institute for Medical Technology Assessment (iMTA) in Rotterdam to research how the assessment of expensive medicines based on outcomes research data could be substantiated. Therefore, iMTA studied the practical feasibility to gather evidence on appropriate drug use and CE with outcomes research in three oncology studies (Delwel and Goettsch, 2012; Franken et al. , 2013). To investigate if effective application of the medicines can be studied with outcomes research treatment regimens, dosages, patient characteristics, reasons for stopping, and treatment outcomes were investigated in the outcomes research that was setup for oxaliplatin in stage III colon cancer, oxaliplatin in mCRC and bortezomib in relapsed/refractory multiple myeloma. It was found that in these three studies most of the evidence needed for assessment of effective application can be collected with outcomes research (as summarized in Table 2)

Table 2. Feasibility to develop evidence on effective application (Franken et al. , 2013)

	Oxaliplatin in stage III colon cancer	Oxaliplatin in metastatic colorectal cancer	Bortezomib in multiple myeloma
Feasibility to use existing databases to identify patients	+	+	+
Feasibility to obtain a complete dataset using hospital records	+	+/–	+/–
Feasibility to develop evidence on:			
Treatments	+	+	+
Dosages	+	+	+
Patients	+	+	+/–
Reasons	+	+	–
Effects: intermediate and final outcomes	+	+	+/–
Effects: safety outcomes	+/–	+/–	+/–
Costs	+	+	+

+ = good; +/– = moderate; – = poor.

For the CE analysis it was investigated if it was feasible to obtain comparable patient groups, identify treatment comparators, obtain information from literature and estimate ICERs. The authors tried to estimate ICERs using the outcomes research data only. This was not feasible even when correcting for confounding because of differences between patients receiving the compared treatments. For the oxaliplatin study in colon cancer this was solved by creating health economic model in which the outcomes research data needed were combined with data from pivotal studies. Although not performed, this was also possible for the other oxaliplatin study. Extreme heterogeneity in the bortezomib study population (because of rapid development in treatment of the disease) lead to modelling with this data being deemed impossible. Table 3 summarizes the feasibility to estimate ICERs with the outcomes research in the indicated studies.

Table 3. Feasibility to estimate incremental cost-effectiveness (Franken et al. , 2013)

	Oxaliplatin in stage III colon cancer	Oxaliplatin in metastatic colorectal cancer	Bortezomib in multiple myeloma
Comparability of baseline characteristics between treatment arms	–	+/–	–
Feasibility of using data from everyday practice:			
To correct for bias	–	+/–	–
To identify treatment comparator	+	+	–
To estimate incremental cost-effectiveness	–	–	–
Comparability of eligible everyday practice patients (treated with oxaliplatin/bortezomib) and clinical trial patients	+	+	+/–
Feasibility of data synthesis:	+	+	–
To obtain additional data from the literature on:			
quality of life	+/–	+/–	–
efficacy	+	+	+/–
effectiveness	–	+/–	–
costs	+/–	+/–	–
Feasibility to estimate (using data synthesis):			
Internally valid incremental cost-effectiveness	+	+	–
Precise incremental cost-effectiveness	+/–	+/–	–
Externally valid incremental cost-effectiveness	+	+	–

+ = good; +/– = moderate; – = poor.

These results show that real-life data gathered with outcomes research can gather valuable evidence on the difference between everyday practice and clinical trials. However, the lack of randomization makes it hard to compare effectiveness between two treatment arms. Therefore outcomes research data seem to be more appropriate to assess effective application of a drug than to assess the CE. Usefulness of data depends on the drug and the indication (Franken et al. , 2013).

3. Cost-Effectiveness of Cetuximab in Chemotherapy Refractory Metastatic Colorectal Cancer Patients

3.1. Introduction

Health economic modelling is crucial in decision making on cost-effectiveness (CE) of medicines. Although the Dutch guidelines clearly ask for a CE estimation in many cases the application for addition to the policy expensive medicines was approved by the CFH without a well described ICER, based on a good model on the available data at the time. The second part of this paper describes the T=0 assessment of cetuximab in third-line treatment of patients with metastatic colorectal cancer (mCRC), for which no estimation of the ICER was presented. Despite that the application was approved and cetuximab was added to the policy for this indication. Was it impossible for the requesting party to deliver a good estimation? To investigate this a model was created to estimate the CE of cetuximab in third line colorectal cancer using data in the public domain.

Cetuximab (Erbitux®) is amongst others indicated in third-line treatment of patients with metastatic colorectal cancer (mCRC). Cetuximab was added to the policy for this indication in 2009 together with a similar drug, panitumumab (NZa , 2011; NZa , 2012b). Cetuximab and panitumumab both inhibit epidermal growth factor receptor (EGFR), a receptor expressed on epithelial cells. EGFR is frequently overexpressed in human tumours including CRC where it can promote proliferation, metastasis, angiogenesis and inhibition of apoptosis of the tumour (Vincenzi et al. , 2008). The WMG party NVZ requested that treatment of mCRC patients with cetuximab in second line and in chemotherapy refractory patients was added to the policy but only the latter indication was approved. Treatment of chemotherapy refractory patients was accepted because there was a relevant study available that described the right patient group and treatment paradigm (Karapetis et al. , 2008) and the expected budget impact was larger than €2.5 million per year.

Although clinically the CFH decided for an added therapeutic value, they were not satisfied with the pharmaco-economic dossier and had several comments (CVZ, 2009). The committee published that the framework for outcomes research was too simple and lacked relevant information, like a clear study protocol. Also the study should include data on both cetuximab and panitumumab vs BSC as this was the basis for the addition to the policy. Furthermore the provided CE information at T=0 was not sufficient. The comments regarding the health economic modelling from the CFH include the following:

- The requester made no CE claim (i.e. an ICER).
- A Markov model was submitted but insufficiently explained, including underlying assumptions.
- Panitumumab treatment was not included.
- No cost data were included
- It is not clear how the presented QALY data were derived
- Used references were not mentioned
- It's not clear if data from the model can be used for the Netherlands
- No sensitivity analyses were included.

The requesting party did include a draft of the health economic model that would be used at reassessment at T=4 to estimate the CE of cetuximab. The model was a relatively simple Markov

model consisting of three health states (progression free, progression and death). Time horizon was four years and outcomes measures used in the model were life-years gained and QALYs which were based on data from the C0.17 trial (Jonker et al. , 2007; Karapetis et al. , 2008). In the model cetuximab treatment in combination with irinotecan was compared with best supportive care (BSC) (CVZ, 2009).

However, the pharmacoeconomic part of the dossier was described insufficiently and no estimation of the cost-effectiveness of cetuximab in third-line treatment of mCRC patients was provided. Despite these shortcomings it was decided that on the basis of the added therapeutic value cetuximab would be added to the policy. As stated in the guidance documents CE is not a primary outcome at T=0 and therefore the lack of an indication was not a reason to block the addition to the policy (Kuijpers and Toenders, 2006). However the guidelines do state clearly that a CE claim should be made and a model should be presented that would be assessed at T=4 (Kuijpers and Toenders, 2006).

To show how in this case a CE claim could be done a health economic model is described below that gives an estimation of the CE of cetuximab compared to best supportive care (BSC) in mCRC patients that are refractory to chemotherapy. The model is based on publically available data. The description of the model roughly follows the formats of the CVZ how a CE claim should be submitted (CVZ, b). Before going into the description of the model, the disease, the patients and the treatment of the disease, including Dutch guidelines, are described. The model is set-up following the Dutch pharmacoeconomic guidelines (CVZ, 2006).

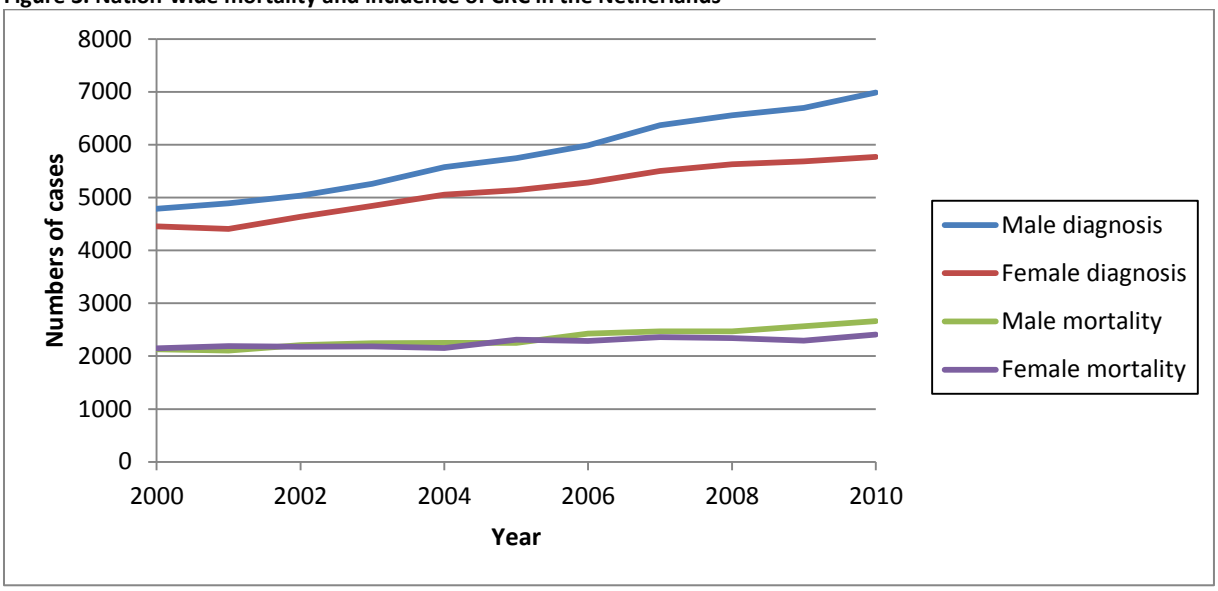
3.2. Description of Colorectal cancer

3.2.1. Introduction

Colorectal cancer (CRC) is cancer in the colon and/or the rectum. Worldwide it is the third most common cancer in men and the second most common in women (10% and 9.4% of the total cases respectively) with the highest incidence rates in Western Europe and Australia/New Zealand and lowest incidence rates in Africa and south-central Asia[9]. Colorectal cancer has the fourth highest mortality rate of all cancers, accounting for 8% of all cancer deaths worldwide[9]. Mortality rates are lower in women than in men. In both men and women the incidence of CRC in Western Europe seems to be stable but in some countries like in the Netherlands the number of newly diagnosed cases of CRC is increasing (Figure 3)[9]. However mortality seems to be more stable for both men and women, which might partly be due to successful treatment of the disease (Figure 3)[9].

[9] Websites: "GLOBOCAN Cancer Fact Sheets: Colorectal Cancer" (Accessed April 2012): http://globocan.iarc.fr/factsheets/cancers/colorectal.asp and "Dutch cancer figures" (Accessed June 2012). www.cijfersoverkanker.nl

Figure 3. Nation-wide mortality and incidence of CRC in the Netherlands[9]



3.2.2. Metastatic CRC

Metastatic CRC (mCRC), which is about 20% of the diagnoses, is usually incurable, although recent advances in therapy have improved survival rates (Markowitz and Bertagnolli , 2009). For mCRC chemotherapy is palliative, but able to lengthen survival, lessen symptoms, improve QoL and downsize metastases (Cunningham et al. , 2010). Three monoclonal antibodies (mABs) are licenced for treatment of mCRC (Cunningham et al. , 2010). In contrast to systemic cytotoxic chemotherapy the mAbs are targeted treatment. Cetuximab and panitumumab inhibit EGFR, a receptor expressed on epithelial cells. EGFR is frequently overexpressed in human tumours including CRC where it can promote proliferation, metastasation, angiogenesis and inhibition of apoptosis of the tumour (Vincenzi et al. , 2008). Bevacizumab is antiangiogenic by inhibiting vascular endothelial growth factor (VEGF). It also improves drug delivery to the target by normalization of tumour vasculature (Cunningham et al. , 2010).

3.2.3. Cetuximab treatment in metastatic CRC

Cetuximab is indicated in mCRC in combination with irinotecan-based chemotherapy, in first-line in combination with FOLFOX, or as monotherapy in third-line in patients who failed oxaliplatin- and irinotecan-based therapy or are incapable of receiving irinotecan. Cetuximab is given as an IV infusion, with an initial dose of 400 mg/m^2 body surface area (BSA) followed by a weekly dose of 250 mg/m^2 BSA (EMA , 2012). Post hoc analyses of clinical trials with cetuximab in mCRC have shown that the drug is less effective in CRC patients that have a mutated KRAS-gene at codon 12 or 13, and therefore the drug is only indicated for patients with wild-type (WT) KRAS (EMA , 2012; Morton and Hammond , 2009). The main undesirable effects of cetuximab are skin reactions (>80% of patients), hypomagnesaemia (>10% of patients) and infusion related reactions (>10% mild/moderate; >1% severe) (EMA , 2012).

The indication for combination with chemotherapy is based on the results of several clinical trials. The CRYSTAL trial studies first-line FOLFIRI vs FOLFIRI + cetuximab and showed a significant gain in progression free survival (PFS). Furthermore the addition of cetuximab to FOLFIRI improved overall survival (OS) in KRAS WT patients (Van Cutsem et al. , 2009; Van Cutsem et al. , 2011).

The OPUS trial compared first-line FOLFOX vs FOLFOX + cetuximab treatment. Although there was a difference in favour of the cetuximab group the difference in overall response rate (ORR) was not significant. However, when looking at the KRAS WT group PFS and ORR was significantly better in the cetuximab group (Bokemeyer et al. , 2009; Bokemeyer et al. , 2011).

In the MRC COIN study patients with advanced CRC that were fit for but had not been treated with chemotherapy were randomly assigned to oxaliplatin and fluoropyrimidine (either capecitabine or infusional 5-FU/LV) chemotherapy, the same combination plus cetuximab, or intermittent chemotherapy. The trial has not confirmed a benefit of addition of cetuximab to oxaliplatin-based chemotherapy in first-line treatment of patients with advanced colorectal cancer. During the trial a toxic effect of the combination of cetuximab + capecitabine-based chemotherapy was identified and the dosing of capecitabine had to be adjusted during the trial (Adams et al. , 2009; Maughan et al. , 2011).

In the EPIC trial patients that were refractory for first-line fluoropyrimidine and oxaliplatin combination treatment received either irinotecan or irinotecan + cetuximab. Although the patients in the cetuximab group had significantly better PFS, response rate and quality of life (QoL) results, the primary endpoint, overall survival, was not significantly better than for patients in the irinotecan group. The fact that almost half of the patients in the irinotecan group received cetuximab after the trial might be a reason for not achieving a significant gain on the primary endpoint (Sobrero et al. , 2008).

In the BOND trial irinotecan refractory patients received either cetuximab alone or irinotecan + cetuximab. The irinotecan + cetuximab group had significantly better response rates, and median time to progression. Although overall survival was longer in the cetuximab group this difference was not significant (Cunningham et al. , 2004). In these trials cetuximab seems to be able to show significantly better results when it comes to progression free survival, but, as seen with most oncology medicines, significantly better overall survival is hard to prove with cetuximab.

The indication for third-line monotherapy is based on the National Cancer Institute of Canada (NCIC) Clinical Trials Group (CTG) C0.17 trial, which will be the basis of the model. In this trial the patients (from Canada, Australia and New Zealand) were refractory to fluoropyrimidine, irinotecan and oxaliplatin or had contraindications to treatment with these medicines. Patients were randomized to treatment with cetuximab plus best supportive care (BSC) or BSC only. BSC was defined as those measures designed to provide palliation of symptoms and improve QoL as much as possible and further chemotherapy was not intended. Cross over to cetuximab was not allowed. Importantly in this trial; cetuximab treatment was associated with a significant improvement in overall survival. Also PFS was significantly better compared to BSC (Jonker et al. , 2007). In a sub-analysis of the CO.17 study in which the KRAS-mutation status was associated with survival in the cetuximab and BSC group (Karapetis et al. , 2008). It was found that effectiveness of cetuximab was significantly associated with KRAS mutation status. In the KRAS WT group patients treated with cetuximab had significantly improved OS and PFS compared to the BSC group, whereas in the KRAS mutation group this difference was not significant. The KRAS mutation status did not affect the survival of the patients treated with BSC (Karapetis et al. , 2008). The same pattern was seen for health-related QoL (HRQoL) endpoints physical function and global health status. In KRAS WT patients HRQoL was

significantly better in the cetuximab group vs the BSC group whereas this was not the case in KRAS mutated patients (Au et al. , 2009).

3.2.4. Cost-effectiveness studies with cetuximab in mCRC

To research the outcomes of existing CE studies performed on cetuximab treatment in mCRC a literature search on PubMed using the following search term: (cetuximab AND "cost effectiveness" AND colorectal AND metastatic). The search term returned 20 results. Of these 14 were not relevant (6 were on CE of KRAS testing; 1 was on ethics; 2 were not in English; 2 were review articles; 3 were in first-line treatment), leaving 6 articles of which the results are summarized in

Table 4 (Annemans et al. , 2007; Hoyle et al. , 2013a; Hoyle et al. , 2013b; Mittmann et al. , 2009; Norum , 2006; Starling et al. , 2007). The table shows the reported CE results in Euros[10]. These results show that cetuximab in mCRC patients that failed chemotherapy compared to BSC seems not to be a good value for money.

Table 4. Results of CE studies comparing cetuximab with BSC in mCRC after failure of chemotherapy

Reference	Year	Trial/Study	Indication	Methods	CE Results
Norum	2006		mCRC	CTX + Iri vs BSC	€205,536 - €323,040 / LYG
Starling	2007		mCRC after CT	CTX + Iri vs BSC	€67,313 / QALY
Annemans	2007	BOND	mCRC after CT	CTX + Iri vs BSC	€30,000-€59,000/QALY
Mittmann	2009	CO.17	mCRC after CT	CTX vs BSC	€140,293 / QALY
Hoyle (Value in Health)	2013		3rd-line mCRC	CTX vs BSC	€111,005 / QALY
				CTX + Iri vs BSC	€102,826 / QALY
				PTM vs BSC	€218,504 / QALY
Hoyle (HTA)	2013		3rd-line mCRC	CTX vs BSC (KRAS WT)	€114,510 / QALY
				CTX + Iri vs BSC (KRAS WT)	€102,826 / QALY
				PTM vs BSC (KRAS WT)	€175,271 / QALY

BSC=Best Supportive Care; CT=Chemotherapy; CTX=Cetuximab; Iri=Irinotecan; mCRC=metastatic CRC; KRAS WT=KRAS Wildtype

3.3. Design of the model

3.3.1 Introduction

To calculate the cost effectiveness (CE) of cetuximab vs BSC a cohort simulation in the form of a Markov model will be done using the data of the earlier mentioned CO.17 trial. The data from this trial is used since this is the trial that the third-line monotherapy indication for cetuximab in mCRC is based on. Because the patient level data is unavailable the CE will be modelled by using the information that is published on the CO.17 trial. The CE will be calculated for the whole population and the KRAS WT population with the efficacy and resource use information from the primary paper (Jonker et al. , 2007), the KRAS subanalysis (Karapetis et al. , 2008) and a CE analysis (Mittmann et al. , 2009). QoL data used in the model is taken from the NICE assessment that has been performed.

3.3.2 Disease states

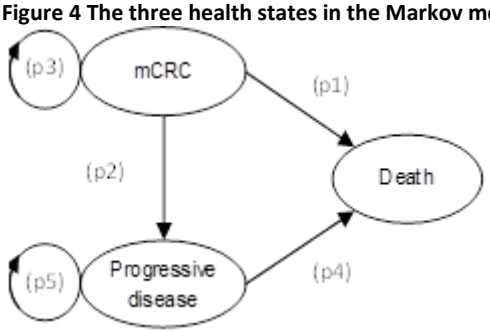
Markov models are structured around mutually exclusive disease states that a patient can be in. The Markov model outcome is based on a set of possible transitions between these exclusive states over

[10] In several case the reported results were other currencies (Pounds and Canadian Dollars). These were transformed to Euros using the exchange rates for those currencies at 22nd May 2013

a series of discrete time periods (cycles) (Briggs, Claxton, and Sculpher 2011). The mCRC model used in this research includes three states (figure 4):

(1) mCRC: mCRC patients in this group have non-progressive disease
(2) Progressive Disease: patients in this group have an objective observation of disease progression.
(3) Death.

Figure 4 The three health states in the Markov model.



3.3.3 Time horizon

To get reliable results around 99% of the patients in the model should die within the time horizon given the low 5-year survival of mCRC patients starting a third-line treatment, so 4 years seems to be a reasonable time horizon. Therefore The time horizon was chosen to be four years, the same as in the incomplete model that was submitted to the Dutch authorities. The patients from the CO.17 trial have failed several treatments and 77% of the cetuximab treated and 82% of the BSC treated patients died within the trial period of approximately 18 months (Mittmann et al. , 2009).

3.3.4 Cycle length

Patients on BSC progress relatively quickly and mortality is high. Therefore the cycle time should not be too short compared to the time between assessments of the patients. In the CO.17 study patients were assessed every four weeks and patients in the cetuximab group received treatment every week (Jonker et al. , 2007). A cycle time of 14 days was chosen. The time horizon of four years combined with a cycle time of 14 days meant that the model was limited to 104 cycles.

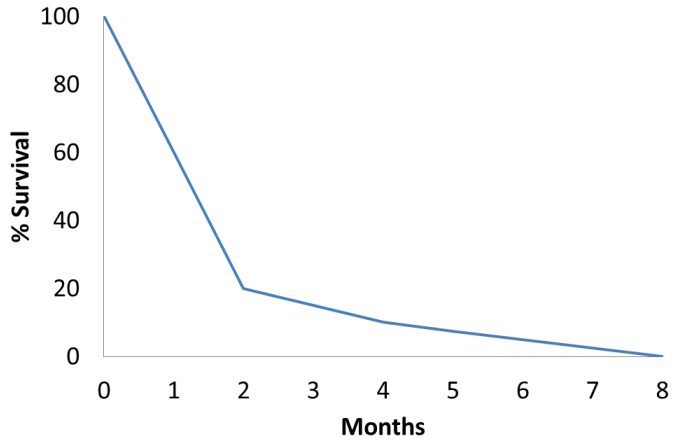
3.3.5 Transition probabilities

Cohort simulation in a Markov model involves multiplying the proportion of patients ending in one state with the probabilities of transitioning to another disease state or die (Drummond et al. 2005). The arrows in figure 4 indicate possible transitions from one cycle to the next. Each arrow represents a transition probability to progress to the indicated state. Non-progressing patients can either die with a probability of *p1*, progress with *p2* or stay in the mCRC state with a *p3* (which is calculated by the following equation: *p3* = 1-*p1*-*p2*). Patients with progressive disease can either die with a *p4* or stay in the progressive disease state with a *p5* (which is calculated by 1-*p4*), but they cannot return to non-progressive mCRC. Obviously the patients that have died stay dead. Some of the transition probabilities that are derived prove not to be constant over time, so time dependency is built into the model. This is done by varying the transition probabilities in the different cycles where needed. The transition probabilities p1,p2 and p4 are calculated as described in the following paragraphs.

(p1) mCRC -> Death

To derive the transition probabilities from non-progressive mCRC to death the number of patients dying without proof of progression mentioned by Jonker et al. are used: 49 patients (out of 287) in the cetuximab group and 91 patients (out of 285) in the BSC group died without progression within the 18 months of the study (Jonker et al. , 2007). In the KRAS sub analysis (Karapetis et al. , 2008) these numbers are not specifically mentioned so it is assumed that the fact that patients died without sign of progression was not influenced by KRAS status and thus the number of patients that died in the KRAS WT groups are divided proportionally. In the cetuximab group 110 patients were KRAS WT, so 49 x (110/287) = 19 patients in this group died without progression. In the BSC group this is 91 x (91/285) = 29 patients. Since >90% of the patients in the study progressed within 8 months (Jonker et al. , 2007) it is assumed that all the patients who died before progression died within these 8 months. Furthermore it can be expected that the survival curve for these patients would be exponential rather than linear with most patients dying within in the first months. Assumed is therefore that 80% of the patients die in the first two months, 10% in month 2-4 and the final 10% die from month 4-8 as shown in Figure 5 (personal communication E. van Rooijen).

Figure 5. Assumed survival curve of patients dying without proof of progression



These assumptions will give three different transition probabilities over time, namely from month 0-2, month 2-4 and month 4-end of the time horizon of the model. From the survival curve in Figure 5 the transition probabilities can be derived as follows. As an example the calculation for month 0-2 for the cetuximab group is taken.

For example in the cetuximab group in the whole population at zero months 49 patients are 'at risk' of dying. At two months, as we assumed, 80% of them died, leaving 9.8 patients alive[11]. This means that in the first two months 39.2 patients died. In other words the 2-month probability of dying in this group of 287 patients is 39.2/287=0.137. The cycle-length in the model is 14 days, so the 2-month probability should be transformed to the 14-day probability of dying. This is done by calculating the (constant) instantaneous rate of dying in this population using the following equation (Briggs, Claxton, and Sculpher 2011):

$$R=-[\ln(1-P)]/T \qquad \text{(equation 1)}$$

[11] 9.8 patients dying is not realistic but for the sake of calculation of the probabilities this will not be rounded up.

Where *R* is the instantaneous rate that an event happens, *P* is the probability over period *T*.
The 14-day probability can be calculated from the instantaneous rate using the following equation from box 3.1 page 51 of Briggs et al. (Briggs, Claxton, and Sculpher 2011):

$$p=1-\exp\{-Rt\} \qquad \text{(equation 2)}$$

Where *p* is the transition probability, *R* the instantaneous rate and *t* the time of interest (in this case 14 days)

Below the probability of dying of 0.137 in two months (60 days[12]) is filled in which results in a 14-day transition probability of 0.03369.

$$R=-[\ln(1-0.137]/60=0.0024477$$

This rate can be transformed into the transition probability over 14 days by filling it in in equation 2:

$$p=1-\exp\{-0.0024477x14\}=0.03369$$

Since the found transition probability is for the first two months this is the case in cycles 1-4. When performing this calculation for all the time points, both the cetuximab and BSC groups and both the full population and KRAS WT population this gives the transition probabilities as shown in Table 5 for the given cycles for both the full model as well as for the KRAS WT model. In the second column of the table the cycle numbers are mentioned in which the transition probabilities will be applied. Although the last probabilities are calculated over month 4-8 they are applied from cycle 9 on to the end (cycle 104).

Table 5. 14-day Transition probabilities Progression free -> Death

		Cetuximab + BSC		BSC	
		Full population*	KRAS WT**	Full population*	KRAS WT**
Month	**Cycle**	**N=287**	**N=110**	**N=285**	**N=105**
1-2	1-4	0,0337	0,0337	0,0660	0,0567
2-4	5-8	0,0027	0,0027	0,0050	0,0044
4-8	9-end	0,0020	0,0020	0,0038	0,0033

**Based on Jonker et al. 2007; **Based on Karapetis et al. 2008*

(p2) mCRC -> Progression

To derive the probability of transitioning from mCRC to progression the Kaplan-Meier curves with the progression free survival can be used. Figure 6 shows the figures from the respective papers with the full population and KRAS WT population (Jonker et al. , 2007; Karapetis et al. , 2008). The results in the Kaplan-Meier curves includes patients dying without progression. Therefore a correction has been applied by subtracting the expected number of patients dying without progression within a certain period as calculated above in the description of p1. It was assumed that during the first month (first two cycles) no patients died without progression, and thus that all patients that died in

[12] For the model it is assumed that 1 month is 30 days.

the first two months died in the second month. Since the curves are not linear the probabilities are time dependent, with in this case changes at 1 month, 2 months and 6 months.

The 14-day transition probabilities can be calculated in a similar way as explained above using the numbers of patient at risk that are shown underneath Figure 6. Therefore linear decrease of PFS should be assumed between time points, as is included in Figure 6, with red lines for cetuximab groups and blue lines for the BSC groups. The probability that a patient progresses within a given time period is the proportion of patients that progressed over that time period. For example for the full population from month 2-6: In the cetuximab group 129 (patients at risk at t=2) – 38 (patients at risk at t=6) = 91 patients progressed over those four months. However it was calculated that during that period 10 patients died without progression, so these were subtracted from the 91 patients that progressed, leaving 81 patients, being 81/129 = 63%. Thus the probability of progression over those four months for this population is 0.63. When filling this information in in equations 1 and 2 the 14-day transition probability to use in the model for month 2-6 (i.e. cycle 5-12) is 0.10937. For month 1 the number of patients at risk is not available. Therefore an estimation had to be made based on the Kaplan-Meier curves. In the full population it is shown that at one month 93% of the total population is at risk (N= 267 in the cetuximab group and N=265 in the BSC group). In the KRAS WT population none of the patients in the cetuximab group (N=110) have progressed at one month and are all still at risk, whereas 92% of the patients in the BSC group are still at risk (N=98). It is not expected that there is a large bias in these estimations since there is no expectation that a large amount of patients will have been censored in the first month.

Table 6 shows the 14-day transition probabilities for all the cycles and treatment groups for both the total population and the KRAS WT population.

Figure 6. Kaplan-Meier curves for progression-free survival for full population (Jonker et al. , 2007) and KRAS WT population (Karapetis et al. , 2008) including numbers at risk

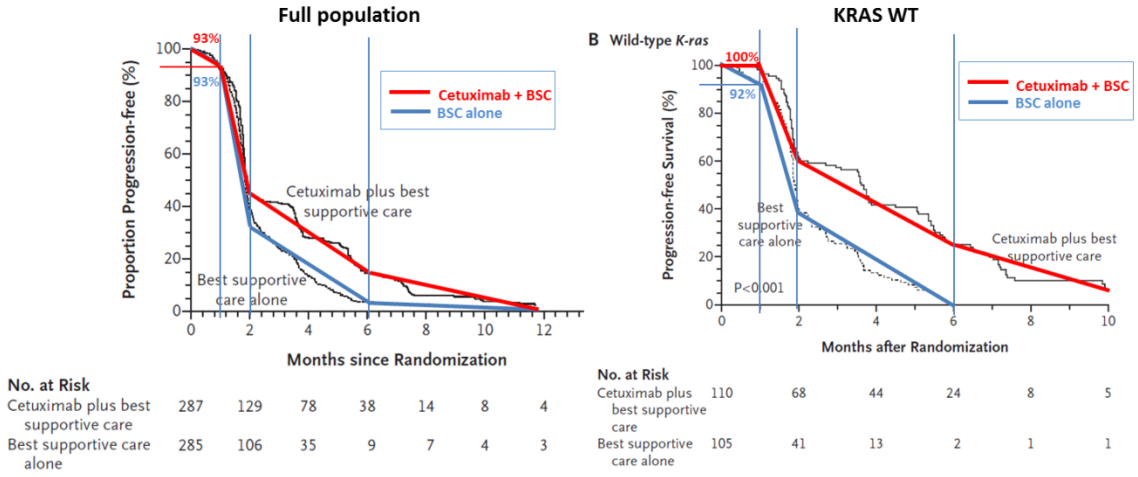


Table 6. 14-day Transition probabilities Progression-free -> Progression

Month	Cycle #	Cetuximab + BSC		BSC	
		Full population*	KRAS WT**	Full population*	KRAS WT*
		N=287	N=110	N=285	N=105
0-1	1-2	0,0331	0,0043	0,0333	0,0333
1-2	3-4	0,1940	0,1193	0,1678	0,1789
2-6	5-12	0,1094	0,0993	0,1467	0,1759
6-end	13-end	0,2743	0,2612	0,2324	0,1862

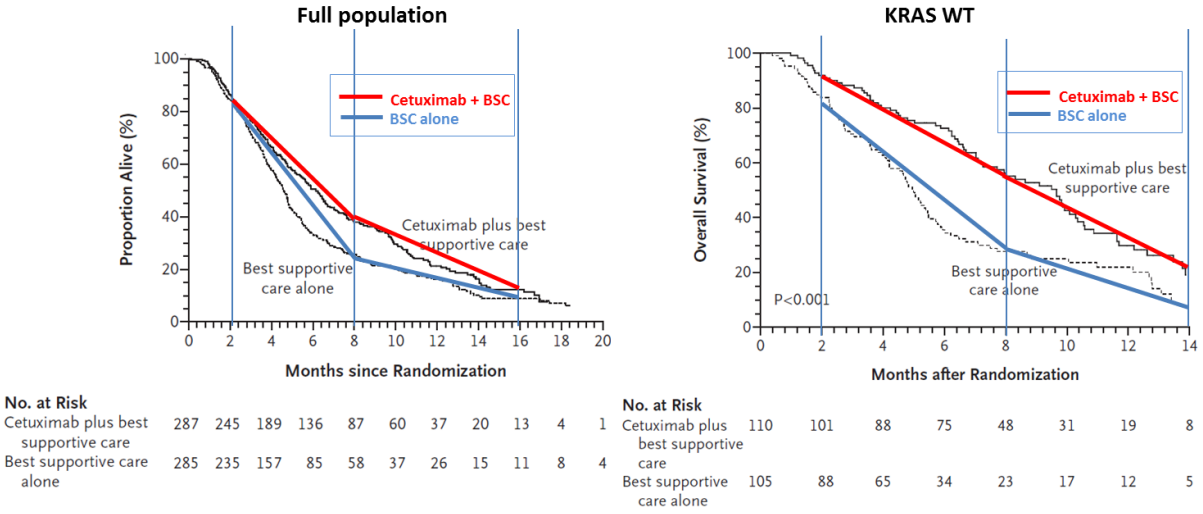
*Based on Jonker et al. 2007; **Based on Karapetis et al. 2008

(p4) Progression -> Death

The probability to transition from progressive disease to death can be derived from the Kaplan-Meier survival curves (Figure 7) that show the overall survival (Jonker et al. , 2007; Karapetis et al. , 2008). Based on the curves it is assumed that the transition probability from progression to death is time dependent. After 8 months (16 cycles) the probabilities are adjusted. The probability of dying in the first two months was not used in the calculations because by then most patients that die without progression would have done so (as was assumed above).

The probability of dying is calculated using the numbers at risk for those time points as indicated in Figure 7. However, the figure includes the survival of progressing and non-progressing patients. To correct for this the number of patients at risk of dying without sign of progression at month two calculated in the previous section (i.e. cetuximab full population: 9.8; cetuximab KRAS WT: 3.4; BSC full population: 18.2; BSC KRAS WT: 5.8) are subtracted from the number at risk at month two.

Figure 7. Kaplan-Meier curves for overall survival for full population (Jonker et al. , 2007) and KRAS WT population (Karapetis et al. , 2008) including numbers at risk



As an example the transition probability of dying for the cetuximab-group in the full population is calculated. At t=2 the number of patients at risk is 245 (Figure 7). In the previous section (mCRC -> Death) it was calculated that over months 2-8 9.8 patients are expected to die without sign of progression. The number of patients at risk of dying after progression is thus 245-9.8=235.2. At t=8 the number of patients at risk is 87, so 148.2 patients died over that time period. The 6-month (or 180-day) probability of dying after progression is thus 148.2/235.2=0.63. Transformation via instantaneous rate to the 14-day probability using equations 1 and 2 gives a transition probability of 0.07444. When performing these calculations for all the patients groups the following 14-day transition probabilities are found (

Table 7), that will be used in all the cycles of the model.

Table 7. 14-day Transition probabilities Progression -> Death

Month	Cycle #	Cetuximab + BSC Full population* N=287	KRAS WT** N=110	BSC Full population* N=285	KRAS WT** N=105
2-8	0-16	0,0744	0,0562	0,0975	0,0991
8-16 (Full) 8-14 (KRAS)	17-end	0,1050	0,1301	0,0924	0,1119

**Based on Jonker et al. 2007; **Based on Karapetis et al. 2008*

3.3.6 Costs

Indirect costs

In the Netherlands the indirect costs within the health care system, ie health care cost due to extra life years, can be left out of pharmacoeconomic evaluations in case no, or little, survival gain is achieved (Hakkaart-van Roijen, et al, 2010). In this case it was decided to leave out these cost because of the relative small survival gain of the patients treated with cetuximab. Regarding indirect costs outside the health care system, which include mainly productivity cost, data on HRQoL is published, including financial impact and social functioning (Au et al. , 2009). The reported outcomes based on analyses of QoL questionnaires are significantly better for the patients treated with cetuximab. However transformation of these data into cost data is not possible because the patient level data are not available. Also the impact of the productivity costs on the total costs is expected to be relatively small in this patient population with end stage mCRC. For example in case of work productivity, it is not expected that many patients, with a median age of 63 year (Jonker et al. , 2007) close to retirement, will go back to work because of the treatment. Therefore it was decided not to include indirect costs outside the health care in the model. A cost factor that could not be included because of the lack of data, but might be important is the productivity of caregivers.

Direct costs outside the health care system

Direct costs outside the health care system include mainly travel costs of the patients. In the literature on the CO.17 trial there is nothing specifically mentioned about the number of hospital visits in the trial. However it is known that the patients in the cetuximab group got the weekly infusion of cetuximab until progression or other event, whereas the BSC group were assessed every four weeks (Jonker et al. , 2007). In the model this was included as follows. The patients in the cetuximab group had to travel weekly for the infusion of cetuximab for a median duration of 8.1 weeks (range 1-60) (Jonker et al. , 2007). Ideally the mean duration of treatment should be used, which is expected to be somewhat higher because of the range. However in the absence of this information the median of 8.1 weeks is used, meaning that for the treated patients the travel costs were applied in the first four cycles. For non-progressing patients not on active treatment it was assumed that they travel to the hospital every four weeks. This means that these costs were applied in the BSC group on non-progressing patients in all cycles and on patients in the cetuximab group from the fifth cycle on, after they stop treatment. Patients in the Netherlands live on average 7 km from the hospital (Hakkaart-van Roijen, et al, 2010). It is assumed that the patients travelled by (private) car, for which the standard calculation costs are €0.20/km and €3.00 parking costs per visit. This will give total travel cost of €5,60 per visit (

Table 8).

Table 8. Travel costs

	CTX group (4 cycles)	Non treated, non-progressing
Distance travelled	14	
Reimbursed / km	€ 0,20	
Total distance costs	€ 2,80	
Parking costs / visit	€ 3,00	
# of visits	Weekly during treatment	Every 4 weeks
Cost per visit	€ 5,80	€ 5,80
Costs per patient per cycle (14 days)	€ 11,60	€ 2,90

Direct costs within the health care system

Direct costs that were made within the health care system in the CO.17 trial are described in the primary paper (Jonker et al. , 2007) and the CE analysis (Mittmann et al. , 2009). There are three categories of direct costs included in the model: (1) hospital and physician costs; (2) Costs of treatment of AEs; (3) Costs of treatment with cetuximab. In the CE analysis information on hospital and physician costs was included. The DBC tariff application from the NZa website was used to search for Dutch prices of hospital use and physicians[13]. From the primary paper information on the management of AEs is found. This information was combined with information from the CVZ website with extramural medicine costs to look up the cost of several treatments of AEs in the Netherlands[14].

Hospital and physician costs

Mittmann et al. present information on the resource utilization and the disaggregated costs per patient per treatment group in the CO.17 study population (
Table 9 and Table 10).
Table 9 shows per category of cost-type what individual units or treatments cost were used (all in Canadian 2007 Dollars), whereas in Table 10 the mean total cost per category per patient is shown for the full population and the KRAS WT patients. Categories for which the disaggregated costs are given are medication and administration, outpatient physician visits, laboratory tests, hospitalization, concomitant medications, management of toxicity, blood products, imaging and other costs. Since there are no big differences between the cetuximab and BSC groups for use of blood products and concomitant medications (i.e. blood products: $163/$201 concomitant medications $100/$100 for cetuximab/BSC group), and it is impossible to identify how the distribution is of the different treatments and care products that are used, it was decided to leave out these costs in the analysis. The unit costs of the individual categories in the Dutch health care system can be either found in the cost manual (Hakkaart-van Roijen, et al, 2010) or with the NZa DBC-tariff application[15], with a preference for the cost manual.

[13] Website "NZa Tariffapplication" (Accessed June 2012): http://dbc-tarieven.nza.nl/Nzatarieven/top.do
[14] Website "Drug cost (Medicijnkosten)" (Accessed June 2012): www.medicijnkosten.nl
[15] Website "NZa Tariffapplication" (Accessed June 2012): http://dbc-tarieven.nza.nl/Nzatarieven/top.do

Table 9. Resource utilization in the CO.17 trial (Mittmann et al. , 2009)

Table 2. Resource utilization, costs, and source information*

Variable	Unit cost, 2007, Can $	Source (reference)
Cetuximab	Cetuximab = 3.24/mg	PMPRB (19)
Dosing: 400 mg/m² initial dose followed by a weekly infusion of 250 mg/m²	Initial dose infusion time/cycle: 103.64/h × 2 h = 207.28	
Infusion time: initial dose infused over 120 min; weekly maintenance dose infused over 60 min	Maintenance dose infusion time: 103.64/h × 1 h = 103.64	
Pharmacy preparation time required (eg, physician preparation, order processing)	Pharmacy preparation time = 40/h × 1 h = 40	
Physician costs		OHIP (20)
Physician outpatient assessments	Consultation = 127.50 Medical-specific assessment = 58.25	
Blood products		Callum (24)
Red blood cells	400	
Autologous (whole) blood	400	
Erythropoietin 40 000 IU/wk for 4–24 wk	1140–2280	
Platelets	500	
Frozen plasma	700	
Cryoprecipitate	225	
Blood group analysis	10	
Antibody screen	25	
Cross matching	15–45	
Treatment of grade 3 and 4 adverse events		
Rash	15–2000	Lacouture (28); OCCI (22)
Non-neutropenic infection	2340	OCCI (22)
Pain	27	
Hospitalization		
Per diem cost	500	Sunnybrook Health Sciences Centre (21)
Imaging		
Diagnostic radiology Colon Air contrast, primary, or secondary, including survey films (Professional fee = $41.00 + technical fee = $62.85)	103.85	OHIP (20)
Concomitant medications		
Antibiotics: ciprofloxacin 500 mg twice daily for 10 d	35.06/infection†	ODB (29)
Opiates: 30 mg SR morphine every 12 h for 30 d	36.97/mo†	ODB (29); Product monograph for MS Contin (30)
Steroids: dexamethasone 4 mg once daily for 30 d	28.28/mo†	ODB (29)
Antidiarrheals: 2 × loperamide 2 mg/d	21.42/mo†	ODB (29)
NSAIDs: 3 × ibuprofen 400 mg once daily	14.37/mo†	ODB (29)
Salicylates: ASA-325 mg once daily	10.84†	ODB (29)
Antiemetics: prochlorperazine 10 mg twice daily	17.74†	ODB (29)
Oral antithrombotics: warfarin 5 mg once daily	13.60†	ODB (29)
Injectable antithrombotics: dalteparin 18 000 U/d for 7 d	258.98†	ODB (29)
Antacid: ranitidine 150 mg twice daily	34.25†	ODB (29)
Blood formation products: darbepoetin, 150 U/kg assuming a 70-kg patient	1216†	ODB (29)
Laboratory		
Laboratory profile: CBC & differential, creatinine, bilirubin, AST, ALT, ALK phos, LDH, electrolytes (sodium, potassium), calcium, magnesium, glucose, albumin (103 U × $0.51/U)	52.53	OHIP (20)

* ALK phos = alkaline phosphatase; ALT = alanine transaminase; ASA = acetylsalicylic acid; AST = aspartate aminotransferase; CBC = complete blood count; IU = international unit; LDH = lactate dehydrogenase; MS = morphine sulphate; NSAID = nonsteroidal anti-inflammatory drug; OCCI = Ontario Case Cost Initiative; ODB = Ontario Drug Benefit; OHIP = Ontario Health Insurance Plan; PMPRB = Patented Medicines Prices Review Board; SR = sustained release.

† Unit cost includes a dispensing fee that was assumed to be $10.

Table 10. Resource use in CO17 trial in Canadian $ (Mittmann et al. , 2009)

Component	Cetuximab + BSC	BSC	Incremental cost per patient with addition of cetuximab
Entire study population			
Medication and administration	21 183	0	21 183
Outpatient physician visits	447	329	118
Laboratory tests	341	26	315
Hospitalization	3803	2785	1018
Concomitant medications	100	100	0
Management of toxicity	1471	385	1086
Blood products	163	201	−38
Imaging	302	72	230
Other costs	392	335	57
Patients with wild-type *KRAS* tumors			
Medication and administration	29 190	0	29 190
Outpatient physician visits	517	325	192
Laboratory tests	432	22	410
Hospitalization	4222	2372	1850
Concomitant medications	100	100	0
Management of toxicity	1915	317	1598
Blood products	125	231	−106
Imaging	385	78	307
Other costs	438	262	176

* Not all categories of costs are included in the table. Costs are presented in 2007 Canadian dollars. BSC = best supportive care.

Table 11 describes the hospitalization costs as found in the cost manual and the DBC-tariff.

Table 11. Unit costs in the Dutch health care system of the hospital and physician costs

Resource used	Reference	Description	Dutch unit cost	
Physician visits	Cost manual	Outpatient consult gastroenterology	€	94,64
Hospitalization	Cost manual	Inpatient day admission	€	251,00
Imaging	DBC code 87042	CT research of the abdomen incl contrast	€	218,04
Laboratory	DBC code 79991	Clinical-chemical and microbiological lab research	€	13,31

When combining the information on unit cost and cost per patient from Table 9 and Table 10 the number of times the resource is used per patient during the study can be calculated for the full population and the KRAS WT population for the cetuximab group (Table 12) and the BSC group (Table 13). For example for imaging: the unit cost in Canadian dollars was $103.85. In the cetuximab group per patient $302 was consumed on imaging which is a mean use per patient of 2.9 imaging scans over the total study.

Table 12. Calculation of mean resource use per patient in cetuximab group

Resource used	Unit cost (Table 9)	cetuximab + BSC Full population		KRAS WT population	
		Mean cost / pt (Table 10)	Mean use / pt	Mean cost / pt (Table 10)	Mean use / pt
Physician visits	$ 185,75	$ 447,00	2,4	$ 517,00	2,8
Hospitalization	$ 500,00	$ 3.803,00	7,6	$ 4.222,00	8,4
Imaging	$ 103,85	$ 302,00	2,9	$ 385,00	3,7
Laboratory	$ 52,53	$ 341,00	6,5	$ 432,00	8,2

Table 13. Calculation of mean resource use per patient in BSC group

Resource used	Unit cost (Table 9)	BSC Full population		KRAS WT population	
		Mean cost / pt (Table 10)	Mean use / pt	Mean cost / pt (Table 10)	Mean use / pt
Physician visits	$ 185,75	$ 329,00	1,8	$ 325,00	1,7
Hospitalization	$ 500,00	$ 2.785,00	5,6	$ 2.372,00	4,7
Imaging	$ 103,85	$ 72,00	0,7	$ 78,00	0,8
Laboratory	$ 52,53	$ 26,00	0,5	$ 22,00	0,4

When combining the information of the previous tables the cost per cycle in the Dutch setting for the different groups can be calculated by multiplying the mean use per patient (from Table 12 and Table 13) with the corresponding unit cost from
Table 11. The outcome represents the cost over the whole study of 18 months, or 540 days. To calculate the cost per cycle the outcome is multiplied with 14 days/540 days. This is done in Table 14 for all the resources, patient groups and treatment groups. In the model the following physician and hospital costs will be applied to the indicated groups: Cetuximab group full population €74.08 and KRAS WT population €85.57 vs the BSC group full population €44.68 and KRAS WT population €39.55 (Table 14).

Table 14. Physician and hospital costs per cycle

Resource used	cetuximab + BSC		BSC	
	Full	KRAS WT	Full	KRAS WT
Physician visits	€ 5,90	€ 6,83	€ 4,35	€ 4,29
Hospitalization	€ 49,50	€ 54,95	€ 36,25	€ 30,87
Imaging	€ 16,44	€ 20,96	€ 3,92	€ 4,25
Laboratory	€ 2,24	€ 2,84	€ 0,17	€ 0,14
Total	€ 74,08	€ 85,57	€ 44,68	€ 39,55

Costs of treatment of AEs

The cost of treatment of AEs was calculated based on Dutch standards of treatment of the AEs that differed significantly between the cetuximab and BSC standard care group, namely rash, non-neutropenic infection and pain (Jonker et al. , 2007).
Table 15 shows the AEs as published in Jonker et al. In the absence of separate data on AEs in the KRAS WT group the cost of treating AEs was assumed to be the same for the full and the KRAS WT groups.

Table 15. Adverse events as seen in the CO17 trial (Jonker et al. , 2007)

Event	Cetuximab plus Best Supportive Care (N=288)	Best Supportive Care Alone (N=274)	P Value
	number (percent)		
Grade 3 or higher with an incidence of ≥5%*			
Any adverse event	226 (78.5)	162 (59.1)	<0.001
Edema	15 (5.2)	16 (5.8)	0.85
Fatigue	95 (33.0)	71 (25.9)	0.09
Anorexia	24 (8.3)	16 (5.8)	0.32
Constipation	10 (3.5)	13 (4.7)	0.53
Nausea	16 (5.6)	15 (5.5)	1.00
Vomiting	16 (5.6)	15 (5.5)	1.00
Non-neutropenic infection	37 (12.8)	15 (5.5)	0.003
Confusion	16 (5.6)	6 (2.2)	0.05
Abdominal pain	38 (13.2)	43 (15.7)	0.40
Other pain†	43 (14.9)	20 (7.3)	0.005
Dyspnea	47 (16.3)	34 (12.4)	0.23
Rash	34 (11.8)	1 (0.4)	<0.001

The Dutch costs of the treatments are found on the CVZ website with cost of outpatient medicines[16]. In case the website indicated that there was a range of prices the lowest possible costs was chosen. Rash is treated with Minocyclin (5600 mg[17]) in 90% of the cases and doxycycline (5600 mg[18]) in 10% of the cases once or twice a day for four weeks. Furthermore other crèmes are prescribed on the basis of personal preference of the treating physician, but the cost of these crèmes are negligible and are not included in this analysis (personal communications E. van Rooijen). In an on-going study in a similar Dutch patient population patients with non-neutropenic infections are treated as follows: 42% patients are treated with amoxicillin/clavulanic acid (28 IV and 20 oral doses[19]), 33% of patients are treated with ciprofloaxacin (28 IV and 28 oral doses[20]) and 25% of patients with cefuroxime (42 IV 1500 mg and 42 IV 750 mg doses[21]) (personal communications E. van Rooijen). Pain in the investigated patient groups are assumed to be of the highest step of the WHO pain ladder[22] and it is assumed that is treated with a 25 µg/hr fentanyl transdermal patch to be replaced once every three days.

[16] Website "Drug cost (Medicijnkosten)" (Accessed June 2012): www.medicijnkosten.nl
[17] 2x/day 100 mg for 4 weeks
[18] 2x/day 100 mg for 4 weeks
[19] Initially IV in a dose of 1000/200 mg 4x/day for 7 days followed by oral 500/125 mg 4x/day for 5 days
[20] Oral dosing 500 mg 2x/day for 14 days. 50% (probably a slight overestimation) of infections are treated with IV dosing 400 mg 2x/day for 14 days.
[21] IV treatment 1500 mg 3x/day (50%) or 750 mg 3x/day (50%) for less serious infections for 14 days.
[22] Website WHO "WHO's pain ladder" (Accessed June 2012): http://www.who.int/cancer/palliative/painladder/en/

Table 16 shows that the cost per cycle for treating AEs in the cetuximab group is €6.00 and for the BSC group €2.54.

Table 16. Calculation of cost per cycle of treatment of AEs

Adverse Event	Treatment	Form	Cost/pt (Dutch €)*	CTX+BSC (N=288) Cost/pt/cycle	BSC (N=274) Cost/pt/cycle
Rash	Minocyclin (90%)	100 mg pill	€ 22,03		
	Doxycyclin (10%)	100 mg pill	€ 6,91		
	Total			€ 0,06	€ 0,00
Non-neutropenic Infection	Amoxicillin/ clavulanic acid (42%)	IV 1000/200 mg	€ 95,30		
		Oral 500/125 mg	€ 1,83		
	Total		€ 97,13	€ 0,13	€ 0,06
	Ciprofloxacin (33%)	IV 400 mg (50%)	€ 1.061,27		
		Oral 500 mg (50%)	€ 3,26		
	Total			€ 0,59	€ 0,25
	Cefuroxime (25%)	IV 1500 mg (50%)	€ 242,10		
		IV 750 mg (50%)	€ 108,54		
	Total			€ 0,15	€ 0,06
Pain	Fentanyl transdermal patch (100%)	25 µg/hr	€ 0,69	€ 0,02	€ 0,01
			Total	€ 0,96	€ 0,38

**From www.medicijnkosten.nl accessed 22/6/2012*

Abbreviations: BSC=Best supportive care; CTX=cetuximab; pt=patiënt;

Costs of cetuximab treatment

A big part of the total costs are the cost of cetuximab, which are obviously only incurred in the cetuximab group. Cetuximab was given as an induction dose of 400 mg/m^2 BSA followed by a weekly maintenance infusion of 250 mg/m^2 . Per protocol treatment was continued until progression, in the absence of the occurrence of unacceptable AEs, patient refusal or death (Jonker et al. , 2007). For the model it was assumed that all the patients that were non-progressing were treated with cetuximab.

Costs that should be included are drug costs and the costs of the infusion. Cetuximab is available in vials with 100 mg (€219.27) and 500 mg (€1096.37) (CVZ, 2011). For the calculation of number of vials an average BSA of 1.79 m^2 is used (Sacco et al. , 2010). Thus for the induction dose 716 mg is needed, which means 1 vial of 500 mg and 3 vials of 100 mg are needed. For the maintenance dose 447.5 mg cetuximab is needed so 1 vial of 500 mg is sufficient. It is assumed that the remainder in the vial was not used to treat other patients. For the cost of the infusion the DBC for gastroenterology day of care (without hospitalization) is used, which is €177,41. Table 17 shows that the costs for cetuximab in the first week (induction dose) is €1,931.59 and for the maintenance dose, the rest of the time, €1.273,78. This means that for the first cycle patients treated with cetuximab have a cost of €3.205,37 and for the following cycles a cost of €2.547,56.

Table 17. Weekly costs of treatment with cetuximab

Costs	Vials		Induction dose		Maintenance dose	
	Content	Cost	# vials	Cost	# vials	Cost
Drug	100 mg	€ 219,27	3	€ 657,81		
	500 mg	€ 1.096,37	1	€ 1.096,37	1	€ 1.096,37
Infusion				€ 177,41		€ 177,41
			Total	€ 1.931,59		€ 1.273,78

Summary of costs

Table 18 summarizes the cost per cycle that will be used in the model including travel costs, cetuximab treatment, treatment of AEs and other hospital or physician costs as explained above.

Table 18. Summary of cost per cycle

Costs	cetuximab +BSC		BSC	
	Full population	KRAS WT	Full population	KRAS WT
Travel costs	€ 11,60	€ 11,60	€ 2,90	€ 2,90
Cetuximab				
Cycle 1	€ 3.205,37	€ 3.205,37	€ -	€ -
Cycle 2 and further	€ 2.547,56	€ 2.547,56	€ -	€ -
Treatment of AEs	€ 0,94	€ 0,94	€ 0,37	€ 0,37
Hospital/Physician costs	€ 158,74	€ 179,80	€ 106,70	€ 92,89

3.3.7 Utilities, Life Years and QALYs

The Dutch guidelines for CE research indicate that the effect should be measured in QALYs, or if not possible in life years (Delwel, 2008). In the mCRC model both QALYs and LY will be presented. A QALY is a health outcomes measure that can capture gains from reduced morbidity (quality) and reduced mortality (quantity) of treatment (Drummond et al. 2005). In the model the QALYs are calculated per cycle by multiplying the number of LY per disease state with the utility that is given to being in that disease state. The number of LY per treatment group is calculated by adding up the amount of patients alive in a cycle multiplied by 2/52 (because of the cycle time of 14 days).

The utility differs per disease state. A patient that has progressive disease probably scores his QoL less than a patient that is not progressing. This information is captured in the CO.17 trial with the generic preference-based QoL measure Health Utility Index-3 (HUI-3) (Mittmann et al. , 2009). In the available literature the utility information per disease state has not been described, but in an appraisal for the British National Institute for Clinical Excellence (NICE) the utility data as presented in

Table 19 (NICE, 2012) was used. This data was based on the HUI-3 data presented by Mittmann et al but it was not explained how it was derived. Therefore there is uncertainty on how representative these utilities are for the Dutch population.

Table 19. Utilities per disease state per treatment group

Disease state	Cetuximab + BSC	BSC
mCRC	0,81	0,75
Progression	0,69	0,69
Death	0	0

For example in a certain cycle the initial cohort of a 1,000 patients per treatment arm has divided as follows: :

Cetuximab group: 500 progression free; 300 progressing; 200 dead
BSC group: 400 progression free; 350 progressing; 250 dead.

The number of life years in this cycle is calculated by summing up the patients that are alive (800 in the cetuximab group and 750 in the BSC group) and multiplying this number with 2/52. The life years in this cycle are:

Cetuximab group: 30.77 LY
BSC group: 28.85 LY

Thus treatment with cetuximab gives a gain of 1.92 LY in this cycle. The number of QALYs in this cycle is:

Cetuximab group: (500x(2/52)X0.81) + (300x(2/52)x0.69) = 23.54 QALYs
BSC group: (400x(2/52)X0.75) + (350x(2/52)x0.69) = 20.83 QALYs

Treatment with cetuximab gives a gain of 2.71 QALYs compared to BSC.

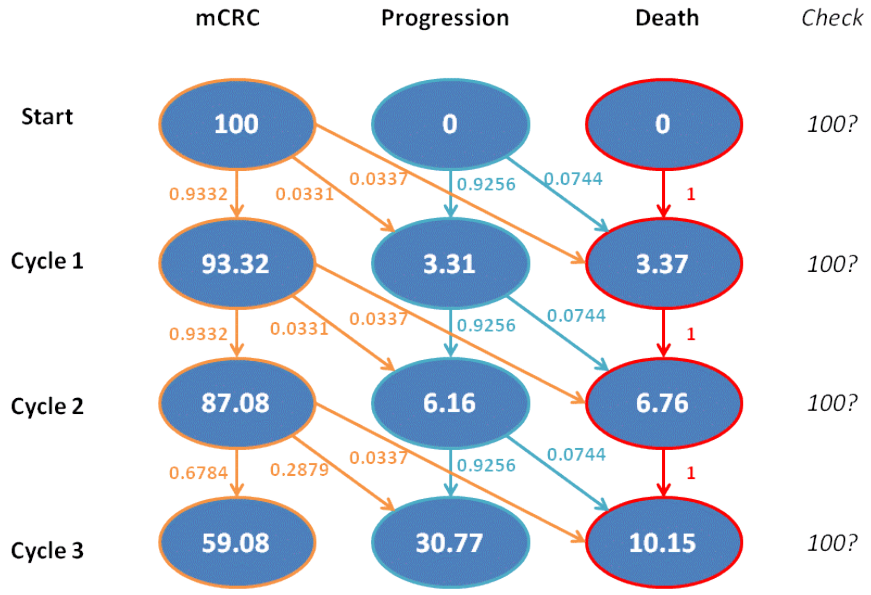
3.3.8 Discounting

As indicated in the guidelines in the Netherlands future cost should be discounted with 4% per year and future effect with 1.5% per year (CVZ, 2006).

3.3.9 Technical details

The mCRC model was built in Microsoft Excel, based on an existing model within iBMG. For every cycle the number of patients in all the disease states is calculated using the transition probabilities as calculated above. Figure 8 shows an example of how this works for the first three cycles with a population of 100 patients. The arrows indicate transitions to disease states in the next cycle. The numbers next to the arrows are the transition probabilities. The numbers in the circles are the number of patients in the disease state. At the start all 100 patients are in the mCRC (non-progressing) group. In cycle one 3.31 patient progress, 3.37 patients die so that leaves 93.32 patients non-progressing. To check if all the calculations are done well a column was added to check if the total number always adds up to 100.

Figure 8. Example of calculation of number of patients per disease state per cycle



Based on the amount of patients per disease state the costs and effects (LY, and QALYs) are calculated as described in the corresponding sections above. The costs and effects for all the cycles are added up and divided by the number of patients to get the mean costs per patient per year. Incremental costs and effects are calculated into ICERs (incremental cost per QALY and per LY).

3.3.10 Univariate deterministic sensitivity analyses

Due to the assumptions made for the model the parameters in the model have a great deal of uncertainty. First of all they are estimates based on information from literature. Furthermore this

literature is based on one clinical trial. However the model should reflect the real life scenario as much as possible, since important decisions, like the reimbursement of the drug, are based on such models. Therefore several deterministic sensitivity analyses (DSAs) are performed in which different parameters are varied. This will be done as univariate analysis (only one parameters varied) or as multivariate analysis (where multiple parameters are varied). The following variables will varied:

SA1 Drug costs of cetuximab

An easy way to improve the CE of a drug is by making the drug cheaper, for example by negotiating a lower price with the manufacturer. To test how the CE is affected by the price of the drug is lowered with 10% and 25%, since these could be discounts that might be negotiated.

DSA2 Utilities

The utilities used in the model are derived from the HUI-3 multi-attribute preference-based questionnaires taken during the CO.17 trial. It has been shown that utility data derived from different preference-based instruments (like the EQ-5D and SF-6D questionnaires) can give different outcomes for the same health state measured in the same patients (Drummond et al. 2005). Therefore the utility scores used in the model will be varied from 7.5% lower to 7.5% higher than used in the original models. Ideally the confidence intervals of the utility scores are chosen as minimum and maximum change in the SA, but these are not publically available. Seven and a a half per cent is chosen because when the mCRC BSC utility is lowered with 7.5% it is still slightly higher than the original utility of progressive disease (Table 20). It would not be realistic that patients with non-progressive disease have a lower utility than patients that are progressing.

Table 20. Utilities used in the DSA-2

	Original	+7.5%	-7.5%
mCRC cetuximab group	0,81	0,871	0,749
mCRC BSC group	0,75	0,806	0,694
Progressive disease	0,69	0,742	0,638

Seven DSAs (DSA2-A to G) are done of which four are univariate and three multivariate analyses as shown in Table 21.

Table 21. Summary of the variations that are done in DSA-2

	Univariate				Multivariate				
Utility	**DSA2-A**	**DSA2-B**	**DSA2-C**	**DSA2-D**	**DSA2-E**	**DSA2-F**	**DSA2-G**	**DSA2-H**	**DSA2-I**
mCRC cetuximab group	+7.5%	-	-	-	+7.5%	+7.5%	-7.5%	0,81	0,75
mCRC BSC group	-	-7.5%	-	-	-7.5%	+7.5%	-7.5%	0,81	0,75
Progressive disease	-	-	+7.5%	-7.5%	-	+7.5%	-7.5%		

In the model it is assumed that there is a difference in the pre-progression utility between the patients in the CTX and the BSC groups. Two separate DSAs (DSA2-H and DSA-I) are done in which this difference is assumed to be non-existent by increasing the utility for patients on BSC to that of patients on CTX (DSA2-H) and vice versa (DSA2-I).

DSA3 Transition probabilities

Performing DSAs on the transition probabilities is important since several assumptions were made when deriving them. To come to a reasonable range for varying the transition probabilities ideally the ranges around the hazard ratios mentioned for OS and PFS are used where available, because

these describe the uncertainty in the CO.17 trial. To adjust the hazard ratio the transition probability for the cetuximab groups in both the full population and the KRAS WT populations will be kept constant while lowering the transition probability for the BSC groups in such a way that the ratios between the transition probabilities of the cetuximab vs the BSC group vary between a certain minimum and maximum. These are described in Table 22 (for the full population) and Table 23 (for the KRAS WT population).

For the mCRC -> Death probabilities the ratio of the patients that died before progression has been taken (0.53) and a range of 0.30 around it has been assumed, since no range has been mentioned in the papers of Jonker and Karapetis. The range of 0.30 was chosen because the other ranges that are found in the papers are similar. The transition probabilities to progress from mCRC are investigated. The tables show for the different cycles the ratios of the probabilities between the cetuximab and BSC groups. The range of 0.24 is found in Jonker et al. Karapetis et al report a range of 0.23 for the KRAS WT population (Jonker et al. , 2007; Karapetis et al. , 2008). Finally for the progression to death after progression the SAs performed will investigate the ranges of 0.62-0.90 for the full population and a range of 0.40-0.73 for ratios of transition probabilities for the cetuximab groups vs the BSC groups based on confidence intervals found in the corresponding papers (Jonker et al. , 2007; Karapetis et al. , 2008).

Table 22. DSA 3: transition probabilities for full population

Full population			Transition Probs Min Ratio		Transition Probs Max Ratio	
Analysis	**Transition probability range**	**Range Ratio**	**CTX**	**BSC**	**CTX**	**BSC**
DSA3-A	mCRC-> Death Cycles 1-4	0.38-0.68	0,0337	0,0884	0,0337	0,0494
	mCRC-> Death Cycles 5-8	0.38-0.68	0,0027	0,0070	0,0027	0,0039
	mCRC-> Death Cycles 9-end	0.38-0.68	0,0020	0,0053	0,0020	0,0029
DSA3-B	mCRC -> Progression cycle 1-2	0.88-1.12	0,0331	0,0379	0,0331	0,0297
	mCRC -> Progression cycle 3-4	1.04-1.28	0,1940	0,1873	0,1940	0,1520
	mCRC -> Progression cycle 5-12	0.63-0.87	0,1094	0,1749	0,1094	0,1264
	mCRC -> Progression cycle 13-end	1.06-1.30	0,2743	0,2588	0,2743	0,2110
DSA3-C	Progression -> Death 1-16	0.62-0.90	0,2743	0,0000	0,2743	0,0000
	Progression -> Death 17-end	1.00-1.28	0,2743	0,1193	0,2743	0,0824

Table 23. DSA3: transition probabilities for KRAS WT population

KRAS WT population			Transition Probs Min Ratio		Transition Probs Max Ratio	
Analysis	**Transition probability range**	**Range Ratio**	**CTX**	**BSC**	**CTX**	**BSC**
DSA3-D	mCRC-> Death Cycles 1-4	0.39-0.69	0,0337	0,0873	0,0337	0,0491
	mCRC-> Death Cycles 5-8	0.39-0.69	0,0027	0,0069	0,0027	0,0039
	mCRC-> Death Cycles 9-end	0.39-0.69	0,0020	0,0052	0,0020	0,0029
DSA3-E	mCRC -> Progression cycle 1-2	0.01-0.24	0,0043	0,3345	0,0043	0,0175
	mCRC -> Progression cycle 3-4	0.55-0.78	0,1193	0,2161	0,1193	0,1526
	mCRC -> Progression cycle 5-12	0.45-0.68	0,0993	0,2209	0,0993	0,1461
	mCRC -> Progression cycle 13-end	1.29-1.52	0,2612	0,2028	0,2612	0,1721
DSA3-F	Progression -> Death 1-16	0.40-0.73	0,0562	0,0000	0,2612	0,0000
	Progression -> Death 17-end	1.00-1.33	0,1301	0,1398	0,2612	0,0768

3.3.11. Probabilistic Sensitivity Analysis

To investigate the uncertainty of the ICER a probabilistic sensitivity analysis (PSA) was performed. In the PSA the parameters that were varied in the DSA were varied simultaneously and the corresponding ICER was captured. The parameters were randomly drawn in such a way that close to 95% of the draws were within the confidence interval that was published, or used in the DSA for that parameter. Drug prices were assumed to be distributed following a gamma-distribution and utilities and transition probabilities as beta-distributions. To be able to apply these distributions means and variances of the original parameters were needed. Because these data were lacking the following assumptions were made. For all parameters the mean was assumed to be the original mean value also used in the base case analysis. Furthermore an estimation of the standard deviation (SD) was made by assuming that the range that was investigated was 4*SD of the population. In a normal distribution this would mean that around 95% of the draws would fall within this range. For the cost data the drug price was varied in such a way that 95% of the times the price was between 25% cheaper to 25% more expensive than the value used in the base case analysis. The utility values were varied over plus or minus 7.5% the original value. For the transition probabilities the ranges as presented in Table 22 and Table 23 were used to estimate the SD.

The alpha and beta for the gamma distribution were calculated using the following equations (in which μ=mean σ=SD and σ^2=variance) (Briggs, Claxton, and Sculpher 2011)

$$\alpha = \mu^2/\sigma^2 \text{ (equation 3)}$$
$$\beta = \sigma^2/\mu \text{ (equation 4)}$$

The alpha and beta for the beta distribution were calculated using the following equations (in which μ=mean σ=SD and σ^2=variance)[23]

$$\alpha = \mu(\mu((1-\mu)/\sigma^2)-1) \text{ conditional } \sigma^2<\mu(1-\mu) \text{ (equation 5)}$$
$$\beta = (1-\mu)(\mu((1-\mu)/\sigma^2)-1) \text{ conditional } \sigma^2<\mu(1-\mu) \text{ (equation 6)}$$

For both the full population and the KRAS WT population the random draw was repeated 1000 times. The results were plotted on a CE plane and in cost-effectiveness acceptability curves (CEACs).

[23] Website Wikipedia "Beta distribution" (Accessed May 2013): http://en.wikipedia.org/wiki/Beta_distribution

3.4 Results

3.4.1 Cost-effectiveness

For the full population the incremental costs per patient in the cetuximab group vs the BSC group were €16.516 whereas there was incremental benefit of 0,09 QALYs or 0,10 LYs. This resulted in an incremental costs / QALY of €191.417 or an incremental costs /LY of €161.975 (Table 24).
For the KRAS WT population the incremental costs per patient in the cetuximab group vs the BSC group were higher than in the full population with €21.429, but the incremental benefit was larger as well, namely 0,15 QALYs or 0,16 LYs per patient. This resulted in an incremental cost / QALY of €144.716 or an incremental cost / LY of €135.661 (Table 24).

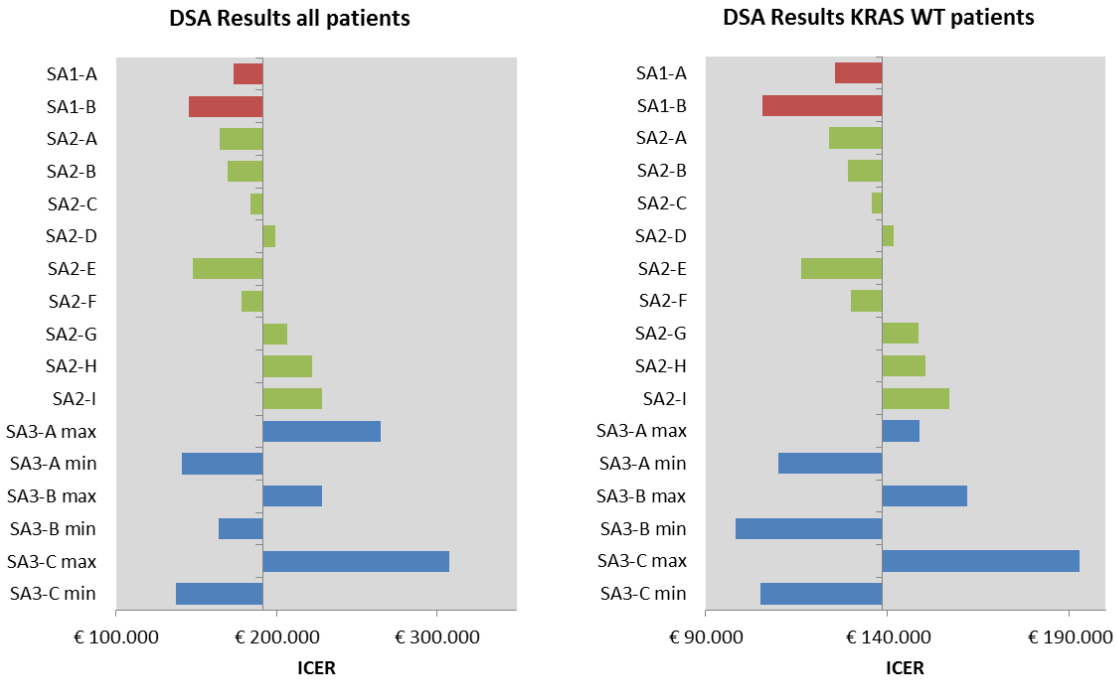
Table 24. Results costs, effects and cost-effectiveness

Full population				**KRAS WT population**			
	Costs	**QALY**	**LY**		**Costs**	**QALY**	**LY**
cetuximab + BSC	€ 17.117	0,45	0,61	cetuximab + BSC	€ 22.608	0,49	0,64
BSC	€ 601	0,36	0,51	BSC	€ 1.180	0,35	0,49
Increment	€ 16.516	0,09	0,10	Increment	€ 21.429	0,15	0,16
Incremental Costs / QALY	€ 191.417			Incremental Costs / QALY	€ 144.716		
Incremental Costs / LY	€ 161.975			Incremental Costs / LY	€ 135.661		

3.4.2 Deterministic Sensitivity Analyses

Figure **9** shows that results from the DSAs in tornado diagrams for all patients and KRAS WT patients. It shows that for all varied parameters there is a considerable change of the ICER. However varying the transition probabilities shows the biggest variation of the ICER indicating the model is most sensitive to changes in transition probabilities. The outcomes are shown in more detail in the sub-chapters below.

Figure 9. Results of the DSAs in tornado diagrams



DSA1 Drug costs of cetuximab

The price of the drug is shown to be a big driver of the outcome of the model. Lowering the price with 10% or 25% causes a 9% to 25% drop of the ICER (
Table 25).

Table 25. DSA1 in which a discount of cetuximab is analysed

Analysis	Cetuximab price	Full population Incr Cost/QALY	KRAS WT population Incr Cost/QALY
Original	100%	€ 191.417	€ 138.689
DSA1-A	90%	€ 172.997	€ 125.477
DSA1-B	75%	€ 145.366	€ 105.659

DSA2 Utilities

This DSA was included because the method of measuring utilities includes uncertainty. These results show that in this model a 7.5% error in the outcomes of utility measurement give a 10% variation of the ICER outcome (Table 26).

Table 26. DSA2 in which utility values are varied

Analysis	Utility adjusted	Full population Incr Cost/QALY	KRAS WT population Incr Cost/QALY
Original	Not applicable	€ 191.417	€ 138.689
DSA2-A	CTX + 7.5%	€ 164.545	€ 124.056
DSA2-B	BSC - 7.5%	€ 169.488	€ 129.216
DSA2-C	Prog + 7.5%	€ 183.865	€ 135.680
DSA2-D	Prog - 7.5%	€ 199.616	€ 141.834
DSA2-E	CTX + 7.5% / BSC - 7.5%	€ 148.076	€ 116.422
DSA2-F	All + 7.5%	€ 178.062	€ 130.003
DSA2-G	All - 7.5%	€ 206.937	€ 148.618
DSA2-H	Pre-progression utilities are like CTX	€ 222.064	€ 150.454
DSA2-I	Pre-progression utilities are like BSC	€ 228.229	€ 156.976

DSA3 Transition probabilities

These results show that the model is especially sensitive to mortality after progression. A 15%-20% variation is seen in DSA3-C and DSA3-F, whereas the spread around the base case ICER seen in the other categories is limited (Table 27).

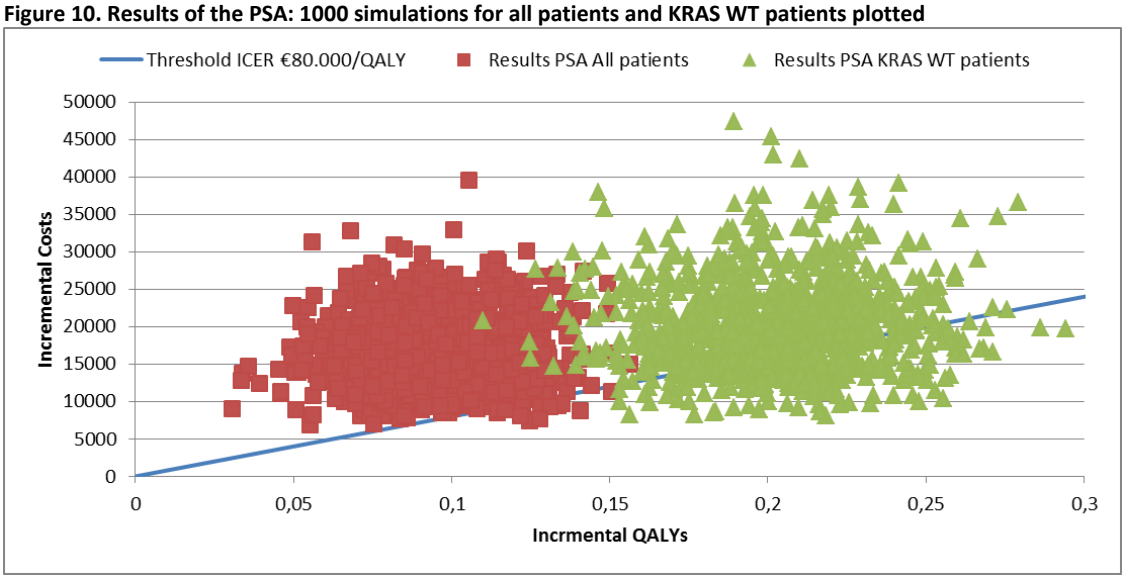
Table 27. DSA 3: transition probabilities are varied

Analysis	Transition probability range	Incr Cost/QALY Min	Max
Original Full population		€ 191.417	
DSA3-A	mCRC-> Death	€ 141.112	€ 265.350
DSA3-B	mCRC -> Progression	€ 163.806	€ 228.351
DSA3-C	Progression -> Death	€ 137.394	€ 307.895
Original KRAS WT population		€ 138.689	
DSA3-D	mCRC-> Death	€ 109.897	€ 148.878
DSA3-E	mCRC -> Progression	€ 98.338	€ 161.852
DSA3-F	Progression -> Death	€ 105.011	€ 192.757

3.4.3. Probabilistic Sensitivity Analysis

The results of 1000 simulations of the PSA are shown in Table 28Table 29, and Figure 10 and Figure 11 below. Figure 10 shows the individual simulations plotted on a CE plane. All simulations fall in the upper right quadrant (higher gains combined with higher costs). In the figure a threshold of €80.000/QALY is included to illustrate that most of the simulations lie above this threshold that is sometimes used in Dutch decision making. The clouds of both patients groups hardly overlap. The KRAS WT patients show larger effect with only slightly higher costs.

Figure 10. Results of the PSA: 1000 simulations for all patients and KRAS WT patients plotted



When analysing the PSA results in Table 28 it shows that the mean ICERs found (€180.243/QALY for the full population and €101.591/QALY for the KRAS WT population) are lower than the point estimates of the deterministic model. Because of the repetition of the simulation and inclusion of the probabilistic factor these results seem to be more reliable.

Table 28. Mean incremental costs, QALYs and ICERs after 1000 simulations of PSA

Population	Cost	QALYs	ICER
All patients	€ 16.594	0,10	€ 180.243
KRAS WT patients	€ 20.214	0,20	€ 101.591

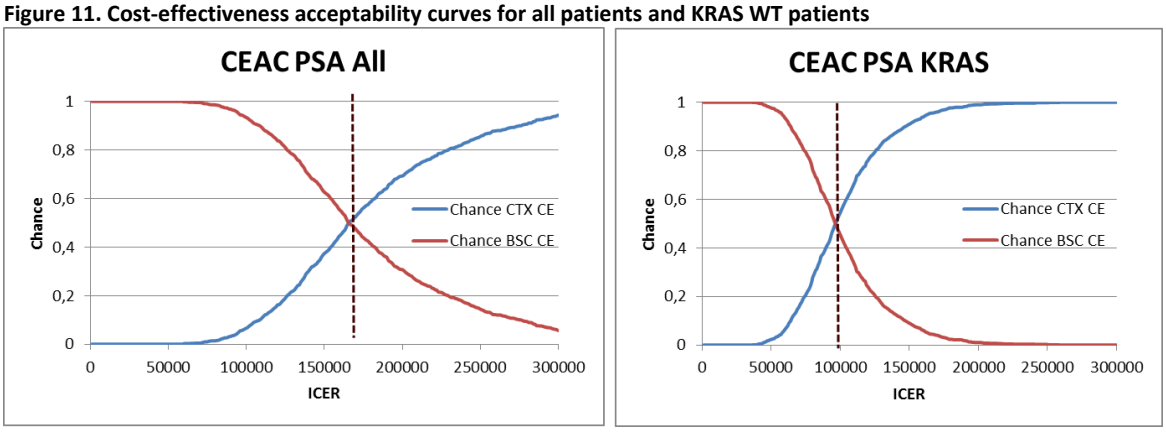
Table 29 summarizes the ICERs found with the PSA. It shows that the ICERs for both patient groups vary largely. The fact that the mean ICERs fall outside the 25th and 75th percentile of the other patient group shows that these populations are statistically different. Minimal ICERs of €59.609 (all patients) and €36.928 (KRAS WT patients) show that, although still high, it could be possible that outcomes sometimes reach more reasonable values.

Table 29. Summary of the ICERs of 1000 simulations of the PSA

ICER	All patients 1000 simulations	KRAS WT patients 1000 simulations
Mean	€ 180.243	€ 101.591
SD	€ 66.943	€ 33.113
Min	€ 59.609	€ 36.928
Max	€ 559.529	€ 258.434
25th percentile	€ 134.310	€ 78.688
75th percentile	€ 212.633	€ 118.825

The cost-effectiveness acceptability curves (CEACs) in Figure 11 show that BSC is the more cost-effective treatment option until very high ICER thresholds: >€150.000/QALY for all patients and around €100.000/QALY for KRAS WT patients. The chance that cetuximab treatment is cost-effective at a threshold of €80.000 (which is sometimes used in the Netherlands) is 0% for all patients and 28% for KRAS WT patients.

Figure 11. Cost-effectiveness acceptability curves for all patients and KRAS WT patients



4. Discussion and Conclusions

4.1. Policy Review

With the introduction of the policy expensive medicines in 2002 the Dutch government introduced a successful method to keep innovative but expensive inpatient medicines available for all patients. A negative consequence of the introduction of the policy was spending on expensive medicines exploded in the years following the introduction (Niezen et al. , 2006). Therefore in 2006 the policy was updated with a list of specific medicines for which hospitals had extra budget available. Coverage with evidence development, a for the Netherlands new policy instrument, was implemented for the medicines listed on the policy. The theory behind the policy maker's idea seems to be good: Give innovative but expensive medicines with limited amount of (real-life) data the benefit of the doubt and let them gather the missing information to show the real-life application and (cost-) effectiveness after four years. Also the assessment pathways, with the CFH assessing the quality of the delivered data and the ACP assessing the effect on society seem to be good (Figure 1). Stakeholders, including representatives of patients, manufacturers, health insurers, hospitals and physicians, are involved in the process and are able to give feedback at several points in time. The different stakeholders all have their own incentive to get new expensive medicines on the policy. Physicians want to be able to prescribe the best treatment for their patients. The hospitals want to get extra funding for the medicines that eat a lot of the hospital budget (Niezen et al. , 2006). Health insurers get the extra listing of expensive medicines, next to DBCs, that show prescribing habits of the physicians which can provide the opportunity to negotiate with hospitals about these prescribing habits. Manufacturers want to have their products on the list because this will make sure that physicians and hospitals will prescribe more and they have extra sales. Finally patients want to get the best treatment for their disease to be reimbursed by the basic benefit package.

A problem with a policy like this is that the different stakeholders have to put a lot of effort into the process. An important question, although hard to answer, is if the policy expensive medicines itself is actual cost-effective. Assuming the point of view of the decision maker the effectiveness of the policy, i.e. the benefit to the patients, should be weighed against the incurred costs, for example due to assessment, time spent by the different stakeholders, extra budget spent on the medicines. It would be interesting if the implementation of such a policy is worth the effort and the investment. An example of a study on the cost-effectiveness of drug policy has recently been performed on the periodic safety updates (PSUR) (Bouvy et al. , 2013). They found an ICER of full regulation (PSUR reporting) vs. limited regulation (no PSUR reporting) of €342.110 / QALY indicating that stringent regulation might not be worth the investment.

Bureaucracy seems to be another problem for the effectiveness of the policy. For example the reassessments by CVZ take a lot of time. The list of medicines added to the policy reveals that as of May 2013 21 medicines have passed T=4 and should have delivered the T=4 dossier. Only four reassessments have been finalized at the time meaning that there is quite a lag in the assessment of the dossier at T=4 at CVZ. The consequences are positive for the patients, hospitals and manufacturers since the medicines are still reimbursed while the reassessment is not final. For society however this could mean that a possible (cost-) ineffective treatment is being given for several years too long, with a possible budget impact of several millions Euros, that could have been spent on other treatments. Another problem that might involve bureaucracy involves the guidance

by CVZ. At the introduction of the mandatory outcomes research in 2006 there was some guidance, namely the policy itself from NZa and the procedural document from CVZ (Kuijpers and Toenders, 2006; NZa , 2006). However, the extensive guidance document was introduced only in 2008 (Delwel, 2008). This was two years after the mandatory outcomes research was introduced, which might have led to inappropriate setup of outcomes research in these first two years. Although this was not published anywhere it is not unthinkable that this could be a reason that T=0 applications were approved relatively easy.

It is of interest to see if the outcomes research provided important new information at T=4. Did the data gathered with outcomes research fill the data gaps at T=0? Franken et al. showed that it is possible to get the data that is needed from outcomes research. They concluded that for every individual case the feasibility is different and that it is more difficult to fill the gaps for CE than for effective application of the medicines (Franken et al. , 2013). When looking at the first four published reassessments this seems to be true. Where the effective application could be determined relatively well, major problems lie with the CE estimation. It should be mentioned that CE modelling in orphan indications might not be feasible at all. With a small patient population higher prices are often justified since manufacturers need to earn back there investment, which is in general not lower than for medicines for non-orphan diseases. High drug cost and no active treatment to which the drug is compared means that the ICER quickly rises (very) high, as was seen in the Pompe and Fabry's disease assessments.

Every case of outcomes research should be individually developed in close collaboration with the different stakeholders, including the government, physicians, patients, health (economic) scientists and manufacturers. The government made the WMG party responsible for the application of the dossiers and the setup of the outcomes research. It turns out that the requesting WMG parties were the Dutch Hospital Association (NVZ) for non-orphan medicines and the Dutch Academic Hospital Association (NFU) for orphan diseases. In theory this seems a good choice since they represent the hospitals prescribing the expensive medicines and have an incentive to have the medicines added to the policy and so receiving extra budget for the hospitals. However, in practice these parties employ only a limited amount of people (NVZ ~60 people; NFU ~10 people) who do not have the specialist knowledge needed for creating the dossiers and setting up the outcomes research. They could hire the extra people but that would mean that extra budget should be created. The question rises if project management of such big dossier and research is the task of the WMG party.

Although it might seem that from the governmental point of view risky to give a commercial party such a responsibility, it could be argued that the manufacturer is a better candidate to be the responsible party for the application. First of all practice showed that they are heavily involved in the process of dossier development and outcomes research (personal communication with CVZ personnel). This makes sense because manufacturers in general own most of the clinical data of their product. Furthermore they have the financial incentive to have their products added to the policy. They have invested already a lot of money for the development of the product (> $1 billon (Munos , 2009)) and there is a significant revenue at stake (these are expensive medicines with an expected revenue of at least €2.5 million in the Netherlands (Kuijpers and Toenders, 2006)). Addition to the policy would be essential and therefore it seems logical that an extra investment in project management, dossier creation and outcomes research is worth it. Also many companies,

especially the larger ones, have already departments in place that are specialized in for example dossier creation, modelling and clinical research. If the manufacturer is responsible the quality of the dossiers might also be improved since a negative assessment (and thus removal of the drug from the policy, and benefit package) because of the bad quality of the dossier is bad for the image of the company. Now, as the responsibility rests with the WMG party, this effect on the image might be less. A negative effect of the manufacturer being responsible might be that the results that are presented are biased in favour of the manufacturer's product. Therefore the assessment of the requests should be done thoroughly. To provide an efficient way of assessment submitted dossiers should be transparent, clear and to the point. Therefore good guidelines and templates should be provided. In case of a clear guidance to what information is needed and why it is needed the dossiers can be created with little bias and assessment can be done efficiently. However the fact remains that all the involved parties have their own incentives. To keep a good working relation between the different parties transparency is very important.

4.2. Cetuximab model

One of the medicines listed on the policy expensive medicines is cetuximab in third-line treatment of metastatic colorectal cancer. The approval was based on an added therapeutic value compared to best supportive care (BSC) and an expected budget impact larger than €2.5 million. The CFH concluded that the framework for outcomes research was too simple. Especially the estimation of the cost-effectiveness was badly done, with only a simple incorrect model lacking the correct data. Also no estimate of the ICER was given. In this paper a Markov model was created to investigate the cost-effectiveness of cetuximab in third-line treatment of metastatic colorectal cancer compared to BSC following Dutch guidelines for health economic research as good as possible. The goal was to investigate if it was possible to create a good model to estimate the cost-effectiveness of cetuximab in this indication at T=0 using only data available in the public domain.

For models in general, and thus also for the cetuximab model, several assumptions were made that make the outcomes uncertain. First of all the disease, mCRC, was simplified into three disease states that patients could be in. This might be an oversimplification. Patients within a disease state were assumed to have similar characteristics, so that costs, LY and utilities could be assigned to the disease state. However in real life a great deal of heterogeneity can be expected between patients which gives uncertainty with respect to the outcomes.

Furthermore, input data for the model were derived from a limited amount of studies and analyses. The question rises if the results from those studies are generalizable to the Dutch situation. For example the transition probabilities were calculated with data from the CO17 study. To be able to generalise the results it was assumed that this patient population is similar to the Dutch population of mCRC patients. Other assumptions made for the calculation of transition probabilities include that the KRAS status does not influence mortality, and that patients who died without signs of progression died within 8 months. The uncertainty of the studied patient population could be investigated when patient level data is available. Then the variation in patient characteristics could be included in the PSA and individual patients with random characteristics could be modelled. However, a more complex model structure than a straightforward Markov model should be applied.

The uncertainties in the model are tested by doing sensitivity analyses (SAs). In the SAs the assumptions made for the transition probabilities, utilities and costs were analysed. Univariate SAs revealed that the model is most sensitive for adjusting the transition probabilities. Adjusting utility values only showed a relatively mild effect on the ICERs when comparing this to the effect of adjusting transition probabilities. However, the uncertainty of the utilities used for the model is high, since they were taken from a NICE report which did not include a clear description of the methods of how the utilities were derived.

How can the data collection with the planned outcomes research could improve the model at T=4? First of all generalizability of the model could be increased by including Dutch real-life data. Also resource use and utilities are model inputs that are expected to vary between regions so focus on these areas would be recommended. Transition probabilities are calculated from randomized data on survival and progression free survival. It is not to be expected that outcomes research, which in general are observational studies without randomization, will be able to improve the uncertainty considering the transition probabilities. In general most reliable clinical (survival) data to include in Markov models is derived from RCTs. Data on resource use in the model was based on the Canadian data from the CO17 trial. Dutch real-life data on resource use by mCRC patients would improve the cost assumptions in the model. However, the major cost was the drug cost.

Based on the results of this study, the easiest way of improving cost-effectiveness would be lowering the price of cetuximab. A 25% price decrease resulted in a 25% lower ICER. However, this ICER was for both populations (all patients and KRAS WT patients) still above the €100.000/QALY. This brings up the question what amount of money we as a society are willing to pay for a QALY gained. In the Netherlands no official thresholds are defined for what ICER is or isn't cost-effective. The Health Care Council (RVZ: In Dutch Raad voor Volksgezondheid & Zorg) has suggested in 2006 to use a maximum threshold of €80.000/QALY for diseases with a high burden (RVZ, 2006). The choice for the €80.000/QALY threshold, which is higher than for example the £20.000/QALY threshold in the UK, was amongst others based on an advice of the WHO in 2002 to put a maximum ICER of three times the GDP, models investigating NICE data, and studies on the value of a human life. However, an official threshold has not been identified by Dutch politics.

For the assessment of applications for the policy expensive medicines the CFH did not give an opinion on the value of the ICER, but only on the quality of the CE research, and how reliable the results were. As explained earlier in case of doubt an appraisal committee (the ACP) reviews the application separately and weighs it from a societal point of view. The ACP should also comment on the value of the ICER. The lack of an official threshold makes this decision very hard and there is a danger of arbitrariness in the decisions of the ACP. Interestingly the ACP decided not to reject the medicines for Pompe and Fabry's disease that showed ICERs up to several millions €/QALY. The fact that there is no other treatment is available for these patients played a big role in this decision. This seems to be a valid argument to approve applications with higher ICERs. The question is however if cost-effectiveness should play a role in reimbursement decisions of orphan diseases. A small amount of patients will in most cases result in limited quantity (and quality) of data. As explained earlier, due to high development cost and the relatively small patient group, it is accepted that the price of orphan medicines is high. Compared to doing nothing, by definition for orphan diseases comparative treatment is lacking or very limited, the incremental costs will most of the time be high. Therefore,

for most orphan medicines to achieve reasonable ICERs the clinical effect should be very big. To reduce the spending on orphan medicines it might be better to only give the medicines to patients for which it works. Risk sharing agreements like pay-for-performance agreements, as has been achieved with omalizumab, could be a solution in this case. A risk sharing agreement would be from the point of view of the government (and payer) a good option a T=0. However, at that time the manufacturer has not yet had a return of investment so there is less space for negotiation. The fact that Dutch government gave four years of reimbursement or extra budget for the drug, there might be a higher chance for successful negotiation of lower price at that time in case the cost-effectiveness is still unacceptable at T=4.

Can something be said about the cost-effectiveness of cetuximab based on the model in this paper? In 2009 the CFH passed the application of cetuximab in third line treatment of mCRC despite the fact that there was no valid estimation of the cost-effectiveness at the time. The model presented in this paper shows that with the data available at the time it was possible to provide a robust estimation of the cost-effectiveness of cetuximab compared to BSC. When using the unofficial threshold of €80.000/QALY, cetuximab in this indication compared to BSC seems to be not cost-effective. From the PSA it can be concluded that the chance that the ICER is below this threshold is almost 0% for the full population and only 28% for the KRAS WT population (Figure 11). It does not seem very likely that the chance that the ICER is significantly lower at T=4. It was shown in the sensitivity analyses that the ICER is especially sensitive to good (overall and progression free) survival data which is not expected to be collected with the outcomes research. Also it is not likely that (big) RCTs are performed in relative small patient populations after a drugs' approval, since RCTs cost a lot of effort and money which is usually paid by the manufacturer. The manufacturer has no incentive to invest in studies that possibly show that their product is not cost-effective. A solution for this issue would be that such studies are financed by public funds, although this seems to be not feasible in the short-term for RCTs. A more feasible option might be to continue centrally organised disease registries, for diseases where, via for example value of information analyses, showed that data collection via registries could deliver useful efficacy data. Also different types of analysis of registry data could be considered. For example matching of patients from observational studies using propensity scoring has shown to give comparable results as RCTs (Kuss, Legler, and Borgermann , 2011).

The CFH has asked at T=0 to include the other EGFR inhibitor, panitumumab, as comparison in the model. Although not included in the model presented here data on panitumumab could have been included in a similar way as presented here, since similar studies has been done and published with panitumumab in mCRC (Van Cutsem et al. , 2007). The NICE assessment of the cost-effectiveness of cetuximab and panitumumab compared to BSC showed high ICERs (>€100.000/QALY) for both medicines compared to BSC (in the KRAS WT population), but the ICER of panitumumab was around €70.000/QALY higher than that of cetuximab (Table 4) (Hoyle et al. , 2013b). The NICE did not present cost-effectiveness estimates comparing cetuximab with panitumumab. In the Dutch situation this seems to be the correct way to present results as the new treatments (here cetuximab and panitumumab) should be compared to the standard treatment (here BSC). However, the CFH asking from the requesting party to include data from competing medicines might not give the most objective results. As mentioned earlier the manufacturers have are significantly involved in the creation of the reimbursement dossiers. Since there is a lot of room for including bias in health

economic models the incentive for the manufacturer is towards a bias to better results for their product.

When looking at the case of cetuximab compared to BSC in mCRC patients that have failed chemotherapy (CT) and basically are dying it seems to be very difficult for an expensive drug like cetuximab to come out cost-effective. As is the case with the orphan medicines the comparator is BSC. As explained earlier an intervention needs to have very good effectiveness to come out cost-effective compared to BSC. A difference with orphan diseases is that the mCRC patients have had several treatments and failed them all. Therefore it would be fairer to include assessment of cost-effectiveness of these 'end-of-life' treatments than of orphan medicines. Whereas patients with an orphan disease have very little options, the mCRC patients have had several options. Giving cetuximab might give a few extra months to live including some increase in QoL. This can be very significant for the individual patient. From a societal point of view however, the question is very relevant if these mCRC patients should receive another treatment of which it is not clear how cost-effective it is. Health economic theory says that there are other treatments for other patients that probably deserve the available health care budget more. Another question is if the government should be deciding via reimbursement decisions if patients get the choice for those extra months or not. It actually might be the best way to make sure the available budget is spent on patients that benefit the most from it. If the government makes the tough decision it might releases pressure from the treating physician, that has a personal relationship with the patient, by not having to make the choice.

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