Cost and Outcome Assessment of a Pharmaceutical Care Service for Cancer Patients treated with Capecitabine

Dissertation

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Meiner Familie

Das Lied von der Wirklichkeit

In der Wirklichkeit gibt es Träume.
In der Wirklichkeit sind sie echt.
Wenn ich Träume hie und da versäume,
ist es nur, weil ich auch schlafen möcht.

Doch die Wirklichkeit ist ein Märchen,
das die Wissenschaft nicht kapiert.
Denn der Wissenschaftler spaltet Härchen,
und der Träumer ist bereits frisiert.

Phantasie ist nichts für die Experten,
die das Leben fürchten und den Tod.
Psychopathen kann man nicht verwerten.
In der Schule gibt´s ein Lexikon:
Was geschrieben ist, gilt als bewiesen.
Wenn´s im Lauf der Zeit, sich als falsch erweist,
schreibt der Professor halt ein neues Buch.
Denn der Mensch will immer was beweisen,
im Gegensatz zur Gans.
Doch er kann´s nicht, und er wird entgleisen,
Solang er glaubt, er kann´s.

In der Wirklichkeit gibt´s nie Beweise,
denn die Wirklichkeit, die ist wahr.
Komm mit mir auf eine wahre Reise
voller Traum und ohne Kommentar!

In der Wirklichkeit sind die Träume,
die kein Physiker je beschreibt.
Komm mit mir in meine Zwischenräume,
wo kein Mensch die Wahrheit übertreibt.
Komm mit mir auf meine Purzelbäume,
wo von Wissenschaft nichts übrig bleibt.

Georg Kreisler

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Content

Abbreviations

AMG	German drug law (Arzneimittelgesetz)
ApBetrO	German pharmacy law (Apothekenbetriebsordnung)
AUC	Area under the curve
AWMF	Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.)
BID	Twice a day (latin: bis in die)
BfArM	Federal Institute of Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte)
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CG	Control group
CL_{CR}	Creatinin clearance
CMA	Cost-minimization analysis
C_{max}	Maximum plasma concentration
CMR	Cancerogen, mutagen, reproduction toxicity
COX	Cyclooxygenase
CT	Computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
CUA	Cost-utility analysis
DMP	Disease management program
DPD	Dihydropyrimidine dehydrogenase
DRG	Diagnosis-related group
DRP	Drug-related problems
EBM (1)	Einheitlicher Bewertungsmaßstab
EBM (2)	Evidence-based medicine

e.g.	For example (latin “exempli gratia”)
Eq.	Equation
FIP	Fédération Internationale Pharmaceutique
FOLFOX	Combination chemotherapy of fluorouracil and oxaliplatin
5-FU / LV	Fluorouracil in combination with folinic acid (leucovorin)
G-BA	Federal joint committee (Gemeinsamer Bundesausschuss)
GKV	Statutory health insurance (Gesetzliche Krankenversicherung)
GKV-WSG	Statutory health insurance - act to promote competition (GKV-Wirtschaftlichkeitsstärkungsgesetz)
GOÄ	Gebührenordnung für Ärzte
GP	General practitioner
HFS	Hand-foot syndrome
HUI	Health utility index
ICUR	Incremental cost-utility ratio
IG	Intervention group
INR	International normalized ratio
IQR	Interquartile range
IQWiG	Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)
ITT	Intention-to-treat
i.v.	Intravenous
KBV	National Association of Statutory Health Insurance Physicians (NASHIP) (Kassenärztliche Bundesvereinigung)
LOCF	Last observation carried forward
MASCC	Multinational Association of Supportive Care in Cancer
MRT	Magnetic resonance tomography
n	Number of patients

NCCN	National Comprehensive Cancer Network
NCCHTA	National Coordinating Centre for Health Technology Assessment (UK)
NICE	National Institute for Health and Clinical Excellence (UK)
No.	Number
OTC	Over-the-counter
PBS	Pharmaceutical benefits schedule (Australia)
PET	Positron emission tomography
PP	Per protocol
PT	Pro-thrombin time
QALD	Quality-adjusted life day
QALY	Quality-adjusted life year
QAPFSD	Quality-adjusted progression-free survival days
RCT	Randomized controlled trial
SD	Standard deviation
SF-6D	Short Form 6D
SOAP	Subjective problems, objective problems, analysis, plan
TK	German statutory health insurance (Techniker Krankenkasse)
TTO	Time-trade-off
ULN	Upper limit of normal
WTP	Willingness-to-pay
X-ACT	Xeloda® Adjuvant Chemotherapy Trial
XELOX	Combination chemotherapy of Xeloda® and oxaliplatin

Preliminary note

For the sake of clarity and to improve readability the use of the female form was largely forgone in the present study (e.g. the patient is mostly referred to as “he”). Generally the respective wording also contains the female form. Furthermore, the author of this work was anxious to consider the copyright of all used texts, figures and data.

1 Introduction

1.1 Pharmacoeconomics

1.1.1 Definition

Pharmacoeconomics is a scientific discipline which evaluates health technologies in terms of costs and outcomes. Health technologies encompass e.g. pharmaceutical products, health services or programmes [1]. As healthcare resources are limited, there is an increased interest in assessing and comparing the values-for-money of alternative treatment strategies [2]. For a meaningful comparison, it is necessary to examine additional costs and effects that one intervention imposes on another. Figure 1-1 illustrates this incremental approach on a four quadrant diagram known as the cost-effectiveness-plane.

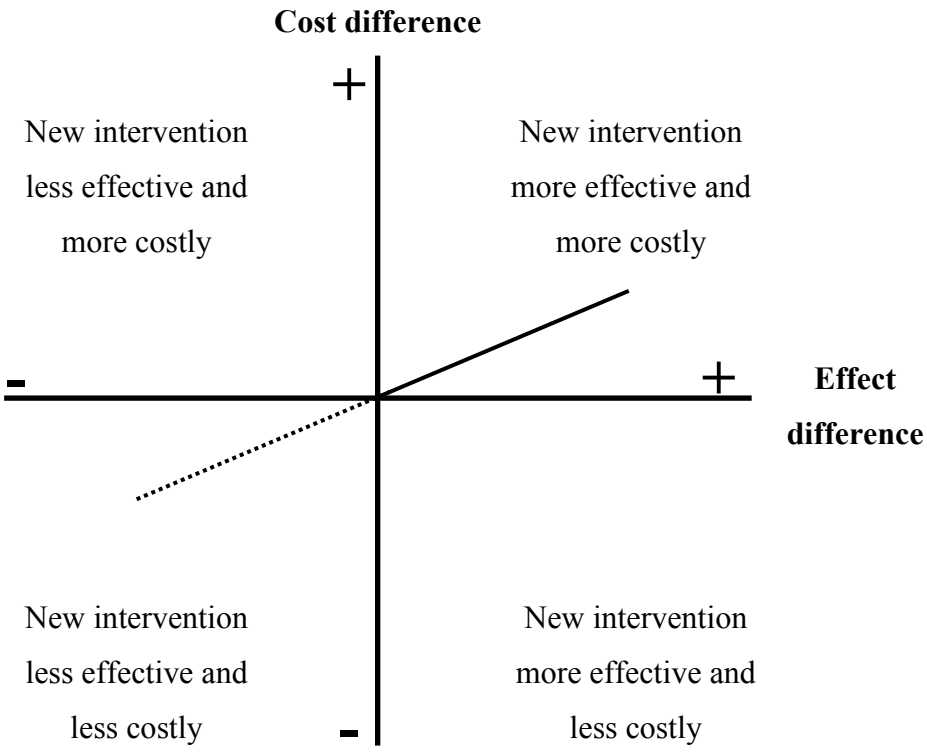


Figure 1-1: Cost-effectiveness-plane [3]

The x-axis represents the difference in effect between the intervention of interest, e.g. a new drug, and the relevant alternative, e.g. the standard medication. The y-axis represents the difference in costs. If the result is in the south-east or in the north-west quadrant the choice between the drugs is clear. In the former case the new intervention is both more effective and less costly than the alternative. This means, it dominates the alternative. In the latter case the opposite is true. In the other two quadrants the choice depends on the maximum cost-

effectiveness ratio one is willing to accept. The slope of the line yields the cost-effectiveness ratio.

1.1.2 Pharmacoeconomics in Germany and other countries

In the light of scarce financial resources several countries implemented different cost containment strategies. Pharmacoeconomic evaluations of health care interventions present one decision-supporting approach for a rational resource allocation in health care. Important motives for performing pharmacoeconomic evaluations appear to be establishing value-for-money of new drugs, to inform decisions on reimbursement and/or pricing. Pharmacoeconomic evaluation is sometimes referred to as "the fourth hurdle", which suggests that the drug company has an additional obstacle to overcome beside the normal marketing authorisation requirements. Australia was the first country in 1993 that required evidence of cost-effectiveness on the basis of pharmacoeconomic studies from pharmaceutical companies beside evidence on safety, efficacy and quality of drugs. In Australia cost-effectiveness of an approved pharmaceutical product is a prerequisite for its listing on the pharmaceutical benefits schedule (PBS; positive list of pharmaceutical products). In the meantime, similar regulations are in force e.g. in Belgium, Austria, Norway and the Netherlands. In France, Switzerland and Finland the submission of clinical studies is sufficient for reimbursement decisions, but the results of pharmacoeconomic evaluations form the basis for price negotiations with pharmaceutical companies in France. In New Zealand, England/Wales and Sweden institutions were established which conduct their own health technology assessments of health care interventions [4–6]. In Germany an independent institution, the Institute for Quality and Efficiency in Health Care (IQWiG), was established in 2004. The legislation contained in the Health Care Reform GKV-WSG (statutory health insurance - act to promote competition) of April 2007 has extended IQWiG's responsibilities. Prior to that, the assessment of drugs was restricted to medical outcome. Now it could also be commissioned to conduct pharmacoeconomic assessments. In October 2009 the final paper on IQWiG`s scientific methods for evaluating costs and outcomes was published and in the meantime the first commissions on pharmacoeconomic evaluations have been submitted by the federal joint committee (G-BA) [7].

1.1.3 Pharmacoeconomic evaluations

There are four main forms of pharmacoeconomic evaluations.

In a *cost-effectiveness analysis* (CEA) the outcomes of health care interventions are measured in the most appropriate natural effects, such as "life year gained" or "symptom free days". The results are expressed in cost-effectiveness ratios, e.g. € 5000 per life year gained. In the rare situations in which the relevant treatment options are identical or very similar in terms of health benefits and risks the evaluation is reduced to a comparison of costs only. The latter evaluation is known as *cost-minimization analysis* (CMA). In a *cost-utility analysis* (CUA), health states are valued in relation to one another through the use of health utility scores. This means that the quality of e.g. life years gained can be quantified, not just the number of years. The common measure in CUAs is the quality-adjusted life year (QALY) which enables the comparison of value-for-money of interventions of different fields of health care. The fourth evaluation is known as *cost-benefit analysis* (CBA). In a CBA attempts are made to value the outcomes of health interventions in monetary terms (e.g. willingness-to-pay approach). Thus, in theory, it represents the broadest form of analysis. However, assessment problems often limit the range of outcomes valued in monetary terms [3, 2].

In the present study a *cost-utility analysis* was chosen to evaluate the impact of pharmaceutical care compared to standard care on costs and outcomes of oncology patients. The combination of quality and quantity of life in the QALY measure is particularly useful in this patient group. Especially in palliative cancer patients the remaining life time should be accompanied with a minimum of treatment side-effects and a high quality of life.

1.1.3.1 Study perspective

Different study perspectives for the evaluation of costs and outcomes may be adopted in a pharmacoeconomic evaluation. The *societal perspective* is preferred by many health economic guidelines, but is rarely applied in practice. This perspective does not only focus on costs in the health care sector but also accounts for the economic consequences of e.g. lost productivity as a result of diseases. A *health care perspective* is concerned with direct medical costs only (see 1.1.3.2 "Costs"), as this is what the health care budget relates to. In case of a *hospital perspective*, only costs and savings that are important for the hospital are taken into account (e.g. less nursing time, less material). From a *patient's perspective* e.g. out-of-pocket payments or a reduced salary due to a disease are important [8].

1.1.3.2 Costs

Costs can be divided into two major categories: direct and indirect costs.

Direct medical costs arise immediately through the treatment of a disease within the health care sector, e.g. costs for drugs, diagnostics, inpatient stays and physician fees. *Direct non-medical costs* accrue due to the disease but beyond the treatment such as travel costs, costs for home help or time spent by family members providing care. The *indirect non-medical costs* result from periods of sick leave and therefore lost productivity. *Indirect medical costs* are related to health care costs which can arise in the future. For example, if a patient lives longer because of an intervention to prevent stroke, the future costs linked to his longer life during which he might develop Alzheimer can also be considered [3, 6].

1.1.4 Pharmacoeconomics in oncology

Understandings of cancer biology and advances in technology have led to the development of a variety of new anti-cancer treatments and diagnostics. Many of these interventions are costly and at the same time only marginally effective [9]. In Germany a debate is going on to which extent pharmacoeconomic evaluations in the field of cancer should form the basis for resource allocation decisions. Ethical concerns are understandable given the potentially life-threatening condition of cancer patients. Aidelsburger et al. published a review on behalf of the German Cancer Society (Deutsche Krebsgesellschaft) on peculiarities associated with the cancer disease that should be considered in pharmacoeconomic analyses in oncology [10]. In clinical studies new anti-cancer drugs are often tested as second- or third-line therapy in cancer patients. In these patients the incremental benefit can only be marginal especially when gained lifetime is considered as an outcome. Add-on therapies or sequential therapy regimens are also common for new anti-cancer therapies. Thus, it is hard to detect their individual additional benefit. In case of advantages for the medication being studied, control patients also have the possibility to switch to the intervention arm. This leads to biased results at the expense of the studied drug. Pharmacoeconomic evaluations mostly require a comparison with standard therapies. In case of last-line therapies this is difficult as generally no definite approved standards exist. In many cases standard therapy means providing best supportive care. The factors mentioned might have consequences regarding the cost-effectiveness of new anti-cancer interventions [10]. Furthermore, certain oncology drugs are orphan drugs. Economic evaluation of orphan drugs is a domain in itself with specific characteristics and limitations[11]. Uyl-de Groot et al. suggest a higher cost-effectiveness threshold for cancer interventions in the field of gastrointestinal cancer and a more prudent price setting by

pharmaceutical companies [12]. An examination of NICE´s decisions based on pharmacoeconomic evaluations of cancer therapies by Drummond and Mason suggested that cancer drugs have faired quite well despite their high costs. Drummond et al. supposed that the seriousness of the health condition and the lack of alternative therapies in some cases led to mainly positive recommendations [13]. In 2008 NICE outlined a new approach for end-of-life drugs appreciating their special role in health care. But it is problematic to set the cost-effectiveness threshold higher for some groups of patients within a fixed budget as it results in other groups being denied treatment [14]. On the whole, it is important to find a balance between the need to promote incentives for innovation of new cancer interventions and potentially competing societal responsibilities [9]. Pharmacoeconomic evaluations may support this balancing act.

For economic evaluations of pharmaceutical care see chapter 1.2.3 “Pharmacoeconomics in pharmaceutical care” and of capecitabine see chapter 1.3.4 “Pharmacoeconomics of capecitabine”.

1.2 Pharmaceutical care

1.2.1 Concept and development

In 1990, Hepler and Strand proposed that pharmacists should deliver “pharmaceutical care”, just as nurses provide “nursing care” and physicians provide “medical care” [15]. They defined pharmaceutical care as *“the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient’s quality of life”*. Some years later the Féderation Internationale Pharmaceutique (FIP) extended the definition emphasising the collaborative approach and the continuous nature of the pharmaceutical care service: *“Pharmaceutical care is the responsible provision of pharmacotherapy for the purpose of achieving definite outcomes that improve or maintain patients´ quality of life. It is a collaborative process that aims to prevent or identify and solve medicinal product and health-related problems. This is a continuous quality improvement process for the use of medicinal products”* [16]. In both definitions the pharmacist is not explicitly named. This indicates that all patient care providers including physicians and nurses can possibly deliver pharmaceutical care. Nevertheless, it is expected that the practitioner who will provide pharmaceutical care as a primary role is the pharmacist [17]. According to the FIP patient counselling and information becomes pharmaceutical care if the following requirements are met: systematic approach, setting a goal, patient-related documentation, and monitoring [16]. The SOAP-method can be a supporting tool to meet these requirements. **S**ubjective patient information

(e.g. headache) and **o**bjective parameters (e.g. high blood pressure) which characterise the patient are **a**nalysed / **a**ssessed (e.g. stage 1 hypertension). On the basis of this analysis therapeutic goals (e.g. blood pressure of 120/80 mmHg) and monitoring parameters (e.g. blood pressure, compliance) are defined in collaboration with the prescribing physician and integrated in a therapeutic **p**lan (e.g. recommendation of antihypertensive medication and monitoring) [18]. In the following, recommendations are implemented and monitoring parameters are evaluated. In certain intervals the plan is re-assessed and adapted if necessary.

1.2.2 Pharmaceutical care for cancer patients

Cancer patients undergoing systemic cancer therapy are at risk of multiple drug-related problems (DRP) as the therapy is highly toxic and particularly complex. Adverse effects, medication errors, drug-drug interactions and non-adherence are the most frequently reported DRP [19]. With his central role as being the only health care provider who may have an overview of all drugs prescribed and self-purchased, the pharmacist can contribute substantially to risk minimisation. Pharmacists have a specific drug-related knowledge which they can add to the clinical team [19]. In addition they can offer patient-oriented activities such as compounding of cytotoxic drugs considering individual patient parameters and therapeutic drug monitoring of critical substances [20]. The concept of pharmaceutical care for cancer patients offers a comprehensive approach to optimize individual drug therapy and solve DRP. Many studies have been conducted which show that pharmaceutical care services have their value in common diseases such as diabetes, hypertension, asthma, chronic pain and psychiatric disorders [21]. Only a few studies are published on pharmaceutical care provided to cancer patients [22, 23]. At the University of Bonn, department of clinical pharmacy the focus is on pharmaceutical care delivery to patients with breast and colorectal cancer. Completed projects could show significant positive impacts of pharmaceutical care on the adverse drug reactions nausea and emesis and on the daily compliance of patients treated with the oral chemotherapeutic agent capecitabine [24–27]. The present study is the first to investigate the cost-effectiveness of pharmaceutical care for cancer patients.

1.2.3 Pharmacoeconomics in pharmaceutical care

In 1998, Plumridge et al. published a review on pharmacoeconomics of pharmaceutical care. They only found a few articles and concluded that *"there is little published research to date that demonstrates the pharmacoeconomic benefit of pharmaceutical care"* [28]. The American College of Clinical Pharmacy has published summaries of the economic literature on pharmacy services before 1988, from 1988 through 1995, from 1996 through 2000 and the

latest from 2001 through 2005 [29–32]. In general they found continued evidence of the economic benefit of clinical pharmacy interventions. At the end of each review they concluded that improvements are needed in the methods used to evaluate pharmaceutical care services. A review by Rijdt et al. focused on pharmacoeconomic analysis of clinical pharmacy interventions in the hospital setting. They found pharmacoeconomic analyses of pharmacy practice in intensive care units, coronary care units, internal medicine wards, general medicine wards and emergency departments. No economic evaluation of pharmaceutical care in oncology could be identified. In addition, they equally concluded that most pharmacoeconomic evaluations of clinical pharmacy interventions exhibited limitations in their methodological quality and applicability to current practice [33].

In the context of pharmacoeconomics of pharmaceutical care the question of reimbursement of these services arises. In Germany a first nationwide pharmaceutical care model known as the family pharmacy program was implemented in 2003. One year later a trilateral integrated care contract was signed that also included general practitioners (GP), combining the family physician with the family pharmacy. In this concept pharmacists are reimbursed for direct communication between the community pharmacist and the GP by the statutory health insurance company 'BARMER Ersatzkasse' [34]. A new reimbursed pharmaceutical service aims at improving the self-monitoring of blood-glucose levels in type 2 diabetes patients. The cognitive service can be charged twice in twelve months and is reimbursed with € 22 per patient by the 'BARMER Ersatzkasse' [35].

Current publications indicate that evidence of the cost-effectiveness of pharmaceutical care services is needed. Reliable study results will probably strengthen the position of pharmacists in oncology treatment teams. Furthermore, evidence on cost-effectiveness may further legitimate and enhance the reimbursement of pharmaceutical care services provided by community pharmacies. The present study tried to contribute a methodologically sound assessment of pharmaceutical care in the field of oncology to the available economic evaluations of pharmacy practice.

1.3 Capecitabine

All patients in the present study were treated with the chemotherapeutic agent capecitabine which is an orally administered prodrug of fluorouracil. There are many advantages of oral treatment compared to intravenous infusions as e.g. higher convenience for patients, avoidance of venepuncture and paravasates, and greater autonomy for the patients. Despite the advantages oral agents are also accompanied by many challenges. The potential toxicity of

anti-cancer agents, the recognition of adverse effects by the patient, the less intense contact between the patient and the physician as well as the importance of patients´ adherence for treatment success are important issues that have to be addressed. Multidisciplinary patient care as e.g. pharmaceutical care services and a good patient education plays a key role in a successful oral anti-cancer treatment [36–39].

1.3.1 Clinical application and drug dosing

Capecitabine is available on the German medical market as tablets with 150 mg or 500 mg under the brandname Xeloda®. It is indicated for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer and for the treatment of metastatic colorectal cancer. Furthermore, it is indicated for first-line treatment of advanced gastric cancer in combination with a platinum-based regimen. Xeloda® in combination with docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. Xeloda® is also indicated as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated. [40].

In the present study capecitabine was also combined with other agents e.g. with paclitaxel and lapatinib in breast cancer patients, in combination with oxaliplatin, irinotecan, bevacizumab and cetuximab in colorectal cancer patients.

Capecitabine tablets should be swallowed with water within 30 minutes after a meal in the morning and in the evening. One capecitabine chemotherapy cycle consists of two weeks of twice daily drug intake followed by seven days of break. Treatment should be discontinued if progressive disease or intolerable toxicity is observed. Standard and reduced dosing according to body surface area for a starting dose of 1250 mg/m^2 twice daily are provided in table 1-1. In case of occurring toxicity the dose should be reduced by 25 and 50 % respectively depending on the severity grade (see 1.3.3 “Adverse effects”).

Table 1-1: Standard and reduced dosing of capecitabine according to body surface area for a starting dose of 1250 mg/m^2 twice daily [40]

Body surface area [m^2]	Standard dose (100%) 1250 mg/m^2 [mg]	Number of 150 mg tablets	Number of 500 mg tablets	Reduced dose (75%) 950 mg/m^2 [mg]	Reduced dose (50%) 625 mg/m^2 [mg]
≤ 1.26	1500	-	3	1150	800
1.27 – 1.38	1650	1	3	1300	800
1.39 – 1.52	1800	2	3	1450	950
1.53 – 1.66	2000	-	4	1500	1000
1.67 – 1.78	2150	1	4	1650	1000
1.79 – 1.92	2300	2	4	1800	1150
1.93 - 2.06	2500	-	5	1950	1300
2.07 – 2.18	2650	1	5	2000	1300
≥ 2.19	2800	2	5	2150	1450

Capecitabine use should be carefully monitored in patients with mild to moderate liver dysfunction. Administration should be interrupted if treatment-related elevations in bilirubin of >3.0 x ULN or treatment-related elevations in aminotransferases (ALT, AST) of >2.5 x ULN occur. Treatment may be resumed when bilirubin decreases to ≤ 3.0 x ULN or aminotransferases decrease to ≤ 2.5 x ULN. In patients with mild renal impairment (CL_{CR} = 51-80 ml/min) no dose reduction is required, in patients with moderate renal impairment (CL_{CR} = 30-50 ml/min) a dose reduction by 25 % is recommended. In case of severe hepatic or renal impairment (CL_{CR} < 30 ml/min) capecitabine is contraindicated [41, 40].

1.3.2 Interaction with other medicinal products and food

The following interactions of capecitabine have been described [41]:

Coumarin-derivative anticoagulants: Altered coagulation parameters and/or bleeding were reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. Patients should be monitored regularly for alterations in their coagulation parameters (PT or INR) and the anticoagulant dose should be adjusted accordingly.

Phenytoin: Increased phenytoin plasma concentrations resulting in symptoms of phenytoin intoxication in single cases were reported during concomitant use of capecitabine with

phenytoin. Patients should be regularly monitored for increased phenytoin plasma concentrations.

Folinic acid: Folinic acid enhances the toxicity of capecitabine.

Sorivudine and analogues: A clinically significant drug-drug interaction between sorivudine and 5-FU, resulting from the inhibition of dihydropyrimidine dehydrogenase (DPD) by sorivudine, was reported. As the DPD catabolizes 5-FU its inhibition is potentially fatal. Therefore, capecitabine must not be administered concomitantly with sorivudine or its chemically related analogues, such as brivudine. There must be at least a four-week intermission between the end of the treatment with sorivudine or its analogues and the start of the capecitabine therapy.

Food interaction: In all clinical trials, patients were instructed to administer capecitabine within 30 minutes after a meal. Since current safety and efficacy data are based upon administration with food, it is recommended that capecitabine is administered with food. The influence of food on the pharmacokinetics of capecitabine was evaluated by Reigner and co-workers. C_{max} as well as the AUC of capecitabine and its metabolites were reduced when the drug was taken within 30 minutes after consumption of a standard breakfast in comparison to a drug intake after an overnight fast. Thus administration with food decreases the extent of capecitabine absorption. The clinical significance of these findings has yet to be investigated [42].

1.3.3 Adverse effects

Many studies show an improved safety profile of capecitabine in comparison to the intravenously administered 5-FU. The most frequently occurring adverse drug reactions are the hand-foot syndrome in 54 % of patients, followed by diarrhoea (48 %), nausea (23 %) and vomiting (23 %). The hand-foot syndrome and diarrhoea are the most frequent therapy limiting toxicities in patients treated with capecitabine. In comparison to 5-FU only the hand-foot syndrome occurs significantly more often under therapy with capecitabine. The adverse effects stomatitis, diarrhoea, nausea, alopecia and neutropenia are less frequent in comparison to 5-FU treatment [43–45]. Concerning the immediate management of adverse effects, a dose reduction or therapy interruption depending on the severity grade is recommended. According to Cassidy et al. a dose reduction of capecitabine as a consequence of occurring toxicity does not lead to a reduced effectiveness of the anti-cancer treatment. No influence on the risk of disease progression or mortality could be observed [45].

The hand-foot syndrome

The hand-foot syndrome (HFS), also known as palmar-plantar-erythrodysesthesia (PPE), is the most frequent and at the same time a dose- and therapy-limiting toxicity in patients under treatment with capecitabine. HFS is also described under treatment with other anti-cancer agents like docetaxel, doxorubicin or the tyrosine kinase inhibitors sorafenib and sunitinib. Zuehlke was the first to describe the HFS in 1974 as adverse drug reaction of intravenous mitotane [46]. HFS starts with mild skin reactions at the hands and feet such as numbness, paraesthesia, dysesthesia, tingling and/or erythema. Painful erythema, swelling of the hands and feet and cracked skin as well as major skin reactions with moist desquamation, ulceration, blistering, bleeding and/or severe pain may follow. Depending on the severity HFS may have a major impact on patients´ quality of life. Activities of everyday life are impaired, patients are unable to work, and they have difficulty in walking and using their hands [47, 48].

Different classification systems for HFS exist. Table 1-2 shows the classification according to the "Common Terminology Criteria for Adverse Events" version 3.0 [49].

Table 1-2: Severity grades of HFS

Grade 0	Grade 1	Grade 2	Grade 3
No problems	Minimal skin changes or dermatitis, without pain	Skin changes (e.g. swelling, blisters, peeling) or pain, no or little impairment	Ulcerative dermatitis or skin changes with severe pain, strong impairment

Until today the patho-mechanism of HFS is not completely clear. An immediate toxic effect of the anti-cancer drug on epidermal cells is discussed. But there is no explanation for the local occurrence of HFS at the hands and feet [47]. Another explanation might be a higher accumulation of capecitabine metabolites due to the expression of the enzyme thymidine phosphorylase in keratinocytes of the skin. A connection between HFS and a higher production of sweat at the hands and feet is also assumed [48]. Furthermore, gender-specific differences of HFS as well as an association with different combination partners in chemotherapy regimens are currently being investigated [50]. As long as the patho-mechanism remains unidentified the prevention and therapy of HFS will be limited to a relief of the clinical symptoms. The most important step in the treatment of HFS is the therapy interruption and dose reduction [51, 52]. Table 1-3 summarises a dose modification scheme for capecitabine.

Table 1-3: Dose reduction schedule depending on HFS grade [40]

HFS severity grade		Step during cycle	Dose following cycle
1		Maintain dose level	100%
2	1st appearance	Interrupt until resolved to grade 0-1	100%
	2nd appearance	Interrupt until resolved to grade 0-1	75%
	3rd appearance	Interrupt until resolved to grade 0-1	50%
	4th appearance	Discontinue treatment permanently	-
3	1st appearance	Interrupt until resolved to grade 0-1	75%
	2nd appearance	Interrupt until resolved to grade 0-1	50%
	3rd appearance	Discontinue treatment permanently	-

Generally the treatment interruption leads to a recovery within the next days. If HFS recurs after interruption and dose reduction the oncologist also has the possibility to change the treatment cycle e.g. extend the therapy-free interval or change the cycle length [53].

Well-educated patients and health care professionals are crucial in the management of HFS. The patient should inform the health care professional immediately about a developing HFS and the health care professional has to identify the severity grade. The patient should know that therapy interruption and dose reductions due to occurring toxicity do not influence the effectiveness of therapy. It has to be clarified that this information does not lead to a higher non-adherence rate as the patient might underestimate the treatment. Ideally the patient should also receive written information about HFS. In addition, continuous care is recommended during the therapy cycle when the patient is at home, especially at the beginning of the treatment. Short telephone calls can help to manage HFS and other toxicities [54].

Several researchers focused on pharmacological strategies to handle or prevent HFS. Lin et al. analysed the influence of celecoxib, a selective COX-2-inhibitor, on HFS. They found a reduced incidence of HFS and a higher survival rate when capecitabine was combined with celecoxib [55]. These results are controversial as in a later randomized multi-centre study celecoxib neither had an effect on HFS nor on the survival rate [56]. Studies with pyridoxine (vitamin B_6) did not show a statistically significant effect on the incidence of HFS either [57, 58]. When capecitabine and cisplatin are used in combination, the use of vitamin B_6 is not advised for symptomatic or secondary prophylactic treatment of HFS because of published reports that it may decrease the efficacy of cisplatin [41]. The supportive administration of vitamin E in a chemotherapy regimen with capecitabine and docetaxel was tested in a Turkish

case study. HFS did not worsen although the chemotherapy was administered without dose reduction. The authors recommended further studies to analyse the effect of vitamin E [59].

Aside from systemic approaches, attempts have been made with topical treatments as e.g. corticosteroid-containing creams. In this context skin atrophy and delayed wound healing also have to be considered if corticosteroids are used for a longer period of time [53]. The pharmacy of the University Hospital Essen, Germany reported positive findings with uridine-containing ointments. Nevertheless, these results have to be confirmed by adequate studies [60].

Finally some empirical recommendations can be given to the patient, which he might consider in his everyday life. Moisturizing creams or emulsions should be applied to his hands and feet; he should avoid heat, pressure and rubbing of the skin. Excoriations should be padded softly. The skin should be aerated as often as possible to avoid excessive sweating. To relieve the symptoms hands and feet can be bathed in cool water; the feet should be elevated as often as possible [53].

Furthermore, it is currently being discussed whether HFS is a valuable marker to monitor the efficacy of capecitabine as its occurrence, at least to a low extent, might be associated with better clinical outcome [61, 62].

1.3.4 Pharmacoeconomics of capecitabine

Some studies evaluated the cost-effectiveness of capecitabine and combinations in the treatment of cancer patients. Eggington et al. undertook a cost-utility analysis of capecitabine compared to bolus 5-FU / LV in the adjuvant treatment of colon cancer patients based on the results of the X-ACT trial (Xeloda® Adjuvant Chemotherapy Trial) [63]. The UK National Coordinating Centre for Health Technology Assessment (NCCHTA) funded the study on behalf of NICE. Their analysis suggested that capecitabine is expected to produce a QALY gain of 0.98 at lower costs per patient than the Mayo Clinic 5-FU / LV regimen, indicating dominance of capecitabine. The safety and tolerability profile of capecitabine was superior to the Mayo Clinic 5-FU / LV regimen, but it has not been compared to other less toxic 5-FU / LV regimens [64]. A recent analysis evaluated the cost-effectiveness of capecitabine plus oxaliplatin (XELOX) in comparison to 5-FU / LV and oxaliplatin (FOLFOX) in patients with metastatic colorectal cancer based on the results of two clinical trials. They used quality-adjusted progression-free survival days (QAPFSD) as outcome parameter. XELOX was associated with a gain in QAPFSD at reduced treatment costs, demonstrating dominance over FOLFOX [65]. An analysis of ixabepilone plus capecitabine versus capecitabine alone in

metastatic breast cancer patients showed an incremental-cost-utility ratio (ICUR) of $ 359000 per QALY gained. This result is far above the common willingness-to-pay for an additional QALY indicating that the combination is not a cost-effective use of health care resources [66]. A similar result was obtained in a cost-utility analysis of lapatinib plus capecitabine versus capecitabine alone in HER-2 positive advanced breast cancer patients [67]. A health technology assessment identified one randomized controlled trial (RCT) on capecitabine in combination with docetaxel versus docetaxel alone. Based on this RCT the combination therapy was likely to be cost-effective [68]. In conclusion, capecitabine either as monotherapy or in combination with oxaliplatin or docetaxel for the treatment of colorectal cancer or metastatic breast cancer seems to be a cost-effective use of health care resources.

2 Aim

The present study aimed at setting up, conducting and evaluating the costs and outcomes of a pharmaceutical care service for cancer patients treated with capecitabine compared to standard care.

A pharmaceutical care intervention as well as an appropriate study design, endpoints and infrastructure had to be developed. For the collection of data on resource use a new infrastructure had to be established as well.

Endpoints within the study were direct disease-related outpatient and inpatient costs, health-related quality of life, the adverse drug reaction hand-foot syndrome and quality-adjusted life years (QALYs). Further endpoints were the indirect disease-related costs, also known as loss of productivity, direct non-medical disease-related costs based on the patients´ need of help with every-day activities and the willingness-to-pay of the intervention patients for the pharmaceutical care service.

A further objective was to determine the cost-effectiveness of the pharmaceutical care service in a cost-utility analysis. The cost-utility analysis should be based on direct disease-related costs and QALYs of retrospectively matched patient pairs from the control and intervention group.

3 Patients and Methods

The present project was initiated as the first study to survey the costs and outcomes of a pharmaceutical care service delivered to cancer patients in Germany. There was no scientific evidence available on pharmacoeconomics of pharmaceutical care research in oncology. Therefore this work was planned as a pilot study.

3.1 Legal status of the study

The legal classification of the study as an observational trial ensued on the basis of the following arguments.

The participating physicians were not influenced with regard to their decision on diagnosis or the choice and implementation of therapy in the individual patient. In the field of supportive therapy the involved physicians were, if required, informed and advised by the participating clinical pharmacists according to the latest therapeutic guidelines. The physicians´ freedom of therapy was not limited during the study. The cooperation between the clinical pharmacists and the physicians was in consent with § 20 ApBetrO (Apothekenbetriebsordnung; German pharmacy law), which regulates the obligation of the pharmacist to give information and advice to patients and physicians. In the present study drugs were not tested. Instead the focus was on testing a service delivered to cancer patients.

With consideration of §§ 4, 40 and 67 of the German drug law (Arzneimittelgesetz, AMG) and the announcement of the Federal Institute of Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) from 12 November 1998 (Bundesanzeiger no. 229, 11 December 1998) the study was accomplished as an observational study.

On 16 September 2005 the ethics committee approved the study. In 2006 two amendments to the study protocol on additional inclusion of breast cancer patients and pharmacoeconomic evaluation of pharmaceutical care were also approved by the committee.

3.2 Participating study centres and cooperating partners

The study was accomplished with the participation of three oncology outpatient wards and three oncology practices (“study centres”) which are listed in table 3-1.

Table 3-1: Participating study centres

	Name of study centre
Oncology outpatient wards	University Hospital Bonn, Centre of Obstetrics and Gynaecology
	University Hospital Bonn, Department of Internal Medicine
	Johanniter Hospital Bonn, Department of Internal Medicine
Oncology practices	PD Dr. Christian M. Kurbacher, Bonn
	Dr. Peter F. Schwindt, Bonn
	Dr. Hartmud Wolter, Bonn

The pharmaceutical care service was delivered by the author of this paper and another research scientist of the Department of Clinical Pharmacy, University of Bonn (in the following referred to as "study pharmacists"). The data collection and analysis was carried out at the Department of Clinical Pharmacy, Institute of Pharmacy of the University of Bonn (in the following to be called "central study office").

Apart from the participating study centres the study was accompanied by the following cooperating partners, listed with job descriptions during the study period:

- Dr. E.S. Dietrich, director of the TK Scientific Institute for Benefit and Efficiency in Health Care, Hamburg (advice concerning study design and method of data analysis)
- Dr. R. Fimmers, Institute of Medical Biometrics, Computer Sciences and Epidemiology, University of Bonn (statistical advice)
- Prof. Dr. S. Hudson, Professor of Pharmaceutical Care, University of Strathclyde, Glasgow, Scotland (advice on pharmaceutical care of oncology patients)
- Pharmacist K. Ruberg, Kronen-Apotheke Marxen, Wesseling (advice on pharmaceutical care, data collection)

3.3 Study design

The gold standard for pharmacoeconomic evaluations is a randomized naturalistic study design in which randomized patients are treated with different therapies or methods under realistic every-day conditions for a long time period [69]. These studies are hard to carry out and are very expensive. Nevertheless, it is important to define and establish standards for pharmacoeconomic and pharmaceutical care research in order to obtain reliable data. The study aimed at approaching the pharmacoeconomic gold standard as closely as possible.

An open, prospective, multi-centred observational cohort study with preceding control group was chosen as study design (figure 3-1). In each study centre the control group was studied before the intervention group. The control group received standard care. The intervention group received intensified pharmaceutical care provided by the study pharmacists. Between December 2006 and February 2007 all study centres switched from recruiting control patients to recruiting intervention patients one by one. For this three-month period control and intervention patients were recruited at the same time but not at the same study centre.

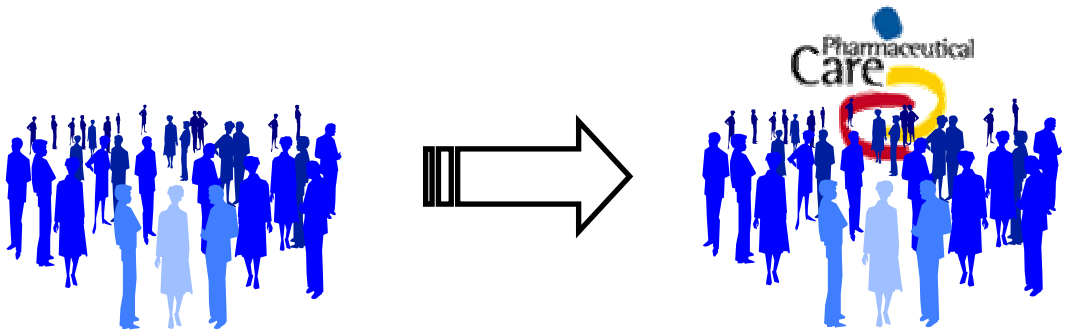


Figure 3-1: Study design

3.4 Selection of patients

To obtain a sufficient number of patients in the study period the following inclusion and exclusion criteria were defined.

Inclusion criteria:

- Patient is diagnosed with colorectal or breast cancer.
- Patient receiving chemotherapy with capecitabine
  - as adjuvant therapy following surgery of colorectal cancer or as mono- or combination chemotherapy for metastatic colorectal cancer.
  - for breast cancer as mono- or combination chemotherapy.
- Patient starting therapy with capecitabine no longer than one week before recruitment and being therapy-naïve concerning orally applied chemotherapeutic agents.
- Patient is at least 18 years old.
- Patient gives written informed consent.
- Patient is able to speak, read and write German.

Exclusion criteria:

- Patient suffers from diseases or mental states which impede that he completely understands the information on the study provided and/or which lead to an impaired capability of reading and completing questionnaires (e.g. Alzheimer´s disease).
- Patient has the intention to change his place of residence (> 100 km).

3.5 Patient recruitment and course of the study

The participating physician informed the patient about the pharmaceutical care project. If the patient was interested in the study the physician handed over a special patient information brochure explaining the aim and the contents of the study (appendix B). The physician informed the patient that his name and telephone number would be passed on to the central study office that would contact him during the following working-day. The physician then transmitted the contact details to the central study office via fax (appendix B). The study pharmacists usually contacted the patient the following day and arranged a meeting for a personal conversation. The meeting either took place in the patient's home, at the oncology outpatient ward / oncology practice or at the central study office. During the first conversation between the study pharmacist and the patient the aim, the content and the course of the study were explained in detail and the patient could ask questions concerning the study. If the patient agreed upon participating in the study, he signed the informed consent (appendix B) that also allowed the study pharmacist to inspect patient records and to analyse the collected data in a pseudonymous manner. Then the study pharmacist documented demographic patient data and the patient received a special study file that contained all needed patient questionnaires arranged according to the chemotherapy cycles of capecitabine. The study file also contained postage-paid, pseudonymously coded and addressed envelopes which were used by the patients to send each set of questionnaires to the central study office.

The study protocol considered a period of six months for each patient. For the whole period the resource utilisation was assessed. The measured resource utilisation included the following direct disease-related costs: costs for pharmacotherapy, oncologist fee, diagnostic costs, administration costs, costs for pharmacist (only in intervention group) and inpatient costs. Indirect disease-related costs were also assessed for six months. The measurement of quality of life and hand-foot syndrome were orientated at the course of the treatment with capecitabine. As mentioned above each chemotherapy cycle with capecitabine consisted of 14 days with twice daily drug intake followed by a seven-day break. Before the first (t_0), after the third (t_3) and after the sixth chemotherapy cycle (t_6) (each time at the first day of therapy

break) the questionnaire on quality of life was completed. After each cycle (each time at the first day of therapy break) the questionnaire on hand-foot syndrome was filled in (t_1, t_2, t_3, t_4, t_5, t_6). At the end of the study after a period of six months the questionnaires on quality of life and hand-foot syndrome were completed again (t_7). In case of discontinuation of capecitabine treatment the measurements were carried out in the same intervals. In the intervention group the patients´ "willingness-to-pay" for the pharmaceutical care service was assessed after six chemotherapy cycles (t_6) (figure 3-2).

Direct non-medical disease-related costs and the current employment situation were assessed with a patient questionnaire before the first (t_0), after the sixth cycle (t_6) and after six months (t_7) (not shown in figure 3-2).

For the cost and outcome assessment tools mentioned see appendix A.

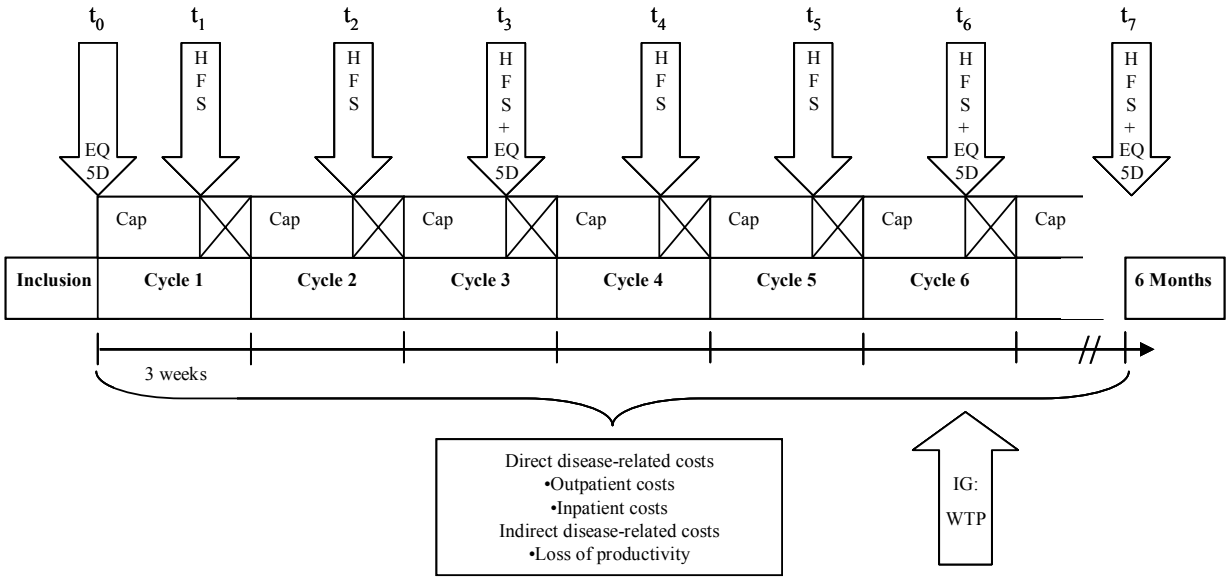


Figure 3-2: Course of treatment, cost and outcome measurement

(HFS = hand-foot syndrome, Cap = capecitabine, EQ-5D = quality of life questionnaire, IG = intervention group, WTP = willingness-to-pay, t = time of measurement)

3.5.1 Control group

According to the study protocol the patients of the control group should not receive additional pharmaceutical care and therefore no pharmaceutical advice was given. In case of questions from the patients the study pharmacists advised the patients to contact their physician. Only in case of urgent questions the patients received short advice from the study pharmacists. To

minimise the contact between the study pharmacists and the patients of the control group during the study period, the patients received a postal reminder at the end of each chemotherapy cycle (appendix C). This card should remind the patients to complete the respective questionnaires. Only if the patient did not respond within a certain period he was contacted by the central study office by telephone.

3.5.2 Intervention group

After signing the informed consent the pharmaceutical care service started immediately during this first personal conversation between the study pharmacist and the patient of the intervention group. During this first meeting the following issues were always discussed with each intervention patient:

- Medication history including all prescribed and over-the-counter (OTC) medication (Why? Since when? How often? Which dose? Before, with or after meal? Does it help? Adverse drug reactions?)
- Education concerning capecitabine
    - Pro-drug and tumour selectivity
    - Adverse drug reactions in general
    - Administration of capecitabine (usually 14 days of twice daily drug intake followed by a seven-day break; to be administered with water within 30 minutes postprandial; dosing interval approximately twelve hours)
- Education concerning hand-foot syndrome, e.g.
    - Prophylaxis
    - Detection
    - Treatment

During the course of this discussion that was completed with additional issues depending on the patient (e.g. concerning concomitant medication beside capecitabine, questions from the patient) the patient received the following information material to support the pharmaceutical care service:

- An information brochure on prophylaxis and treatment of certain important adverse drug reactions (appendix C). This brochure was developed by the Department of Clinical Pharmacy at the University of Bonn in cooperation with the participating physicians.
- A patient brochure containing advice concerning prophylaxis and management of hand-foot syndrome developed by Roche Pharma AG.
- A patient video about the chemotherapeutic agent Xeloda® of Roche Pharma AG.

- Relevant “Blaue Ratgeber” developed by the ‘Deutsche Krebshilfe’ (German Cancer Aid), also offering the possibility to order further copies.

All important issues of this first patient-pharmacist consultation were documented in a documentation sheet (appendix C). Within the next few days after that consultation the study pharmacist sent an individual information letter to the patient repeating important subjects in a written form. This letter also contained a detailed drug administration plan considering all current medication and the result of a computer-based interaction check (DrugDex®, DIMDI PharmSearch®) as well as, if necessary, other information material (appendix C).

In case of interactions that needed further discussion with the attending physician, the study pharmacist contacted the physician to find a common solution. During the course of the study, the study pharmacist had access to the patient files at regular intervals and stayed in close contact with the attending physicians. The study pharmacist contacted the patient at least every three weeks at the end of the drug intake period of each capecitabine cycle. The beginning and the end of the current and next cycle were discussed. The patient was questioned about adverse drug events during the last cycle, new medication and he had the opportunity to ask questions. Advice was given and/or the attending physician was contacted if necessary. Discussions with the patient as well as physician were documented in a specially prepared documentation sheet and were based on the pharmaceutical care plan in order to standardise the care process (both appendix C). In case of new medication the computer-based interaction check was repeated, the result was documented and communicated to the patient and/or the attending physician if necessary. The patients of the intervention group also had the possibility to contact the study pharmacists at certain times during the week via phone (Monday till Friday from 9 a.m. to 4 p.m.) if they had specific pharmaceutical questions that could not wait until the next regular patient-pharmacist contact.

3.6 Study perspectives

For the cost-utility analysis (see 3.9 “Cost-utility analysis”) a health insurance perspective was used. Hence only direct medical costs were taken into account as the health insurance had to reimburse these costs only. The outcomes also had to reflect the health insurance perspective which means that outcomes had to be valuated by the community insured. In the following cost section (see 3.7 “Cost assessment”) not only direct medical costs were taken into account but also indirect and direct non-medical costs which referred to a societal perspective. The willingness-to-pay of intervention patients (see 3.8. “Outcome assessment”) referred to a patient perspective.

3.7 Cost assessment

In general, costs are calculated by multiplying the used amount of resources with their specific unit price. In the German health care system almost all prices are administrated prices. These prices are influenced by different stakeholders or determined by administrative proceedings and do not develop due to supply and demand. The latter are called market prices [69]. For example prices for pharmacotherapy are partly market-based but are influenced by many administrative processes [70]. Physician fees or prices for diagnostic tests in the statutory health insurance are determined by the National Association of Statutory Health Insurance Physicians (NASHIP, Kassenärztliche Bundesvereinigung, KBV) in cooperation with the German health insurances [71]. Prices for inpatient stays are also administrated prices. Although administrated prices do not reflect the real price of the resource used, they are relevant for the health insurances as these are the prices they have to pay.

All costs refer to 2008. More precise details are mentioned in each cost section.

3.7.1 Direct disease-related outpatient and inpatient costs

3.7.1.1 Costs for pharmacotherapy

The costs for disease-related pharmacotherapy can be divided into costs for antineoplastic therapy, e.g. capecitabine, and supportive therapy, e.g. ondansetrone against nausea and emesis.

In three study centres the resource use of disease-related pharmacotherapy was obtained from directly searching the patient files. The resource use was documented in the resource use documentation form (appendix A). In the other three study centres these resource use data were obtained from hardcopies of electronic patient files (appendix A). In addition, study patients completed a questionnaire on pharmacotherapy after each chemotherapy cycle and after six months. They were asked to indicate all medication they were treated with (appendix A). If additional disease-related pharmacotherapy which was not documented in the patient files could be identified in these medication overviews, this was also considered in the cost calculation. All resource use data were transferred into Excel®-sheets for the calculation of costs.

The prices for proprietary medicinal products were obtained from the ‘Lauer-Fischer-Taxe’ and refer to the cut-off date 15 March 2008. The ‘Lauer-Fischer-Taxe’ is an index of all announced proprietary medicinal products and the standard pharmacy goods that are admitted for trade in Germany and their corresponding price [72]. In case of exact naming of the

medicinal product including dose, package size and company the corresponding price could be found in the 'Lauer-Fischer-Taxe'. If only the substance with dose and package size was documented, the cheapest product was chosen. If, in addition, the information on dose and/or package size was missing the lowest dose and the biggest package size was chosen.

Prices for sterile preparations were calculated according to the cooperating pharmacy, Kronen Apotheke Marxen, in Wesseling. Their calculations were in agreement with general pharmacy practice and the recommendations of the German 'Hilfs-Taxe'. The purchase prices of the medicinal products and the corresponding excipients taken from the 'Lauer-Fischer-Taxe' formed the basis of the calculation. An additional charge of 3 % as well as labour costs of € 53 in case of cytostatic drugs were added to the sum of the purchase prices. For preparations that do not contain CMR substances (CMR = cancerogen, mutagen, reproduction toxicity) the additional labour costs amounted to € 40. Finally, value-added tax of 19 % was added. A calculation example is shown in table 3-2.

Table 3-2: Calculation of the sterile preparation oxaliplatin (Eloxatin®) 112 mg in 500 ml Glucose 5 % (as of 2008)

Purchase price Eloxatin® 100 mg:	€ 517.10
Purchase price Eloxatin® 50 mg:	€ 264.55
Purchase price glucose solution 5 %:	€ 2.70
Sum:	€ 784.35
Additional charge 3 %:	€ 23.53
Additional labour costs:	€ 53.00
Sum:	€ 860.88
Value-added tax 19 %:	€ 163.57
Sum:	€ **1024.45**

Erythrocyte concentrates have fixed prices. Information on these prices was obtained from the blood donor service of the German Red Cross (Deutsches Rotes Kreuz). Prices for filtered erythrocyte concentrates amounted to € 81.00 as of 2008.

Patients´ out-of-pocket payment for medicinal products and sterile preparations were subtracted from the assessed prices, as these did not account for the costs of the health insurances. This was done for patients with a statutory health insurance as well as for patients with a private health insurance. It was neglected if individual patients were completely exempted from any out-of-pocket payment.

3.7.1.2 Oncologist fee

In the statutory health insurance oncologist fees as well as diagnostic and administration services are coded by the so called EBM-system (Einheitlicher Bewertungsmaßstab). The EBM-system consists of digits that code for a certain service in the health care system. The same is true for the private health insurance. Here the GOÄ-system (Gebührenordnung für Ärzte) is applied. The digits in both systems stand for a certain number of points. Each point has a certain value. For the EBM-system as of 2008 the value of one point was assumed to be 3.72 cents and in the GOÄ-system 5.83 cents. In some cases the digits of the EBM-system code directly for a certain amount of money, e.g. laboratory tests. In case of privately insured patients the accounts for medical services can be charged up to 2.3-fold depending on the medical service. For example accounts for laboratory tests are generally multiplied by 1.15, accounts for oncologist consultations by 2.3.

The EBM and GOÄ digits discounted in this study population were classified on the basis of their literal meaning into the three categories oncologist fee, diagnostics and administration. Information on the charged oncologist fees were obtained either from directly searching patient files followed by a documentation in the resource use documentation form, from hardcopies of electronic patient file cards or hardcopies of accounting files from the ambulatory hospital administration (appendix A). The EBM digits were searched for digits coding for physician fees by comparing the digits with their actual literal meaning, e.g. 01311 stands for "Basic charge for insurants from the beginning of the 6th until the end of the 59th year of life" and has a value of 175 points or € 6.51. The EBM digits coding for physician fees were then documented in an Excel®-sheet, translated into points and the points multiplied by the corresponding cent value to obtain the amount of money the health insurance had to pay. The same procedure was carried out with the GOÄ digits unless there were patient accounting files available that already contained the needed information. From the same data source the number of oncologist visits per patient plus visits to carry out diagnostic tests (e.g. CT scans, if documented in the patient file) during the study period was assessed. Visits at other physicians e.g. general practitioners were not assessed.

3.7.1.3 Costs for diagnostics and administration

The same procedure as described in chapter 3.7.1.2 "Oncologist fee" was used to assess the costs for diagnostics and administration that had to be paid by the health insurances.

3.7.1.4 Costs for the pharmacists

In the intervention group costs for pharmacists presented yet another direct disease-related cost category of interest.

The time spent by the study pharmacists to deliver pharmaceutical care was used as a measure for pharmacist costs. The pharmacists spent time for the following tasks:

- the first pharmacist-patient consultation,
- the following pharmacist-patient or pharmacist-physician consultations,
- writing individual patient letters, including medication administration plans and interaction checks and
- other pharmaceutical services (e.g. literature search, contact with pharmaceutical companies).

The first pharmacist-patient consultations as well as the following pharmacist-patient or pharmacist-physician consultations were documented on the above-mentioned documentation sheets (appendix C). In most cases the documented time spent for the first pharmacist-patient consultation not only included the total time but also differentiated between time spent on explaining the study and time spent on pharmaceutical care issues. Only the median of the latter was used as a measure for pharmacist costs. For the time spent on writing patient letters and other pharmaceutical services plausible estimations were used. The assessed pharmaceutical care time per patient was then multiplied by an hourly wage of € 22.99. This complies with an hourly wage of an employed pharmacist in his second to fifth year on the job plus associated employer outlay of 23 % (gross wage € 2991 + 23 % = € 3679, 40 hours / week; € 3679 / (4 x 40) = 22.99 € / hour) and is in agreement with the national collective wage agreement of 2008 for employed pharmacists [73, 74].

3.7.1.5 Direct disease-related inpatient costs

Diagnosis related groups (DRGs) form the basis for charges of hospitalisations in the statutory health insurance as well as in the private health insurance since 2003. DRGs are used to classify hospital cases into 500 to 1000 different groups according to e.g. diagnoses, procedures and the presence of complications. To obtain the case-based lump sum for a hospitalisation the so called base rate which is a certain charge for each hospital is multiplied with the relative weight of the DRG. For example the University Hospital Bonn had a base rate of € 2728.09 in 2008. The DRG J23Z, which means “Big intervention at the breast with malignant growth”, had a relative weight of 1.545. The product of the base rate and the

relative weight equals to the case-based lump sum of € 4214.90 that had to be paid by the health insurance [75, 76].

The receipts on hospitalisations of the study patients during the study period were directly received from the hospital controlling centres in case of hospitalisations in cooperating hospitals. In case of hospitalisations in other hospitals the patients themselves requested receipts of their hospitalisation charges from the corresponding controlling centre and sent hardcopies to the central study office (appendix A). The hospitalisations were checked for disease-relation and those related with cancer were chosen for further evaluation. Hospitalisations with debatable disease-relation were discussed with the attending oncologist. The DRGs indicated on the receipts were used to find their relative weighting in 2008 and multiplied by the hospital's base rate of 2008 to receive the corresponding case-based lump sum. From the same data material the number of disease-related hospitalisations per patient during the study period was assessed.

The case-based lump sum that has to be paid by the health insurance covers all procedures during an inpatient stay including pharmacotherapy and diagnostic tests. These inpatient costs for pharmacotherapy and diagnostics are not to be confused with the above-mentioned outpatient costs for pharmacotherapy and diagnostics.

3.7.2 Direct non-medical disease-related costs: help with every-day activities

Direct non-medical costs are not paid by the health insurance and reflect the societal perspective. As an example of direct non-medical costs, the need of help with every-day activities and also who mostly provided the help was queried with a patient questionnaire at t_0, t_6 and t_7 (appendix A). If the patient answered the question "Did you need help with every-day activities during the last two weeks? (e.g. eating, dressing, making coffee)" with "yes" he should indicate who mostly provided the help: family members/friends, professional nursing services, voluntary organisations or others. As it is a qualitative question in which the first part can only be answered with yes or no, no quantitative time measurement was done. The received information should give an overview whether these costs play a role in the studied patient group.

3.7.3 Indirect non-medical disease-related costs: loss of productivity

The indirect disease-related costs generally reflect the perspective of the society as these costs result from loss of productivity. Patients were questioned about their present employment situation at t_0, t_6 and t_7 (appendix A). Patients that were still employed or currently unable to

work were questioned in more detail at the end of their study participation about their time of sick leave during the last six months (absenteeism from work). If a patient was unable to work during the whole study period 128 days of sick leave were assumed (study period = six months = 180 days including 26 weekends x 2 (Saturday, Sunday) = 52 days; 180 days – 52 days = 128 days of sick leave). The days of sick leave were valuated in money terms according to the human capital approach. The gross average income in Germany amounted to € 3127 per month as of 2008 [77]. The number of days on sick leave was multiplied by € 142.14 to estimate the indirect disease-related costs in the present study. € 142.14 resulted from dividing € 3127 by 22 days assuming five working days per week and 30 days per month minus four weekends.

Reduced productivity at work due to the patients´ illness was not measured.

3.8 Outcome assessment

3.8.1 Patients´ quality of life

Patients´ quality of life was measured with the EQ-5D questionnaire, a generic instrument that was developed by the EuroQol Group, at t_0, t_3, t_6 and t_7 [78]. As it can be transformed into a single index or utility score it has considerable potential for use in pharmacoeconomic analysis and thus it is used very often in that field of research. The EQ-5D questionnaire consists of two parts, the descriptive system and the visual analogue scale (VAS) (appendix A).

The EQ-5D descriptive system

The descriptive system defines health in terms of the following five dimensions:

- Mobility
- Self-care
- Usual activities
- Pain / discomfort
- Anxiety / depression

Each dimension has three response categories corresponding to no problems (=1), some problems (=2) and extreme problems (=3). It defines a total of 243 possible health states (3^5 = 243) to which two further states were added (dead and unconscious). The level of the reported problem (1, 2 or 3) on each of the five dimensions determines one out of the 243 possible health states and can be defined by a five-digit number. For example, state 21223 would

indicate level two on mobility (“I have some problems…”), no problems with self-care, some problems with usual activities and some pain / discomfort and extreme anxiety / depression. From that five-digit number the EQ-5D health status index, that can be used to calculate QALYs, can be derived. The generated utility score lies on a scale on which full health has the value 1 and death has the value 0. In the present study the EQ-5D self-classified health states were converted to that single summary index by applying scores from the standard set of preference weights derived from the German population [79]. The German standard set of preference weights was developed between 1997 and 1998 with 339 randomly selected subjects. A total of 35 health states was evaluated based on the TTO method (time-trade-off, see 3.8.3.2 “QALYs from hand-foot syndrome questionnaire”). A linear additive model specification was used to value all 245 possible health states. According to this model certain values were subtracted from 1 (= perfect health) depending on the patient’s self-classified health state (see table 3-3).

Utility scores were only calculated if no cross was missing in the EQ-5D descriptive system. The absolute changes in utility scores between t_0 and t_3, t_6 and t_7, respectively, were calculated.

Table 3-3: Summary of the calculation of utility scores [79]

German TTO set of preference weights	**Example: utility score for health state 21223**
Full health (11111) = 1	Full health (11111) = 1
At least one 2 or 3: -0.001	-0.001
At least one 3: -0.323	-0.323
Mobility = 2: -0.099	-0.099
Mobility = 3: -0.327	/
Self care = 2: -0.087	-0.000
Self care = 3: -0.174	/
Usual activities = 2: -0.000	-0.000
Usual activities = 3: -0.000	/
Pain/discomfort = 2: -0.112	-0.112
Pain/discomfort = 3: -0.315	/
Anxiety/depression = 2: -0.000	/
Anxiety/depression = 3: -0.065	-0.065
	Health state 21223 = 0.400

The EQ-5D visual analogue scale (VAS)

In the second part of the EQ-5D questionnaire patients were asked to mark their current health state on a vertical 20 cm visual analogue scale ("thermometer") calibrated from zero (= worst imaginable health state) to 100 (= best imaginable health state). The VAS is generally used in conjunction with the 5-digit classification of the descriptive system to build an accurate profile of the patient's health status. The absolute changes in VAS scores between t_0 and t_3, t_6 and t_7, respectively, were calculated.

The two parts of the EQ-5D questionnaire were only assessed for patients under treatment with capecitabine. If treatment with capecitabine was discontinued or a new antineoplastic therapy without capecitabine was started the completed questionnaires of that period were not analysed.

3.8.2 Adverse effect hand-foot syndrome (HFS)

HFS is a dose- and therapy-limiting toxicity in cancer patients under treatment with capecitabine. If not managed properly it can develop from mild skin reactions at the hands and feet (grade 1) to major skin reactions with bleeding, ulceration and severe pain (grade 3).

The HFS grade was assessed after each capecitabine cycle and after six months (t_1, t_2, t_3, t_4, t_5, t_6, t_7) by a patient questionnaire (appendix A). The patients were asked to mark the particular grade of HFS with a cross that best characterised their current condition. The different HFS grades on the questionnaire were described according to the "Common Terminology Criteria for Adverse Events" (CTCAE) Version 3.0 of the National Cancer Institute, USA. Only those HFS questionnaires were evaluated in which the patient was under treatment with capecitabine. If treatment with capecitabine was stopped or a new antineoplastic therapy without capecitabine was started the completed questionnaires of that period were not analysed.

3.8.3 Quality-adjusted life years (QALYs)

QALYs present the outcome parameter in a cost-utility analysis. The background of the QALY is the combination of quality and quantity of life in one concept. Figure 3-3 illustrates the basic principle of the QALY.

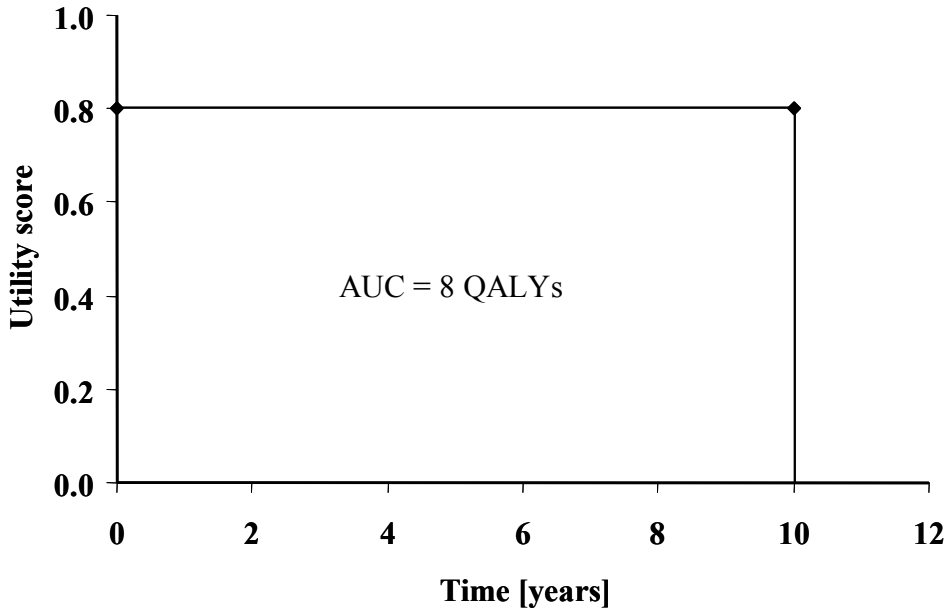


Figure 3-3: Concept of the QALY

The Y axis represents the utility score between 0 and 1 which can be considered, simply put, as a "quality of life" level. The X axis stands for a certain time period. The patient in figure 3-3 has lived for 10 years since the time of diagnosis. His average quality of life during these 10 years had a value of 0.8 on the scale. In terms of QALYs that means that he had 0.8 x 10 = 8 QALYs. Each of the 10 life years had a utility score of 0.8 and the number of life years, in his case 10, is adjusted to their respective quality [8].

3.8.3.1 QALYs from EQ-5D questionnaire

As mentioned in chapter 3.8.1 “Patients´ quality of life”, the answers to the descriptive system of the EQ-5D questionnaire during treatment with capecitabine were transferred into utility values by the German TTO set of preference weights. These utility values were then used to calculate QALYs as illustrated in figure 3-4.

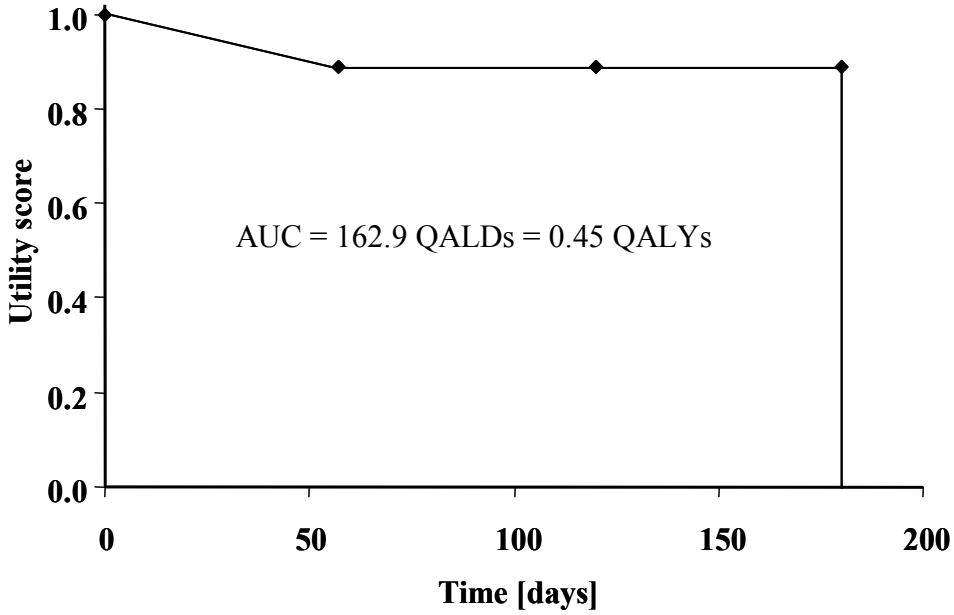


Figure 3-4: QALYs from EQ-5D questionnaire

The Y axis again represents the utility score between 0 and 1. The X axis represents the time in days, with the four points of measurement at t_0 (day 0), t_3 (day 57), t_6 (day 120) and t_7 (day 180). The area under the curve (AUC) corresponds to the number of quality-adjusted life days (QALDs). In the present study the QALDs were divided by 365 days to obtain QALYs. The AUC was assessed with Microsoft Excel® according to the trapezoidal method, where the area under the curve is defined through the function $f(x)$ for the interval $[0, h]$:

$$\int_0^h f(x)d(x) \approx h \cdot \frac{f(h) + f(0)}{2} \qquad \textit{(Eq. 1)}$$

The best achievable QALD or QALY result was 180 QALDs or 0.49 QALYs respectively according to this formula and the study period of 180 days (180 days divided by 365 days = 0.49 years). To achieve this result a patient would need a utility score of 1.000 (= perfect health) at all four points of measurement.

QALDs and QALYs were only calculated for those patients whose measurement was available for all four points (= analysis of completers´ data).

3.8.3.2 QALYs from hand-foot syndrome questionnaire

The assessed HFS grades during therapy with capecitabine (see 3.8.2 “Adverse effect hand-foot syndrome (HFS)”) were converted into utility scores. The completed HFS questionnaires during periods without capecitabine treatment were not evaluated in this respect. The utility scores used were generated earlier in a diploma thesis at the Department of Clinical Pharmacy, University of Bonn [80]. In that diploma thesis a survey was conducted in a German community pharmacy in 2007. 53 randomly chosen subjects were introduced to the symptoms of HFS using cards explaining the different HFS grades by pictures of hands and feet, a clinical definition and citations of patients who had suffered from the particular HFS grade. Participants were first asked to value their own health state using the EQ-5D questionnaire followed by a test exercise in which the subjects had to assess a particular severity grade of heart failure using the VAS and the time-trade-off method (TTO). Then they valuated the different severity grades of HFS using the VAS and the TTO method. Both methods are two direct approaches to generate utility scores. The TTO method was developed specifically for use in health care by Torrance et al. in 1972 [81]. The application of the TTO technique to a chronic HFS state is illustrated in figure 3-5.

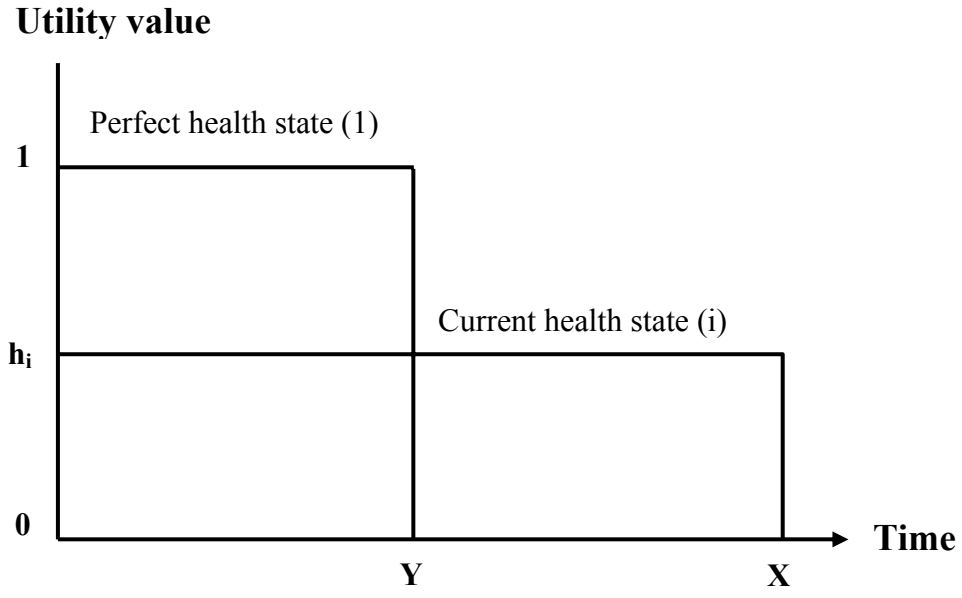


Figure 3-5: TTO method to generate utility scores for HFS grades [3]

During the application of the TTO technique the subject was offered two alternatives:

- State *i* (current health state) for time *X* (here 10 years) followed by death, or
- State 1 (perfect health state) for time *Y* followed by death.

Time Y was varied until the respondent was indifferent between the two alternatives. At this point the utility score was calculated using the following formula:

$$h_i = \frac{Y}{X} \qquad \textit{(Eq. 2)}$$

Table 3-4 shows the HFS grades and the corresponding assessed median utility scores.

Table 3-4: HFS grades and corresponding utility scores [80]

HFS grade	Utility score (median) (TTO technique)
0	1.00
1	0.97
2	0.72
3	0.34

The utility scores listed in table 3-4 were used to calculate QALYs according to the approach presented in chapter 3.8.3.1 "QALYs from EQ-5D questionnaire". In contrast to the utility scores obtained from the EQ-5D questionnaire the HFS-based utilities were assessed seven times: at t_1, t_2, t_3, t_4, t_5, t_6 and t_7 (days: 15, 36, 57, 78, 99, 120, 180). The utility score on day 0 (t_0) was assumed to be 1.00. If one of the first six measurement points was missing the utility – time - curve was plotted without that point of measurement and the QALYs were calculated. If the last measurement point or more than one measurement point were missing QALYs were not calculated for that patient.

3.8.4 Patients´ "willingness-to-pay" for pharmaceutical care service

The "willingness-to-pay" survey is a measurement technique often used in a cost-benefit analysis. Outcomes of health programmes such as the pharmaceutical care service are broadly defined in a cost-benefit analysis. Outcomes might comprise improvements in health status, the value of being better informed or the value associated with the process of care. Cost-benefit analysis that use the "willingness-to-pay" approach can be understood as attempts to examine unknown markets and to measure underlying consumer demand and valuation for non-marketed social goods such as health care programmes [3].

In the present study the patients of the intervention group were asked to complete the "willingness-to-pay" questionnaire at t_6 (appendix A). This questionnaire was specifically developed for the study. The patients were required to imagine that there is an actual market existing for the pharmaceutical care service they had experienced and to reveal the maximum

amount of money they would be willing to pay for such a service per month. Furthermore, they were asked to state their household net income and size of household.

3.9 Cost-utility analysis

In a cost-utility analysis the outcome is measured in quality-adjusted life years (QALYs), a complex measure that links a time period with the patient's quality of life during that time. The results can be expressed as an incremental cost-utility ratio (ICUR) in costs per QALY gained.

3.9.1 Retrospective identification of matched-pairs

To be able to compare patients of the control group with patients of the intervention group in a cost-utility analysis it was important to identify matched-pairs between these two patient groups as the patients of the present study were not randomized. The matching is an alternative approach to control for the effects of a covariate. It is a common technique in case-control and cohort studies. Each member of a group is matched to one or more members of the other group with respect to the values of one or more covariates. However, the risk of bias persists as there might be unknown differences or differences difficult to determine also known as "confounders" [82].

The following main matching parameters were defined:

- Tumour entity (breast or colorectal cancer),
- Treatment setting (adjuvant, neoadjuvant or palliative),
- Antineoplastic regimen at the time of inclusion (e.g. capecitabine monotherapy, capecitabine oxaliplatin combination therapy,…), not considering anti-estrogen therapy,
- Treatment with bisphosphonates at the time of inclusion,
- Type of health insurance (statutory or private health insurance).

Only those patients were allowed to enter the matching process whose complete outpatient and inpatient cost data as well as EQ-5D descriptive system measurements were available. Also those EQ-5D questionnaires were analysed in which the patient stopped treatment with capecitabine or started a new antineoplastic therapy without capecitabine. If a patient died during the study the utility score for the following points of measurement was supposed to be 0.000 (= dead) for that patient.

3.9.2 Incremental cost-utility ratio

For the matched patient pairs the ICUR should be calculated according to the following formula:

$$\frac{Costs_{IG} - Costs_{CG}}{QALYs_{IG} - QALYs_{CG}} \qquad (Eq.\ 3)$$

where IG stands for intervention group and CG for control group. The mean direct disease-related costs including outpatient and inpatient costs plus pharmacist costs were considered in the intervention group. The considered direct disease-related costs of the control group included outpatient and inpatient costs. Concerning the outcome QALYs there were two different QALY values available: QALYs based on the EQ-5D questionnaire and QALYs based on the HFS questionnaire. The ICUR should be calculated separately for both mean QALY values. Equation 3 leads to an estimate of the cost and effect differences. To present the uncertainty in that estimate a nonparametric bootstrapping was performed and a cost-effectiveness acceptability curve was plotted.

3.9.3 Nonparametric bootstrapping

Bootstrapping is a resampling procedure that employs computing power to estimate the empirical distribution of cost-effectiveness. The approach involves a three-step procedure:

1. Sample with replacement n_{CG} Cost/QALY pairs from the patients in the control group (where n_{CG} is the number of patients observed in the control group) and calculate the mean cost and effect in this bootstrap resample.
2. Sample with replacement n_{IG} Cost/QALY pairs from the patients in the intervention group (where n_{IG} is the number of patients observed in the intervention group) and calculate the mean cost and effect in this bootstrap resample.
3. Using the bootstrapped means from the steps above, calculate the difference in QALYs between the groups, the difference in cost between the groups and an estimate of the incremental cost-effectiveness.

This three-step procedure provides one bootstrap replication of the incremental cost-utility [83]. This process was repeated 10000 times to generate the empirical distribution of cost-effectiveness.

Furthermore, a cost-effectiveness acceptability curve was drawn plotting the proportion of bootstrap replications whose ratios fell below a certain cost-effectiveness threshold ratio (λ). λ

was varied from 0 through ∞. This graphic illustrates the probability of cost-effectiveness for different threshold ratios (costs/QALY) [83].

3.9.4 Sensitivity analysis

A sensitivity analysis is a technique to handle uncertainties in a pharmacoeconomic evaluation. During the analysis of cost and outcome data the author of this work identified critical methodological assumptions. On the basis of these the following sensitivity analyses were accomplished to investigate the robustness of the ICUR:

- Two simple one way analyses:
  - Double costs for pharmacists of € 45.98/hour were assumed, as the hourly wage of € 22.99 is based on the national collective wage agreement for employed pharmacists. If pharmacists provided the pharmaceutical care service as e.g. a freelancer they would have to charge more money.
  - The transformation of the EQ-5D digit into utilities was based on the UK TTO set of preference weights. This set is widely used in pharmacoeconomic analyses and was generated with more participants (n = 3235) than the German TTO set [84].
- One analysis of extremes:
  - Following the matching process some patients had to be selected at random which is an established approach. Due to the limited sample size of the cost-utility analysis the selection of patients probably had an influence on the result of the ICUR. Therefore those patients leading to the best possible ICUR (best case) and those patients leading to the worst possible ICUR (worst case) were combined and evaluated in two separate sensitivity analyses.

3.10 Study hypotheses

The following hypotheses were investigated in the pilot study:

- The direct disease-related outpatient costs are reduced by pharmaceutical care.
- The direct disease-related inpatient costs are reduced by pharmaceutical care.
- Patients´ quality of life is increased by pharmaceutical care.
- The adverse drug reaction hand-foot syndrome is improved by pharmaceutical care.
- More quality-adjusted life years (QALYs) are gained by pharmaceutical care.
- Indirect disease-related costs are reduced by pharmaceutical care.
- The need of help with every-day activities as a measure of direct non-medical disease-related costs is reduced by pharmaceutical care.

- The intervention patients´ willingness-to-pay for the pharmaceutical care service is as high as the pharmacist costs to deliver pharmaceutical care.
- The cost-utility analysis shows that the pharmaceutical care intervention is a cost-effective service. It is considered cost-effective if the additional cost per QALY lies below € 29000 / QALY (=£ 20000 / QALY). This threshold is based on a review on NICE`s recommendations [85].

3.11 Statistical analysis

For all statistical analyses the software SPSS® version 17 was used except for the nonparametric bootstrapping which was performed with SAS®.

Patient characteristics

Differences in age between control and intervention as well as between breast and colorectal cancer patients were tested with the parametric t-test for independent samples. Other patient characteristics were evaluated in respect of their absolute and relative frequency distribution. Differences between the control and intervention group in the other patient characteristics at the time of inclusion were tested with the Fisher`s exact test.

Direct disease-related outpatient and inpatient costs

Differences in outpatient, inpatient and total costs, in number of oncologist visits, in number of hospitalisations and in number of days in the study between the control and intervention group were tested with the nonparametric Mann-Whitney-U test for independent samples. Also mean, median and standard deviation were calculated. Costs for the pharmacist in the intervention group were evaluated descriptively.

Direct non-medical disease-related costs: help with every-day activities

The need of help with every-day activities in control and intervention patients at t_0, t_6 and t_7 was evaluated in respect of its absolute and relative frequency distribution. Differences between the control and intervention group at these three times were tested with the Fisher`s exact test for nominal data. The differences within the control and intervention group respectively between the first and the second measurement and between the first and the last measurement were tested with the McNemar test for nominal data. The answer concerning the help provider was evaluated regarding the absolute and relative frequency distribution.

Indirect non-medical disease-related costs: loss of productivity

The current employment situation in control and intervention patients at t_0, t_6 and t_7 was evaluated in respect of its absolute and relative frequency distribution. Differences between the control and intervention group at these three times were tested with the Fisher`s exact test. The differences within the control and intervention group, respectively, between the first and the second measurement and between the first and the last measurement were tested with the McNemar test for nominal data. For this test the patients were arranged in two groups: one group for patients that were able to work (full-time or part-time job) and one group for patients that were unable to work. Other categories like housewife or pensioner were not considered. Differences between control and intervention group concerning the days on sick leave and indirect costs were tested with the Mann-Whitney-U test.

Quality of life measurement with EQ-5D questionnaire

The results of the descriptive system of the EQ-5D questionnaire were evaluated with the help of relative frequency distributions at t_0, t_3, t_6 and t_7 separately for control and intervention patients. Mean, median and standard deviation were calculated for each of the five dimensions.

Utility scores as well as EQ-5D VAS scores were evaluated descriptively calculating mean, median, standard deviation and interquartile range at t_0, t_3, t_6 and t_7. Differences in absolute changes in utility / VAS scores at t_0 and t_3 (t_6, t_7) between control and intervention patients were tested with the Mann-Whitney-U test. The absolute changes were illustrated as boxplots.

Adverse effect hand-foot syndrome

Descriptive statistics calculating median and interquartile range of hand-foot syndrome grades at seven different points in time (t_1, t_2, t_3, t_4, t_5, t_6, t_7) were performed. Boxplots were chosen for graphical presentation. Differences between the control and intervention patients were analysed with the Cochran-Armitage test for trends.

HFS-based utility scores were evaluated descriptively calculating median and interquartile range at t_1, t_2, t_3, t_4, t_5, t_6, and t_7.

Quality-adjusted life years

QALYs and QALDs (quality-adjusted life days) were analysed descriptively by assessing mean, median, standard deviation and interquartile range for both patient groups. The Mann-

Whitney-U test was used to test for statistically significant differences between the two patient groups. A utility-time curve was used for graphical presentation.

Willingness-to-pay

The willingness-to-pay (WTP) in the intervention group was analysed descriptively. It was tested for a correlation with the household net income as well as the net income per household member by applying a trend line and calculating the coefficient of determination (R^2). The difference in WTP between patients with a statutory and a private health insurance was evaluated with the Mann-Whitney-U test.

Cost-utility analysis

Differences in outpatient and inpatient costs between the selected control group and the selected intervention group were tested with the nonparametric Mann-Whitney-U test for independent samples. Also mean, median and standard deviation were calculated. QALYs and QALDs (quality-adjusted life days) were analysed descriptively by assessing mean, median and standard deviation for both selected patient groups. The Mann-Whitney-U test was used to test for statistical significant differences between the two selected patient groups. Concerning the incremental cost-utility ratio the non-parametric bootstrapping as described in chapter 3.9.3 was used to estimate the empirical distribution of cost-effectiveness and a cost-effectiveness acceptability curve was plotted. Furthermore sensitivity analyses as described in chapter 3.9.4 were applied.

Study drop-outs and missing data

Patients who dropped out of the study, e.g. because they withdrew their informed consent, were not analysed. All outcome data collected until then were not used for further analysis. This is known as a per protocol analysis (PP).

In case of missing patient data for a certain outcome, only the available data of a patient were evaluated (analysis of completers´ data). Imputation methods as e.g. last observation carried forward (LOCF) were not used.

4 Results

4.1 Patient recruitment

Patients were recruited on three oncology outpatient wards (two Departments of Internal Medicine and one Department of Obstetrics and Gynaecology) and three oncology practices. Between May 2006 and April 2008, 100 ambulatory patients were reported to the central study office by the cooperating oncologists. From these 100 patients, 78 were included into the study and 76 were finally analysed. Figure 4-1 shows the patient recruitment in the control group and the intervention group in a flow diagram.

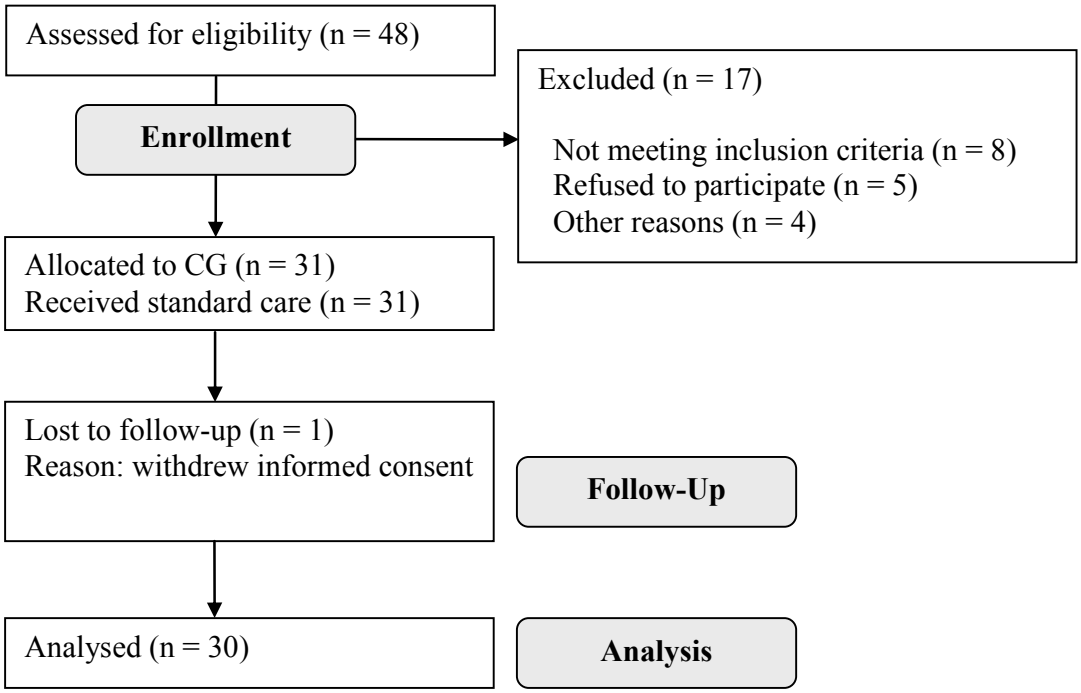
In each patient group one patient was lost to follow-up (study drop-out). Both patients withdrew their informed consent. Reasons for the control patient to drop out were bad news from his oncologist regarding his progression of disease. In the intervention group the patient refused to receive pharmaceutical care. The patient wanted to receive information from his attending oncologist and general practitioner only.

4.2 Patient characteristics

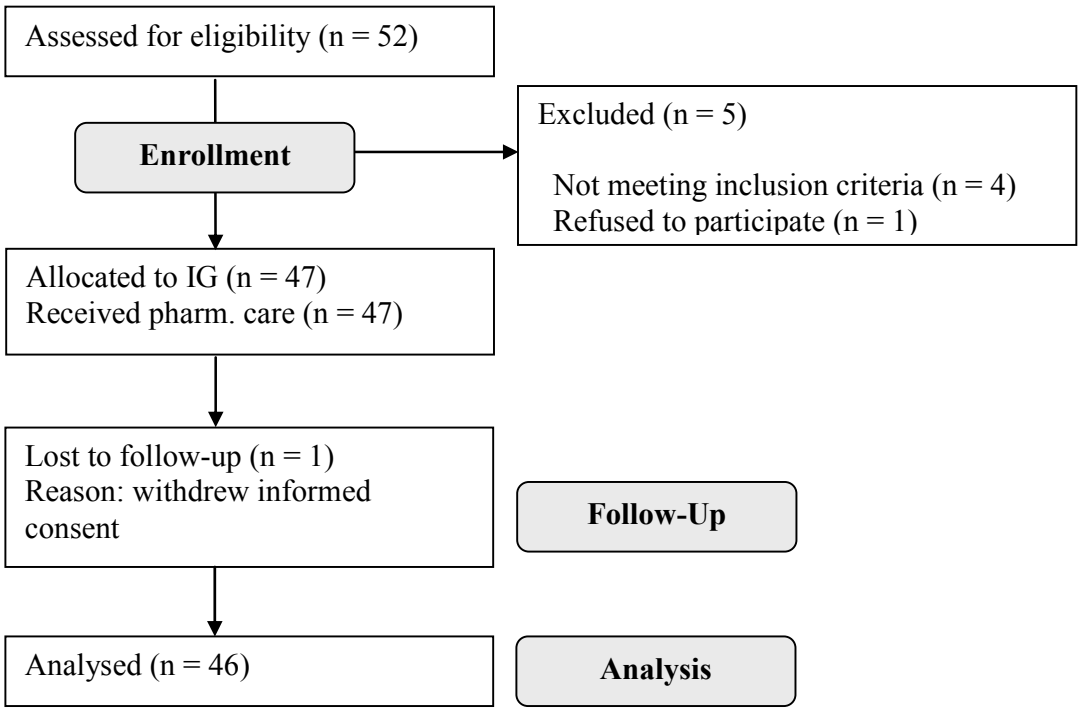
As shown in figure 4-1 76 patients were analysed, 30 belonged to the control group and 46 to the intervention group. At the time of inclusion control patients had a mean age of 63.0 years (SD: 12.8; median: 64.5; IQR: 53-71.3; min.: 33; max.: 85) and intervention patients of 57.5 years (SD: 12.5; median: 58.0; IQR: 49.8-65; min.: 28; max.: 93 years). The intervention patients were 5.5 years younger in the mean. This difference was not statistically significant ($p = 0.067$, t-test). At the time of inclusion breast cancer patients had a median age of 55 years (25 % percentile: 48; 75 % percentile: 64; minimum: 28; maximum: 80 years), while colorectal cancer patients showed a median of 64 years (25 % percentile: 57.5; 75 % percentile: 71.5; minimum: 30; maximum: 93 years). This difference observed was statistically significant ($p = 0.001$, t-test).

The socio-demographic and disease-related patient characteristics of both groups are listed in table 4-1 and table 4-2.

Control Group: First patient in 05/2006, Last patient in 02/2007, Last patient out 08/2007



Intervention Group: First patient in 12/2006, Last patient in 04/2008, Last patient out 10/2008



CG = control group, IG = intervention group

Figure 4-1: Patient recruitment flow diagram

Table 4-1: Socio-demographic patient characteristics at the time of inclusion (control group n=30; intervention group n=46)

Socio-demographic variable		Control group		Intervention group		P value*
		n	%	n	%	
Age	< 50 years old	3	10.0	11	23.9	0.301
	50-60 years old	10	33.3	14	30.4	
	> 60 years old	17	56.7	21	45.7	
Sex	Female	24	80.0	33	71.7	0.589
	Male	6	20.0	13	28.3	
Health insurance	Statutory	29	96.7	32	69.6	0.003
	Private	1	3.3	14	30.4	
Marital status	Married / partner	19	63.3	39	84.8	0.085
	Single	4	13.3	4	8.7	
	Divorced	1	3.3	1	2.2	
	Widow	6	20.0	2	4.3	
	No answer	0	0.0	0	0.0	
Current living situation	Living alone	8	26.7	2	4.3	0.011
	With family / partner	21	70.0	43	93.5	
	Living in institution	0	0.0	0	0.0	
	Other	1	3.3	1	2.2	
	No answer	0	0.0	0	0.0	
Education	Elementary school	8	26.7	11	23.9	0.306
	Secondary school	8	26.7	9	19.6	
	O-levels	2	6.7	2	4.3	
	Journeyman	5	16.7	6	13.0	
	Master of a trade	1	3.3	1	2.2	
	Bachelor	3	10.0	3	6.5	
	University / College	2	6.7	14	30.4	
	No answer	1	3.3	0	0.0	
Current employment situation	Full-time job	3	10.0	5	10.9	0.458
	Part-time job	2	6.7	4	8.7	
	Unemployed	0	0.0	0	0.0	
	Unable to work	6	20.0	14	30.4	
	Pensioner	18	60.0	18	39.1	
	Housewife/ -man	1	3.3	5	10.9	
	Student	0	0.0	0	0.0	
	No answer	0	0.0	0	0.0	

**Fisher`s exact test (the category no answer was not considered)*

Table 4-2: Disease-related patient characteristics at the time of inclusion (control group n=30; intervention group n = 46)

Disease-related variable		Control group		Intervention group		P value*
		n	%	n	%	
Tumour entity	Breast cancer	16	53.3	23	50.0	0.818
	Colorectal cancer	14	46.7	23	50.0	
Treatment	Curative (adjuvant/neoadjuvant)	7 (3/4)	23.3 (13.3/10.0)	14 (13/1)	30.4 (28.2/2.2)	0.604
	Palliative	23	76.7	32	69.6	
Therapy regimen at inclusion[1]	Cap	12	40.0	15	32.6	0.387
	Cap Beva	4	13.3	6	13.0	
	Cap Beva Iri	1	3.3	2	4.3	
	Cap Beva Ox	2	6.7	1	2.2	
	Cap Cet Iri	0	0.0	3	6.5	
	Cap Lap	0	0.0	2	4.3	
	Cap Mil	0	0.0	1	2.2	
	Cap Mit	1	3.3	0	0.0	
	Cap Ox	3	10.0	8	17.4	
	Cap Pac	1	3.3	5	10.9	
	Cap Tras	3	10.0	3	6.5	
	Cap Tras Vin	2	6.7	0	0.0	
	Cap Vin	1	3.3	0	0.0	
Time since diagnosis	< ½ year	8	26.7	14	30.4	0.834
	½ year to 2 years	10	33.3	12	26.1	
	> 2 years	12	40.0	20	43.5	
Therapy setting	Oncology outpatient ward	18	60.0	36	78.3	0.121
	Oncology practice	12	40.0	10	21.7	

**Fisher`s exact test*

[1]Therapy regimen: Cap = capecitabine monotherapy; Cap Beva = capecitabine + bevacizumab; Cap Beva Iri = capecitabine + bevacizumab + irinotecan; Cap Beva Ox = capecitabine + bevacizumab + oxaliplatin; Cap Cet Iri = capecitabine + cetuximab + irinotecan; Cap Lap = capecitabine + lapatinib; Cap Mil = capecitabine + miltefosin; Cap Mit = capecitabine + mitomycin; Cap Ox = capecitabine + oxaliplatin; Cap Pac = capecitabine + paclitaxel; Cap Tras = capecitabine + trastuzumab; Cap Tras Vin = capecitabine + trastuzumab + vinorelbin; Cap Vin = capecitabine + vinorelbin

[1]Endocrine therapies (e.g. tamoxifen, exemestan, fulvestrant), treatment with bisphosphonates and radiation therapy are not considered.

4.3 Direct disease-related outpatient and inpatient costs

Direct disease-related outpatient costs

Table 4-3 gives an overview of the different outpatient cost categories that were paid for by the respective health insurance in both patient groups. The number of oncologist visits during the study period is also shown.

Table 4-3: Direct disease-related outpatient costs, number of oncologist visits and study period

	Anti-neopl. therapy [€]	**Supp. therapy [€]**	**Oncologist fee [€]**	**Diagn. cost [€]**	**Admin. cost [€]**	**No. visits [n]**	**Study period [days]**
Control group							
n:	30	30	30	30	30	30	30
Sum:	466949	63113	18025	8521	572	459	4912
%:	83.8	11.3	3.2	1.5	0.1	/	/
Median cost/patient:	8543	1257	369	238	17	14	180
Mean cost/patient:	15565	2104	601	284	19	15	164
SD:	19449	2450	637	319	13	9	38
Intervention group							
n:	46	46	45	45	45	45	46
Sum:	691210	72949	25537	26209	306	561	7631
%:	84.7	8.9	3.1	3.2	0.03	/	/
Median cost/patient:	13748	1443	490	260	1	11	180
Mean cost/patient:	15026	1586	568	582	7	12	166
SD:	11667	1177	454	719	10	6	41
P value*:	0.366	0.903	0.871	0.230	0.000	0.235	0.874

**Mann-Whitney-U test, SD = standard deviation, Supp. = supportive, Diagn. = diagnostic, Admin. = administration, No. = number*

In both patient groups most of the money was spent on antineoplastic therapy, followed by supportive therapy. In the control group more money was spent on the oncologist fee than on diagnostics in contrast to the intervention group. In both groups administrative costs were negligibly small. The cost differences between control and intervention patients were not statistically significant except in the category administration costs. The median number of oncologist visits was 14 in the control and 11 in the intervention group; the difference was not statistically significant. The median study period was 180 days in both patient groups.

Appendix D shows the EBM and GOÄ digits assessed in this study and their respective value and meaning. The digits were classified into the categories oncologist fee, diagnostics or administration according to their literal meaning. The direct disease-related outpatient costs are also shown in appendix D separately for each patient.

Costs for pharmacist

The first pharmacist-patient consultation lasted 78 minutes in the median (n = 46; mean: 83 minutes, SD: 21, min.: 44, max.: 140). In 15 cases it was differentiated between the time spent

on explaining the study (protocol-driven time) and time spent on pharmaceutical care issues [3]. A median of 46 minutes were spent on explaining the study (mean: 47 minutes, SD: 15, min.: 19, max.: 80) and a median of 40 minutes were spent on pharmaceutical care issues (mean: 41 minutes, SD: 18, min.: 16, max.: 70). For the following pharmacist-patient or pharmacist-physician consultations a median of 131 minutes per patient were needed (mean: 123 minutes, SD: 59, min.: 9, max.: 256). For writing individual patient letters including medication administration plans and interaction checks 60 minutes per patient were estimated as well as 15 minutes per patient for other pharmaceutical services.

In total the study pharmacist spent 246 minutes per patient (4.1 hours) to deliver pharmaceutical care during the study (40 + 131 + 60 + 15 minutes). This amounted to pharmacist costs of € 22.99 x 4.1 hours = € 94.26 per patient for a pharmaceutical care period of six months or € 4335.91 for the whole patient population in a study period of six months. As some intervention patients received pharmaceutical care for a shorter time period since they died before the end of the study, the total cost for the whole intervention population amounted to € 3996.10 (7631 study days x € 94.26/180 days). This represented 0.41 % of total direct costs in the intervention group. An overview of the documented pharmacist time can be seen in appendix D.

Direct disease-related inpatient costs

Eighteen of 30 control (60 %) and 19 of 46 intervention patients (41 %) had disease-related inpatient stays during the study period. Twelve control (40 %) and 27 intervention patients (59 %) were not hospitalised.

There was a total number of 32 hospitalisations in the control and of 30 hospitalisations in the intervention group. Hospitalisations were necessary in the control group due to: i.v. administration of chemotherapy (6), surgery (6), disease-related complications (5), toxicity/adverse drug reaction (4), progression (4), surgery following neoadjuvant treatment (4), unknown reasons (2) and diagnostic tests (1). Hospitalisations were necessary in the intervention group due to: disease-related complications (14), diagnostic tests (6), progression (6), surgery following neoadjuvant treatment (2), toxicity /adverse drug reaction (1) and i.v. administration of chemotherapy (1).

The median number of inpatient stays per patient was 1.0 in the control group (mean: 1.1, SD: 1.4) and 0.0 in the intervention group (mean: 0.7, SD: 0.9). The difference in the number of hospitalisations per patient was not statistically significant ($p = 0.201$, Mann-Whitney-U). A total amount of € 114327.35 was paid for inpatient stays in the control group and of

€ 137194.02 in the intervention group. The median inpatient costs per patient in the control group amounted to € 1959.13 (mean: € 3810.91, SD: € 4617.88) and to € 0.00 (mean: € 2982.48, SD: € 6127.89) in the intervention group. The difference was not statistically significant (p = 0.112, Mann-Whitney-U).

For more details concerning inpatient costs per patient and for an overview of cancer-related DRGs see appendix D.

Total direct disease-related costs (outpatient and inpatient)

Figure 4-2 shows the distribution of direct disease-related outpatient and inpatient costs for the control and intervention group as boxplots.

In both patient groups most costs arose through the antineoplastic therapy (control group 70 %, intervention group 73 %), followed by inpatient costs (control group 17 %, intervention group 14 %) and then costs for supportive therapy (control group 9 %, intervention group 8 %). In the intervention group the oncologist fee and costs for diagnostics were equal (3 % and 3 %). In the control group the oncologist fee (3 %) was higher than costs for diagnostics (1 %). In both patient groups costs for administration were negligible small (control group 0.1 %, intervention group 0.0 %).

The mean total costs per patient amounted to € 22384 (median: € 16224, SD: € 20362) in the control group. In the intervention group the mean total cost per patient amounted to € 20726 (median: € 20020, SD: € 12790). The difference was not statistically significant (p = 0.832, Mann-Whitney-U).

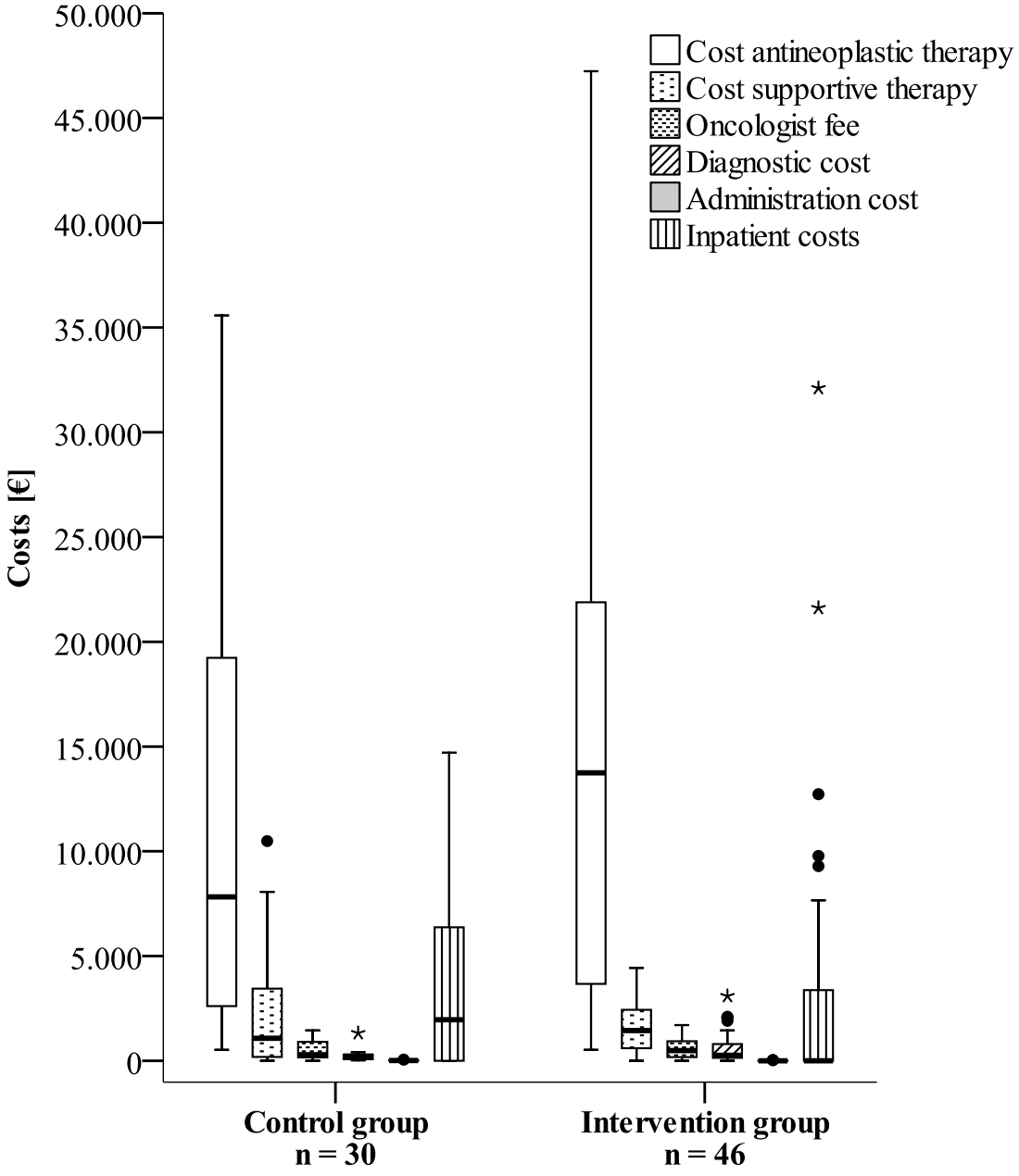


Figure 4-2: Direct disease-related outpatient and inpatient costs as boxplots

(For reasons of clarity two extreme values in the control group were excluded (costs for antineoplastic therapy of € 93319 and € 51112). In the intervention group the categories oncologist fee, diagnostic cost and administration cost have an n of 45 because of missing values.)

4.4 Direct non-medical disease-related costs

Help with every-day activities

Table 4-4 shows the answers of the control and intervention patients to the question if they needed help with every-day activities. The question was answered three times during the study.

Table 4-4: Need of help with every-day activities at three different time-points

Time	Need of help	Control group		Intervention group		P value*
		n	%	n	%	
t_0	Yes	6	20.0	14	30.4	0.426
	No	24	80.0	32	69.6	
	Questionnaire missing	0	0.0	0	0.0	
t_6	Yes	6	24.0	9	22.0	1.000
	No	19	76.0	31	75.6	
	Questionnaire missing	0	0.0	1	2.4	
t_7	Yes	4	16.0	4	10.3	0.700
	No	18	72.0	29	74.4	
	Questionnaire missing	3	12.0	6	15.3	

**Fisher´s exact test*

At t_6 five patients had died in each group (17 % control group, 11 % intervention group). At t_7 five patients were dead in the control group (17 %) versus seven in the intervention group (15 %).

The differences between the control and intervention group were not statistically significant (see p values in table 4-4). The differences within the control group between the three time-points showed the following p values (McNemar test): t_0 versus t_6: p = 1.000 (not significant); t_0 versus t_7: p = 1.000 (not significant). The differences within the intervention group between the three time-points showed the following p values (McNemar test): t_0 versus t_6: p = 1.000 (not significant); t_0 versus t_7: p = 0.687 (not significant).

In case the patients indicated that they needed help with every-day activities they were asked who mostly provided the help. The answers are shown in table 4-5.

Table 4-5: Help provider (Evaluation for t_0, t_6, t_7 at once)

Help provider	Control group		Intervention group	
	n	%	n	%
Family / friends	12	75.0	26	96.3
Professional care service	1	6.2	1	3.7
Voluntary organisation	0	0.0	0	0.0
Others	0	0.0	0	0.0
No answer	3	18.8	0	0.0

The option "family / friends" was indicated most frequently in both patient groups (75 % in control group and 96 % in intervention group). "Voluntary organisations" and "others" did not provide help for any patient.

4.5 Indirect non-medical disease-related costs

Loss of productivity

Table 4-6 shows the employment situation of control and intervention patients at three different time-points during the study.

Table 4-6: Employment situation at three different time-points

Time	Employment situation	Control group		Intervention group		P value*
		n	%	n	%	
t_0	Full-time job	3	10.0	5	10.9	0.458
	Part-time job	2	6.7	4	8.7	
	Unable to work	6	20.0	14	30.4	
	Pensioner	18	60.0	18	39.1	
	Housewife	1	3.3	5	10.9	
	No answer / missing	0	0.0	0	0.0	
t_6	Full-time job	1	4.0	7	17.1	0.089
	Part-time job	2	8.0	4	9.8	
	Unable to work	7	28.0	11	26.8	
	Pensioner	15	60.0	13	31.7	
	Housewife	0	0.0	5	12.2	
	No answer / missing	0	0.0	1	2.4	
t_7	Full-time job	0	0.0	6	15.4	0.012
	Part-time job	2	8.0	5	12.8	
	Unable to work	7	28.0	5	12.8	
	Pensioner	15	60	13	33.3	
	Housewife	0	0.0	6	15.4	
	No answer / missing	1	4.0	4	10.3	

**Fisher's exact test (the category no answer / missing was not considered)*

No patient indicated "unemployed" or "student" as current employment situation at any time. Table 4-6 shows that from three control patients with full-time jobs at t_0 no one was left after

six months. During the study period two control patients were working part-time. In the intervention group five patients were on a full-time job at t_0 and six at t_7. There were five patients with a part-time job at t_7 in comparison to four at t_0. A reduction took place in the section “unable to work” in the intervention patients from fourteen at the beginning via eleven in the middle and five at the end of the study. Four answers were missing at t_7. The differences between the control and intervention group were statistically significant at t_7 (see p value in table 4-6).

The differences within the control patients in the groups “able to work” versus “unable to work” between the three points of measurements showed the following p values (McNemar): t_0 versus t_6: p = 0.500 (not significant); t_0 versus t_7: p = 0.625 (not significant). The differences within the intervention patients in the groups “able to work” versus “unable to work” between the three points of measurements showed the following p values (McNemar): t_0 versus t_6: p = 0.625 (not significant); t_0 versus t_7: p = 0.125 (not significant).

From those patients who indicated “full-time job”, “part-time job” or “unable to work” at the time of inclusion the number of days on sick leave were evaluated at the end of the study. Nineteen control patients and 23 intervention patients had stated “pensioner” or “housewife” and were therefore not asked for days on sick leave. From the remaining eleven control and 23 intervention patients, information about days on sick leave could be received from eight control and 17 intervention patients (three and six missing values, respectively). Four out of eight control patients (50 %) and eight out of 17 intervention patients (47 %) were unable to work during the whole study period. The results are illustrated in figure 4-3 as boxplots.

The median number of days on sick leave amounted to 121 days in the control and 93 days in the intervention group. The days on sick leave were then multiplied by the average German gross wage per day of € 142.14. In patients that stated pensioner or housewife costs of € 0.00 were assumed. This amounted to mean indirect costs of € 4206.29 per control patient (min: € 0.00; max: € 18193.92; median: € 0.00; SD: € 7174.93) and of € 4992.67 per intervention patient (min: € 0.00; max: € 18193.92; median: € 0.00; SD: € 7371.50). The differences were not statistically significant (p = 0.464, Mann-Whitney-U). When adding the indirect costs to the total cost calculation indirect costs amounted to 14 % of total costs in the control and of 17 % in the intervention group (table 4-7).

For more information on indirect cost per patient see appendix D.

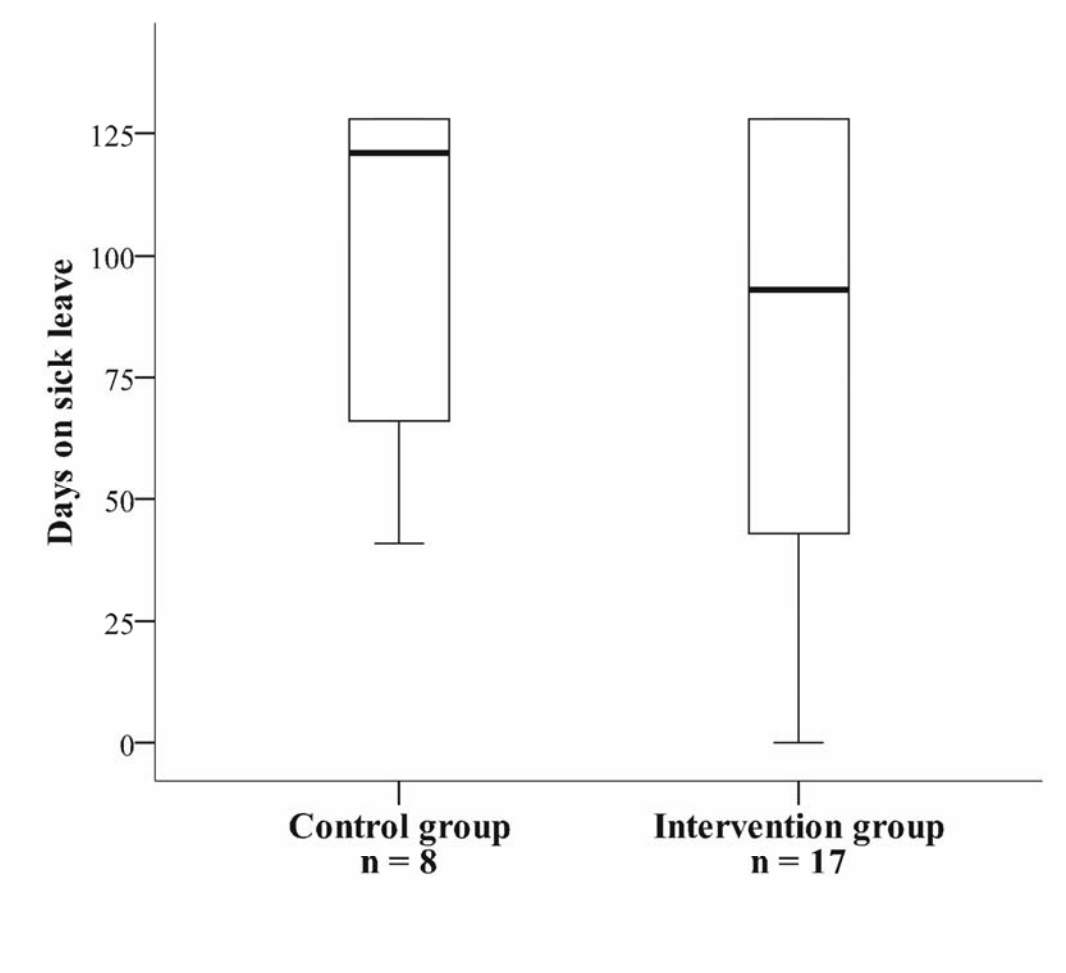


Figure 4-3: Days on sick leave in the control and intervention group

Table 4-7: Direct costs (outpatient and inpatient costs) and indirect costs

	Direct costs [€]	Indirect costs [€]
Control group		
Total costs:	671527	113570
%:	86	14
Median costs/patient:	16224	0
Mean costs/patient:	22384	4206
SD:	20362	7175
Intervention group		
Total costs:	953405	199707
%:	83	17
Median costs/patient:	20020	0
Mean costs/patient:	20726	4993
SD:	12790	7372
p value*:	0.832	0.464

**Mann-Whitney-U*

4.6 Patients´ quality of life

EQ-5D descriptive system

Table 4-8 summarises the results of the descriptive system of the EQ-5D questionnaire. A value of 1.0 implies "no problems", 2.0 "some problems" and 3.0 implies "severe problems".

Table 4-8: Median, mean and standard deviation of the EQ-5D descriptive system at four different times for the control and intervention group during treatment with capecitabine

EQ-5D dimension	Control group				Intervention group			
	t_0	t_3	t_6	t_7	t_0	t_3	t_6	t_7
n	28	16	9	11	46	39	30	18
Mobility								
Median	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Mean	1.43	1.44	1.22	1.27	1.46	1.38	1.37	1.39
SD	0.50	0.51	0.44	0.47	0.50	0.54	0.49	0.50
Self-Care								
Median	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Mean	1.21	1.06	1.0	1.09	1.15	1.10	1.10	1.11
SD	0.50	0.25	0.0	0.30	0.42	0.31	0.31	0.32
Usual Activities								
Median	2.0	2.0	1.0	1.0	2.0	2.0	2.0	1.0
Mean	1.61	1.75	1.33	1.45	1.70	1.64	1.63	1.33
SD	0.57	0.68	0.50	0.52	0.73	0.71	0.62	0.59
Pain / Discomfort								
Median	2.0	2.0	2.0	1.0	2.0	2.0	2.0	2.0
Mean	1.79	1.81	1.78	1.55	1.72	1.74	1.67	1.78
SD	0.50	0.54	0.67	0.69	0.58	0.60	0.48	0.65
Anxiety / Depression								
Median	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Mean	1.36	1.50	1.22	1.27	1.43	1.33	1.40	1.28
SD	0.56	0.63	0.44	0.47	0.54	0.58	0.56	0.58

SD = standard deviation

At the time of inclusion the median values for all five dimensions were the same in both patient groups (see table 4-8). There were, however, differences in the mean values. In three dimensions ("mobility", "usual activities" and "anxiety/depression") the mean values were higher in the intervention group than in the control group (e.g. usual activities 1.61 vs. 1.70) indicating slightly more problems. In both patient groups there was no increase in median values at any time. In the control group there was a decrease in median values in two categories: in the dimension "usual activities" from 2.0 (= some problems) at t_3 to 1.0 (= no problems) at t_6 and t_7 and in the dimension "pain" from 2.0 (= moderate pain) at t_6 to 1.0 (=

none) at t_7. In the intervention group there was a decrease in median value in the dimension "usual activities" from 2.0 (= some problems) at t_6 to 1.0 (= no problems) at t_7. For the frequency distribution of the EQ-5D scores at the four different points of measurement see appendix D.

Utility scores from the EQ-5D descriptive system

The five-digit number of the descriptive system was converted into the EQ-5D utility score. For these results see chapter 4.8.1 "QALYs from EQ-5D questionnaire".

EQ-5D VAS

Table 4-9 shows the patients´ own assessment of their health states during treatment with capecitabine using the EQ-5D VAS as mean scores plus standard deviation and median scores plus interquartile range.

Table 4-9: EQ-5D VAS score

	Control group				Intervention group			
	t_0	**t_3**	**t_6**	**t_7**	**t_0**	**t_3**	**t_6**	**t_7**
n	29	19	11	11	46	40	29	18
Mean	55.9	58.4	65.0	69.1	63.2	59.1	65.3	69.7
SD	19.8	20.1	21.5	18.3	21.3	23.2	20.4	25.1
Median	52.5	60.0	65.0	70.0	62.5	60.0	70.0	80.0
IQR	47.5-70.0	40.0-70.0	50.0-80.0	60.0-80.0	50.0-80.0	40.0-73.8	52.5-80.0	40.0-90.0

SD = standard deviation, IQR = interquartile range

At the time of inclusion the intervention group started at a higher VAS score than the control group (not statistically significant: p = 0.133, Mann-Whitney-U test). In the intervention group there was a minimal deterioration of VAS scores at t_3 and an improvement again at t_6 and also at t_7. Figure 4-4 shows the above-mentioned data in a VAS score-time curve.

For data on absolute changes in the VAS scores between t_0 and t_3, t_6, t_7 for control and intervention patients see appendix D.

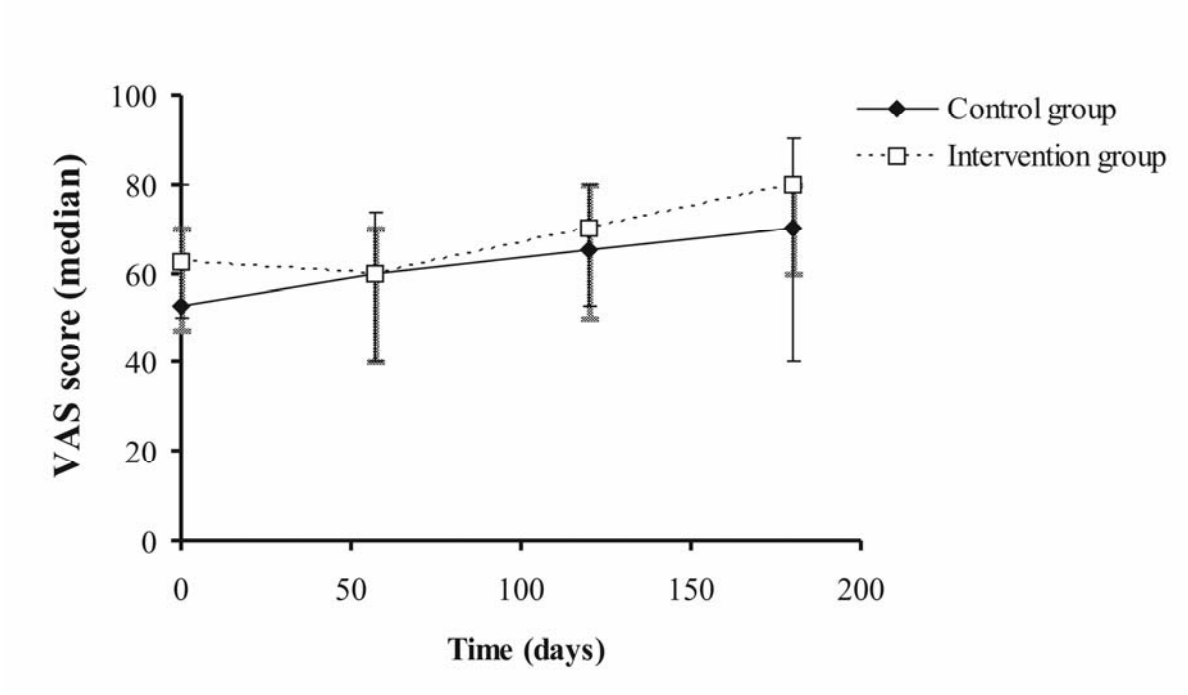


Figure 4-4: VAS score-time curve

(n control group: t_0: 29, t_3: 19, t_6: 11, t_7: 11; n intervention group: t_0: 46, t_3: 40, t_6: 29, t_7: 17; error bars = interquartile range (thick, grey = control group, thin, black = intervention group))

4.7 Adverse effect hand-foot syndrome

Figure 4-5 gives an overview of HFS grades at seven different points of measurement in the control and intervention group. The figure summarises only the results of those HFS questionnaires in which the patients were under treatment with capecitabine.

In the intervention group the median HFS grade did not exceed grade 1 at any time during the study period. In the control group the median HFS grade was grade 2 twice: at t_5 and at t_7. Here the differences between the intervention and control group were statistically significant (t_5: $p = 0.023$, t_7: $p = 0.019$, Cochran-Armitage test for trend).

Concerning HFS grade 3 six out of 30 control patients (20 %) experienced HFS grade 3 at least once during the treatment with capecitabine versus only seven out of 46 intervention patients (15 %) ($p = 0.588$, Chi-Square test).

For more information on the number of missing questionnaires, patients without treatment of capecitabine and the number of dead patients at the seven different points of measurement see appendix D.

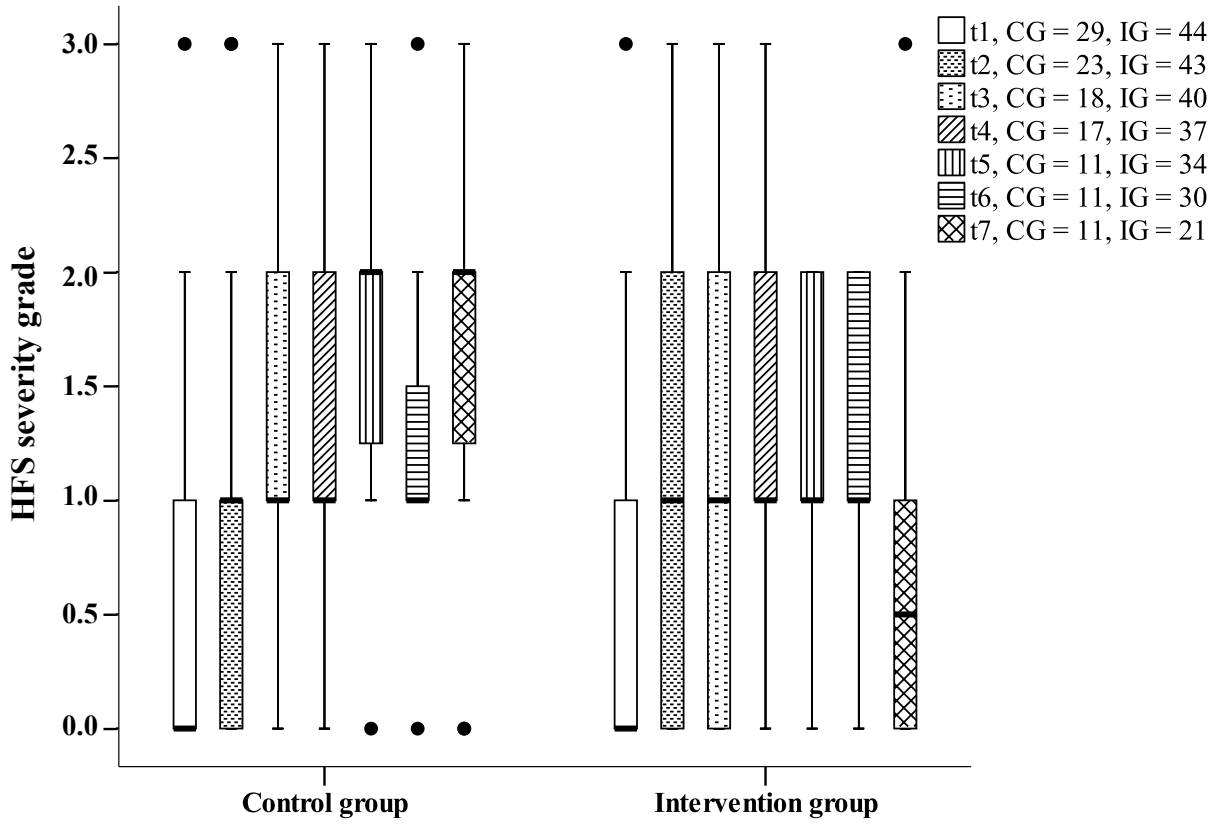


Figure 4-5: HFS grades under treatment with capecitabine

(CG = control group, IG = intervention group; numbers in the legend represent number of analysed control and intervention patients)

Utility scores from the HFS questionnaire

The patient-reported HFS grades were converted into HFS utility scores using the TTO-based utility scores generated earlier in the diploma thesis of D. Güney (Department of Clinical Pharmacy, University of Bonn). For these results see chapter 4.8.2 "QALYs from hand-foot syndrome questionnaire".

4.8 Quality-adjusted life years

4.8.1 QALYs from the EQ-5D descriptive system

The five-digit number of the descriptive system during treatment with capecitabine was converted into the EQ-5D utility score. Table 4-10 gives a summary of the generated utility scores in both patient groups.

Table 4-10: Utility scores in control and intervention group during treatment with capecitabine

	Control group				Intervention group			
	t_0	**t_3**	**t_6**	**t_7**	**t_0**	**t_3**	**t_6**	**t_7**
n	28	16	9	11	46	39	30	18
Mean	0.810	0.789	0.844	0.866	0.797	0.781	0.845	0.796
SD	0.206	0.212	0.199	0.225	0.230	0.239	0.179	0.255
Median	0.887	0.887	0.887	0.999	0.887	0.887	0.887	0.887
IQR	0.723-0.897	0.788-0.897	0.788-1.000	0.788-1.000	0.788-1.000	0.788-1.000	0.788-0.999	0.766-1.000

SD = standard deviation, IQR = interquartile range

Intervention and control patients started at the same median utility score and nearly the same mean utility score at the time of inclusion. The intervention patients were stable in their median utility score during the whole study period. The control patients were stable in their median utility score until t_6 and showed an improvement at t_7. Figure 4-6 shows the absolute changes in utility scores between t_0 and t_3, t_6, t_7 for the control and intervention group.

In the median there was no change in utility scores at any time in both patient groups.

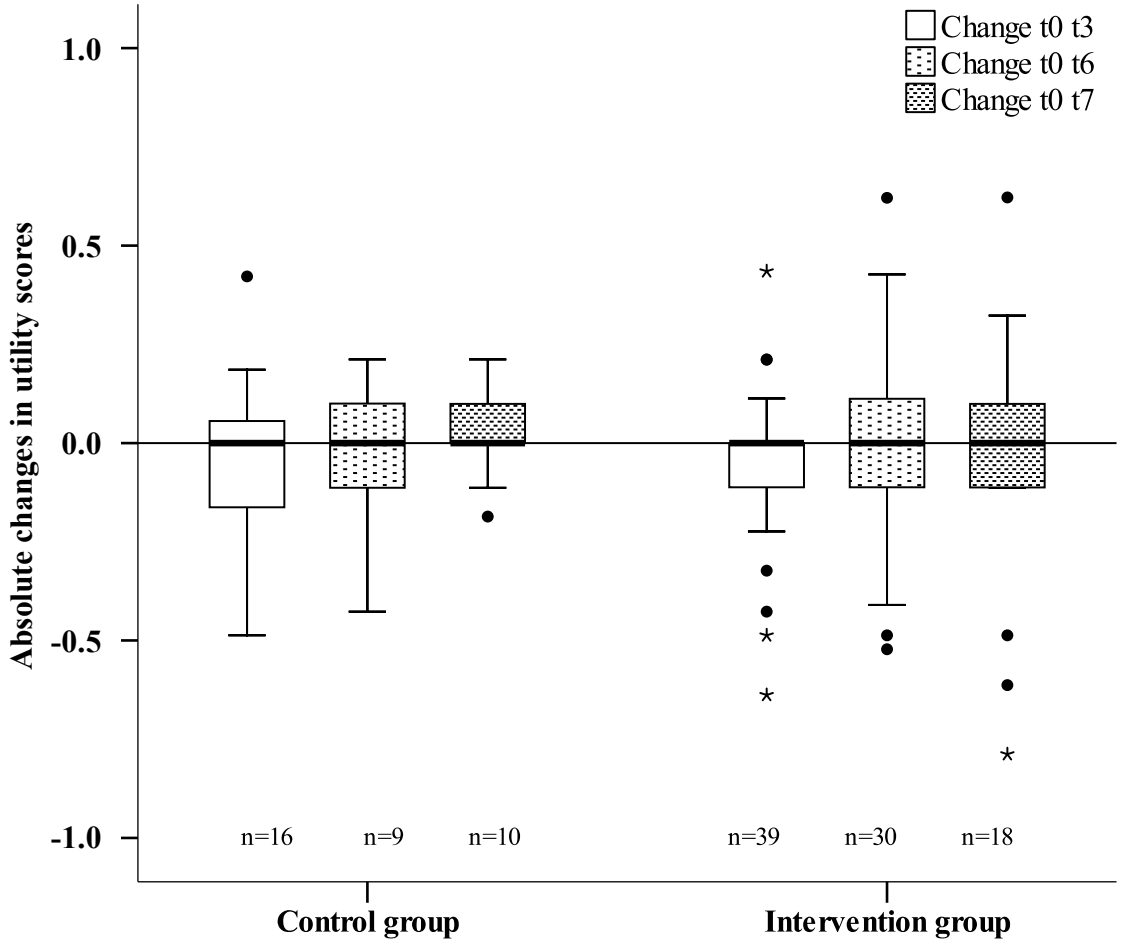


Figure 4-6: Absolute changes in EQ-5D utility scores between t_0 and t_3, t_0 and t_6 and t_0 and t_7 for control and intervention patients

(t_0 and t_3: control group median = 0.0, intervention group median = 0.0 (p = 0.947, Mann-Whitney-U); t_0 and t_6: control group median = 0.0, intervention group median = 0.0 (p = 0.603, Mann-Whitney-U); t_0 and t_7: control group median = 0.0, intervention group median = 0.0 (p = 0.694, Mann-Whitney-U))

In the control group QALYs based on the utility scores from the EQ-5D descriptive system could be calculated for eight patients (27 %). In three patients (10 %) at least one of four utility scores (t_0, t_3, t_6, t_7) during treatment with capecitabine was missing, in 14 patients (47 %) capecitabine treatment was stopped before the end of the study period for different reasons and five patients (17 %) died before the end of the study period and therefore QALYs were not calculated. In the intervention group QALYs could be calculated for 17 patients (37 %). In four patients (9 %) at least one of four utility scores during treatment with capecitabine was missing, in 18 patients (39 %) capecitabine treatment was stopped before the

end of the study period for different reasons and seven patients (15 %) died before the end of the study period and therefore QALYs were not calculated. Table 4-11 summarises the results of the QALY and QALD calculation per patient in both patient groups.

Table 4-11: QALYs and QALDs in the control and intervention group

	Control group	Intervention group	P value*
n	8	17	
QALY [year]			
Median	0.44	0.42	
IQR	0.41-0.48	0.37-0.47	0.364
Mean	0.43	0.41	
SD	0.07	0.08	
QALD [day]			
Median	160.0	154.9	
IQR	148.8-174.8	134.9-170.1	0.414
Mean	155.1	148.6	
SD	26.5	28.6	

**Mann-Whitney-U test, IQR = interquartile range, SD = standard deviation, QALY = quality-adjusted life year, QALD = quality-adjusted life day*

There was nearly no difference in QALYs and QALDs between the two patient groups. The control group gained slightly more QALYs than the intervention group: a median of 0.44 QALYs versus 0.42 QALYs. In terms of QALDs the control group gained 5.1 more QALDs in the median than the intervention group. The differences were not statistically significant.

Figure 4-7 illustrates the utility-time curve for both patient groups. The calculation of QALDs and QALYs was based on the results of table 4-10. This approach also considered the available utility scores of those patients with at least one of four utility scores missing during the study period.

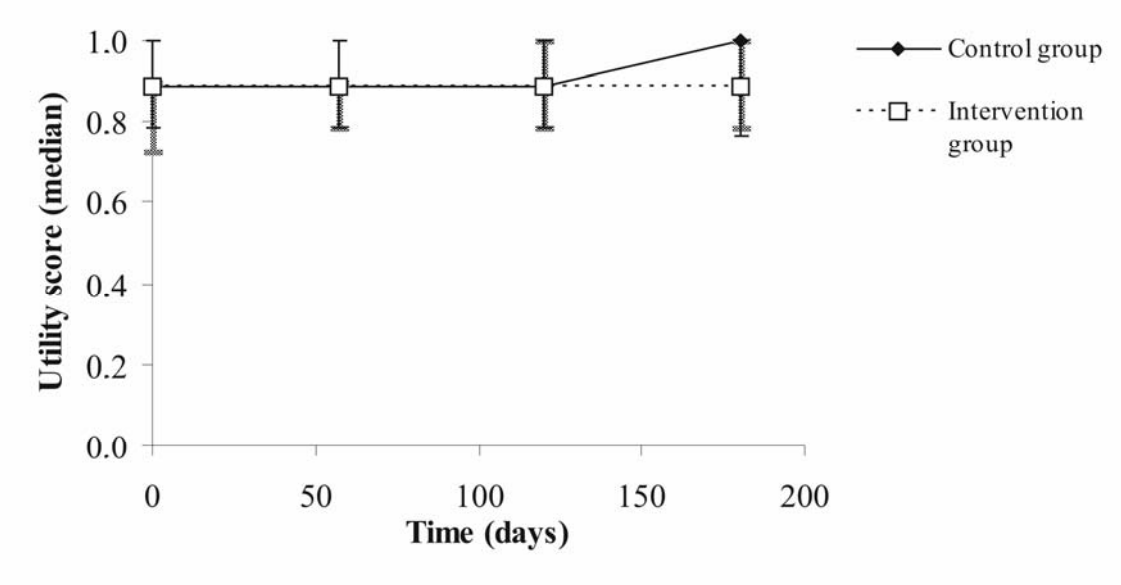


Figure 4-7: Utility-time curve during treatment with capecitabine for calculation of QALDs and QALYs

(n control group: t_0: 28, t_3: 16, t_6: 9, t_7: 11; n intervention group: t_0: 46, t_3: 39, t_6: 30, t_7: 18; AUC control group: 163.1 QALDs, AUC intervention group:: 159.7 QALDs; error bars = interquartile range (thick, grey = control group, thin, black = intervention group))

This approach also shows that there is nearly no difference between the control and the intervention group. The control group gained 0.45 QALYs and the intervention group 0.44 QALYs. With regard to the QALDs 3.4 more QALDs were gained in the control group compared to the intervention group.

4.8.2 QALYs from hand-foot syndrome questionnaire

In the control group QALYs based on the utility scores of the HFS grades could be calculated for 11 patients (37 %). In 19 patients (63 %) either more than one of seven utility scores (t_1, t_2, t_3, t_4, t_5, t_6, t_7) or the last utility score (t_7) was missing or capecitabine treatment was stopped before the end of the study period and therefore QALYs were not calculated. In the intervention group QALYs could be calculated for 20 patients (44 %). In 26 patients (57 %) either more than one of seven utility scores (t_1, t_2, t_3, t_4, t_5, t_6, t_7) or the last utility score (t_7) was missing or capecitabine treatment was stopped before the end of the study period and therefore QALYs were not calculated. For more information also see appendix D, table D-19. Table 4-12 summarises the results of the QALY and QALD calculation per patient in both patient groups.

Table 4-12: QALYs and QALDs based on HFS utility scores in the control and intervention group

	Control group	Intervention group	P value*
n	11	20	
QALY [year]			
Median	0.44	0.46	
IQR	0.40-0.47	0.44-0.48	0.420
Mean	0.44	0.45	
SD	0.04	0.04	
QALD [day]			
Median	162.1	167.5	
IQR	146.0-171.4	161.3-175.6	0.420
Mean	160.4	164.7	
SD	14.0	14.8	

**Mann-Whitney-U test, IQR = interquartile range, SD = standard deviation, QALY = quality-adjusted life year, QALD = quality-adjusted life day*

With the HFS-based approach the intervention group gained more QALYs then the control group: a median of 0.46 QALYs versus 0.44 QALYs. In terms of QALDs the intervention group gained 5.4 more QALDs in the median than the control group. The differences were not statistically significant.

Figure 4-8 illustrates the HFS-based utility-time curve for both patient groups. This approach also considered the available utility scores of those patients with more than one of seven utility scores or the last utility score missing.

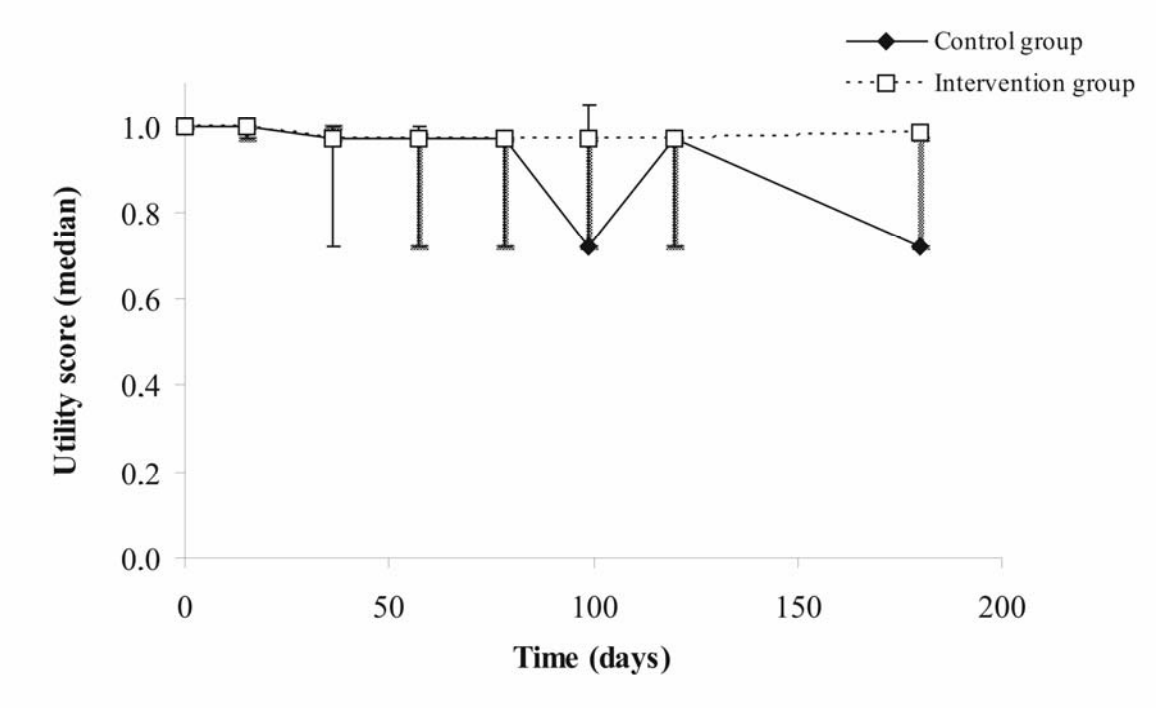


Figure 4-8: Utility-time curve and HFS-based calculation of QALDs and QALYs

(n control group: t_0: 30, t_1: 29, t_2: 23, t_3: 18, t_4: 17, t_5: 11, t_6: 11, t_7: 11; n intervention group: t_0: 46, t_1: 44, t_2: 43, t_3: 40, t_4: 37, t_5: 34, t_6: 30, t_7: 21; AUC control group: 162.6 QALDs; AUC intervention group: 175.8 QALDs; error bars = interquartile range (thick, grey = control group, thin, black = intervention group))

With this approach the intervention group also gained slightly more QALYs than the control group: 0.48 versus 0.45 QALYs. The difference between the QALDs amounts to 13.2 more QALDs in the intervention group. Table 4-13 summarises the HFS utility scores that formed the basis for figure 4-8.

Table 4-13: HFS utility scores in control and intervention group during treatment with capecitabine

		t_1	t_2	t_3	t_4	t_5	t_6	t_7
CG	n	29	23	18	17	11	11	11
	median	1.000	0.970	0.970	0.970	0.720	0.970	0.720
	IQR	0.970-1.000	0.970-1.000	0.720-0.978	0.720-0.970	0.720-0.970	0.720-0.970	0.720-0.970
IG	n	44	43	40	37	34	30	21
	median	1.000	0.970	0.970	0.970	0.970	0.970	0.985
	IQR	0.970-1.000	0.720-1.000	0.720-1.000	0.720-0.985	0.720-0.978	0.720-0.970	0.970-1.000

CG = control group, IG = intervention group, IQR = interquartile range

4.9 Patients´ "willingness-to-pay" for pharmaceutical care service

Thirty-two intervention patients (70 %) stated their willingness-to-pay for the received pharmaceutical care service on a monthly basis. 10 patients gave no answer (22 %) and 4 patients (9 %) were already dead at the time of assessment. The median "willingness-to-pay" amounted to € 45.00 / month (mean: € 72.20, SD: € 99.60, min: € 5.00, max: € 500.00). Table 4-14 gives an overview of the corresponding median and mean "WTP" and the household net income.

Table 4-14: Willingness-to-pay (WTP) per month and household net income

Net income of the household	**€ 1000 - < € 1500**	**€ 1500 - < € 2000**	**€ 2000 - < € 2500**	**€ 2500 - < € 3000**	**€ 3000 - < € 3500**	**≥ € 3500**	**no answer**
n	4	4	2	6	4	7	5
WTP/month (€)							
Median	10.0	75.0	45.0	17.5	100.0	50.0	30.0
Mean	31.3	95.0	45.0	30.0	87.5	107.1	87.0
SD	45.9	75.9	7.0	34.8	25.0	175.9	121.1

SD = standard deviation

The highest median "willingness-to-pay" per month with € 100.0 was stated by the second highest net income group of € 3000 to < € 3500. The lowest "willingness-to-pay" with € 10.0 was stated by the group with the lowest net income of € 1000 to < € 1500. Concerning the other net income groups no linear correlation could be found. As the group sizes were small no statistical tests were performed. No linear correlation could be found between the "willingness-to-pay" and the household net income per household member (adults and children) (see appendix D). The patients with a statutory health insurance (n=21) were willing to pay a median value of € 50.0 (mean: € 86.0, SD: € 118.7) while privately insured patients (n=11) were willing to pay a median of € 30.0 (mean: € 45.9, SD: € 37.5). The difference was not statistically significant (p = 0.547, Mann-Whitney-U test).

According to section 4.3 "Costs for pharmacists" the pharmaceutical care service provided by a pharmacist amounted to € 94.26 for six months. The intervention patients were willing to pay € 45.0 per month amounting to € 270.0 per six months thus leading to a surplus of € 175.74 in six months. This showed that the benefit for the patient was higher than the money that had to be invested for the service when considering the costs for pharmacists only.

4.10 Cost-utility analysis

4.10.1 Matched-pairs between control and intervention group

All outpatient and inpatient cost data as well as the EQ-5D measurements were available from 21 out of 30 control patients (70 %) and 36 out of 46 intervention patients (78 %). Only these patients entered the matching process. Concerning the main matching parameters tumour entity, treatment setting, antineoplastic regimen at the time of inclusion, treatment with bisphosphonates at the time of inclusion and type of health insurance 15 intervention and eleven control patients were identified, resulting in eleven matched patient pairs (table 4-15):

Table 4-15: Number of control and intervention patients in coinciding matching parameters

Tumour Entity	Treatment setting	Therapy regimen	Bis-phosphonate	Health insurance	CG [n]	IG [n]
Breast	Adjuvant	Cap Pac	No	Statutory	1	2
Breast	Palliative	Cap	Yes	Statutory	4	4
Breast	Palliative	Cap	No	Statutory	1	1
Breast	Palliative	Cap Tras	Yes	Private	1	1
Colorectal	Neoadjuvant	Cap Ox	No	Statutory	1	1
Colorectal	Palliative	Cap	No	Statutory	1	3
Colorectal	Palliative	Cap Beva	No	Statutory	2	3
Sum					11	15

Therapy regimen: Cap = capecitabine monotherapy; Cap Beva = capecitabine + bevacizumab; Cap Ox = capecitabine + oxaliplatin; Cap Pac = capecitabine + paclitaxel; Cap Tras = capecitabine + trastuzumab

Where more than one intervention patient matched with one control patient (e.g. 2:1) one intervention patient was selected at random to form a ratio of 1:1. Appendix D shows the random selection of matched patient pairs. At the time of inclusion the selected control patients had a mean age of 63.3 years (SD: 13.1; median: 66.0; min: 39; max: 80 years) and selected intervention patients of 55.8 years (SD: 10.0; median: 55.0; min: 35; max: 75 years). This difference was not statistically significant ($p = 0.172$, t-test). Concerning quality of life represented by the utility score at the time of inclusion there was no statistically significant difference between the two selected patient groups ($p = 0.519$, Mann-Whitney-U). Both groups started with a median utility score of 0.887 and a mean score of 0.813 (SD: 0.171) in the control and of 0.829 (SD: 0.237) in the intervention group. The socio-demographic characteristics of the eleven matched patient pairs at the time of inclusion are shown in appendix D.

4.10.2 Direct disease-related costs of matched-pairs

Table 4-16 summarises the direct disease-related costs of the eleven matched patient pairs.

Table 4-16: Direct disease-related costs of eleven matched-pairs

	Anti-neopl. therapy [€]	Supp. therapy [€]	Oncol. fee [€]	Diagn. cost [€]	Admin. cost [€]	In-patient cost [€]	Total direct costs[1] [€]
Control group							
Sum	104397	31780	4652	3015	171	32867	176879
%	59.0	18.0	2.6	1.7	0.1	18.6	100.0
Median cost/patient	4721	1442	234	204	16	0	15755
Mean cost/patient	9491	2889	423	274	16	2988	16080
SD	10717	3523	401	369	13	5148	11308
Intervention group							
Sum	122050	17896	4337	2778	126	23508	171662
%	71.1	10.4	2.5	1.6	0.1	13.7	100.0
Median cost/patient	4721	1356	204	208	12	0	9071
Mean cost/patient	11095	1627	394	253	11	2137	15606
SD	12739	1617	407	329	10	6485	13816
p value*:	0.797	0.562	0.949	0.949	0.606	0.519	0.748

**Mann-Whitney-U test, SD = Standard deviation, Antineopl. = antineoplastic, Supp. = supportive, Oncol. = oncologist, Diagn. = diagnostic, Admin. = administration*

[1]Total direct cost of the intervention group also contains the cost for pharmacist of € 968 (0.6 %; median: € 94; mean: € 88; SD: € 21).

The corresponding study period of the eleven control patients was 1561 days (median: 180.0, mean: 141.9, SD: 53.8) and therefore shorter than of the eleven intervention patients with 1848 days (median: 180.0, mean: 168.0, SD: 39.8). The difference was not statistically significant (p = 0.365, Mann-Whitney-U).

For both patient groups most costs arose through the antineoplastic therapy, followed by inpatient cost, costs for supportive therapy, oncologist fee, diagnostics, and finally, with a very small portion, administration costs. In the intervention group costs for pharmacists were between costs for diagnostics and administration. In the selected control patients the costs for supportive therapy were nearly as high as the costs for inpatient stays (€ 31780 versus € 32867).

The main difference between both selected patient groups existed between the costs for antineoplastic therapy. These costs were higher in the intervention group than in the control group. The main reason for the difference observed was the colorectal cancer patient C 10 who was treated with capecitabine and bevacizumab at the time of inclusion but declined the

treatment after one cycle and died on day 61 of the study resulting in very low costs of € 525 for antineoplastic therapy. The treatment with bevacizumab was applied during an inpatient stay and was considered there. In comparison the cost for antineoplastic therapy of a matching intervention patient (e.g. CI 16) amounted to € 25304.

Costs for supportive therapy were vice versa. These costs were higher in the control group than in the intervention group. The main reasons were the supportive treatments of the two control patients B 4 and B 6 and to a smaller extent B 12. B 4 and B 6 both received supportive therapy with Neulasta® containing the substance pegfilgrastim, a human granulocyte-colony-stimulating factor. Treatment with one pre-filled syringe costs about € 1550. Besides, B 4 received parenteral nutrition after one and a half months in the study causing costs of about € 3300. B 6 received i.v. iron dextrane (Cosmofer®) for iron insufficiency amounting to costs of about € 710. B 12 was treated four times for chemotherapy-induced anaemia with Aranesp® containing darbepoetin-alpha resulting in costs of about € 2300. No intervention patient received any of these therapies, except for BI 16 who was treated with Aranesp® once. Instead of treatment with epoetin-analoga e.g. CI 3 and CI 20 were treated with human erythrocyte concentrates resulting in costs of € 162 each.

Concerning inpatient costs the costs were again higher in the control group in comparison to the intervention group. From the selected eleven control patients four showed inpatient stays, whereas only two intervention patients were hospitalised during the study period. One patient in the selected control group (B 12) was hospitalised due to an adverse drug reaction of the chemotherapy (fever under chemotherapy). No patient in the selected intervention group was hospitalised due to adverse drug reactions.

Regarding oncologist fees, costs for diagnostics and administration only small differences were observed between the selected patient groups in relation to the cost categories discussed above.

Finally, the total costs were higher in the selected control group than in the selected intervention group. For all details on resource-utilisation and cost calculation of the matched patient pairs see appendix D.

4.10.3 QALYs of matched-pairs

QALYs and QALDs based on the EQ-5D questionnaire of the matched-pairs are shown in table 4-17.

Table 4-17: QALYs and QALDs based on the EQ-5D questionnaire

	Control group		Intervention group	
	QALY [year]	**QALD [day]**	**QALY [year]**	**QALD [day]**
Sum	3.52	1286	4.37	1594
Median/patient	0.44	160	0.45	163
Mean/patient	0.32	117	0.40	145
SD	0.19	68	0.14	52

QALY = quality-adjusted life year, QALD = quality-adjusted life day, SD = standard deviation

The highest achievable sum of QALYs and QALDs were 5.39 (0.49 QALYs x 11) and 1980 (180 QALDs x 11) respectively. The selected intervention patients led to a higher sum of QALYs (84 % of highest achievable score) than the control patients (65 % of highest achievable score). The differences were not statistically significant (p = 0.797, Mann-Whitney-U).

The QALYs and QALDs based on the HFS questionnaire could only be calculated for three control patients and for four intervention patients. In the other patients either more than one utility score was missing or the patients were not treated with capecitabine for the whole study period. Because of the small sample size these data were not used for further analysis.

4.10.4 Incremental cost-utility ratio

For the eleven matched patient pairs the ICUR should be calculated. There was a gain in QALYs at reduced costs indicating that the intervention ‘pharmaceutical care’ dominates the comparator ‘standard care’. Therefore the incremental cost-utility ratio (costs per QALY gained) was not calculated.

- The difference in mean QALYs amounted to:

  $$0.40\ QALYs_{IG} - 0.32\ QALYs_{CG} = 0.08\ QALYs$$

- The difference in mean direct costs amounted to:

  $$€\,15605.63_{IG} - €\,16079.92_{CG} = -\,€\,474.29$$

Through the delivery of pharmaceutical care for six months to one patient 0.08 QALYs could be gained in comparison to not delivering that service and at the same time € 474 could be saved.

4.10.5 Nonparametric bootstrapping

Figure 4-9 shows the estimate of the empirical distribution of cost-effectiveness.

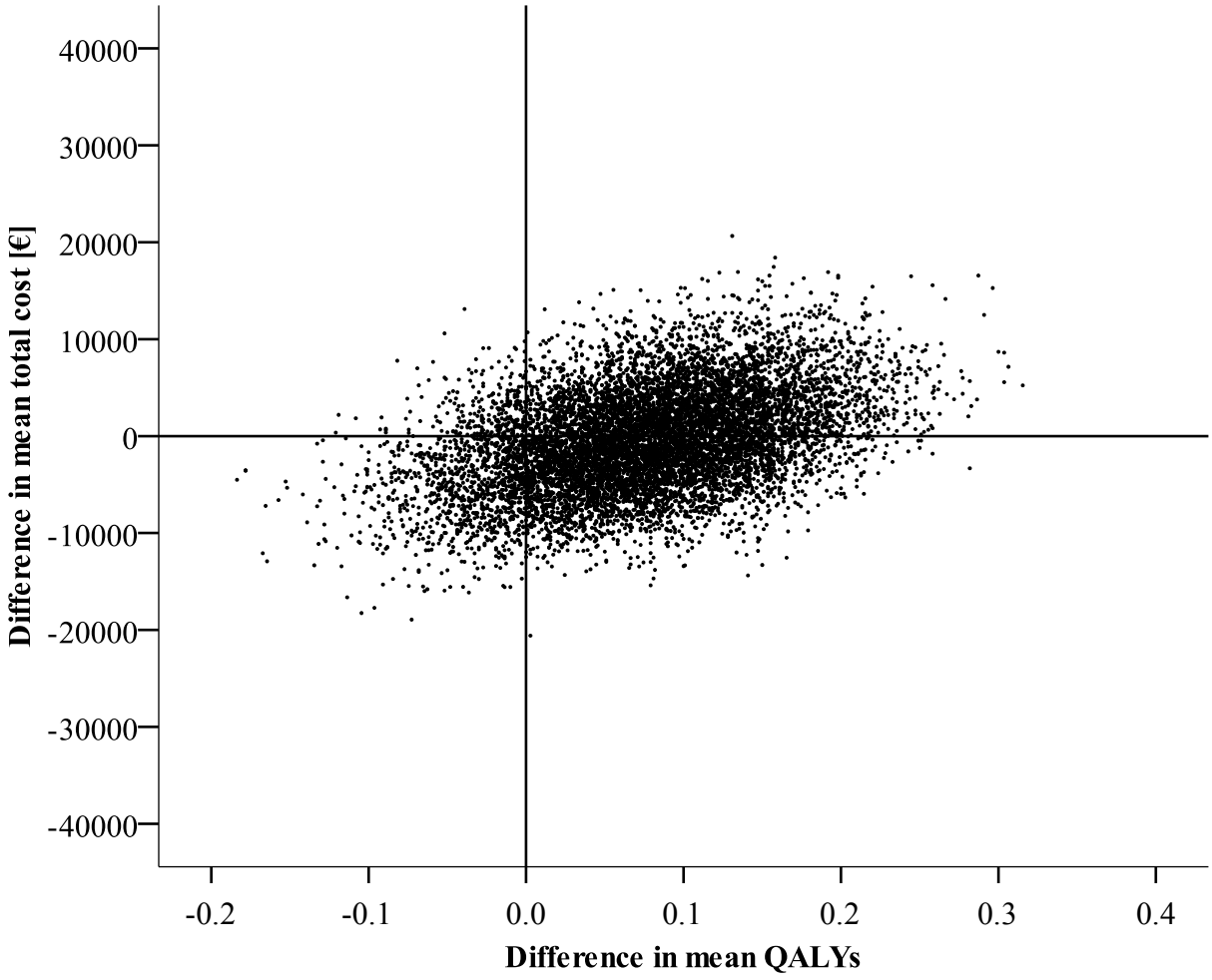


Figure 4-9: Cost-effectiveness plane showing differences between intervention and control group after 10000 bootstrap replications

The intervention group showed lower costs and more QALYs than the control group in 43 % of all replications (south-east quadrant); more costs and more QALYs in 44 % of all replications (north-east quadrant); lower costs and less QALYs in 10 % of all replications (south-west quadrant) and more costs and less QALYs in 3 % of all replications (north-west quadrant). The bootstrap results of the south-east and north-east quadrants (together 87 % of

all replications) were then used to plot the cost-effectiveness acceptability curve (figure 4.10). The highest achievable probability was therefore 87 %.

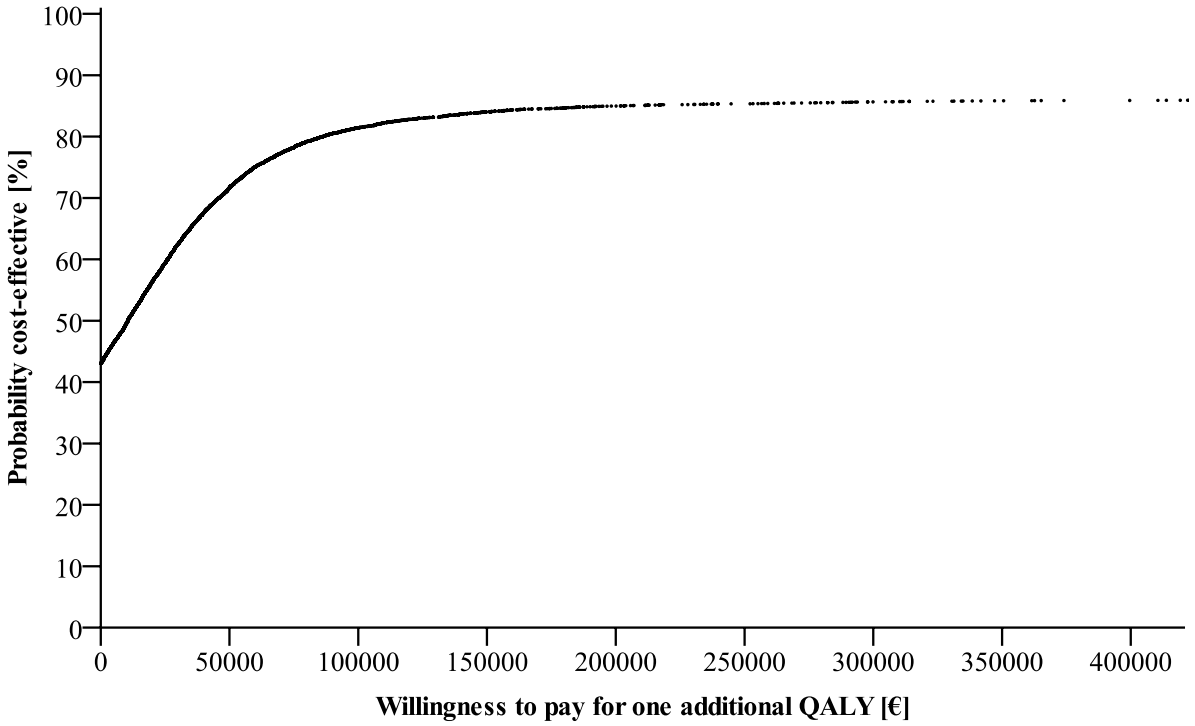


Figure 4-10: Cost-effectiveness acceptability curve

The probability that pharmaceutical care was more cost-effective than standard care was 43 % at a willingness to pay (WTP) for an additional QALY of € 0, reaching 62 % probability at a WTP of € 29000 per additional QALY.

4.10.6 Sensitivity analysis

Two simple one-way analyses were performed with the cost and outcome data of the eleven matched-pairs.

The assumption of **double cost for pharmacists** of € 45.98 / hour led to the following results:

- The difference in mean QALYs amounted to:

  $0.40\ QALYs_{IG} - 0.32\ QALYs_{CG} = 0.08\ QALYs$

- The difference in mean direct costs amounted to:

  $€\ 15685.04_{IG} - €\ 16079.92_{CG} = -\ €\ 394.88$.

The transformation of the EQ-5D digits into utilities based on the **UK TTO** set of preference weights resulted in the following results:

- The difference in mean QALYs amounted to:

  $$0.36\ QALYs_{IG} - 0.29\ QALYs_{CG} = 0.07\ QALYs$$

- The difference in mean direct costs amounted to:

  $$€\,15605.63_{IG} - €\,16079.92_{CG} = -\,€\,474.29$$

Furthermore, an analysis of extremes was accomplished.
By replacing the randomly selected patients BI 16 and CI 16 by the equally matching patients BI 21 and CI 17 the **"best case"-scenario** was received:

- The difference in mean QALYs amounted to:

  $$0.40\ QALYs_{IG} - 0.32\ QALYs_{CG} = 0.08\ QALYs$$

- The difference in mean direct costs amounted to:

  $$€\,15262.01_{IG} - €\,16079.92_{CG} = -\,€\,817.91$$

By replacing the randomly selected patients CI 13 and CI 1 by the also matching patients CI 17 and CI 20 the **"worst case"-scenario** was received:

- The difference in mean QALYs amounted to:

  $$0.41\ QALYs_{IG} - 0.32\ QALYs_{CG} = 0.09\ QALYs$$

- The difference in mean direct costs amounted to:

  $$€\,18002.76_{IG} - €\,16079.92_{CG} = €\,1922.84$$

As in the "worst case"-scenario the intervention no longer dominated the comparator, as money had to be invested to gain QALYs, the $ICUR_{worst\ case}$ could be calculated:

$$ICUR_{worst\ case} = \frac{€\,18002.76_{IG} - €\,16079.92_{CG}}{0.41\ QALYs_{IG} - 0.32\ QALYs_{CG}} = \frac{€\,1922.84}{0.09\ QALYs} = \frac{€\,21364.89}{QALY}.$$

The mean total costs in the "worst case" intervention patients were so high mainly because of a colorectal cancer patient (CI 20) who was treated with capecitabine for the first three months and was then switched to 5-FU, irinotecan and bevacizumab due to disease progression of his liver metastasis. The latter treatment resulted in costs of about € 20000.

The matched control patient (C 7) was treated with capecitabine only during the whole study period.

For all details on resource utilisation and cost calculation of the additional patients BI 21, CI 17 and CI 20 see appendix D.

5 Discussion

5.1 Study set-up

The present study on pharmaceutical care used a prospective, multi-centred observational cohort **study design** with a control group. The control group received standard care and was studied before the intervention group which received intensified pharmaceutical care.

Randomization is the most robust method of preventing selection bias; however a randomization of individual patients was not suitable to evaluate the present intervention for several reasons which will be discussed in the following. Pharmaceutical care must be regarded as a complex intervention since the service aims at both organisational and service modifications. At the same time it is targeted on other health care professionals with educational interventions in the form of e.g. supportive treatment guidelines or consideration of drug-drug interactions. Furthermore, pharmaceutical care has a direct influence on the individual patient with its behavioural aspect, the patient monitoring and education [86]. A recent review on economics of clinical pharmacy interventions recognized this peculiarity of studies on pharmaceutical care. They stated that physicians can learn from recommendations made by clinical pharmacists ("learning effects") and apply these recommendations to other patients who are not reviewed by pharmacists. When intervention and control patients are part of the same ward or practice population, this may have an effect on the outcomes of the control group. Rijdt et al. concluded that intervention and control groups should be selected from different wards or practices. The populations should have similar demographic characteristics and a comparable severity of disease [33]. Moreover, it would have been unethical if the pharmacist had reviewed e.g. the supportive therapy of the intervention patients and made guideline-based recommendations for adjustment while control patients were kept on the initial supportive therapy. Furthermore, intervention patients might have communicated advice of the study pharmacist to control patients in the same practice. It is known that patients who are treated concurrently in the same ward / practice intensively exchange their experiences with one another. As the pharmaceutical care service somehow also affected the organization on the practice / ward level it was impossible to recruit control and intervention patients at the same time [87]. A cluster randomization of study centres could have minimised some of these problems by randomizing, e.g., practices and outpatient wards rather than individual patients. Generally speaking, studies with only a few clusters (less than four) per group should be avoided [88]. In the present study the number of study centres was limited to six by practical and also financial constraints, thus not allowing for a

reasonable cluster randomization. Because of the above-mentioned reasons some limitations with regard to the study design in the present study had to be accepted. A cost-utility analysis of a disease management program (DMP) for patients with asthma was conducted in the Netherlands [89]. The researchers also collected control group data before the implementation of the DMP without any randomization, thus using a similar study design as in the present study. Steuten et al. also had substantive arguments to justify their study design. There was a lack of a "fair" comparison-region as in all potential comparison-regions innovations were being implemented that would have biased the measure of usual care.

The present study evaluated the contribution of two clinical pharmacists on costs and outcomes of cancer patients**.** Thus, the measured impact of **pharmaceutical care** depended on the skills and competence of the two clinical pharmacists rather than the potential of pharmaceutical care in general. To minimise an individual influence it was attempted to standardise the pharmaceutical care service. Each pharmacist-patient consultation followed a certain course, based on the pharmaceutical care plan. It was specified in which cases it was necessary to contact the attending oncologist. The pharmacists had received prior training to deliver a high quality service tailored to the particular needs of cancer patients treated with capecitabine. To promote a more sustained effect of education, the information of patients and physicians was not only based upon spoken words but also written material (e.g. individual patient letters, summaries of supportive guidelines). The study pharmacists informed patients and physicians according to the principles of evidence-based medicine, which is a prerequisite for a high quality pharmaceutical care service [90]. During the course of the study the clinical pharmacists received a lot of important information from the patient. These details, e.g. concerning self-administered medication and adverse drug effects, were mandatory for a successful pharmaceutical care service. This flow of information from the patient to the pharmacist was only possible in an atmosphere of mutual trust and was very important to solve and prevent drug related problems.

The two clinical pharmacists who delivered the care service collected cost and outcome data and analysed the results. This procedure possibly presents a conflict of interest. It would have been more suitable if the pharmaceutical care service and the research and evaluation of the service had not been conducted by the same persons. Furthermore, it would have been more appropriate if the researcher who evaluated the service had been blinded in respect of the group identity. However, due to the method of outcome data collection in both patient groups via pseudonymous, questionnaires and envelopes that were sent via mail to the central study office, the possible influence of the pharmacist on the patients´ response behavior was

limited. The patients did not complete the questionnaires in the presence of the pharmacist but independently at home. The questionnaires in both patient groups were evaluated in the same way independent of the group identity. Concerning cost data the method of data collection and evaluation was the same in both patient groups. Hence, despite the mentioned limitations, everything was done to assure a reliable and sound assessment of cost and outcome data.

According to Kennie et al. it is crucial to identify appropriate **outcomes** in studies evaluating the impact of pharmaceutical care [91]. In any evaluation of quality, the pharmacist should document structure (e.g. patient file), process (e.g. monitoring the drug regimen), and outcomes (e.g. adverse drug reactions) and evaluate these measures to provide appropriate care [92]. According to the Association of the Scientific Medical Societies in Germany (AWMF), a combination of traditional (e.g. adverse drug reactions, survival rate) and hermeneutic (e.g. quality of life) outcome measures should be used [93]. The selected measures in the present study meet those demands and are thus applicable to investigate the impact of pharmaceutical care.

The studied **patient population** consisted of 30 control and 46 intervention patients. The different sample sizes were due to the longer recruiting period for intervention patients (ten months versus 17 months). Since this work was planned as a pilot study no sample size calculation was conducted. In both patient groups the tumour entities breast and colorectal cancer were distributed evenly (control group: 53 % breast and 47 % colorectal cancer, intervention group: both 50 %). Patients were recruited on three oncology outpatient wards and three oncology practices. Relatively more control patients were recruited in oncology practices than intervention patients (40 % versus 22 %). One oncology outpatient ward recruited a lot more intervention patients than control patients leading to the observed result. One reason might have been a more fluent recruitment process in that study centre after the oncologist became more familiar with the study. Another reason might have been their conviction of the benefit of the pharmaceutical care service thus leading to a higher patient recruitment. Between May 2006 and April 2008, 100 ambulatory patients were reported to the study centre by the cooperating oncologists. It is not clear whether every patient who met the requirements was reported to the central study office or whether the oncologists selected patients beforehand. It is striking that in the intervention group 30 % had a *private health insurance* compared to only 3 % in the control group. It might be possible that oncologists pushed the recruitment of privately insured patients for the intervention group as a special benefit could be expected from the pharmaceutical care service. Since private insurances generally pay more money for the same medical service as statutory insurances it might have

been of interest to the oncologists to please these patients with this service. This circumstance could have contributed to a selection bias. Ten percent of the German population is covered by a private health insurance [94]. Thus privately insured patients are underrepresented in the control and overrepresented in the intervention group. A similar distribution could be found concerning the highest *level of education*: 30 % of intervention patients versus only 7 % of control patients hold a university / college degree. It is possible that this fact had an impact on the capability of understanding the patient questionnaires. However, the questionnaires were not evaluated in this respect. Regarding the current *living situation* and *marital status* more intervention patients were married / with partner and living with family / partner than control patients. A recent study in Israel assessed the impact of marital status and gender on psychological distress, coping and social support in colorectal cancer patients. Married patients coped better with cancer than unmarried patients and women coped better than men [95]. As there are a higher percentage of men in the intervention group the possibly positive effect of the marital status might be balanced. In a study on patients with non-small cell lung cancer no impact of marital status on quality of life could be observed [96]. Another difference could be seen concerning age at the time of inclusion: intervention patients were 6.5 years younger in the median than control patients. It is discussed in section 5.4 “Cost-utility analysis” that age is not as important as e.g. quality of life at the time of inclusion. The older age of the control patients was also reflected by the higher percentage of pensioners in the control group compared to the intervention group (60 % versus 37 %). This probably had an impact on indirect costs (see section 5.2 “Cost assessment”). Regarding the therapy regimen at the time of inclusion most patients were treated with capecitabine monotherapy in both patient groups (CG: 40 %, IG: 33 %). The higher percentage of monotherapy in the control group could have had a positive effect on quality of life as monotherapies generally have less adverse effects than combination therapies. The same is true for the higher percentage of palliative treatments in the control group compared to the intervention group (77 % versus 70 %, see section 5.3 “Outcome assessment”). Concerning combination chemotherapy twelve different combinations were observed in the study with different distributions among the two patient groups. Depending on the therapy regimen different effects on costs and outcomes could be expected. In conclusion, heterogeneity in the discussed patient variables was apparent. The presented cost and outcome results of the whole study population need to be interpreted carefully. It was decided to find matched patient pairs for the cost-utility analysis based on some of the discussed parameters to limit their possible biasing impact (see section 5.4 “Cost-utility analysis”).

In the present study patients who dropped out were not analysed (**study drop-outs**). All outcome data collected until then were not used for further analysis. This stands in contrast to international recommendations of the intention-to-treat analysis (ITT) according to which all patients should be analysed as allocated to the groups [97]. However, the way of handling drop-outs in the present non-randomized cohort study is not as important as in a randomized controlled study in which the group consistency is a prerequisite for the internal validity of the study. The cost-utility analysis was only conducted after matching the patients of the control group with patients of the intervention group thus establishing consistent groups. Furthermore, drop-outs were not a problem in the present study, as there was only one drop-out in each group. The same is true for **missing data**. There was not a substantial amount of missing data. This was probably because of the close contact between the central study office and the patients assuring an intensive follow-up of patients.

5.2 Cost assessment

Before discussing the results presented in the cost section of this work, the author would like to comment on the conditions of and her experience with data collection and cost assessment. It was not an easy task to receive all relevant data to assess disease-related costs. The establishment of an atmosphere of trust through personal relationships was obligatory to receive resource use data from the cooperating physicians, hospitals and their administrative staff. To smooth the way was hard work and took more than a year in some cases. The quality of resource use data was very heterogenic depending on the study centre and great effort was needed to transfer it into a comparable format. For future cost analysis of pharmaceutical care from a health insurance perspective a cooperation with, e.g., a major health insurance company would be recommended rather than trusting in receiving all needed data from cooperating study centres – here the focus should be the assessment of clinical and subjective outcomes and not economic ones. However, Germany is not as progressed in terms of health economic assessments as e.g. the UK and Sweden. Economic data are widespread between different parties and high data privacy protection hampers pharmacoeconomic analyses [98].

Concerning the **direct costs** in both patient groups most money was spent on costs for antineoplastic therapy (CG: 70 %, IG: 73 %), followed by inpatient stays (CG: 17 %, IG: 14 %), and then costs for supportive therapy (CG: 9 %, IG: 8 %). In both groups the oncologist fee amounted to 3 % and costs for administration were almost 0 % of total direct costs. In the intervention group costs for diagnostics presented 3 % and in the control group 1 % of total direct costs. The median costs in each category were always higher in the

intervention group except for the categories administration and inpatient costs. The mean costs in each category were higher in the control group for the categories antineoplastic and supportive therapy, oncologist fee, administration and inpatient costs.

It is uncertain whether all relevant cancer-related outpatient costs could be identified, as patients probably did not only consult physicians in the cooperating study centres but also other physicians for their cancer disease. It can be assumed that this possible lack of data is about the same in both patient groups and therefore negligible.

Since the patient population is heterogenic, as described in the section before, it is hard to draw conclusions from the cost differences between the two patient groups. In the intervention group a higher percentage of patients received combination chemotherapy than in the control group at the time of inclusion (CG: 60 %, IG: 67 %) thus leading to higher median costs for antineoplastic therapy. The fact that 30 % of the intervention patients and only 3 % of the control patients were privately insured further biased the cost results as e.g. other supportive therapies can be prescribed and more diagnostic tests are reimbursed by a private insurance company than by a statutory insurance company. For a meaningful comparison of costs it was obligatory to match the patients according to their therapy regimen and also their type of insurance, which was done for the cost-utility analysis. Concerning the percentage distribution of cost categories in both patient groups, the high amount of money for antineoplastic therapy and the relatively low amount of money for inpatient stays is striking. A systematic review from 2009 on cost-of-illness studies for breast-, colorectal and prostate cancer patients showed that inpatient stays were responsible for 50-98 % of all direct costs [99]. Especially in the field of colorectal cancer the latest included study analysed direct costs from the year 2004 in France [100]. Two highly expensive medicinal products, cetuximab and bevacizumab, for the treatment of advanced colorectal cancer were approved only in June of the analysed year and January of the following year (2005) in Europe [101, 102]. This latest study by Clerk et al. maybe covered a fraction of applications of cetuximab but the other included studies definitely did not. The application of bevacizumab could not be considered in any study due to the later marketing authorisation. Clerk et al. found the following cost distribution in a French setting for the first twelve months following diagnosis: hospitalisation charges 55 %, medical purchases 24 %, outpatient care 18 % and transportation 3 %. A more recent cost-of-illness study would probably show a different cost distribution with a higher percentage of medical purchases. Nevertheless, the low amount of inpatient costs in the present study may lead to false conclusions without further explanation. The result is probably due to the choice of study onset as e.g. adjuvant patients entered the study after their main

inpatient period with costly surgical intervention. Inpatient stays are therefore underrepresented in the present study. However, if the purpose of the present study had been the conduction of a cost-of-illness study a different observation period would have been needed. Despite these limitations the overwhelming amount of money that had to be paid for antineoplastic therapies needs to be discussed. This observation is in agreement with two recent publications by Garattini et al. and Danzon et al. [103, 104]. According to them, Germany is Europe's largest spender on drugs, and it also has the most new drugs available. In case of cancer therapy this circumstance especially plays a role as in this indication very costly innovative drugs are used. This was the case in the present study with e.g. bevacizumab and cetuximab for the treatment of advanced colorectal cancer and trastuzumab for the treatment of HER-2/neu positive breast cancer patients. The National Institute for Health and Clinical Excellence (NICE) in London published a technology appraisal about bevacizumab and cetuximab for the treatment of metastatic colorectal cancer in 2007. On the basis of the available evidence they concluded that both therapies showed health outcomes in colorectal cancer patients. Nevertheless, according to this appraisal the assessed cost-effectiveness ratio was not compatible with the best use of NHS resources as the industry-set prices for the two medicinal products were extremely high [105, 106]. The latest major health care system reform in Germany in 2007 amended the social legislative code to allow insurance funds to set maximum drug prices and negotiate prices with the industry. It also enabled the German Institute for Quality and Efficiency in Health Care (IQWiG) to assess the cost-effectiveness ratio that could help the insurance funds with their negotiations [94]. A judgment of the federal constitutional court from 6 December 2005 also known as the St-Nicholas judgment, said that it is not in agreement with the basic human rights to exclude a statutory insured patient suffering from a life-threatening disease from treatment options that might cure him or might have a positive influence on the course of his disease [107]. On the basis of this decision, negotiations between insurance funds and industry in the field of cancer are probably not possible as insurance funds have to pay whatever price is set. Moreover, there is a high risk that the insurance fund sets a maximum drug price and the industry does not lower its price resulting in patients who are able to pay the price difference and patients who are not. Nevertheless, the German health care system is under pressure and rational drug prices, *possibly also in the field of cancer* [in italics: note from the author], are essential for long-term stability of a system founded on the principle of communal responsibility [108].

When looking closer at **inpatient costs**, and keeping in mind the heterogeneity of patients limiting the validity, it is striking that 60 % of control patients and only 41 % of intervention

patients were hospitalised during the study period. There were four neoadjuvant control patients versus one neoadjuvant intervention patient, thus increasing the hospitalisation rate in the control group. But aside from these hospitalisations due to surgery following neoadjuvant treatments and other reasons that are hard to influence, such as inpatient i. v. administration of chemotherapy and disease-related complications, there were four hospitalisations (13 % of hospitalisations) in the control group due to drug toxicity / adverse drug reactions versus only one in the intervention group (3 % of hospitalisations). Maybe one or more of those inpatient stays in the control group could have been prevented with the help of a pharmaceutical care service. It is widely known that serious adverse effects may lead to hospitalisation [109, 110]. A recent prospective multi-centre study in the Netherlands found that from about 13000 unplanned hospital admissions 714 (6 %) were medication-related and almost half of these admissions were potentially preventable drug-related problems [111]. Westfeld et al. showed that pharmaceutical care can contribute to a reduction of adverse effects in cancer patients during chemotherapy concerning nausea and vomiting [25]. The effect of pharmaceutical care on hospitalisation rates was not evaluated in this study. Stewart et al. showed a reduced hospital readmission rate for patients with congestive heart failure who received a home-based intervention by a pharmacist and a nurse to optimize medication management [112].

The **costs for pharmacists** assessed in the present study amounted to € 94 per patient for a period of six months. This amount was obtained by multiplying the time to deliver pharmaceutical care (4.1 hours) with the gross wage of an employed community pharmacist in his second to fifth year on the job (€ 23). The assessed time is subject to uncertainty. The times assumed for writing individual patient letters and for other pharmaceutical services were estimated as they were not documented during the study. The pharmacist fee of € 23 might not be the correct charge for an hour of pharmaceutical care service either. This uncertainty was accounted for by conducting a sensitivity analysis assuming the double fee of € 46 within the cost-utility analysis (see 5.4 “Cost-utility analysis”). Other publications that accounted for pharmacist costs also multiplied the net time spent by the pharmacist with an hourly wage. McMullin et al. used a mean hourly rate of $ 30 (= € 25.42, 1999 exchange rate 1.18 $ / €) for a clinical pharmacist. Van den Bemt et al. assumed a salary of € 51 per hour (2002) for a hospital pharmacist indicating that pharmacist salaries vary a lot between countries [113–116]. Despite the mentioned uncertainties in the assumed pharmacist time, the assessed amount of 4.1 hours per patient to deliver pharmaceutical care for six months might demonstrate to some critical colleagues that a pharmaceutical care service is not as time consuming as they might fear. Furthermore, for possible payers of a pharmaceutical care fee

of about € 188 for one year of service (or € 377 if a double fee is assumed) the amount of money is probably a comparatively low charge.

Indirect costs were calculated based on the human capital approach by multiplying the number of days on sick leave with the average German gross wage per day. They amounted to a mean of € 4206 per patient in the control group and € 4993 per patient in the intervention group ($p = 0.464$). As data were neither available on the number of working hours per day in the case of part-time jobs nor on the exact date in the case of a switch from a full-time to a part-time job, missing days in part-time employment situations were valued like a whole day missing. The percentage of part-time working patients was higher in the intervention group thus leading to a slight overestimation of indirect costs in intervention patients. It is frequently argued that the human capital approach applied in the present study overestimates the true cost for the society. For example, in case of short-term absences from work, losses in production could be compensated for by colleagues and in case of long-term absences the employer is likely to hire a replacement worker. Both examples probably were the case in some of our patients. At the same time retired patients and housewives / -men were valued with € 0 in terms of indirect costs although they are definitely also of value for the society [3]. When adding the indirect costs to the total cost calculation, indirect costs amounted to 15 % of total costs in the control and to 17 % in the intervention group indicating that indirect costs play a role in the studied patient population. The slightly higher indirect costs in the intervention group were probably due to the younger age of the intervention patients (58 years versus 64.5 years, median) thus leading to a higher risk of production losses. The higher percentage of pensioners in the control group at the time of inclusion emphasises this argument (CG: 60 % versus IG: 37 %). Lidgren et al. who studied the cost of breast cancer in Sweden in 2002 found significantly higher amounts of indirect costs resulting in a share of 70 % of total costs [117]. One reason for this higher amount is that they did not only include days on sick leave for indirect cost calculation as in the present study but also early retirement and premature mortality, the latter amounting to 52 % of indirect costs. The other reason is that in the present study the included colorectal cancer patients were older than the included breast cancer patients (55 years versus 64 years), thus reducing the indirect costs as more patients were already retired.

Direct non-medical costs, also known as costs for informal care, were assessed in a qualitative manner. In the control group 16 to 24 % of patients needed help with every-day activities versus 10 to 30 % in the intervention group. Most of those patients indicated that they received help from family members or friends (CG: 75 %, IG: 96 %). As the patients

were not asked to state the number of hours of informal care these costs could not be valued in money terms as was done, e.g., in a study by Lidgren et al. for patients with breast cancer [118]. They multiplied the number of hours of informal care per week by the cost of leisure time lost, which was estimated to be 35 percent of the gross wage rate (53 Swedish kronor = € 7.38). Lidgren et al. found a mean number of 3.0 hours of informal care per week for metastatic breast cancer patients resulting in annual costs of 8350 Swedish kronor (= € 1163). There was no information available on how many percent of metastatic patients needed informal care. In a study by Yabroff et al. approximately 99.6 % of cancer patients reported that they did need some informal care [119]. They interviewed patients with bladder, breast, colorectal, kidney and other cancers about received informal care in the two years after their diagnosis. In this study informal care was not only defined as help with every-day activities but included four different categories: emotional, instrumental, tangible and medical support. This is probably one reason for the much higher amount of patients that needed informal care compared to the present study. Here the median wage rate in 2006 ($ 16.28 = € 12.33, 2006 exchange rate $ / € 1.32) was used to value caregiver time [113]. These two examples show that the valuation of leisure time is not straightforward and different methods lead to different approximations of informal costs. Yabroff et al. found an average caregiver time of 8.3 hours per day for 13.7 months for all cancers. The average value of caregiver time over two years after diagnosis was $ 38334 (= € 29041) for breast and $ 45699 (= € 34620) for colorectal cancer patients.

5.3 Outcome assessment

As patient outcomes, quality of life measured with the EQ-5D questionnaire, the adverse drug reaction hand-foot syndrome and quality-adjusted life years were assessed. Moreover, in the intervention group the patients´ willingness-to-pay for the pharmaceutical care service was evaluated.

Both patient groups started with the same median values in all five dimensions of the **EQ-5D** descriptive system. Most problems were evident in the dimensions “usual activities” and “pain / discomfort”. There was no deterioration in median values at any time. There were improvements in both patient groups for the dimension “usual activities” and an improvement in the dimension “pain / discomfort” in the control group. The corresponding utility scores calculated on the basis of the EQ-5D descriptive system showed a stable median utility score of 0.887 for the intervention patients at all times. The same median utility score was assessed for the control patients until t_6 followed by an improvement to 0.999 at t_7. These results

indicate a very high quality of life for both patient groups throughout the course of the study. Only the mean utility scores showed that there was a slight deterioration in quality of life in both patient groups from t_0 to t_3 (control group: 0.810 to 0.789, intervention group: 0.797 to 0.781). In terms of absolute changes in utility scores there was no difference at any time for both groups. Concerning the visual analogue scale (VAS) the intervention group started with a higher score than the control group (IG: 62.5 versus CG: 52.5; median). Through all times of measurement the median VAS score improved in both groups. The mean VAS score deteriorated only for the intervention patients from t_0 to t_3.

The EQ-5D questionnaire was evaluated only for those patients who were under treatment with capecitabine. In case capecitabine treatment was stopped, the answers to the questionnaire were not considered. This was done in order to receive more comparable patient groups as quality of life under treatment with completely different chemotherapy regimens or even no chemotherapy at all can hardly be compared. But still patients received different chemotherapy regimens at the time of inclusion although all contained capecitabine. For example there were more intervention patients with a curative treatment than control patients (CG: 23 % versus IG: 30 %). Curative regimens mostly accept a higher toxicity which probably has a negative effect on quality of life, whereas in palliative regimens the relief of symptoms and an improvement or stabilisation of quality of life is most important.

It is striking that concerning the five dimensions and utility scores there was no deterioration in median values and an improvement in VAS scores although chemotherapy was started. It is widely known that especially curative chemotherapy has a negative influence on quality of life. A comparable study by Westfeld et al. on pharmaceutical care of adjuvant breast and ovarian cancer patients showed partly similar results: in the median there were no absolute changes between the utility scores from t_0 to t_1 and from t_0 to t_2 [25]. In that study also “pain” and “usual activities”, beside “anxiety / depression” were the dimensions with the most predominant problems. In the course of the study there were deteriorations in the control group in the dimensions “mobility”, “usual activities” and “pain / discomfort” and an improvement in “anxiety / depression”. In the intervention group there was an improvement in the dimension “mobility”, “anxiety / depression” and “self care” and a deterioration in “usual activities”. These changes did not result in absolute changes in utility scores as already mentioned. The changes that Westfeld et al. observed in the descriptive system might be due to the solely adjuvant treatment setting resulting in higher toxicity and a higher impact on quality of life than in the patient group studied in this piece of work. Due to the more toxic chemotherapy there was probably a higher possibility of alleviating effects of pharmaceutical

care. The median utility scores at the time of inclusion were 0.830 for the control and 0.796 for the intervention group which was below the utility scores of the patients of the present study (in both groups 0.887). This might be due to the method of utility calculation: in the study by Westfeld et al. the utilities were generated with the UK TTO utility set and in the present study with the German TTO utility set in order to represent the preferences of the German insured population. A sensitivity analysis in the context of the cost-utility analysis showed that the UK set leads to lower utility scores than the German set. Another possible reason is that the present study also included colorectal cancer patients thus leading to different utility scores. In a study by Zhou et al. quality of life was assessed with the EQ-5D questionnaire in patients with metastatic breast cancer under treatment with lapatinib plus capecitabine versus capecitabine alone [120]. Quality of life for patients in both treatment groups could be maintained during 24 weeks of follow-up, which is in agreement with the here found results. The utility index showed a mean of 0.64 versus 0.66 at baseline. Conner-Spady et al. found a mean EQ-5D utility score of 0.770 (SD 0.16) for breast cancer patients at baseline prior to the beginning of high-dose chemotherapy [121]. In a study by Wilson et al. colon cancer patients showed a utility index of 0.824 and rectal cancer patients of 0.761 six weeks after hospital discharge and potentially curative surgery [122]. In all three studies the utility scores were based on the UK TTO utility set, providing one reason for the lower utility scores at baseline compared to the here found results. The VAS utility scores at the time of inclusion in the study by Westfeld et al. lay below the utility scores from the descriptive system as was the case in the present study. This is a known phenomenon as valuations of quality of life that are not represented in the five dimensions are also included in the VAS score [123]. Others found that the VAS utility score is generally lower than a utility score from a TTO-based approach [124]. The latter formed the basis of the UK and German utility set used to transfer the EQ-5D into utility scores. Unlike the here presented results the VAS scores in the study by Westfeld et al. showed deterioration in median values for both patient groups during the course of the study. In conclusion, it seems that the generic EQ-5D questionnaire is either not sensitive enough to display the impact of the present antineoplastic therapy on quality of life of the studied patient population or the applied antineoplastic therapy did not affect quality of life considerably considering the high portion of palliative treatments. If the former is true, it would be very hard to detect an effect of pharmaceutical care on quality of life in the studied patient population, especially in the light of the heterogenic population considering the fact that the effect might be biased. Westfeld et al. also concluded that the EQ-5D questionnaire was not able to detect differences in quality of

life due to pharmaceutical care between the control and intervention group. Furthermore, the subsequently discussed positive impact of pharmaceutical care on the occurrence of the hand-foot syndrome showed that the EQ-5D questionnaire could not display the impact of this adverse drug reaction on quality of life. A solution might be the application of a disease-specific quality of life questionnaire like the EORTC-QLQ-C30. A limitation of this questionnaire is that it cannot be transferred into a single quality of life index which is essential for the use in cost-utility analyses. It remains to be evaluated whether other instruments like the Short Form 6D (SF-6D) or the Health Utilities Index (HUI) that can also be used in cost-utility analyses are more suitable for the present patient population [125–127].

The **hand-foot syndrome (HFS)** was measured with a patient questionnaire at seven times during the course of the study. Both patient groups started with HFS grade 0 at t_1. In the intervention group the median HFS grade was 1 until t_6 and ended with 0.5 at t_7. In the control group the median HFS grade was grade 2 twice: at t_5 and t_7, with statistically significant differences between the two patient groups. At the other measurements HFS reached grade 1 in the control group. Concerning the severest HFS grade 3, six out of 30 control patients (20 %) experienced HFS grade 3 at least once during the treatment with capecitabine versus only seven out of 46 intervention patients (15 %). The HFS utility scores were lowest in the control group with a median of 0.720 at t_5 and t_7. In the intervention group the lowest median score was 0.970.

As the HFS grades were characterised by the patients themselves and not by a physician the above-mentioned results might be biased. Patients might have confused HFS with adverse drug reactions of combination partners that showed similar symptoms; e.g. cetuximab leads to skin changes and oxaliplatin causes peripheral neuropathy, both also possibly affecting hand and feet. Cetuximab was only applied in intervention patients and oxaliplatin was used in a higher percentage in intervention patients than in control patients, thus possibly worsening the reported HFS grades in the intervention group. Despite this possible bias the intervention patients showed milder HFS grades than the control group, indicating a positive effect of pharmaceutical care on the occurrence of HFS in the studied patient population. The positive impact of pharmaceutical care is not only presented by the two statistically significant results at t_5 and t_7, but also by the reduction of the risk to develop HFS grade 3 (CG: 20 %, IG: 15 %). Especially the latter is of great importance to patients as HFS grade 3 has a corresponding utility score of 0.340 indicating a major impact on patients´ quality of life. In a study by Cassidy et al. 17 % of colorectal cancer patients treated with capecitabine developed HFS grade 3 [45]. Thus the intervention patients showed less and the control patients more

HFS grade 3 than these patients. Walko et al. summarised safety results of capecitabine from three trials in breast and colorectal cancer patients. They found that the median time to HFS onset is 79 days but can range from 11 to 360 days [43]. In the present study a median HFS grade of 1 was first reported at the end of cycle two (day 36) in both patient groups. In the control group a median HFS grade 2 primarily occurred after the fifth chemotherapy cycle (day 99), then it improved again to grade 1 and finally reached grade 2 once more at t_7. This observed phenomenon is hard to explain, especially as the capecitabine dose in the control group was only known at the time of inclusion. Maybe the capecitabine dose was reduced in cycle six in the corresponding patients. As HFS symptoms had disappeared, it was increased again in cycle seven and HFS got worse. However, this procedure would not have been according to the common recommendations of managing HFS [40]. Maybe it was just an artefact due to the small sample size of eleven remaining control patients under treatment with capecitabine at that point in the study and there is no logical explanation. A longitudinal model to predict HFS dynamics in patients receiving capecitabine was recently developed by Hénin et al. with data from two phase III trials in metastatic colorectal cancer [128]. They found an obvious relationship between the proportional distribution of HFS grades and the time of treatment and therefore the exposure to treatment with capecitabine. For example at treatment week 14 (= treatment for five cycles) the probabilities for the different HFS grades were as follows: grade 0 = 55 %, grade 1 = 15 %, grade 2 = 25 % and grade 3 = 5 %. Furthermore, the lower the calculated creatinine clearance at inclusion, the higher was the risk of HFS. In conclusion, the author wants to emphasise the importance of further research in the field of HFS. Hitherto no evidence-based prophylaxis and treatment strategies, except dose reduction and treatment stop, have been available. The observed positive results in the intervention group were probably due to the intense education and monitoring of the patients in regard to their HFS. This and a good pharmacist-physician communication probably resulted in a faster HFS management by the physician. Further strategies could possibly further reduce the occurrence of HFS grades 2 and 3. The above-mentioned dynamic model of HFS by Hénin et al. might be an interesting tool to develop individual treatment adaptations for capecitabine patients [128].

Quality-adjusted life years (QALYs) were calculated on the basis of the EQ-5D and HFS utility scores. QALYs based on the EQ-5D utility score could be calculated for eight control and 17 intervention patients. Both groups almost gained the same amount of QALYs: control patients gained a median of 0.44 QALYs and intervention patients 0.42 QALYs. On the basis of the utility-time curve that included all existing EQ-5D utility scores the difference was

even smaller: 0.45 QALYs for control and 0.44 for intervention patients. The EQ-5D VAS score was not used for QALY calculation as in comparison to the utility scores derived from the EQ-5D descriptive system the scores are said to be *"inherently flawed"* and should therefore not be used if more reliable scores are available [125]. QALYs based on the HFS utility score could be calculated for eleven control and 20 intervention patients and amounted to 0.44 QALYs for the control and 0.46 QALYs for the intervention group. On the basis of the HFS utility-time curve the difference between the two groups increased: 0.45 QALYs for the control and 0.48 QALYs for the intervention group. The difference was more obvious in terms of quality-adjusted life days (QALDs) resulting in 13.2 more QALDs for the intervention group. These two contrasting QALY results depending on the utility score used were not astonishing following the discussion of the EQ-5D and HFS results in the previous two sections. The HFS QALYs showed the positive impact of pharmaceutical care on quality of life that could not be detected by the EQ-5D questionnaire. Still, it might seem logical that HFS grades 2 and 3 have an impact on the EQ-5D dimensions "mobility", "self-care", "usual activities" and "pain". Nevertheless, the observed differing results are in agreement with the familiar but still discussed problem concerning QALYs: there is a lot of evidence that different utility elicitation methods used in the calculation of QALYs yield different results [126]. The sentence *"A rose is a rose is a rose is a rose…"* written by Gertrud Stein as part of the poem Sacred Emily is obviously not transferable to *"A QALY is a QALY is a QALY is a QALY…"*. Other concerns are e.g. the utilitarian thinking behind the QALY concept and the smaller capacity to benefit of older, sicker or disabled patients [129]. These are some reasons why e.g. the IQWiG refused to accept QALYs as a single outcome parameter. It preferred indication-specific outcome parameters for its evaluation of costs and outcomes [7]. Despite the limitations, the QALY approach was used in the present study and a cost-utility analysis of pharmaceutical care was conducted as it also has a lot of strengths; otherwise it would not be in the centre of health measurement of some decision makers including the National Institute for Health and Clinical Excellence in the UK. One big advantage of the QALY is the simultaneous capture of quality and quantity gains (quality of life and mortality) and their combination into a single generic measure so that comparisons between studies with different outcomes are possible [127].

The maximum **"willingness-to-pay" (WTP)** per month for the pharmaceutical care service was assessed in the intervention group. The median WTP amounted to € 45 per month (min: € 5, max: € 500, n = 32, € 270 per six months). There was no correlation between the WTP and the net income per household member. Ten intervention patients gave no answer. During

the conduction of the WTP assessment different problems evolved. Some patients called the central study office and said that they did not understand the questionnaire. After an oral explanation this problem could be solved and the patients stated their WTP. But the presence of the clinical pharmacist might have biased the results in terms of a higher WTP in these cases. One patient thought that he should actually pay money for the received service and he had to be appeased that it was a misunderstanding. Others returned the questionnaire with a question mark or a diagonal line; in these cases "missing answers" were assumed. It was not clear whether some of these patients actually meant a WTP of € 0. The described problems indicated that patients need to become familiar with the WTP approach and that it is not a trivial undertaking to pose the question in a way that it is clear to the respondent as has been observed by others [3]. It was not easy for some patients to imagine this theoretical payment situation. Nor was it easy to set the benefit they received from the pharmaceutical care service in relation to the benefits they might get from other goods of daily life in the context of a resource allocation decision. For future WTP assessments a face-to-face interview by a non-involved investigator is recommended rather than a questionnaire format in order to prevent misunderstandings and to improve response rates. The results obtained in the study need to be interpreted carefully. The amount of € 45 per month or € 270 per six months is quite high in comparison to the costs for pharmacists of € 94 per six months. This result may indicate that the pharmaceutical care service was perceived as useful by the patients even though no quality of life changes were measured with the EQ-5D questionnaire. The WTP approach has been used in some studies to investigate the intangible benefits of pharmaceutical care services [130–132]. Suh et al. measured WTP for pharmacists´ services directed toward reducing the risk of medication-related problems [130]. They found a mean WTP from $ 4.02 to $ 5.48 per prescription (€ 3.68 - € 5.03, 2000 exchange rate $ / € 1.09), depending on the level of risk reduction [113]. If the patients´ insurance covered the service they would be willing to pay $ 28.79 to $ 36.29 per year (€ 26.41 to € 33.29) as an extra premium. Overall, the average WTP for a pharmacist's consultation was $ 5.57 (€ 5.11) and increased by $ 0.87 (€ 0.80) as consultation time increased by 1 minute. If this last result was used to calculate the WTP for the delivered 246 minutes of pharmaceutical care within six months in the present study, it would amount to € 196.80 (246 minutes x € 0.80). Thus it would lie below the maximum WTP of € 270 of the intervention patients of this study. But there is a time difference of about eight years between the WTP assessment by Suh et al. and the present study. Moreover, the mixed US American patient collective in the study by Suh et al. probably had different preferences than a German cancer patient.

5.4 Cost-utility analysis

A cost-utility-analysis was conducted for retrospectively **matched patient pairs** from the control and intervention group. Patients were matched according to the parameters tumour entity (breast, colorectal cancer), treatment setting (adjuvant, neoadjuvant, palliative), therapy regimen at the time of inclusion, treatment with bisphosphonates at the time of inclusion and type of health insurance (statutory or private) resulting in eleven matched patient pairs. Some other typical variables used in matching procedures include gender, age, socioeconomic status or hospital, which complies with therapy setting (outpatient ward or oncology practice) in our case [133]. A matching approach has also been used by Mangiapane et al. in a study on pharmaceutical care of asthma patients. They matched a subgroup of intervention patients according to gender, age, date of recruitment and amount of prescribed anti-asthmatics with control patients [134]. In the present study quality of life at the time of inclusion could also have been a considered matching parameter. The inclusion of the above-mentioned additional parameters would have further reduced the number of matching patient pairs possibly resulting in a case report. Therefore they were not applied. When comparing the eleven matched patient pairs regarding gender and quality of life at the time of inclusion there were no differences between the two groups. Concerning age the selected intervention patients were eleven years younger in the median than the control patients. But it is much more important that the groups were consistent with quality of life rather than age at the time of inclusion as there might be older patients who are fit and younger patients who are frail. In respect of the therapy setting outpatient ward versus oncology practice the distribution in both selected groups was almost equal. Seven control patients versus six intervention patients were treated on an oncology outpatient ward, thus limiting the possible bias of the slightly different charging modalities depending on the therapy setting.

For the cost-utility analysis only **direct costs** were considered as the indirect costs were regarded to be too uncertain. The distribution of different cost categories in the selected patient groups followed the same order as the cost categories in the whole patient population (see section 5.2 “Cost assessment”). One peculiarity were the costs for supportive therapy in the selected control group as they were almost as high as the costs for inpatient stays. The reason was the application of several highly expensive supportive treatments in the control group as discussed below. Costs for antineoplastic therapy were higher in the intervention group than in the control group mainly because of one control patient who declined treatment after one cycle leading to low costs of € 525. He died on day 61 of the study. The costs of one matching intervention patient reached about € 25000 as he received the antineoplastic

treatment until the end of the study. This example reflects the problem of the small sample size of eleven matched-pairs. Within a larger patient group one patient would not have had such an immense weight in terms of cost differences. In case of costs for supportive care and inpatient stays it was vice versa – higher costs arose for the selected control patients. Reasons for the higher supportive costs were treatments with Neulasta® (pegfilgrastim), parenteral nutrition, Cosmofer® (iron dextrane) and Aranesp® (darbepoetin alpha). No intervention patient received any of these treatments, except for Aranesp® which was applied once. Two other intervention patients who also suffered from anaemia were treated with human erythrocyte concentrates instead. Especially concerning treatment with erythropoietin analogues for chemotherapy-induced anaemia the pharmacist-physician consultations in the intervention period might have influenced that result. In these consultations the pharmacist gave oral and written information on a technology appraisal in progress of the NICE on erythropoietin analogues in cancer-treatment induced anaemia. The final appraisal does not recommend the routine use of erythropoietin analogues as was true for the interim recommendations. The only exception is ovarian cancer patients receiving platinum-based chemotherapy and patients who cannot receive blood transfusions [135, 136]. In the selected intervention group one patient received transfusion with erythrocyte-concentrates instead of erythropoietin analogues. Whether the treatment with Cosmofer® of one control patient was clinically necessary or an oral iron preparation would have been sufficient cannot be tracked. The same is true for treatment with Neulasta®. Intensive discussions also took place regarding guideline compatible prophylaxis of nausea and emesis in different study centres. In both patient groups Kevatril® (granisetron) was used in all patients receiving treatment with paclitaxel / capecitabine. According to the NCCN and MASCC guidelines of 2007 only 8 mg of dexamethasone on day 1 would be necessary as the mentioned combination is a low emetic risk chemotherapy regimen [137, 138]. As the clinical pharmacist was not a real member of the clinical team the implementation was slow, but also because of the needed consent from different team members. In the meantime the implementation was successful, mainly because of a new clinical pharmacist who now works in one study centre and who could support the process. An emetic prophylaxis as recommended by the clinical pharmacist would have saved additional money for supportive therapy in the intervention group. Inpatient costs were higher in the selected control group as four control patients showed inpatient stays versus only two intervention patients. One selected control patient was hospitalised due to the adverse drug reaction “fever under chemotherapy”. No selected intervention was hospitalised due to an adverse drug reaction. It is hard to say whether “fever under chemotherapy” could have been

avoided by the pharmaceutical care service. But it is true that intervention patients receiving chemotherapy with a high risk of neutropenia and related fever received special information from the pharmacist. This information consisted of behavioural advice in case of neutropenia thus maybe influencing the occurrence of neutropenic fever [139]. Concerning other publications on impact of pharmaceutical care on hospitalisation rates see chapter 5.2 “Costs assessment”.

The median **quality-adjusted life years (QALYs)** were almost the same in the two selected groups 0.44 QALYs versus 0.45 QALYs in favour of the intervention group. This advantage was more obvious when looking at the mean QALYs: 0.32 versus 0.40. The slightly positive result for the intervention group, in contrast to the result in the whole patient population (see 5.2 “Outcome assessment”), may be due to the more comparable patients following the matching process. The matching parameters might have biased the QALY results in the whole patient group. But the result might also be an artefact due to the limited sample size of eleven patient pairs. In contrast to the QALYs in the whole patient population, here also those EQ-5D utility scores were evaluated during periods without chemotherapy or regimens without capecitabine. When a patient died his utility score was assumed to be zero (= dead) to act as a counterbalance for no further costs from that period onwards. In other words the last observed utility score of a living patient was extrapolated to a utility score of zero at the normally following time of measurement. Otherwise an early death would present a cost-effective situation if it was not accounted for on the outcomes side. That possibility is actually the advantage of the QALY because it combines quality and quantity of life. In a Markov model based cost-utility analysis of cancer drugs in patients with advanced small-cell lung cancer a utility score of zero was also assigned to the state “death” [140]. QALY calculations based on the HFS utility scores on the other hand only make sense for those patients under treatment with capecitabine as it is a specific capecitabine-related side effect. Due to this prerequisite HFS-based QALYs could only be calculated for three control and four intervention patients and thus could not be used for further analysis.

The pharmaceutical care service was associated with a gain in mean QALYs compared to standard care of 0.08 QALYs (0.40 QALYs ± 0.14 versus 0.32 QALYs ± 0.19) at lower mean costs of - € 474 (€ 15606 ± 13816 versus € 16080 ± 11308). Thus the intervention ‘pharmaceutical care’ dominated the comparator ‘standard care’. The bootstrapping showed lower costs and more QALYs than the control group in 43 % of all replications; more costs and more QALYs in 44 % of all replications; lower costs and less QALYs in 10 % of all replications and more costs and less QALYs in 3 % of all replications. According to the cost-

effectiveness acceptability curve the probability that pharmaceutical care was a cost-effective strategy was 43 % at a willingness-to-pay (WTP) for an additional QALY of € 0, reaching 62 % probability at a WTP of € 29000 per additional QALY. The bootstrap results indicated that there was a quite high probability of the pharmaceutical care service being associated with a QALY gain (87 % of all replications showed a QALY gain). The cost-effectiveness acceptability curve indicated a moderate to high probability of the pharmaceutical care service to be a cost-effective service in the selected patient population.

Due to the small sample size of 22 patients this result has limited validity as is emphasised by the worst and best case **sensitivity analyses**. In the worst case scenario € 1922.84 would have to be paid to gain 0.09 QALYs in one intervention patient ($ICUR_{worst\ case}$ = € 21365/QALY). In the best case scenario €817.91 would have been saved and 0.08 QALYs would have been gained. But also if the $ICUR_{worst\ case}$ reflected the true ratio this would probably still be considered cost-effective by the NICE. According to a review on NICE´s recommendations between 1999 and 2005, NICE requires *"[…] more explicit reference to factors including the range of uncertainty […], the innovative nature of the technology, the particular features of the condition and the population receiving the technology, and where appropriate the wider societal costs and benefits. […]"* when the cost per QALY is above £ 20000 (€ 29000) [85]. The $ICUR_{worst\ case}$ still was below this threshold. The highest cost per QALY that NICE has accepted is an estimated £ 39000 (€ 57000) for riluzole to treat motor neurone disease indicating that the clinical situation of the patients plays a key role in the decision making. The two further sensitivity analyses evaluating the impact of the pharmacist costs and the applied utility set showed that both parameters did not change the result considerably. To the knowledge of the author no prospective cost-utility analysis of a pharmaceutical care service has been published up to now. Only one recent model-based analysis of interventions aimed at preventing medication errors at hospital admission was found. Pharmacist-led medicines reconciliation was the intervention with the highest expected net benefits and a probability of being cost-effective of 60 % for an additional cost per QALY of £ 10000 (€ 15000) [141]. The recent review by Rijdt et al. focused on economic effects of clinical pharmacy interventions in the hospital setting. The results of pharmacoeconomic analyses suggested that general clinical pharmacy interventions are associated with cost-savings. This trend could be confirmed in the present cost-utility analysis. Rijdt et al. criticized that most evaluations suffered from a number of methodological limitations relating to the absence of a control group, exclusion of pharmacist employment costs, exclusion of health outcomes, use of intermediate outcome measures, absence of incremental and sensitivity analyses, limited

scope of costs and outcomes and focus on direct health care costs only [33]. Except for the last point the present economic evaluation of pharmaceutical care service considered all recommendations mentioned. Indirect costs were assessed in the whole patient population but not incorporated into the cost-utility analysis for the above-mentioned reason. According to Rijdt et al. the present study could be classified as a study of high methodological quality but with one big limitation of a small sample size.

5.5 Conclusion and perspectives

Costs for antineoplastic therapy played a dominant role in the direct disease-related costs in both patient groups, followed by inpatient stays. Indirect costs have been identified as a cost category that should not be underestimated in the present patient population. Costs for pharmacists were very low compared to other cost categories in the intervention group. Because of the heterogenic patient population especially concerning the therapy regimen at the time of inclusion, conclusions regarding cost differences between the two patient groups were drawn for the matched patient pairs only. Pharmaceutical care showed a statistically significant impact on hand-foot syndrome (HFS), the most frequent and at the same time dose- and therapy-limiting toxicity under treatment with capecitabine, at particular points of time. No impact of pharmaceutical care on quality of life measured with the EQ-5D questionnaire could be found. In general quality of life was very high and stable. The intervention patients´ willingness-to-pay (WTP) per month for the pharmaceutical care service was quite high in comparison to the actual pharmacist costs but also in comparison to other reported WTP amounts. This high WTP indicated that the pharmaceutical care service was perceived as valuable by the intervention patients.

The cost-utility analysis of the eleven matched patient pairs showed that in terms of common understanding of cost-effectiveness the pharmaceutical care service was a cost-effective service in the studied patient population. The very small sample size of 22 patients limits the validity of the observed positive result.

For future analyses of costs and outcomes of pharmaceutical care services from a health insurance perspective, cooperation with a major health insurance company is recommended for the collection of patient-level cost data. Moreover, different quality of life instruments that can also be transferred into a single utility index should be investigated in a similar patient population to evaluate quality of life changes during chemotherapy and the impact of pharmaceutical care. As the WTP questionnaire had to be explained to some patients an oral WTP interview should be conducted by an independent interviewer to confirm the high WTP

of the intervention patients. For future cost-utility analyses a larger sample size is mandatory to investigate the cost-effectiveness of pharmaceutical care. If possible the inclusion criteria should be narrower in terms of acceptable therapy regimens at the time of inclusion to achieve better comparable patient groups. If feasible in terms of manpower, a cluster randomization of study centres should be conducted to control for bias followed by a retrospective matching of control and intervention patients. Ideally, clinical pharmacists should be integrated into the clinical team not only at selective points of time but during the whole study period.

The present project was the first study to survey the costs and outcomes of a pharmaceutical care service delivered to cancer patients. Before, no scientific evidence was available on pharmacoeconomics of pharmaceutical care research in oncology.

Despite the limitations of the present study which were discussed in detail, the used methods and gained results might serve as a valuable basis for future analyses of costs and outcomes not only of pharmaceutical care services but also of other complex interventions such as disease management programs (DMPs).

6 Summary

Objective: The present pharmacoeconomic pilot study aimed at evaluating the costs and outcomes of a pharmaceutical care service delivered to cancer patients treated with capecitabine compared to standard care.

Methods: An open, prospective, multi-centred cohort study with a preceding control group was chosen as the study design. Colorectal and breast cancer patients treated with capecitabine were included in the study. For a study period of six months control patients received standard care whereas intervention patients received intensified pharmaceutical care. Endpoints within the study were direct disease-related outpatient and inpatient costs, health-related quality of life, the most frequent and at the same time dose- and therapy-limiting toxicity hand-foot syndrome (HFS) and quality-adjusted life years (QALYs). Further endpoints were the indirect disease-related costs, direct non-medical disease-related costs and the willingness-to-pay of the intervention patients for the pharmaceutical care service. Another objective was to determine the cost-effectiveness of the pharmaceutical care service in a cost-utility analysis. Resource use data on direct disease-related outpatient costs (pharmacotherapy, oncologist fee, diagnostics and administration) were retrieved from patient files. Data on inpatient stays during the study period were obtained from the hospital controlling centres. As a measure for pharmacist costs the time spent by the study pharmacists on delivering pharmaceutical care was used. Information on the number of days on sick leave were obtained from patients and used to calculate indirect costs. Quality of life was assessed with the EQ-5D questionnaire. HFS was assessed with a patient questionnaire after each chemotherapy cycle. QALYs were calculated on the basis of the EQ-5D index score and on the basis of HFS grade-related utility scores. The cost-utility analysis was based on direct-disease-related costs and QALYs of retrospectively matched patient pairs from the control and intervention group. Matching parameters were tumour entity, treatment setting, antineoplastic regimen and treatment with bisphosphonates at the time of inclusion and type of health insurance.

Results: Thirty patients were analysed in the control group and 46 patients in the intervention group. Costs for antineoplastic therapy played a dominant role in the direct costs in both patient groups (control group: 70 %, intervention group: 73 % of total direct costs), followed by costs for inpatient stays (control group: 17 %, intervention group: 14 % of total direct costs). Indirect costs accounted for 14 % and 17 % of total costs in the control group and intervention group, respectively. Costs for pharmacists were very low compared to other cost

categories (0.41 % of total direct costs). Because of the heterogenic patient population especially concerning the therapy regimen at the time of inclusion, conclusions regarding cost differences between the two patient groups were drawn for the matched patient pairs only. However, inpatient stays due to adverse drug reactions were higher in the control group compared to the intervention group. Furthermore, pharmaceutical care showed a statistically significant impact on HFS at particular points of time. No impact of pharmaceutical care on quality of life measured with the EQ-5D questionnaire could be monitored. In general, quality of life under treatment with capecitabine was very high and stable with a median utility index of 0.887 in both patient groups and a slight improvement in the control group for the last point of measurement. QALYs based on the HFS and EQ-5D questionnaire reflected the positive impact of pharmaceutical care on HFS and no impact on quality of life. The intervention patients stated a median willingness-to-pay (WTP) of € 45 per month for the pharmaceutical care service, thus exceeding the costs for pharmacists of € 16 per month. The retrospective identification of matched-pairs for the cost-utility analysis yielded eleven patient pairs. In the analysis 0.08 QALYs could be gained and € 474 could be saved in comparison to the selected control group, thus demonstrating dominance of the pharmaceutical care service. The result was robust to changes in pharmacist costs and the EQ-5D utility set used. It was sensitive to the analysis of extremes. In the worst case scenario € 1923 had to be invested to gain 0.09 QALYs in an intervention patient resulting in an ICUR of € 21365 / QALY. In the best case scenario 0.08 QALYs could be gained and € 818 could be saved per intervention patient. The bootstrapping showed that in 87 % of all replications the pharmaceutical care service was associated with a gain in QALYs. According to the cost-effectiveness acceptability curve the probability that pharmaceutical care was a cost-effective strategy was 43 % at a WTP for an additional QALY of € 0, reaching 62 % probability at a WTP of € 29000 per additional QALY.

Conclusion: In this pharmacoeconomic pilot study costs for antineoplastic therapy played a dominant role in the direct disease-related costs in both patient groups. The results of the study indicated that pharmaceutical care might be associated with improved HFS. The high WTP of the intervention patients for the pharmaceutical care service showed that the service was perceived as valuable by them. The results of the cost-utility analysis indicated that in terms of common understanding of cost-effectiveness the pharmaceutical care service was a cost-effective service in the studied patient population. The very small sample size of 22 patients included in the cost-utility analysis limits the validity of the observed positive result. Further studies with a larger sample size are needed to confirm these findings.

7 Disclosure

Partial funding of the study was provided by Roche Pharma AG, Basel. However, the researchers were entirely independent during all phases of this work.

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9 Appendix

Appendix A: Cost and outcome assessment tools

EQ-5D

Socio-demographic patient characteristics, help with every-day activities and current employment situation

Hand-foot syndrome (HFS)

Willingness-to-pay (WTP)

Pharmacotherapy

Resource use documentation form

Hardcopy of electronic patient file

Receipt of inpatient stay

Appendix B: Informed consent

Patient information brochure

Recruitment fax

Consent form

Appendix C: Pharmaceutical care service

Pharmaceutical care plan

Patient brochure on adverse drug reactions

Patient letter containing medication plan

Consultation documentation forms

Reminding card control group

Appendix D: Results

EBM digits

GOÄ digits

Direct disease-related outpatient costs

Pharmacist time spent for intervention patients

Inpatient costs

Indirect costs

Quality of life

Hand-foot syndrome (HFS)

Willingness-to-pay (WTP)

Cost-utility analysis

Appendix A: Cost and outcome assessment tools

EQ-5D questionnaire, part 1

Bitte geben Sie an, welche Aussagen Ihren heutigen Gesundheitszustand am besten beschreiben, indem Sie ein Kreuz in ein Kästchen jeder Gruppe machen.

Beweglichkeit/Mobilität

Ich habe keine Probleme herumzugehen ❑

Ich habe einige Probleme herumzugehen ❑

Ich bin ans Bett gebunden ❑

Für sich selbst sorgen

Ich habe keine Probleme, für mich selbst zu sorgen ❑

Ich habe einige Probleme, mich selbst zu waschen oder mich anzuziehen ❑

Ich bin nicht in der Lage, mich selbst zu waschen oder anzuziehen ❑

Allgemeine Tätigkeiten *(z.B. Arbeit, Studium, Hausarbeit, Familien- oder Freizeitaktivitäten)*

Ich habe keine Probleme, meinen alltäglichen Tätigkeiten nachzugehen ❑

Ich habe einige Probleme, meinen alltäglichen Tätigkeiten nachzugehen ❑

Ich bin nicht in der Lage, meinen alltäglichen Tätigkeiten nachzugehen ❑

Schmerzen/Körperliche Beschwerden

Ich habe keine Schmerzen oder Beschwerden ❑

Ich habe mäßige Schmerzen oder Beschwerden ❑

Ich habe extreme Schmerzen oder Beschwerden ❑

Angst/Niedergeschlagenheit

Ich bin nicht ängstlich oder deprimiert ❑

Ich bin mäßig ängstlich oder deprimiert ❑

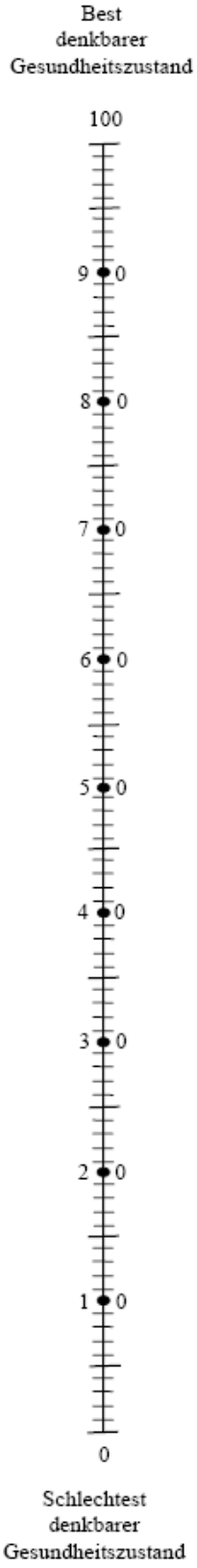
Ich bin extrem ängstlich oder deprimiert ❑

EQ-5D questionnaire, part 2

Um Sie bei der Einschätzung, wie gut oder wie schlecht Ihr Gesundheitszustand ist, zu unterstützen, haben wir eine Skala gezeichnet, ähnlich einem Thermometer. Der best denkbare Gesundheitszustand ist mit einer "100" gekennzeichnet, der schlechteste mit "0".

Wir möchten Sie nun bitten, auf dieser Skala zu kennzeichnen, wie gut oder schlecht Ihrer Ansicht nach Ihr persönlicher Gesundheitszustand heute ist. Bitte verbinden Sie dazu den untenstehenden Kasten mit dem Punkt auf der Skala, der Ihren heutigen Gesundheitszustand am besten wiedergibt.

Ihr heutiger Gesundheitszustand



Questionnaire on socio-demographic patient characteristics, help with every-day activities and current employment situation, part 1

1) Lebensalter in Jahren : _____

2) Geschlecht (Zutreffendes bitte ankreuzen):

❑ weiblich ❑ männlich

3) Familienstand (Zutreffendes bitte ankreuzen):

❑ verheiratet/ Lebensgemeinschaft ❑ ledig

❑ geschieden ❑ verwitwet

4) Aktuelle Wohnsituation (Zutreffendes bitte ankreuzen):

❑ allein lebend ❑ mit Familie/ Lebenspartner lebend

❑ in Institution lebend (z.B.: Altenheim/ Pflegeheim...) ❑ sonstiges (bitte angeben): _____

5a) Benötigten Sie in den letzten zwei Wochen Hilfe bei alltäglichen Tätigkeiten? (wie z.B. Essen, Anziehen, Kaffee kochen) (Zutreffendes bitte ankreuzen)

❑ ja ❑ nein

5b) Falls ja, von wem haben Sie die meiste Hilfe erhalten? (Zutreffendes bitte ankreuzen)

❑ Ehe-/Lebenspartner/-in, Verwandte, Freunde

❑ professioneller Pflegedienst

❑ freiwillige/ehrenamtliche Organisation

❑ andere (bitte angeben): _____

Questionnaire on socio-demographic patient characteristics, help with every-day activities and current employment situation, part 2

6) Höchster Ausbildungsabschluss (Zutreffendes bitte ankreuzen):

- ❑ Volksschulabschluss
- ❑ Hauptschulabschluss
- ❑ Mittlerer Reife (Fachhochschulreife)
- ❑ Gesellenprüfung
- ❑ Abitur (Hochschulreife)
- ❑ Meisterschule
- ❑ Fachhochschulabsolvent/-in
- ❑ Hochschulabsolvent/-in
- ❑ Höherer universitärer Abschluss (Doktor, Priv.Doz., Prof. etc.)

7) Aktuelles Beschäftigungsverhältnis (Zutreffendes bitte ankreuzen):

- ❑ Vollzeittätigkeit (mehr als 30 Std./Woche)
- ❑ Rentner/-in
- ❑ Teilzeittätigkeit (weniger als 30 Std./Woche)
- ❑ Hausfrau/-mann
- ❑ arbeitssuchend
- ❑ Schüler/-in / Student/-in
- ❑ arbeitsunfähig aufgrund Krankheit oder Behinderung

8) Welchen Beruf haben Sie erlernt? (z.B. Lehrer/-in, Einzelhandelskauffrau/-mann)

_____

9) In welchem Beruf arbeiten Sie momentan oder haben Sie als letztes gearbeitet?
(Zutreffendes bitte ankreuzen)

Ich arbeite/arbeitete als _____ (z.B. Lehrer/-in, Bäcker/-in) und bin/war

- ❑ Beamte/-r
- ❑ Handwerker/-in
- ❑ Angestellte/-r
- ❑ Selbständige/-r
- ❑ Arbeiter/-in
- ❑ sonstiges (bitte angeben):

_____

Hand-foot syndrome (HFS)

Fragebogen zu Hautreaktionen

Sehr geehrte Patientin, sehr geehrter Patient,

bitte geben Sie auf diesem Bogen kurz an, ob Sie während des letzten Zyklus Ihrer Chemotherapie mit Xeloda® Probleme mit Hautreaktionen an Ihren **Händen und Füßen** hatten.

Kreuzen Sie hierzu bitte das Feld unter der für Sie zutreffenden Beschreibung an:

Keine Probleme	Minimale Hautveränderungen (z.B. Rötungen), **KEINE Schmerzen**	Hautreaktionen (z.B. Risse, Blasen, Schwellungen) **und/oder Schmerzen, NICHT beeinträchtigend**	Sehr starke Reaktionen (z.B. Hautablösungen, Blasen, Bluten) **und/oder starke Schmerzen, BEEINTRÄCHTIGEND**

Platz für zusätzliche Kommentare:

_____

_____

_____

_____

Willingness-to-pay (WTP), part 1

Patientenzufriedenheit mit der Dienstleistung „Pharmazeutische Betreuung" im Rahmen der Studie „Pharmazeutische Betreuung von onkologischen Patienten unter Behandlung mit Capecitabin (Xeloda®)"

Sehr geehrte Patientin, sehr geehrter Patient,

bitte beantworten Sie die folgenden Fragen offen und spontan.

In den Kästchen sind Noten von „1" (sehr gut, sehr, ja) bis „5" (mangelhaft, überhaupt nicht, nein) zu vergeben.

Alle Angaben sind freiwillig und bleiben wie immer anonym!

Datum: _____

	☺ ☹
Wie zufrieden sind Sie **insgesamt** mit der pharmazeutischen Betreuung?	1 2 3 4 5
Wie zufrieden sind Sie mit der **Erreichbarkeit** der Studienapotheker?	1 2 3 4 5
Wie zufrieden sind Sie mit der **Zeit**, die sich die Studienapotheker für Sie nehmen?	1 2 3 4 5
Wie zufrieden sind Sie mit der Aufklärung über mögliche **Nebenwirkungen** und **Wechselwirkungen** Ihrer Krebsbehandlung und anderer Medikamente, über **Arzneimitteleinnahme bzw. -anwendung** sowie **ergänzende Therapien** durch die Studienapotheker?	1 2 3 4 5
Waren die Informationen, die Sie rund um Ihre Arzneimitteltherapie von den Studienapothekern erhalten haben, für Sie **nützlich**?	1 2 3 4 5
Konnten Sie **Ihre Fragen** zur Arzneimitteltherapie zu Ihrer Zufriedenheit mit den Studienapothekern besprechen?	1 2 3 4 5
Würden Sie sich in Zukunft für die Dienstleistung „Pharmazeutische Betreuung" entscheiden, wenn sie beispielsweise von einer öffentlichen Apotheke oder einem Apotheker im Krankenhaus angeboten würde?	1 2 3 4 5

Willingness-to-pay (WTP), part 2

Haben Sie mit Ihrem behandelnden Onkologen oder einem anderen Arzt über Informationen, die Sie von den Studienapothekern erhalten haben, gesprochen?

□ ja □ nein

Wie ist Ihre Haushaltsgröße?

- □ 1 Person
- □ 2 Personen
- □ 3 Personen
- □ 4 Personen
- □ 5 Personen oder mehr

Wie hoch ist Ihr Haushaltsnettoeinkommen?

- □ unter € 1000
- □ € 1000 bis unter € 1500
- □ € 1500 bis unter € 2000
- □ € 2000 bis unter € 2500
- □ € 2500 bis unter € 3000
- □ € 3000 bis unter € 3500
- □ € 3500 und mehr

Sie wurden 4,5 Monate lang zusätzlich durch eine/-n Apotheker/-in betreut. Was wären Sie theoretisch bereit, für eine pharmazeutische Betreuung wie Sie sie erfahren haben, maximal pro Monat zu zahlen?

maximal _____ Euro pro Monat

Gibt es noch etwas, das Sie uns mitteilen möchten (z.B. was Ihnen besonders gut gefallen hat oder was wir verbessern könnten)?

_____

_____

Pharmacotherapy

universitätbonn

Fragebogen zur Begleitmedikation

Sehr geehrte Patientin, sehr geehrter Patient,
in unserer Studie spielen die Arzneimittel, die Sie im Rahmen Ihrer Therapie mit Xeloda® zur Behandlung von Magenproblemen (z.B. Pantozol®), des Hand-Fuß-Syndroms (z.B. Vitamin B_6, Handsalben) und anderer Nebenwirkungen erhalten, eine wichtige Rolle.
Auch Vitaminpräparate, Spurenelemente (z.B. Selen, Zink), Mineralstoffe (z.B. Calcium, Magnesium) und andere ergänzende Therapien (z.B. Mistelpräparate), die Sie anwenden, sind für unsere Studie wichtig.
Daher bitten wir Sie, die von Ihnen während dieses Zyklus verwendeten Arzneimittel **(egal ob von Ihrem Arzt verordnet oder von Ihnen selbst erworben)** zu notieren und auch die Stärke und Packungsgröße zu vermerken.

Zyklus _____ Datum: _____

Arzneimittel:

	Stärke:	Packungsgröße:
_____	_____mg	_____Stück/ml
_____	_____mg	_____Stück/ml
_____	_____mg	_____Stück/ml
_____	_____mg	_____Stück/ml
_____	_____mg	_____Stück/ml
_____	_____mg	_____Stück/ml
_____	_____mg	_____Stück/ml
_____	_____mg	_____Stück/ml
_____	_____mg	_____Stück/ml

Vitamine/Spurenelemente/Mineralstoffe/ergänzende Therapien:

	Stärke:	Packungsgröße:
_____	_____mg	_____Stück/ml
_____	_____mg	_____Stück/ml
_____	_____mg	_____Stück/ml

Hand-Fuß-Pflege

_____

_____

Resource use documentation form, part 1

Universität Bonn, Klinische Pharmazie
Pharmazeutische Betreuung Dokumentationsbogen: Patientenakte - Titelblatt

Datum Akteneinsicht:	Zeit: ___ : ___ Uhr bis ___ : ___ Uhr = ___ min
Patient/-in:	Code:
Erstdiagnose:	
Tumorentität und Tumorstatus:	
OP: (Wann? Was?)	
Krebstherapien in der Vergangenheit? (Chemotherapie, Bestrahlung, Hormontherapie,...)	
Krankenkasse: Versichertennummer:	
Hausarzt:	
Sonstiges: (bei Bedarf auch Rückseite)	
Akteneinsicht durch wen ?	Susanne □ Andere □ (_____)

Resource use documentation form, part 2

Universität Bonn, Klinische Pharmazie,
Pharmazeutische Betreuung Dokumentationsbogen: Patientenakte

Datum Akteneinsicht:	Zeit: ___ : ___ Uhr bis ___ : ___ Uhr = ___ min
Patient/-in:	Code:
Datum in Akte:	(z.B. Arztbesuch)
Pharmakotherapie: (Chemo- und Supportiv-Therapie)	
Diagnostik: (CT, Blutuntersuchung, erhöhte oder erniedrigte Laborwerte eintragen,...)	Gewicht: Größe: KOF:
Verwaltung: (z.B. Arztbrief)	
Infos zu Krankmeldungen?	
Infos zu stationären Aufenthalten?	
Abrechnungsziffern:	
Sonstiges: (bei Bedarf Rückseite)	
Akteneinsicht durch wen?	Susanne ▫ Andere ▫ (_____)

Hardcopy of electronic patient file (extract)

Karteikarte [redacted] von: **01.05.2006** bis: **20.12.2006**

Geschlecht	W	ChipIdent:	4491707.41105040
Geburt	[redacted]	Patienten-ID:	25547
Strasse:	[redacted]	Letzter Kontakt:	20.12.2006 16:08:1
Ort		Behandler:	[redacted]
Telefon		IK/VKNR/Kass-Name:	[redacted] NOVITAS Vereinigte BKK

2/06Org 12.06.06 Kasse: 25420 Kassenname: NOVITAS Vereinigte BKK IK 4491707 Abgerechnet: Nein

*	**23.05.2006**	D	Dauerdiagnose	WO	(ICD:C50.9G) Mammakarzinom
*	**23.05.2006**	F	Formulare	WO	Überweisung(#317072)
*	**23.05.2006**	F	Formulare	WO	Taxischein(#317089)
*	**23.05.2006**	F	Formulare	WO	Taxischein(#317087)
*	**23.05.2006**	M	Medikament	WO	M:MCP Trp. 100ml>□M:Xeloda 500mg FTbl 120 ST(#0410399)><
*	**23.05.2006**	F	Formulare	WO	Kassenrezept(#317086)
*	**23.05.2006**	DI	Langdiagnose	WO	Mamma Karzinom links 08/05 Z.n,. Ablatio mammea und Axilla Dissection Histologie: TU.Stadium: Rez.Status: HER2: postoperative Strahlentherapie postoperative Therapie mit Tamoxifen Hautmetastasen/Narbenrezidiv 05/06 Therapie mit Xeloda
*	**23.05.2006**	SS	Sonographie	WO	Sonographie des Abdomens anamnestisch heute unauffällig,
*	**23.05.2006**	R	Röntgen	WO	Rö-der Lunge anamnestisch unauffällig
*	**23.05.2006**	F	Formulare	WO	Überweisung(#317073)
*	**23.05.2006**	Z	Ziffer	WO	80112, 32012, 13500, 86503, 13502, 32019, 90909, 01600
*	**23.05.2006**	T	Therapie	WO	Pat. war im Elisabeth Krhs. Habe sie dort konsiliarisch gesehen. □Therapiebeginn mit Xeloda 2-0-2

Receipt of an inpatient stay

UNIVERSITÄTSKLINIKUM BONN
ANSTALT DES ÖFFENTLICHEN RECHTS
Der Kaufmännische Direktor

Geschäftsbereich 3 Abt. 3.1 Az: 5016409/3

53105 Bonn, 12.10.06

Telefon: **(0228) 287 - 0**
Durchwahl:
Bearb.: [redacted]
Telex:
Telefax:
IKZ : **260530103**

Universitätsklinikum Bonn
Sigmund-Freud-Str. 25, 53105 Bonn
BKK Gruner + Jahr
Timm-Kröger-Str. 2
25524 Itzehoe

Bei Zahlung bitte angeben:
Debitorennummer: 1004963
Rechnungsnummer: 10547882

Abrechnungsdatum: 12.10.06
zahlbar bis: 02.11.06

Rechnung

Fall
AufnDatum: 10.08.06 Uhrzeit: 10:35
EntlDatum: 25.08.06 Uhrzeit: 19:31
EntlGrund: 01 FallNr: 5016409
EntlDiagnose: C50.9

Patient
Name:
Vorname:
GebDatum: [redacted] PatNr.: [redacted]

Versicherter
Name:
Vorname:
Strasse/Nr:
PLZ,Ort:

GebDatum:
MitglArt: M VSt: 1000 1
VersNr: [redacted]
AktZeichen:

Leistung anf.Fachabt.	Bezeichnung von	bis	Menge	Preis/EUR	Basisfallwert Rel.gewicht Anteil in %		Schlüssel §301 Betrag/EUR
ASZS	Ausbildungszuschlag stationär, nach §17a						75105002
GYN	10.08.2006	10.08.2006	1	102,83	100,00		102,83
DRG06J11A	Andere Eingriffe an Haut, Unterhaut und Mamma mit mäßig komplexer Prozedur				3.054,43	0,828	7010J11A
GYN	10.08.2006	24.08.2006	1	2.529,07	100,00		2.577,38

Zwischensumme: 2.680,21

Fachrichtung	OPS-301	HC	Diagnose
1500	5-399.5	X	
1500			C50.9
2400			C50.9
2400	3-820		
2400	3-823		

Leistung anf.Fachabt.	Bezeichnung von	bis	Menge	Preis/EUR	Basisfallwert Rel.gewicht Anteil in %	Schlüssel §301 Betrag/EUR
				Übertrag Summe:		2.680,21
QS	Qualitätssicherungszuschlag					46005000
GYN	10.08.06	10.08.06	1	1,27	100,00	1,27
SGBS	Systemzuschlag gem.Bundesausschuss §91 S					47100001
GYN	10.08.06	10.08.06	1	0,65	100,00	0,65
SYS	DRG-Systemzuschlag					48000001
GYN	10.08.06	10.08.06	1	0,90	100,00	0,90
davon Summe AiP-Zuschl.+ Arbeitszeitverbesserung			1,91 %	auf DRG und Zusatzentgelt		(48,31)
				Rechnungsbetrag:		**2.683,03**

Appendix B: Informed consent

Patient information brochure (example Johanniter Hospital, Bonn)

Pharmazeutische Betreuung onkologischer Patienten unter Behandlung mit Capecitabin (Xeloda®)

- Eine Anwendungsbeobachtung -

Patienteninformation

Verantwortlicher Leiter:

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Klaus Ruberg, Apotheker, Kronen-Apotheke Marxen, Wesseling

Beate Niemann, Apothekerin, Apotheke im Stadthaus, Bonn

Kooperationspartner:

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Universität Bonn
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Fax:	0228 – 73-9757	0228 – 73-9757
e-mail:	s.simons@uni-bonn.de	s.roth@uni-bonn.de

Sehr geehrte Patientin,
Sehr geehrter Patient,

Sie erhalten momentan eine Chemotherapie mit dem Arzneimittel Xeloda®. Über den gesamten Verlauf Ihrer Therapie kümmert sich ein Team aus Ärzten, Pflegenden und anderen besorgten Menschen um Sie, um Ihre Behandlung möglichst gut und belastungsarm zu gestalten.

Wir möchten in dieser Studie herausfinden, ob es sinnvoll ist, Chemotherapiepatienten rund um ihre Therapie zusätzlich intensiv durch einen Apotheker zu betreuen und zu informieren.

Dabei sind wir auf Ihre Hilfe angewiesen.

In dem Ihnen vorliegenden Informationsmaterial wird Ihnen die geplante Studie genau vorgestellt. Es wird beschrieben, welche Überlegungen zur Planung der Studie geführt haben, wie die Studie ablaufen soll und was eine Teilnahme für Sie als Patient/-in ganz praktisch bedeuten würde.

Nehmen Sie sich für das Lesen ruhig viel Zeit. Legen Sie die Unterlagen zwischendurch beiseite, um darüber nachzudenken. Machen Sie sich überall im Heft Notizen zu den Dingen, die Sie gerne noch mit uns klären würden.

Sollte Ihnen während des Lesens irgend etwas unklar erscheinen oder Fragen aufwerfen, so scheuen Sie sich nicht, Ihren behandelnden Arzt, oder die verantwortlichen Apotheker Sven Simons und Susanne Roth anzusprechen.

Vielen Dank für Ihr Interesse und Ihre Mühe und

viel Erfolg bei Ihrer Behandlung!

Prof. Dr. Yon Ko
(Studien-Arzt)

Dipl.-Pharm. Sven Simons
Dipl.-Pharm. Susanne Roth
(Studien-Apotheker)

INHALT **Seite**

1. Hintergründe und Ziele des Projektes

Diese Studie ist ein Projekt der Arbeitsgruppe „Klinische Pharmazie“ der Universität Bonn. Pharmazie ist das Fach, welches Apotheker für ihren Beruf ausbildet. Klinische Pharmazie ist ein relativ neues Gebiet innerhalb der Pharmazie. Durch die Entwicklung des Gesundheitssystems haben sich neue Anforderungen an den Apothekerberuf ergeben. Die Rolle der Patienten und auch ihrer Bedürfnisse haben sich gewandelt. Das Fach Klinische Pharmazie soll daher dazu beitragen, die Ausbildung und Berufsausübung der Apotheker verstärkt im Dienste der Patienten auszurichten. In diesem Zusammenhang werden Untersuchungen durchgeführt, anhand derer der Nutzen und die Durchführbarkeit patientenorientierter Leistungen des Apothekers unter Beweis gestellt werden sollen.

In Deutschland sind heute ca. 45.000 zugelassene Arzneimittel am Markt erhältlich. Mit der wachsenden Zahl an Medikamenten gehen verschiedene Probleme einher. Zum einen wird es immer schwieriger, das Angebot zu überblicken und alle Neuerungen kritisch zu bewerten, zum anderen steigt die Gefahr, Medikamente zu kombinieren, die sich in ihrer Wirkung gegenseitig beeinflussen, was möglicherweise zu unerwünschten Wirkungen führen kann.

Diese Entwicklung macht es notwendig, dass alle an einer Therapie Beteiligten, also sowohl Sie als Patient/-in, wie auch die Ärzte und Apotheker, möglichst gut zusammenarbeiten, um eine optimale Therapie zu erreichen.

Die Hauptaufgabe des Apothekers besteht darin, Sie rund um Ihre Arzneimitteltherapie zu informieren und zu beraten. Gerade in einer Dauertherapie ist es wichtig, dass der Patient durch den Apotheker begleitet wird und möglicherweise aufkommende Fragen und Probleme zu den Medikamenten direkt beantwortet bzw. Probleme beseitigt werden können.

Die Realität der gegenwärtigen Apothekenpraxis sieht jedoch häufig anders aus. Patienten erwerben die vom Arzt verordneten oder selbst gewählten freiverkäuflichen Arzneimittel in der Apotheke und erhalten zu den Medikamenten Einnahme- oder Anwendungshinweise. Danach besteht jedoch oft wochenlang kein Kontakt mehr zum behandelnden Arzt oder Apotheker.

Um dieser Aufgabe gerecht zu werden, wurde das Konzept der Pharmazeutischen Betreuung entwickelt. Durch eine fortlaufende Betreuung soll der Apotheker eine sinnvolle und sichere Arzneimitteltherapie für Sie als Patient/-in gewährleisten.

Für Krebspatienten hat es bislang in dieser Form erst sehr wenige Untersuchungen gegeben, obwohl gerade diese Patientengruppe besonders betreuungsbedürftig ist.

Ziel dieser Untersuchung ist es:

- ◊ die Qualität und Sicherheit der Arzneimitteltherapie zu erhöhen
- ◊ die Zusammenarbeit von Arzt, Patient und Apotheker zu verbessern
- ◊ die Patientenbetreuung in Apotheken weiter zu entwickeln
- ◊ die Lebensqualität der Krebspatienten zu steigern

Was bedeutet das konkret für Sie als Krebspatient/-in?

In Ihrem Fall ist eine Chemotherapie - nach dem heutigen Stand der wissenschaftlichen Erkenntnisse - Teil einer optimalen Behandlung Ihrer Erkrankung. Die für Sie vorgeschlagene Therapie sieht die Gabe des Wirkstoffs Capecitabin in Form von Filmtabletten (Xeloda®) vor. Diese Therapie zeichnet sich, wie die Erfahrungen gezeigt haben, durch eine gute Wirksamkeit aus.

Es ist schwierig, die Wirkung der Krebsbehandlung auf die Krebszellen allein zu beschränken. Das hat zur Folge, dass auch gesunde Zellen geschädigt werden, was zu unangenehmen Nebenwirkungen führen kann.

Das Ausmaß der Nebenwirkungen beim einzelnen Patienten bei gleichbleibender Wirksamkeit der Behandlung zu senken, ist das Ziel dieser Studie.

Apotheker bringen sich mehr als bisher üblich in die Gestaltung und Durchführung der Therapie ein und sollen durch ihr Wissen Ihnen als Patient/-in einen weiteren Nutzen bringen.

Wenn im Zusammenhang mit dieser Studie von Therapieverbesserung gesprochen wird, so ist damit vor allem die sogenannte „Supportivtherapie" gemeint. „Supportiv" bedeutet im eigentlichen Sinne „unterstützend". Auf die Therapie einer Krebserkrankung bezogen sind damit alle Behandlungsmaßnahmen gemeint, die zur Vorbeugung und/oder Therapie von unerwünschten Wirkungen (z. B. Durchfall) eingesetzt werden, die mit der eigentlichen Therapie der Krebserkrankung einhergehen können. Auf diese unterstützenden Therapien soll besonderes Augenmerk gerichtet werden.

Es soll an dieser Stelle ausdrücklich darauf hingewiesen werden, dass es sich bei der geplanten Studie **nicht** um eine klinische Prüfung von Arzneimitteln handelt. Es werden also keine neuen, noch nicht erprobten Arzneimittel zum Einsatz kommen.

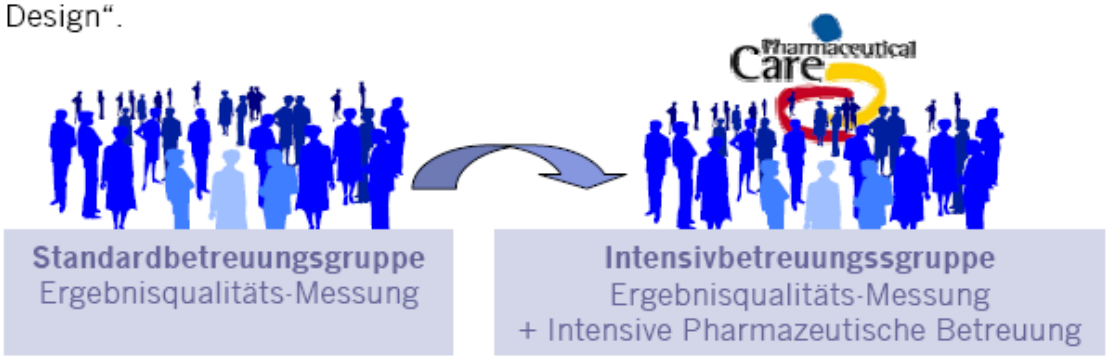
Des Weiteren möchten wir Sie darauf aufmerksam machen, dass sich der betreuende Apotheker zwar mit Ihrer Arzneimitteltherapie befasst und diese gemeinsam mit Ihnen und den behandelnden Ärzten zu optimieren sucht, es aber keine Rolle spielt, woher Sie Ihre Arzneimittel beziehen. Sie können also auch während der Teilnahme an dieser Studie, so wie Sie es gewohnt sind, weiter bei den von Ihnen bevorzugten Apotheken die Arzneimittel beziehen.

2. Konzept der Studie

a. Studiendesign

Der Ausdruck „Studiendesign“ beschreibt, welche Untersuchungs-Methode der Studie zugrunde liegt und auf welche Weise die Ergebnisse zustande kommen sollen.

Diese Studie basiert auf dem sogenannten „sequenzierten Kontrollgruppen-Design“.



Dieser Ausdruck bedeutet, wie auch aus der oben gezeigten Grafik hervorgeht, dass zunächst nur eine Gruppe Patienten (**„Standardbetreuungsgruppe“**) in die Studie aufgenommen wird, bei der die Therapie inkl. der gewohnten Betreuung durch Ärzte und Pflegepersonal sowie durch die Apotheke Ihrer Wahl wie bisher üblich durchgeführt wird. Die Patienten dieser Standardbetreuungsgruppe werden gebeten, bestimmte Fragebögen zu festgelegten Zeitpunkten (siehe 3.b.) auszufüllen. Außerdem werden alle möglicherweise auftretenden Nebenwirkungen von den Ärzten in Dokumentationsbögen festgehalten, sowie die zeitlichen Einnahmegewohnheiten der verordneten Xeloda®-Filmtabletten durch ein speziell für diese Art von Studien entwickeltes Arzneimittelbehältnis (siehe 3.b.) beobachtet. Dieses Verfahren ist notwendig, um Vergleichswerte zu erhalten, die es später ermöglichen, Veränderungen, die durch die intensivierte Betreuungsmaßnahme eingetreten sein könnten, zu messen.

Sobald diese Vergleichswerte vorliegen, wird die nächste Gruppe von Patienten in die Studie aufgenommen. Diese Patienten gehören der **„Intensivbetreuungsgruppe“** an und werden intensiv durch den Studienapotheker betreut. Eine genaue Beschreibung des Betreuungsablaufes finden Sie unter Punkt 3 dieses Heftes.

Auch diese Patienten werden gebeten, die gleichen Fragebögen zu den gleichen Zeitpunkten im Laufe ihrer Therapie auszufüllen, wie die Patienten in der ersten Gruppe und auch hier findet eine Beobachtung der Einnahmegewohnheiten der verordneten Xeloda®-Filmtabletten statt.

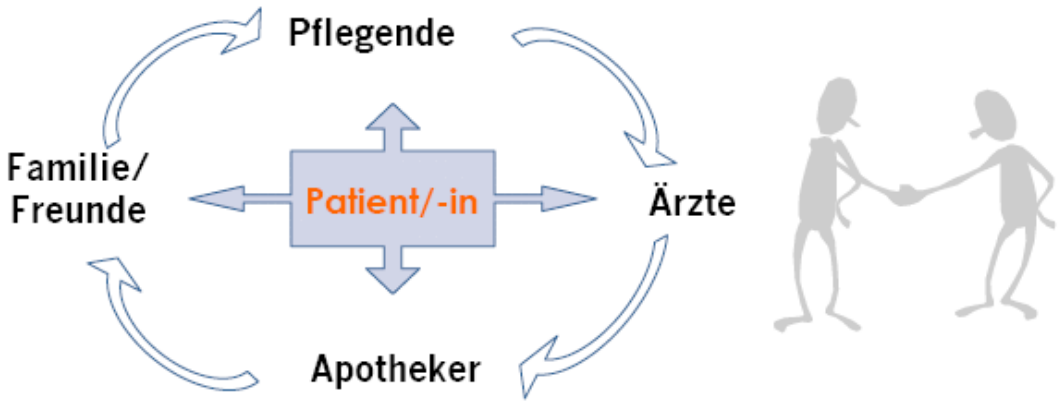
Auch bei den Patienten der Intensivbetreuungsgruppe werden von den behandelnden Ärzten alle möglicherweise auftretenden Nebenwirkungen genau aufgezeichnet.

Abschließend werden die Ergebnisse der Fragebögen und Aufzeichnungen beider Gruppen verglichen. Dieser Vergleich wird dann zeigen, ob die intensivierte Betreuung durch einen Apotheker für Krebspatienten einen Nutzen hat oder nicht.

b. Kommunikation

Rund um die Therapie Ihrer Erkrankung sind viele Menschen in sehr unterschiedlichen Funktionen darum bemüht, Ihnen die bestmögliche Versorgung zukommen zu lassen.

Es wird angestrebt, alle an Ihrem Betreuungsprozess Beteiligten in ein Kommunikationsnetzwerk einzubinden (siehe Grafik).



Dadurch soll gewährleistet werden, dass keine wichtigen Informationen verloren gehen, die für Ihre Behandlung von Bedeutung sein könnten.

3. Ablauf der Studie

Die Betreuung findet im Rahmen Ihrer Chemotherapie statt.

Der Studien-Apotheker steht zur Beantwortung aller aufkommenden arzneimittelbezogenen Fragen zur Verfügung.

Eine fortlaufende Dokumentation der aktuellen Medikation ist erforderlich, um einen Überblick zu bekommen, wie die Arzneimittel vertragen werden.

Die Daten werden ständig verarbeitet und ausgewertet, so dass eine bestmögliche Therapiebegleitung erfolgen kann.

Der Nutzen der durchgeführten Betreuung soll durch einen Vergleich mit der bisherigen Betreuungssituation gezeigt werden. Hierzu soll die Qualität der durchgeführten Betreuung mit verschiedenen Fragebögen zu Lebensqualität und Patientenzufriedenheit überprüft werden (siehe 3.b.).

Unter Anwendung eines modernen, speziell für diese Art von Studien entwickelten, Arzneimittelbehälters werden die zeitlichen Einnahmegewohnheiten der Patienten beobachtet (siehe 3.b.).

Die intensivierte Pharmazeutische Betreuung im Rahmen dieser Studie wird von Apothekern durchgeführt, die besondere Erfahrungen in der Patientenbetreuung haben. Der Kontakt zum Apotheker wird über Ihren behandelnden Arzt hergestellt, der Sie auch über die Möglichkeit informiert hat, an dieser Studie teilzunehmen.

a. Studienverlaufsplan

Die Betreuung soll sich dadurch auszeichnen, dass sie Ihren individuellen Bedürfnissen gerecht wird. Einen Eindruck, wie Sie sich den Ablauf dieser Studie in etwa vorstellen können, soll der folgende Studienverlaufsplan vermitteln.

Im **Aufklärungsgespräch** werden Sie von dem betreuenden Apotheker über die Ziele und Hintergründe der geplanten Studie informiert.

- In diesem Gespräch sollte Ihnen vermittelt werden, was Sie von der Studie erwarten können und was als Patient auf Sie zukommt.
- Sie erhalten Informationsmaterial zur Studie, welches Sie zu Hause in Ruhe lesen können, bevor Sie eine Entscheidung über Ihre Teilnahme treffen.

Im Verlauf dieses Gespräches haben Sie die Gelegenheit, Fragen zu stellen und sich Dinge erläutern zu lassen, die Ihnen unklar erscheinen.

Im **folgenden Gespräch** können Sie Ihre Entscheidung mitteilen, ob Sie bereit sind, an der Studie teilzunehmen oder lieber davon absehen möchten. Zuvor besteht die Möglichkeit, weitere Fragen zu klären.

Falls Sie bereit sind, an der Studie teilzunehmen

- werden Sie gebeten, Ihr Einverständnis zur Teilnahme an der Studie und zur Speicherung Ihrer persönlichen Daten schriftlich zu bestätigen.
- werden Ihnen die Studienunterlagen (z.B. Fragebögen), sowie das in dieser Studie für die Aufbewahrung Ihrer Tabletten zu verwendende Arzneimittelbehältnis ausgehändigt und vollständig erläutert sowie Ihre Fragen diesbezüglich beantwortet.

⇒ Die Patienten der ***Standardbetreuungsgruppe*** werden von diesem Gespräch an hauptsächlich telefonisch mit dem Studien-Apotheker in Kontakt stehen, wenn es zum Beispiel um das Ausfüllen der Fragebögen geht. Außerdem werden auch von ihnen bestimmte personenbezogene Daten erhoben (z.B. Alter usw.)

⇒ Für die Patienten **der *Intensivbetreuungsgruppe*** verläuft der Betreuungsplan etwa wie folgt:

- ◊ Zunächst werden ein Termin und der Ort für das **erste intensivierte Betreuungsgespräch** vereinbart.

Das **erste intensivierte Betreuungsgespräch** sollte vor dem ersten Therapiezyklus stattfinden. Wenn dies nicht möglich sein sollte, wird ein anderer passender Termin gesucht. Während des Gespräches ist geplant,

- ◊ Ihre persönlichen Daten, die für die Betreuung sinnvoll sind (z.B. Alter u.ä.) aufzunehmen.
- ◊ eine Übersicht über die Arzneimittel, die Sie regelmäßig einnehmen, zu erstellen.
- ◊ Fragen zur Arzneimitteltherapie zu klären.
- ◊ Ihre persönlichen Ziele und Hoffnungen verbunden mit der Arzneimitteltherapie zu erörtern und daraus gemeinsam einen Plan zu erstellen.

Die **folgenden intensivierten Betreuungsgespräche** sollten möglichst mindestens ein Mal zwischen den Therapiezyklen stattfinden. Während dieser Gespräche werden

- ◊ in der Zwischenzeit aufgekommene Fragen zur Arzneimitteltherapie geklärt.
- ◊ Probleme und Wünsche im Zusammenhang mit der Arzneimitteltherapie gemeinsam erörtert.
- ◊ Ziele gesteckt, um Ihren Bedürfnissen bestmöglich gerecht zu werden.
- ◊ Sie über zusätzliche Maßnahmen informiert, die Sie zur Vermeidung von Nebenwirkungen, die möglicherweise eintreten können, ergreifen können.

In beiden Gruppen endet Ihre Teilnahme an der Studie nach dem letzten oder spätestens nach dem achten Zyklus (also nach ca. sechs Monaten) der verordneten Chemotherapie oder selbstverständlich jederzeit, wenn Sie dies wünschen.

b. Ergebnisqualitätsmessungen

Im Folgenden werden Ihnen die „Messinstrumente“ vorgestellt, mit denen ermittelt werden soll, ob die Pharmazeutische Betreuung in den angestrebten Punkten eine Verbesserung herbeiführen kann.

i. Fragebogen zur Begleitmedikation

In unserer Studie spielen die Arzneimittel, die Sie im Rahmen Ihrer Therapie mit Xeloda zur Behandlung von Magenproblemen (z.B. Pantozol®), des Hand-Fuß-Syndroms (z.B. Vitamin B6, Handsalben) und anderer Nebenwirkungen erhalten, eine wichtige Rolle. Auch Vitaminpräparate, Spurenelemente (z.B. Selen, Zink), Mineralstoffe (z.B. Calcium, Magnesium) und andere ergänzende Therapien (z.B. Mistelpräparate), die Sie anwenden, sind für unsere Studie wichtig. Daher bitten wir Sie, die **zu jedem Zyklus** von Ihrem Arzt verordneten bzw. von Ihnen selbst erworbenen Arzneimittel zu notieren und auch die Stärke, Packungsgröße und Dosierung zu vermerken

ii. Fragebogen zur Messung der Lebensqualität

Man stellt immer wieder fest, dass die Lebensqualität der Patienten für den Therapieverlauf von entscheidender Bedeutung ist. Um einen Eindruck zu bekommen, inwieweit die Therapie Einfluss auf die Lebensqualität hat, soll zu dieser Fragestellung ein Fragebogen ausgefüllt werden. Dieser Fragebögen wurde speziell für Krebspatienten entwickelt. Während der Studienphase werden Sie gebeten, den Fragebogen **zu drei Zeitpunkten** auszufüllen: vor Beginn, in der Mitte (nach vier erhaltenen Zyklen Chemotherapie mit Xeloda® bzw. drei Monaten) und am Ende Ihrer Teilnahme an der Studie (nach spätestens acht Zyklen bzw. sechs Monaten).

iii. Fragebogen zur Messung der Patientenzufriedenheit mit der Information zu ihrer Behandlung

Nicht zuletzt ist auch Ihre Zufriedenheit ein Ziel der Studie. Um die Qualität der Betreuung festzustellen, soll Ihre Zufriedenheit als Patient/-in ermittelt werden. Hierbei wird ein besonderes Augenmerk auf die Information gelegt, die Sie zu Ihrer Behandlung erhalten. Anhand der ermittelten Ergebnisse können Strategien entwickelt werden, wie Patienten gemäß ihren individuellen Bedürfnissen informiert werden sollten. Sie werden gebeten, auch diesen Fragebogen **drei Mal** auszufüllen: zu Beginn, in der Mitte und am Ende Ihrer Teilnahme an der Studie (spätestens nach acht Zyklen bzw. sechs Monaten).

iv. Beobachtung der zeitlichen Einnahmgewohnheiten

Um mehr über Ihre zeitlichen Einnahmegewohnheiten der Ihnen verordneten Chemotherapie mit Xeloda® zu erfahren, wird in dieser Studie ein speziell entwickeltes Arzneimittelbehältnis verwendet (siehe Abbildung unten). Im Deckel dieses Behältnisses befindet sich ein kleiner elektronischer Prozessor, der Datum und Uhrzeit jeder Öffnung und Schließung des Behälters registriert. Dieses System wurde von der Schweizer Firma Aardex Ltd. entwickelt und wird als MEMS®- Medication Event Monitoring System bezeichnet. Sie werden gebeten, während Ihrer Studienteilnahme ausschließlich dieses Behältnis zur Aufbewahrung und Entnahme Ihrer Xeloda®-Tabletten zu verwenden.

Das Behältnis wird hierzu den gesetzlichen Vorgaben entsprechend beschriftet sein und Sie erhalten zusätzlich selbstverständlich die Original-Packungsbeilage des Ihnen verordneten Arzneimittels Xeloda®.

Die Tabletten werden zur Umfüllung in dieses Behältnis in ihren originalen einzelnen Folienverpackungen verbleiben, so dass kein Risiko einer Beschädigung der Tabletten beim Umfüllungsvorgang besteht.

Bitte beachten Sie die Hinweise zur Verwendung des Studien-Arzneimittelbehältnisses, die Ihnen gesondert ausgehändigt werden!

Abbildung: das MEMS®-Arzneimittelbehältnis

4. Datenschutz und Patienteneinwilligung

a. Datenschutz

Die Information, die Sie bisher über diese Studie erhalten haben, lässt schon vermuten, dass eine Vielzahl von Daten über Ihre Person im Zusammenhang mit dieser Studie erfasst werden sollen. Dies geschieht allerdings auch erst, wenn Ihr schriftliches Einverständnis dazu vorliegt.

Zum einen sollen bestimmte, für die Betreuung notwendige Daten aus Ihrer vom Arzt geführten Patientenakte übertragen werden (z.B. Laborwerte u.ä.).

Weiterhin sollen hilfreiche Informationen, die gemeinsam mit Ihnen im Gespräch erörtert werden, gespeichert werden (z.B. Schwierigkeiten oder Unsicherheiten mit der Arzneimitteltherapie).

Außerdem sollen Daten gespeichert werden, die neben Ihrer Betreuung speziell zur Auswertung der Studie benötigt werden. Das sind zum Beispiel die Ergebnisse der Fragebögen.

Alle Informationen, die zu Ihrer Person erfasst werden sollen, werden in einer computergestützten Datenbank gespeichert. Diese Datenbank wurde speziell für diese Studie entwickelt und unterstützt den Apotheker bei seiner Aufgabe, Sie umfassend zu betreuen. Die Ergebnisse der Studie sollen mit einem Statistikprogramm (SPSS®) ausgewertet werden. Dadurch soll auch in Zahlen dargestellt werden können, ob die Betreuung durch Apotheker einen Nutzen gezeigt hat.

Die im Zusammenhang mit dieser Studie erhobenen Daten unterliegen den Bestimmungen des Datenschutzes und werden ausschließlich zum Zweck der Durchführung der Studie erhoben und ausgewertet. Das bedeutet, dass Sie der Verwendung Ihrer Daten für Studienzwecke zustimmen müssen, bevor mit der Dokumentation begonnen wird. Außerdem ist gewährleistet, dass aus Veröffentlichungen der in der Studie erhobenen Daten Ihr Name nicht hervorgeht. Die Ergebnisse der Studie werden anonymisiert veröffentlicht und stehen Ihnen dann selbstverständlich auf Anfrage zur Verfügung.

b. Patienteneinwilligung

Die Teilnahme an dieser Studie birgt für Sie keine zusätzlichen Risiken.

Sie haben selbstverständlich das Recht, jederzeit und ohne Angabe von Gründen von der Teilnahme an der Studie zurückzutreten. Es entstehen Ihnen dadurch keine Nachteile in Ihrer Behandlung.

Wenn Sie dieses Informationsmaterial eingehend gelesen haben und die Ihnen aufgekommenen Fragen beantwortet wurden, können Sie frei über die Teilnahme an der Studie entscheiden. Ihre Teilnahme und Ihr Einverständnis mit den erläuterten Bestimmungen zum Datenschutz bestätigen Sie schriftlich mit einer so genannten **Patienten-Einwilligungserklärung**, die sie gesondert erhalten.

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53121 Bonn

Recruitment fax (example Johanniter Hospital, Bonn)

universitätbonn

Absender:
Prof. Dr. Yon Ko
Johanniterstraße 3-5
53113 Bonn

An:
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Pharmazeutische Betreuung onkologischer Patienten unter Behandlung mit Capecitabin (Xeloda®)

Patientenname: _____

Anschrift: _____

_____

Telefon: _____

Stärke: ☐ 150mg ☐ 500 mg (bitte ankreuzen)

Dosierungsschema: _____ (z.B. 2 – 0 – 2)

Bitte ankreuzen:

☐ Mamma-Ca ☐ Kolorektal-Ca ☐ andere: _____

Consent form, part 1

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Rheinische
Friedrich-Wilhelms-
Universität Bonn

Pharmazeutisches Institut

Prof. Dr. U. Jaehde

Klinische Pharmazie
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Einwilligungserklärung

Name: _____

Geburtsdatum: _____

Das Original dieser Einwilligungserklärung verbleibt bei den Unterlagen. Eine Kopie der Einwilligungserklärung wird dem Patienten ausgehändigt.

Ich erkläre, dass ich die Patienteninformation zur wissenschaftlichen Untersuchung:

Pharmazeutische Betreuung onkologischer Patienten
unter Behandlung mit Capecitabin (Xeloda®)

und diese Einwilligungserklärung erhalten habe.

☐ Ich wurde für mich ausreichend mündlich und schriftlich über die wissenschaftliche Untersuchung informiert.

☐ Ich weiß, dass ich jederzeit meine Einwilligung, ohne Angaben von Gründen, widerrufen kann, ohne dass dies für mich nachteilige Folgen hat.

☐ **Ich bin damit einverstanden, dass die im Rahmen der wissenschaftlichen Untersuchung über mich erhobenen Krankheitsdaten sowie meine sonstigen mit dieser Untersuchung zusammenhängenden personenbezogenen Daten aufgezeichnet werden. Es wird gewährleistet, dass meine personenbezogenen Daten nicht an Dritte weitergegeben werden. Bei der Veröffentlichung in einer wissenschaftlichen Zeitung wird aus den Daten nicht hervorgehen, wer an dieser Untersuchung teilgenommen hat. Meine persönlichen Daten unterliegen dem Datenschutzgesetz.**

Consent form, part 2

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Universität Bonn

☐ Ich bin bereit, die in dieser Studie eingesetzten Arzneimittelbehältnisse zu verwenden, die an mich ausgegebenen Fragebögen zu „Begleitmedikation“, "Lebensqualität" und „Patientenzufriedenheit“ ordnungsgemäß auszufüllen und die Beratungstermine mit dem/der betreuenden Apotheker/-in wahrzunehmen.

☐ Mit der vorstehend geschilderten Vorgehensweise bin ich einverstanden und bestätige dies mit meiner Unterschrift.

_____, den _____ _____

Ort Datum Unterschrift

_____ _____

Unterschrift der/des Ärztin/Arztes

Unterschrift der/des Apothekerin/Apothekers

Appendix C: Pharmaceutical care service

Pharmaceutical care plan, part 1

PHARMAZEUTISCHER BETREUUNGSPLAN: XELODA (Vers. 01-06) - SEITE 1/2

Name:	Geschlecht:	Patientencode:	Geb.datum:
Akt. Krebstherapie:		Diagnose:	Metastasen: ja ☐ nein ☐
			Erstdiagnose:
Arzt:	Krankenkasse:	Start MEMS:	Monitor-Nr.:

RELEVANTE KRANKHEITSGESCHICHTE

	Datum	Problembeschreibung		Datum	Problembeschreibung
1			3		
2			4		

Bekannte Arzneimittel-Allergien:

BISHERIGE UND AKTUELLE KREBSTHERAPIE

Chemotherapie (+ RT?) **1.** **2.** **3.** **4.**	**Datum**	**Zyklen**	**Besonderheiten**
Hormontherapie **1.** **2.** **3.** **4.**	**Datum**	**Dosierung**	**Besonderheiten**
OP **1.** **2.**	**Datum**	**Besonderheiten**	

XELODA-Therapie

Zyklusnr. / Daten							
Stärke							
Dosierung							

AKTUELLE MEDIKATION (zu Beginn jedes Zyklus zu aktualisieren)

		Start	Stop			Start	Stop
1				8			
2				9			
3				10			
4				11			
5				12			
6				13			
7				14			

Pharmaceutical care plan, part 2

PHARMAZEUTISCHER BETREUUNGSPLAN: XELODA (Vers. 01-06) - SEITE 2/2

Betreuungsprotokoll: X = kein Problem / √ = aufgetretenes Problem (Erläuterung im Individualfeld unten)			
Hand-Fuß-Syndrom ☐ ☐ ☐ ☐ ☐ ☐ ☐	Diarrhoe ☐ ☐ ☐ ☐ ☐ ☐ ☐	Obstipation ☐ ☐ ☐ ☐ ☐ ☐ ☐	Mukositis/Mundpflege ☐ ☐ ☐ ☐ ☐ ☐ ☐
Übelkeit und Erbrechen ☐ ☐ ☐ ☐ ☐ ☐ ☐	Alopezie ☐ ☐ ☐ ☐ ☐ ☐ ☐	Schmerzkontrolle ☐ ☐ ☐ ☐ ☐ ☐ ☐	Angst/Depressionen ☐ ☐ ☐ ☐ ☐ ☐ ☐
Schlaflosigkeit ☐ ☐ ☐ ☐ ☐ ☐ ☐	Betreuung / Schulung ☐ ☐ ☐ ☐ ☐ ☐ ☐	Andere ☐ ☐ ☐ ☐ ☐ ☐ ☐	

INDIVIDUELLE PROBLEME			
Datum	Problem	Maßnahme	Ergebnis (Initialen)

Mögliche Nebenwirkung	Vorbeugende Maßnahmen	Im Falle des Falles
Verstopfung (Obstipation)	○ Ausreichend trinken! (Pflaumensaft, Tee, Wasser) ○ Bewegung (z.B. Spazieren gehen) ○ Jedem Reiz, zur Toilette zu gehen, nachgeben ○ Ballaststoffreiche Ernährung (Vollkornbrot, Gemüse, Weizenkleie)	○ Ursache mit dem Arzt klären, evtl. Abführmittel einnehmen ○ Viel trinken!
Geschmacksver-änderungen	○ Mundschleimhaut feucht halten durch häufiges Trinken (z.B. Salbeitee)	○ Bonbons lutschen ○ Zur Geschmacksverstärkung trockene Nahrung in Flüssigkeiten einweichen (z. B. Saucen, Brot in Kaffee tunken)
Fieber/Infektionen	○ Ausreichende Ruhephasen ○ Ungekochtes Obst/Gemüse vermeiden ○ Gründliche Körperhygiene ○ Kontakt meiden zu: - Menschen mit ansteckenden Erkrankungen - Frisch geimpften Menschen	○ Bei Fieber > 38°C sofort den Arzt verständigen! ○ Erkältungsanzeichen genau beobachten ○ Bei längerer Heilungsdauer üblicher Erkrankungen den Arzt aufsuchen ○ Vom Arzt verordnete Antibiotika regelmäßig und gemäß der Verordnung einnehmen
Müdigkeit und Erschöpfung (Fatigue)	○ Entspannungsübungen ○ Ruhephasen einplanen ○ Angemessene körperliche Bewegung (Spaziergänge im Freien) ○ Koffein und Alkohol vor dem Einschlafen vermeiden ○ Alltagspflichten auf andere übertragen (z.B. Familienmitglieder)	○ Bei länger anhaltender Erschöpfung und Müdigkeit, die auch durch ausreichende Ruhepausen nicht deutlich verringert wird, den Arzt informieren ○ Vorbeugende Maßnahmen weiter verfolgen
Haarausfall (Alopezie)	Wie fast alle Nebenwirkungen tritt auch Haarausfall nicht bei jedem Patienten auf, ist aber leider nicht durch vorbeugende Maßnahmen zu vermeiden oder zu lindern. Sorgen Sie vorsorglich für geeigneten Haarersatz oder eine Kopfbedeckung anderer Art, die Ihnen gefällt.	○ Kopfhaut vor Kälte, Hitze und direkter Sonneneinstrahlung schützen ○ Bei Verlust der Wimpern, das Auge vor intensivem Licht und Staub bewahren

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Chemotherapie und die Nebenwirkungen

Was Sie darüber wissen sollten,
wie Sie Nebenwirkungen vorbeugen können,
und was Sie im Falle des Falles tun können!

Klinische Pharmazie universitätbonn

Sehr geehrte Patientin, sehr geehrter Patient,

im Rahmen Ihrer Behandlung bekommen Sie eine Chemotherapie in Tablettenform. Sie erhalten das Arzneimittel Xeloda® (Wirkstoff: Capecitabin) und dazu möglicherweise noch weitere Kombinationspartner, die individuell auf Ihre Erkrankung abgestimmt wurden.

Anders als eine Operation oder eine Strahlentherapie wirken die in der Chemotherapie eingesetzten Wirkstoffe im ganzen Körper (systemisch), da sie über das Blut verteilt werden. Die Wirkstoffe sind gegen möglicherweise im Körper verteilte Krebszellen gerichtet. Die Wirkstoffe können jedoch nicht zwischen kranken und gesunden Zellen unterscheiden, so dass auch gesunde Zellen betroffen sein können. Das führt zu unerwünschten Nebenwirkungen. Hiervon sind hauptsächlich die Zellen in Ihrem Körper betroffen, die sich häufig teilen und dadurch erneuern. Dazu gehören zum Beispiel Haarzellen, Schleimhautzellen des Mundes und des Magen-Darmtraktes, Hautzellen und auch Zellen des Knochenmarks, welches Ihr Blut bildet.

Wichtig für Sie zu wissen ist, dass nicht alle der beschriebenen Nebenwirkungen auch tatsächlich auftreten. Falls es jedoch dazu kommen sollte, ist es gut, wenn Sie bereits davon gehört haben und wissen, was Sie dagegen tun können.

Im Zweifel sprechen Sie Ihren betreuenden Arzt an und unterrichten ihn genau über die Nebenwirkung und die Maßnahmen, die Sie dagegen eingeleitet haben.

Die Wirkstoffe, die Sie in Ihrer Chemotherapie erhalten, heißen:

_____

_____

_____

Mögliche Nebenwirkung	Vorbeugende Maßnahmen	Im Falle des Falles
Hand-Fuß-Syndrom	○ Hautpflege mit milder, parfümfreier Feuchtigkeitslotion ○ Milde Seifen und Spülmittel verwenden ○ Druck vermeiden (offene, lockere Schuhe tragen, schwere Hand- und/oder Gartenarbeit vermeiden) ○ Lauwarm duschen bzw. baden, heiße Fußbäder vermeiden	○ Hautpflege mit milder, parfümfreier Feuchtigkeitslotion ○ Bei starker Verschlechterung und/oder Beeinträchtigung den behandelnden Arzt informieren!
Übelkeit und Erbrechen (Nausea und Emesis)	○ Vorbeugende Medikation wie verordnet einnehmen (nicht nur im Bedarfsfall!) ○ Generell gilt: Essen Sie, worauf Sie Appetit haben! ○ Große Mahlzeiten vermeiden; 5-6 kleinere Mahlzeiten pro Tag essen ○ Kalte Speisen und Getränke werden häufig besser toleriert als warme ○ Appetit durch säuerliche Bonbons, Speisen oder Getränke anregen ○ Schlaf, entspannende Musik oder Spaziergänge im Freien ○ Süße, fette, stark riechende und gebratene Speisen vermeiden	○ Viel frische Luft zuführen ○ Ausruhen ○ Bedarfsmedikation einnehmen ○ Ausreichend trinken
Entzündungen im Mundraum (Mukositis)	○ Zahnsanierung beim Zahnarzt ○ Gründliche, schonende Mundhygiene ○ Weiche Zahnbürsten verwenden ○ Alkoholfreie Mundwässer verwenden ○ Spülung mit lauwarmem Salbeitee ○ Zahnreinigende Kaugummis zur Speichelanregung kauen ○ Ausreichend trinken ○ Nikotin und Alkohol vermeiden ○ Scharfe, heiße und sehr saure Speisen vermeiden	○ Bei Anzeichen einer Mundschleimhautentzündung rechtzeitig den Arzt informieren und verordnete Medikamente einsetzen ○ Mundhygiene entsprechend der Vorbeugung fortsetzen ○ Weiche Speisen bevorzugen ○ Ananassaft-Eiswürfel lutschen ○ Zusätzliche Verletzungen vermeiden
Durchfall (Diarrhoe)	○ Bei Durchfallneigung Ernährung umstellen (auf z.B. Weißbrot, Kartoffeln, Bananen, Äpfel, Mais usw.) ○ Vermeiden: Süßstoffe, Vollkornbrot, Kaffee, stark gewürzte Speisen, Fruchtsäfte, Obst (mit Ausnahmen s. o.), rohe Milch ○ Mineralwässer mit geringem Sulfatgehalt (SO_4^{2-}) trinken	○ Ausreichend trinken ○ Ursache mit dem Arzt klären, evtl. Medikamente (Loperamid) einnehmen ○ Weiches Toilettenpapier und feuchte Tücher verwenden

Patient letter containing medication plan

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Ihre Arzneimitteleinnahme und weitere Informationen

Bonn, 19.12.2007

Liebe Frau Musterfrau,

wie bei unserem gestrigen Termin in der Universitätsfrauenklinik besprochen, haben wir alle Medikamente, die Sie derzeit einnehmen, auf Wechselwirkungen überprüft und können Ihnen mitteilen, dass, bis auf eine Ausnahme, keines der Arzneimittel einen Einfluss auf die Wirksamkeit und Sicherheit eines anderen nimmt, wenn man sich an die empfohlenen Einnahmezeitpunkte hält.
Die einzige Ausnahme betrifft eine vorhandene Wechselwirkung zwischen Ihren Codeintropfen und dem Beruhigungsmittel Lorazepam. Hier kann es zu einer Wirkverstärkung und damit Beeinflussung der Atmung kommen. Eventuell könnte man die Codeintropfen durch Capval-Tropfen ersetzen. Der Wirkstoff, der in Capval-Tropfen enthalten ist, heißt Noscapin und zeigt diese mögliche Wirkverstärkung nur zu einem geringeren Ausmaß. Bitte besprechen Sie das mit Ihrem Hausarzt oder den Ärzten der Frauenklinik.

Im Folgenden finden Sie einige Hinweise zu Ihrer momentanen Arzneimitteltherapie.

Ihr Ehemann berichtete uns weiterhin von Ihren erhöhten Leberwerten, und dass Sie aus diesem Grund Silymarin-Kapseln und Ubichinon-Ampullen anwenden. Bei genauerer Betrachtung Ihrer Arzneimittel ist uns aufgefallen, dass Ihr Medikament TRI-Normin® 25 zur Behandlung des Bluthochdrucks, neben dem Betablocker Atenolol und dem Entwässerungsmittel (Diuretikum) Chlortalidon, auch den Wirkstoff Hydralazinhydrochlorid enthält. Dieser Wirkstoff kann zu Leberschäden führen, was sich in erhöhten Leberwerten widerspiegeln kann. Unser Vorschlag wäre eine andere Wirkstoffkombination zur Behandlung Ihres Bluthochdrucks anzuwenden. Die aktuelle Leitlinie zur Behandlung des Bluthochdrucks schlägt beispielsweise eine

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Dreierkombination aus einem Diuretikum, einem Betablocker (z.B. Bisoprolol comp. – CT) und einem ACE-Hemmer (z.B. Wirkstoff Enalapril) vor. Bitte besprechen Sie dies mit Ihrem Hausarzt bzw. dem Arzt, der für die Einstellung Ihres Blutdrucks verantwortlich ist.

Darüber hinaus berichtete Ihr Ehemann, dass Sie zurzeit nicht an der frischen Luft spazieren gehen können, da Ihre Bronchialmuskulatur durch den Kältereiz der Einatmungsluft verkrampft. Damit Sie sich in diesen Situationen behelfen können, wäre ein Vorschlag von unserer Seite die Anwendung eines Dosieraerosols mit einem Wirkstoff, der die Atemmuskulatur entspannt. Hier käme z.B. das Dosieraerosol Salbutamol der Firma CT in Frage, das man zur Akutbehandlung plötzlich auftretender Bronchialkrämpfe und anfallsweise auftretender Atemnot inhalieren kann. Auch dies sollten Sie noch einmal ausführlich mit Ihrem Arzt besprechen.

In Bezug auf Ihre Schlafprobleme, bei denen es sich meist um Einschalfprobleme handelt, wie ihr Ehemann uns mitteilte, empfehlen wir Ihnen von der Einnahme des Lorazepams abzusehen und stattdessen ein Schlafmittel mit dem Wirkstoff Zolpidem oder Zopiclon (Handlesnamen z.B. Zolpidem® ratiopharm, Zopiclon® ratiopharm) einzunehmen.

Bezüglich Ihrer Vitamin-Präparate ist uns aufgefallen, dass Sie über das Präparat Livol Multi® bereits 2400 Einheiten Vitamin A zuführen und gleichzeitig mittags 3000 Einheiten Vitamin A als Kapsel zu sich nehmen. Eventuell erübrigt sich die doppelte Einnahme, aber vielleicht ist es von Ihrem Hausarzt auch genauso beabsichtigt.

Als Anlage zu diesem Schreiben senden wir Ihnen einen Vorschlag für einen Einnahmezeitplan, der sich an Ihren Mahlzeiten im Laufe des Tages orientiert. Dieser Plan wurde von uns nach bestem Wissen und Gewissen zusammengestellt und ist hinsichtlich der unterschiedlichen Wirkweisen der Medikamente optimiert. Sollte sich aufgrund unserer Vorschläge oder auch sonst Änderungen in Ihrer Medikation ergeben, übernehmen wir diese gerne in den Einnahmeplan.

Sollten Sie das sogenannte Hand-Fuß-Syndrom unter der Xeloda®-Therapie entwickeln, geben Sie bitte früh genug Bescheid. Ein leichtes Hand-Fuß-Syndrom (Grad 1) ist als normal einzustufen.
Im Falle von wässrigem Durchfall als Nebenwirkung der Xeloda®-Therapie, sollten Sie viel Flüssigkeit mit Elektrolyten (z.B. Elotrans®-Beutel) zu sich nehmen. Außerdem

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sollten Sie Loperamid (z.B. Loperamid®-ratiopharm (verschreibungspflichtig), Loperamid®-ratiopharm akut, Imodium® akut) vorrätig zu Hause haben.
Außerdem übersenden wir Ihnen wie besprochen einige Kopien aus dem erwähnten Buch von Prof. Beuth aus Köln zum Thema ergänzende Therapien. Sollten Sie zu speziellen Bereichen bzw. Themen der Komplementärmedizin weitere Fragen haben, stehen wir natürlich jederzeit zur Verfügung.
Weiterhin legen wir Ihnen die Adresse und einen Flyer einer Psychoonkologin aus Siegburg bei, für den Fall, dass Sie und Ihr Ehemann einmal Beratungsbedarf haben. Es handelt sich dabei um eine kostenlose Dienstleistung der Caritas für den Rhein-Sieg-Kreis. Es gibt auch eine Krebsberatungsstelle des Tumorzentrums Bonn e.V. (Tel. 0228 – 299161) an der Uniklinik in Bonn.

Bitte rufen Sie uns an, wenn Sie noch Fragen zu diesen Unterlagen haben, über die Sie natürlich gerne mit Ihrem Hausarzt oder den Ärztinnen und Ärzten der Frauenklinik sprechen können.
Wir werden uns wie vereinbart in einigen Tagen wieder telefonisch bei Ihnen melden.

Beste Grüße

Susanne Roth

Einnahmeplan für Frau Petra Musterfrau, Stand 19.12.2007

Nach dem Aufstehen (circa 6:30 Uhr)
- Bromelain 200 mg (2 Tabletten circa 1 bis 2 Stunden vor dem Frühstück mit einem Glas Wasser einnehmen)

Vor dem Frühstück (circa 7:25)
- TRI-Normin 25 (1 Tablette unzerkaut mit etwas Flüssigkeit vor dem Frühstück einnehmen)

Frühstück (circa 7:30 Uhr)

Nach dem Frühstück (circa 8:00 Uhr)
- Silymarin-CT (1 Hartkapsel unzerkaut mit etwas Flüssigkeit einnehmen)
- Selen-graf 100 (3 Tabletten unzerkaut mit etwas Flüssigkeit einnehmen, **Hinweis:** da der Wirkstoff Natriumselenit durch Vitamin C bei gleichzeitiger Zufuhr in eine für den menschlichen Körper nicht verfügbare Form umgewandelt wird, sollte der zeitliche Abstand zwischen dem Verzehr von Natriumselenit und Vitamin C mindestens 1 Stunde betragen.)
- Xeloda (innerhalb von 30 Minuten nach dem Essen mit Wasser einnehmen, Anzahl wie verordnet, bisher 3 Tabletten)

Nach dem Frühstück (circa 9:00 Uhr)
- Codeintropfen-CT 1mg/Tropfen (Erwachsene und Kinder ab 12 Jahren nehmen 15-44 Tropfen

Nach dem Frühstück (circa 9:30 Uhr)
- Lorazepam (1 Tablette unzerkaut mit etwas Flüssigkeit einnehmen)

Mittagessen

Nach dem Mittagessen
- Omega-3-Lachsöl Kapseln (2 Kapseln unzerkaut mit etwas Flüssigkeit einnehmen)
- Vitamin A 3000 Einheiten (1 Kapsel unzerkaut mit etwas Flüssigkeit einnehmen)
- Vitamin E 200mg Kapseln (1 Kapsel unzerkaut mit etwas Flüssigkeit einnehmen)
- Vitamin C 850mg + 5mg Zink (1 Kapsel unzerkaut mit etwas Flüssigkeit einnehmen)

Vor dem Abendessen (circa 18:00 Uhr)
- Miltex-Lösung (Tragen Sie die beigefügten Einweghandschuhe. Nach dem Auftropfen auf die Haut wird die Lösung unter leichtem Druck einmassiert, unter Einbeziehung eines etwas 3 cm breiten Randes über den erkennbar befallenen Hautbereich hinaus. Sobald die Lösung eingezogen ist, kann die behandelte Haut mit geeignetem, luftdurchlässigem Verbandmaterial abgedeckt werden.)

Abendessen (circa 19:30 Uhr)

Nach dem Abendessen (circa 20:00 Uhr)
- Livol Multi (Multivitamin-Mineral-Dragees) (1 Tablette unzerkaut mit etwas Flüssigkeit einnehmen)
- Silymarin-CT (1 Hartkapsel unzerkaut mit etwas Flüssigkeit einnehmen)
- Xeloda (innerhalb von 30 Minuten nach dem Essen mit Wasser einnehmen, Anzahl wie verordnet, bisher 3 Tabletten)

Nach dem Abendessen (circa 21:00 Uhr)

- Codeintropfen-CT 1mg/Tropfen (Erwachsene und Kinder ab 12 Jahren nehmen 15-44 Tropfen

Zur Nacht (bei Bedarf)

- Lorazepam (1 Tablette unzerkaut mit etwas Flüssigkeit vor dem Schlafengehen einnehmen)

Sonstiges:

- Iscador (3 x / Woche eine Ampulle subkutan injizieren)
- Ubichinon (2 x / Woche eine Ampulle)

Bitte beachten Sie die weiteren Hinweise im Begleitbrief!

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Einnahmeplan für Frau Petra Musterfrau, Stand 19.12.2007

Nach dem Aufstehen		Früh-Stück			Mittag-essen			Abend-Essen		Zur Nacht
Bromelain 2 Tabletten	**TRI-Normin 25** 1 Tablette		**Silymarin** 1 Tablette			**Omega-3-Lachsöl** 1 Kapsel	**Miltex-Lsg.** Anwendung wie verordnet		**Livol Multi** 1 Tablette	**Lorazepam** bei Bedarf
			Selen-graf 100 3 Tabletten			**Vitamin A 3000 Einheiten** 1 Kapsel			**Silymarin** 1 Tablette	
			Xeloda 3 Tabletten			**Vitamin E 200mg** 1 Kapsel			**Xeloda** 3 Tabletten	
			Codeintr. 15-44 Tropfen			**Vitamin C 850mg + 5mg Zink** 1 Kapsel			**Codeintr.** 15-44 Tropfen	
			Lorazepam 1 Tablette						**Bromelain** 2 Tabletten	

Sonstiges:

- Iscador (3 x / Woche eine Ampulle subkutan injizieren)
- Ubichinon (2 x / Woche eine Ampulle)

Bitte beachten Sie die Angaben im Begleitbrief!

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Consultation documentation form, first patient-pharmacist consulation

Dokumentationsbogen Einschlussgespräch Intensivbetreuung

Datum:	Zyklus-Nr. _____
Patient/-in:	Code _____
Zeit:	Von ____ : ____ Uhr bis ____ : ____ Uhr = _____ Minuten
Was:	**Patient erhalten:** Broschüre Chemotherapie & Nebenwirkungen Video Xeloda Broschüre „Richtiges Verhalten“ Blaue Ratgeber: _____
Probleme/Fragen beim Ausfüllen?	nein □ ja □
Rückrufdatum/ Termin:	
Wer führte das Gespräch?	Sven □ Susanne □ Andere □ (_____)

Consultation documentation form, follow-up consultations

(For patient-pharmacist and pharmacist-physician consultations)

Dokumentationsbogen: Telefonat

Datum:	Zyklus-Nr. _____
Patient/-in:	Code _____
Zeit:	Von ____ : ____ Uhr bis ____ : ____ Uhr = _____ Minuten
Was: (neuer Zyklus wann? Dose ok? UAWs?...)	
Probleme/Fragen beim Ausfüllen?	nein □ ja □
Ambulante Arztbesuche im letzten Zyklus?	_____ Mal
Krankmeldung im letzten Zyklus?	_____ Tage (auch bei Hausfrau/-mann)
Stationärer Aufenthalt im letzten Zyklus?	_____ Tage
Rückrufdatum:	
Wer rief an?	Wir □ Patient/-in □
Wer führte das Gespräch?	Sven □ Susanne □ Andere □ (_____)

Reminding card, control group

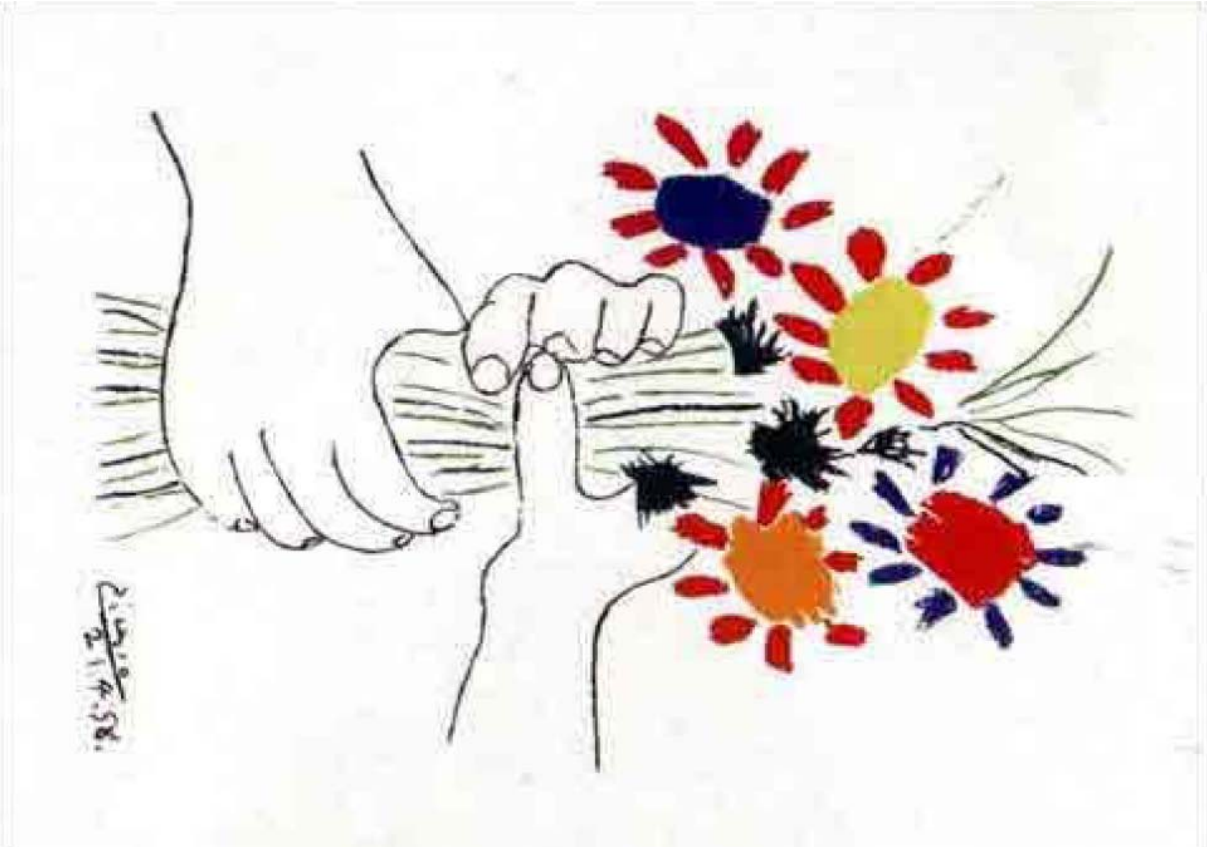
Mit diesem Kärtchen möchten wir Sie freundlich daran erinnern, an uns und unsere Fragebögen zu denken.

Sollten Sie Fragen zum Ausfüllen oder zu unserem Behältnis haben,
zögern Sie bitte nicht uns anzurufen!

Vielen Dank und beste Grüße

&

An



Appendix D: Results

EBM digits

Table D-1: EBM digits coding for oncologist fee

EBM digit	Points / € (2008)	Meaning (2008)
01311	175	Grundpauschale für Versicherte ab Beginn des 6. bis zum vollendeten 59. Lebensjahr
01312	205	Grundpauschale für Versicherte ab Beginn des 60. Lebensjahr
01510	1420	Zusatzpauschale für ambulante Beobachtung und Betreuung, > 2 h
01511	2700	Zusatzpauschale für ambulante Beobachtung und Betreuung, > 4 h
01512	3970	Zusatzpauschale für ambulante Beobachtung und Betreuung, > 6 h
02100	160	Infusion, mind. 10 min Dauer
02101	445	Infusionstherapie, obligat: i.v. Zytostatika, Virustatika, Antimykotika und/oder Antimykotika mit konsumierender Erkrankung, mind. 60 min Dauer
02110	600	Erste Transfusion der ersten Blutkonserve/ Blutpräparation/ Frischblut
02111	240	Jede weitere Transfusion im Anschluss an die Position 02110
02341	330	Punktion II (z.B. Mammae, Knochenmark, Leber, Pankreas)
02343	725	Entlastungspunktion des Pleuraraums und/oder nichtoperative Pleuradrainage
02511	30	Elektrotherapie unter Anwendung niederfrequenter und/oder mittelfrequenter Ströme
03115	35	Konsultationskomplex
08215 (only 2007)	50	Konsultationskomplex, weiterer persönlicher oder anderer Arzt-Patientenkontakt (=frauenärztliche Grundleistung)
08220 (only 2007)	235	Beratung, Erörterung und/oder Abklärung, mind. 10 min Dauer (=frauenärztliche Grundleistung)
08345 (not 2007)	540	Zusatzpauschale Behandlung und/oder Betreuung eines Patienten mit einer gesicherten onkologischen Erkrankung bei laufender Therapie oder Betreuung im Rahmen der Nachsorge

EBM digit	Points / € (2008)	Meaning (2008)
13215 (only 2007)	50	Konsultationskomplex, weiterer persönlicher oder anderer Arzt-Patientenkontakt (=internistische Grundleistung)
13220 (only 2007)	235	Beratung, Erörterung und/oder Abklärung, mind. 10 min Dauer (=internistische Grundleistung)
13491	865	Grundpauschale für Versicherte ab Beginn des 6. bis zum vollendeten 59. Lebensjahr (Hämato-/Onkologie)
13492	905	Grundpauschale für Versicherte ab Beginn des 60. Lebensjahrs (Hämato-/Onkologie)
13500	540	Zusatzpauschale Behandlung einer laboratoriumsmedizinisch oder histologisch/zytologisch gesicherten, primär hämatologischen und/oder onkologischen und/oder immunologischen Systemerkrankung
13502	540	Zusatzpauschale intensive, aplasieinduzierende und/oder toxizitätsadaptierte antiproliferative Behandlung
16215 (only 2007)	50	Konsultationskomplex, weiterer persönlicher oder anderer Arzt-Patientenkontakt (=neurologische Grundleistung)
16220 (only 2007)	235	Beratung, Erörterung und/oder Abklärung, mind. 10 min Dauer (=neurologische Grundleistung)
30400	210	Massagetherapie (z.B. manuelle Lymphdrainage)
30420	265	Krankengymnastik (Einzelbehandlung), mind. 15 min Dauer
80111	175	Grundpauschale für Versicherte ab Beginn des 6. bis zum vollendeten 59. Lebensjahr, Gemeinschaftspraxis und MVZ
80112	205	Grundpauschale für Versicherte ab Beginn des 60. Lebensjahr, Gemeinschaftspraxis und MVZ
86503	€ 25.56	Behandlung solider Tumoren
86505	€ 255.65	Intravasale Polychemotherapie pro Behandlungsfall

Table D-2: EBM digits coding for diagnostics (laboratory parameter / blood test)

EBM digit	Charge [€] (2008)	Meaning (2008)
32030	€ 0.50	Orientierende Untersuchung
32031	€ 0.25	Mikroskopische Untersuchung des Harns
32042	€ 0.25	BSG (Blutkörperchensenkungs-geschwindigkeit)
32056	€ 0.25	Gesamteiweiß
32057	€ 0.25	Glucose
32058	€ 0.25	Bilirubin gesamt
32059	€ 0.40	Bilirubin direkt
32060	€ 0.25	Cholesterin gesamt
32061	€ 0.25	HDL-Cholesterin
32063	€ 0.25	Triglyceride
32064	€ 0.25	Harnsäure
32065	€ 0.25	Harnstoff
32066	€ 0.25	Kreatinin (Jaffé-Methode)
32067	€ 0.40	Kreatinin enzymatisch
32068	€ 0.25	Alkalische Phosphatase
32069	€ 0.25	GOT
32070	€ 0.25	GPT
32071	€ 0.25	Gamma-GT
32072	€ 0.40	Alpha-Amylase
32073	€ 0.40	Lipase
32074	€ 0.25	Creatinkinase (CK)
32075	€ 0.25	LDH
32081	€ 0.25	Kalium
32082	€ 0.25	Calcium
32083	€ 0.25	Natrium
32084	€ 0.25	Chlorid
32085	€ 0.25	Eisen
32086	€ 0.40	Anorganisches Phosphat
32094	€ 4.00	HbA_1 und/oder HbA_{1c}
32101	€ 3.00	Quantitative Bestimmung mittels Immunoassay, Thyrotropin (TSH)
32103	€ 0.60	Gesamt-IgA
32104	€ 0.60	Gesamt-IgG
32105	€ 0.60	Gesamt-IgM
32107	€ 0.75	Elektrophoretische Trennung von Proteinen oder Lipoproteinen im Serum
32110	€ 0.75	Blutungszeit
32112	€ 0.60	Partielle Thromboplastinzeit (PTT)
32113	€ 0.60	Quick, Thromboplastinzeit (TPZ) aus Plasma
32115	€ 0.75	Thrombingerinnungszeit (TZ)
32116	€ 0.75	Fibrinogen

EBM digit	Charge [€] (2008)	Meaning (2008)
32120	€ 0.50	Bestimmung von mind. 2 der folgenden Parameter: Erythrozytenzahl, Thrombozytenzahl, Leukozytenzahl, Hämoglobin, Hämatokrit, mechanisierte Retikulozytenzählung
32122	€ 1.10	Vollständiger Blutstatus mittels automatisierter Verfahren (obligater Leistungsinhalt: Erythrozytenzahl, Thrombozytenzahl, Leukozytenzahl, Hämoglobin, Hämatokrit, mechanisierte Zählung der Neutrophilen, Eosinophilen, Basophilen, Lymphozyten und Monozyten)
32123	€ 0.40	Zuschlag zu 32121 oder 32122 bei nachfolgender mikroskopischer Differenzierung
32169	€ 15.30	Vergleichende hämatologische Begutachtung von mikroskopisch differenzierten Ausstrichen des Knochenmarks und des Blutes einschl. Dokumentation
32248	€ 1.40	Magnesium
32324	€ 4.90	CEA (Carcinoembryonales Antigen)
32325	€ 4.90	Ferritin
32354	€ 5.60	LH (Lutropin)
32355	€ 5.10	Prolaktin
32356	€ 5.10	Östradiol
32357	€ 4.60	Progesteron
32390	€ 9.70	CA 125
32391	€ 8.20	CA 15-3
32392	€ 9.20	CA 19-9
32395	€ 19.90	NSE (Neuronenspezifische Enolase)
32426	€ 4.60	Gesamt-IgE
32435	€ 6.90	Albumin
32446	€ 8.70	Kappa-Ketten
32447	€ 8.70	Lambda-Ketten
32448	€ 10.20	Immunglobulin A, G oder M im Liquor
32460	€ 5.40	CRP (C-reaktives Protein)
32494	€ 7.70	Antimitochondriale Antikörper (AMA), auch Subtypen, z. B. AMA-M2
32540	€ 9.20	Nachweis der Blutgruppenmerkmale A, B, 0 und Rh-Faktor D
32542	€ 7.20	Coombs-Test
32545	€ 7.20	Antikörper-Suchtest

Table D-3: EBM digits coding for diagnostics (CT / MRT)

EBM digit	Points / € (2008)	Meaning (2008)
34311	2100	CT von Teilen der Wirbelsäule
34330	1865	CT Thorax
34340	1875	CT Oberbauch
34341	2315	CT Abdomen
34342	1875	CT Becken
34345	545	CT-Zuschlag bei Kontrastmitteleinbringungen
34411	3430	MRT von Teilen der Wirbelsäule
34421	3430	MRT Schädelbasis
34440	3430	MRT Oberbauch
34441	3430	MRT Abdomen
34442	3430	MRT Becken

Table D-4: EBM digits coding for diagnostics (other)

EBM digit	Points / € (2008)	Meaning (2008)
01741	4325	Koloskopischer Komplex
01756	215	Histologische Untersuchung eines durch Biopsie gewonnenen Materials
13251	565	Belastungs-EKG
13422	2645	Zusatzpauschale (Teil-) Koloskopie (inklusive Kolon transversum)
17311	1860	Ganzkörperszintigraphische Untersuchung
17312	475	Zuschlag zu 17311
17362	1900	Zuschlag SPECT
27320	225	EKG
32045	€ 0.25	Mikroskopische Untersuchung eines Körpermaterials
32687	€ 5.10	Kulturelle mykologische Untersuchung
32722	€ 7.70	Stuhluntersuchung
32749	€ 12.80	Nachweis bakterieller Toxine
32750	€ 2.60	Differenzierung gezüchteter Bakterien mittels mono- oder polyvalenter Seren
32760	€ 4.10	Bakterienreinkultur-Differenzierung, bis zu 3 Reaktionen
33011	245	Sonographie der Gesichtsweichteile und/oder Halsweichteil und/oder Speicheldrüsen
33020	760	Echokardiographische Untersuchung (Sonographie) mittels M-Mode und B-Mode Verfahren
33040	360	Sonographie Thorax
33041	465	Sonographische Untersuchung einer oder beider Brustdrüsen mittels B-Mode-Verfahren, ggf. einschl. der regionalen Lymphknoten, je Sitzung
33042	445	Sonographische Untersuchung des Abdomens

EBM digit	Points / € (2008)	Meaning (2008)
33044	400	Sonographie der weiblichen Genitalorgane
34220	270	Röntgenaufnahme des knöchernen Thorax
34221	430	Röntgenaufnahme von Teilen der Wirbelsäule (mind. 2 Ebenen)
34234	210	Röntgenaufnahme des Beckens und/oder dessen Weichteile
34241	430	Röntgenaufnahme der Brustorgane (2 Ebenen)

Table D-5: EBM digits coding for administration

EBM digit	Points / € (2008)	Meaning (2008)
01430	35	Verwaltungskomplex (z.B. Ausstellung von Wiederholungsrezepten ohne persönlichen Arzt-Patientenkontakt)
01600	110	Ärztlicher Bericht über das Ergebnis einer Patientenuntersuchung
01601	210	Ärztlicher Brief in Form einer individuellen schriftlichen Information des Arztes an einen anderen Arzt über den Gesundheitsstatus des Patienten
01602	35	Mehrfertigung (z.B. Kopie) eines Berichtes oder Briefes
01610	40	Bescheinigung zur Feststellung der Belastungsgrenze
01620	85	Kurze Bescheinigung oder kurzes Zeugnis, nur auf besonderes Verlangen der Krankenkasse
01621	125	Krankheitsbericht, nur auf besonderes Verlangen der Krankenkasse oder Ausstellung der vereinbarten Vordrucke nach den Mustern 11, 53 oder 56
01622	235	Schriftlicher Kurplan / Gutachten, auf besonderes Verlangen der Krankenkasse
32008	/	Kennnummer, Abrechnungsscheine sind damit zu kennzeichnen
32012	/	Kennnummer „Tumorerkrankung unter parenteraler tumorspezifischer Behandlung oder progrediente Malignome unter Palliativbehandlung“, Abrechnungsscheine sind damit zu kennzeichnen
32019	/	Kennnummer “Erkrankungen unter systematischer Zytostatikatherapie und/oder Strahlentherapie” Abrechnungsscheine sind damit zu kennzeichnen

EBM digit	Points / € (2008)	Meaning (2008)
32022	/	Kennnummer “Manifester Diabetes Mellitus” Abrechnungsscheine sind damit zu kennzeichnen
40120	€ 0.55	Kostenpauschale für die Versendung bzw. den Transport von Briefen und/oder schriftlichen Unterlagen bis 20g oder Übermittlung Telefax
40144	€ 0.13	Kostenpauschale für fotokopierte oder EDV-technisch reproduzierte Befundmitteilungen, Berichte, Arztbriefe, je Seite
80032	/	Patient ist von Zuzahlungen befreit (auch Praxisgebühr)
90909	/	Praxisbesonderheitsziffer “orale und parenterale Chemotherapie bei Tumorpatienten einschließlich zugelassener Hormonanaloga, Zytokine und Interferone sowie Rezepturen”
90914	/	Kennzeichungsziffer “Substitution von Plasmafaktoren bei Faktormangelkrankheiten”
90916	/	Praxisbesonderheitsziffer “Schmerztherapie mit Opioiden und mit dazugehörigen Laxantien”
90925	/	Praxisbesonderheitsziffer “Antithrombotische Mittel (nur Heparin und Heparinoide, parenteral)”
90929	/	Praxisbesonderheitsziffer “Bisphosphonate und selekitve Östrogenrezeptormodulatoren bei Osteoporsose”
99970	/	Versicherter wünscht explizit keinen Bericht. Abrechnungen sind damit zu kennzeichnen.

GOÄ digits

Table D-6: GOÄ digits coding for oncologist fee:

GOÄ digit	Points	Rate in € (2008)	Meaning (2008)
1	80	Basic: € 4.66 2.3: € 10.72	Beratung – auch mittels Fernsprecher
3	150	Basic: € 8.74 2.3: € 20.11	Eingehende Beratung, mind. 10 Min – auch mittels Fernsprecher
31	450	Basic: € 26.23 2.3: € 60.33	Homöopathische Folgeanamnese
34	300	Basic: € 17.49 2.3: € 40.22	Erörterung der Auswirkungen einer Krankheit (mind. 20 Min.)
45	70	Basic: € 4.08 2.3: € 9.38	Visite im Krankenhaus
60	120	Basic: € 6.99 2.3: € 16.09	Konsiliarische Erörterung
78	180	Basic: € 10.49 2.3: € 24.13	Behandlungsplan für die Chemotherapie und/oder schriftlicher Nachsorgeplan
250	40	Basic: € 2.33 1.8: € 4.20	Blutentnahme mittels Spritze, Kanüle oder Katheter aus der Vene
252	40	Basic: € 2.33 2.3: € 5.36	Injektion, subkutan, submukös, intrakutan oder intramuskulär
261	30	Basic: € 1.75 2.3: € 4.02	Einbringung von Arzneimitteln in einen parenteralen Katheter
265	60	Basic: € 3.50 2.3: € 8.04	Auffüllung eines subkutanen Medikamentenreservoirs oder Spülung eines Ports
271	120	Basic: € 6.99 2.3: € 16.09	Infusion, intravenös, bis zu 30 Min. Dauer
272	180	Basic: € 10.49 2.3: € 24.13	Infusion, intravenös, > 30 Min.
275	360	Basic: € 20.98 2.3: € 48.26	Dauertropfinfusion von Zytostatika, > 90 Min.
297	45	Basic: € 2.62 2.3: € 6.03	Entnahme und Aufbereitung von Abstrichmaterial zur zytologischen Untersuchung
506	120	Basic: € 6.99 1.8: € 12.59	Krankengymnastische Ganzbehandlung als Einzelbehandlung
1103	185	Basic: € 10.78 2.3: € 24.80	Probeexzision aus dem Gebärmutterhals/ Muttermund /Vaginalwand

Table D-7: GOÄ digits coding for diagnostics (laboratory parameter / blood test)

GOÄ digit	Points	Rate in € (2008)	Meaning (2008)
3502	120	Basic: € 6.99 1.15: € 8.04	Differenzierung des Blutausstrichs, mikroskopisch
3503	70	Basic: € 4.08 1.15: € 4.69	Hämatokrit
3512	70	Basic: € 4.08 1.15: € 4.69	Alpha-Amylase
3513	70	Basic: € 4.08 1.15: € 4.69	Gamma-Glutamyltranspeptidase
3514	70	Basic: € 4.08 1.15: € 4.69	Glukose
3515	70	Basic: € 4.08 1.15: € 4.69	GOT (ASAT, AST)
3516	70	Basic: € 4.08 1.15: € 4.69	GPT (ALAT, ALT)
3517	70	Basic: € 4.08 1.15: € 4.69	Hämoglobin
3518	70	Basic: € 4.08 1.15: € 4.69	Harnsäure
3519	70	Basic: € 4.08 1.15: € 4.69	Kalium
3520	70	Basic: € 4.08 1.15: € 4.69	Kreatinin
3550	60	Basic: € 3.50 1.15: € 4.02	Blutbild und Blutbildbestandteile
3551	20	Basic: € 1.17 1.15: € 1.34	Differenzierung der Leukozyten
3555	40	Basic: € 2.33 1.15: € 2.68	Calcium
3556	30	Basic: € 1.75 1.15: € 2.01	Chlorid
3557	30	Basic: € 1.75 1.15: € 2.01	Kalium
3558	30	Basic: € 1.75 1.15: € 2.01	Natrium
3560	40	Basic: € 2.33 1.15: € 2.68	Glukose
3570	30	Basic: € 1.75 1.15: € 2.01	Albumin, photometrisch
3573	30	Basic: € 1.75 1.15: € 2.01	Gesamt-Protein im Serum oder Plasma
3574	200	Basic: € 11.66 1.15: € 13.41	Proteinelektrophorese im Serum
3580	40	Basic: € 2.33 1.15: € 2.68	Anorganisches Phosphat
3581	40	Basic: € 2.33 1.15: € 2.68	Bilirubin, gesamt
3583	40	Basic: € 2.33 1.15: € 2.68	Harnsäure

GOÄ digit	Points	Rate in € (2008)	Meaning (2008)
3584	40	Basic: € 2.33 1.15: € 2.68	Harnstoff
3585	40	Basic: € 2.33 1.15: € 2.68	Kreatinin
3587	40	Basic: € 2.33 1.15: € 2.68	Alkalische Phosphatase
3588	50	Basic: € 2.91 1.15: € 3.35	Alpha Amylase
3592	40	Basic: € 2.33 1.15: € 2.68	Gamma-GT (Gamma-Glutamyltranspeptidase)
3594	40	Basic: € 2.33 1.15: € 2.68	GOT (Glutamatoxalazetattransaminase)
3595	40	Basic: € 2.33 1.15: € 2.68	GPT (Glutamatpyruvattransaminase)
3597	40	Basic: € 2.33 1.15: € 2.68	LDH (Laktatdehydrogenase)
3598	50	Basic: € 2.91 1.15: € 3.35	Lipase
3605	50	Basic: € 2.91 1.15: € 3.35	PTT (Partielle Thromboplastinzeit)
3607	50	Basic: € 2.91 1.15: € 3.35	TPZ (Thromboplastinzeit)
3620	40	Basic: € 2.33 1.15: € 2.68	Eisen im Serum oder Plasma
3652	35	Basic: € 2.04 1.15: € 2.35	Streifentest im Urin
3711	40	Basic: € 2.33 1.15: € 2.68	Blutkörperchensenkungsgeschwindigkeit (BSG, BKS)
3741	200	Basic: € 11.66 1.15: € 13.41	CRP (C-reaktives Protein)
3742	250	Basic: € 14.57 1.15: € 16.76	Ferritin, Ligandenassay
3901.H3	450	Basic: € 26.23 1.15: € 30.16	CA 15-3, Ligandenassay
3902	300	Basic: € 17.49 1.15: € 20.11	CA 19-9
3905	250	Basic: € 14.57 1.15: € 16.76	CEA (Carcinoembryonales Antigen)
4021	250	Basic: € 14.57 1.15: € 16.76	FSH (Hormonbestimmung mittels Ligandenassay)
4026	250	Basic: € 14.57 1.15: € 16.76	LH (Luteinisierendes Hormon) (Hormonbestimmung mittels Ligandenassay)
4030	250	Basic: € 14.57 1.15: € 16.76	TSH (Hormonbestimmung mittels Ligandenassay)
4039	350	Basic: € 20.40 1.15: € 23.46	Estradiol (Hormonbestimmung mittels Ligandenassay)
4040	350	Basic: € 20.40 1.15: € 23.46	Progesteron (Hormonbestimmung mittels Ligandenassay)

GOÄ digit	Points	Rate in € (2008)	Meaning (2008)
4062	480	Basic: € 27.98 1.15: € 32.17	Untersuchungen mit ähnlichem methodischen Aufwand

Table D-8: GOÄ digits coding for diagnostics (CT / MRT / PET)

GOÄ digit	Points	Rate in € (2008)	Meaning (2008)
5371	2300	Basic: € 134.06 1.8: € 241.31	CT Hals- und/oder Thoraxbereich
5372	2600	Basic: € 151.55 1.8: € 272.78	CT Abdomen
5488	6000	Basic: € 349.72 1.8: € 629.50	PET
5700	4400	Basic: € 256.46 1.8: € 461.64	MRT Bereich Kopf
5705	4200	Basic: € 244.81 1.8: € 440.65	MRT Bereich Wirbelsäule
5715	4300	Basic: € 250.64 1.8: € 451.14	MRT Bereich Thorax
5720	4400	Basic: € 256.46 1.8: € 461.64	MRT Bereich Abdomen und/oder Becken
5730	4000	Basic: € 233.15 1.8: € 419.67	MRT einer oder mehrerer Extremitäten

Table D-9: GOÄ digits coding for diagnostics (other)

GOÄ digit	Points	Rate in € (2008)	Meaning (2008)
2	30	Basic: € 1.75 1.8: € 3.15	Messung von Körperzuständen
5	80	Basic: € 4.66 2.300: € 10.72	Symptombezogene Untersuchung
7	160	Basic: € 9.33 2.3: € 21.45	Vollständige körperliche Untersuchung mind. eines der folgenden Organe: Hautorgan, Stütz- und Bewergungsorgane, Brustorgane, Bauchorgane, weibl. Genitaltrakt
11	60	Basic: € 3.50 2.3: € 8.04	Digitaluntersuchung des Mastdarms und/ oder Prostata
401	400	Basic: € 23.31	Zuschlag zu den sonographischen Leistungen nach den Numnern 410-418 bei zusätzlicher Anwendung des Duplex-Verfahrens
403	150	Basic. € 8.74 1.8: € 15.74	Zuschlag zu den sonographischen Leistungen bei transkavitärer Untersuchung

GOÄ digit	Points	Rate in € (2008)	Meaning (2008)
404	250	Basic: € 14.57	Zuschlag zur Doppler-sonographischen Leistung bei zusätzlicher Frequenzspektrumanalyse
405	200	Basic: € 11.66	Zuschlag zu den Leistungen 415 oder 424 – cw Dopplerzuschlag
406	200	Basic: € 11.66	Zuschlag zu der Leistung 424 – bei zusätzlicher Farbkodierung
410	200	Basic: € 11.66 2.3: € 26.81	Ultraschalluntersuchung eines Organs (Leber)
420	80	Basic: € 4.66 2.3: € 10.72	Ultraschalluntersuchung von bis zu drei weiteren Organen (Gallenblase, Niere, Milz)
424	700	Basic: € 40.80 2.3: € 93.84	Zweidimensionale Doppler-echokardiographische Untersuchung
651	253	Basic: € 14.75 1.8: € 26.54	Elektrokardiographische Untersuchung
4851	130	Basic: € 7.58 1.8: € 13.64	Zytologische Untersuchung zur Krebsdiagnostik
5030	360	Basic: € 20.98 1.8: € 37.77	Röntgenaufnahme Oberarm, Unterarm, Ellenbogengelenk, Oberschenkel, Unterschenkel,… jeweils in 2 Ebenen
5120	260	Basic: € 15.15 1.8 fach: € 27.28	Strahlendiagnostik Rippen einer Thoraxhälfte, Schulterblatt oder Brustbein in einer Ebene
5121	140	Basic: € 8.16 1.8 fach: € 14.69	Ergänzende Ebene(n)
5137	450	Basic: € 26.23 1.8: € 47.21	Brustorgane-Übersicht, gegebenenfalls einschließlich Breischluck und Durchleuchtungen-, in mehreren Ebenen (= Röntgen Thorax)
5330	750	Basic: € 43.72 1.8: € 78.69	Venographie einer Extremität

Table D-10: GOÄ digits coding for administration

GOÄ digit	Points	Rate in € (2008)	Meaning (2008)
2	30	Basic: € 1.75 1.8: € 3.15	Ausstellung von Rezept/ Überweisung/ Befund/ Anordnung auch mittels Fernsprecher
70	40	Basic: € 2.33 2.3: € 5.36	Kurze Bescheinigung oder kurzes Zeugnis, Arbeitsunfähigkeitsbescheinigung
75	130	Basic: € 7.58 2.3: € 17.43	Ausführlicher schriftlicher Krankheits- und Befundbericht

Direct disease-related outpatient costs

Table D-11: Direct disease-related outpatient costs of the control patients

Patient	Anti-neoplastic therapy [€]	Supp. therapy [€]	Oncologist fee [€]	Diagn. cost [€]	Admin. cost [€]	No. visits [n]	Study period [days]
B 1	1049.10	1807.67	211.28	278.96	16.72	12	180
B 2	5072.71	3384.66	725.07	308.73	12.45	26	180
B 3	27677.38	4729.38	1150.24	150.90	19.87	17	180
B 4	7611.07	8066.81	913.23	90.20	11.14	16	81
B 5	34967.39	3886.19	1049.77	280.44	15.62	25	180
B 6	4296.84	10488.42	926.41	26.50	17.09	14	180
B 7	35572.82	3705.90	439.73	1321.41	0.00	11	180
B 8	1049.10	1442.31	67.69	41.52	8.36	8	98
B 9	8042.81	2116.21	469.03	411.94	23.43	18	180
B 10	1049.10	31.84	64.62	84.48	8.36	2	61
B 11	3711.24	3367.17	524.09	373.34	45.16	21	180
B 12	9585.79	3600.73	234.12	18.70	25.08	10	180
B 13	4328.70	3501.59	697.60	233.60	43.03	26	180
B 14	20144.61	151.45	234.13	67.45	8.36	10	180
B 15	31069.92	94.02	297.20	52.60	28.98	13	180
B 16	2121.61	213.17	98.01	69.08	12.45	9	180
C 1	15396.24	755.08	1.86	155.87	15.62	3	180
C 2	20374.30	703.43	1449.86	306.13	25.08	25	180
C 3	14796.51	1379.52	924.99	406.96	56.32	21	180
C 4	93318.49	3639.58	1264.36	1370.01	31.24	28	180
C 5	51111.80	1588.65	3101.99	575.99	19.32	42	180
C 6	9042.78	1133.41	148.78	303.21	0.00	10	180
C 7	4720.95	36.84	96.14	271.69	23.43	12	180
C 8	16013.13	845.87	195.26	294.14	0.00	15	180
C 9	18316.82	1018.61	278.76	242.09	4.09	15	180
C 10	524.55	130.26	51.79	288.99	15.62	3	61
C 11	524.55	344.16	178.54	37.30	16.54	4	180
C 12	2098.20	0.00	195.84	111.30	34.74	22	180
C 13	3098.26	906.97	895.62	142.90	16.72	14	111
C 14	20262.03	63.39	1139.20	204.15	16.72	10	180
Sum:	466948.80	63133.29	18025.22	8520.58	571.54	459	4912
(%):	(83.8)	(11.3)	(3.2)	(1.5)	(0.1)	/	/
Median:	8542.80	1256.47	368.47	237.85	16.72	14	180
Mean:	15564.96	2104.44	600.84	284.02	19.05	15	164
SD:	19448.64	2450.10	636.45	319.32	13.28	9	38

Table D-12: Direct disease-related outpatient costs of the intervention patients

Patient	Anti-neoplastic therapy [€]	Supp. therapy [€]	Oncologist fee [€]	Diagn. cost [€]	Admin. cost [€]	No. visits [n]	Study period [days]
BI 1	3671.85	52.46	91.30	145.58	14.32	11	180
BI 2	41408.63	4411.40	472.14	1216.57	0.00	10	180
BI 3	18749.81	2909.26	504.65	798.47	3.15	16	180
BI 4	16158.43	1950.75	674.75	3094.72	17.43	24	180
BI 5	1049.10	1356.25	38.69	31.20	8.18	6	48
BI 6	34889.82	3534.95	1703.72	104.29	2.40	12	180
BI 7	11284.61	2488.63	298.34	19.50	4.09	11	180
BI 8	4720.95	3440.09	203.64	123.11	24.54	9	180
BI 9	21317.76	337.24	489.74	364.16	0.00	15	180
BI 10	2126.18	1210.53	0.00	0.00	0.00	0	18
BI 11	3185.71	2204.33	186.74	208.24	0.00	8	180
BI 12	3147.30	2182.00	104.88	1451.91	17.43	5	180
BI 13	3192.36	2383.57	137.64	203.31	0.00	8	162
BI 14	22820.91	1763.13	missing	missing	missing	missing	180
BI 15	1208.84	448.32	8.74	255.19	0.00	3	62
BI 16	10432.25	3131.06	299.65	105.18	1.10	11	180
BI 17	5943.01	2700.05	109.00	224.54	0.00	14	180
BI 18	3621.75	2432.76	96.91	54.78	0.00	8	169
BI 19	3845.44	2475.70	350.14	2101.44	10.72	16	180
BI 20	22575.78	4436.22	187.86	260.49	0.00	11	180
BI 21	10259.76	1856.73	175.58	24.15	0.55	11	180
BI 22	12110.26	1261.19	815.34	259.96	35.41	11	180
BI 23	9110.55	1387.32	459.21	153.76	4.25	20	118
CI 1	2622.75	127.98	108.41	34.40	25.67	6	180
CI 2	16455.08	1497.74	876.20	1452.89	0.00	21	180
CI 3	3404.26	367.79	509.42	264.00	19.88	13	180
CI 4	29880.87	2768.38	1045.28	935.36	0.00	16	180
CI 5	13380.53	744.54	1119.30	143.60	0.00	18	180
CI 6	9004.36	1781.67	936.19	417.55	0.00	12	180
CI 7	22109.75	1188.52	1125.26	437.34	0.00	14	180
CI 8	524.55	0.00	0.00	0.00	0.00	0	34
CI 9	15051.45	1863.47	272.71	2065.30	0.00	11	180
CI 10	18183.12	199.19	264.17	1107.85	3.15	11	180
CI 11	2622.75	279.52	68.27	1088.57	3.15	10	180
CI 12	47228.59	2405.67	795.12	304.90	0.00	26	180
CI 13	20306.74	18.42	1172.50	209.95	12.27	9	180
CI 14	15160.36	1259.42	621.50	610.89	0.00	18	180
CI 15	14115.50	759.93	630.22	65.80	8.74	7	180
CI 16	25304.31	86.31	1145.53	215.10	19.71	12	180
CI 17	23195.06	85.01	1119.68	233.05	10.76	13	180
CI 18	17411.20	754.42	744.61	506.23	0.00	10	180
CI 19	34316.34	2511.99	1254.03	2056.25	0.00	22	180
CI 20	21887.16	605.33	1399.23	269.35	25.67	25	180
CI 21	21226.37	690.99	1148.51	513.99	0.00	17	180

Patient	Anti-neoplastic therapy [€]	Supp. therapy [€]	Oncologist fee [€]	Diagn. cost [€]	Admin. cost [€]	No. visits [n]	Study period [days]
CI 22	38115.96	1513.63	1105.90	1909.06	33.51	18	180
CI 23	12872.07	1085.15	665.96	167.00	0.00	12	180
Sum:	691210.19	72949.01	25536.66	26208.98	306.08	561	7631
(%):	(84.69)	(8.94)	(3.13)	(3.20)	(0.03)	/	/
Median:	13748.02	1442.53	489.74	259.96	0.55	11	180
Mean:	15026.31	1585.85	567.48	582.42	6.80	12	166
SD:	11666.85	1176.92	453.95	718.88	10.01	6	41

Pharmacist time spent for intervention patients

Table D-13: Pharmacist time spent for intervention patients

Patient-code	First consultation			Follow-up consultations
	Total time [min]	Protocol driven time [min]	Time for pharmaceutical care [min]	Time [min]
BI 1	44	n.d.	n.d.	27
BI 2	60	n.d.	n.d.	45
BI 3	140	n.d.	n.d.	90
BI 4	115	n.d.	n.d.	132
BI 5	70	n.d.	n.d.	166
BI 6	105	n.d.	n.d.	203
BI 7	72	n.d.	n.d.	30
BI 8	65	n.d.	n.d.	48
BI 9	81	65	16	173
BI 10	55	n.d.	n.d.	15
BI 11	60	n.d.	n.d.	148
BI 12	66	n.d.	n.d.	150
BI 13	75	n.d.	n.d.	121
BI 14	60	n.d.	n.d.	99
BI 15	106	n.d.	n.d.	95
BI 16	70	50	20	180
BI 17	105	46	59	256
BI 18	77	n.d.	n.d.	243
BI 19	97	40	57	212
BI 20	85	58	27	154
BI 21	73	n.d.	n.d.	139
BI 22	70	n.d.	n.d.	95
BI 23	50	32	18	163
CI 1	100	n.d.	n.d.	147
CI 3	85	n.d.	n.d.	135
CI 2	80	n.d.	n.d.	148
CI 4	90	n.d.	n.d.	188
CI 5	70	n.d.	n.d.	64
CI 6	105	36	69	154
CI 7	90	n.d.	n.d.	61
CI 8	80	n.d.	n.d.	9
CI 9	110	65	45	168
CI 10	75	n.d.	n.d.	140
CI 11	107	n.d.	n.d.	90
CI 12	55	n.d.	n.d.	56
CI 13	70	n.d.	n.d.	43
CI 14	72	n.d.	n.d.	130
CI 15	90	49	41	121
CI 16	120	80	40	107
CI 17	120	n.d.	n.d.	149
CI 18	101	46	55	41
CI 19	75	n.d.	n.d.	181

Patient-code	First consultation			Follow-up consultations
CI 20	70	36	34	125
CI 21	89	19	70	177
CI 22	64	37	27	121
CI 23	79	40	39	114
Median	78	46	40	131
Mean	83	47	41	123
SD	21	15	18	59
Min	44	19	16	9
Max	140	80	70	256

n.d. = not documented

Inpatient costs

Table D-14: Base rates of relevant hospitals 2006 until 2008 according to AOK

Hospital	Base rate 2006 [€]	Base rate 2007 [€]	Base rate 2008 [€]
University Bonn	2990.99	2822.36	2728.09
Johanniter Bonn	2506.74	2546.13	2605.07
St. Marien Bonn	2369.68	2541.14	2591.11
St. Antonius Schleiden	Not known	Not known	2715.95
Malteser Bonn	2671.18	2648.98	2677.36
University Cologne	2954.89	2778.39	2672.10
Waldkrankenhaus Bonn	2446.65	2507.81	2593.24

Table D-15: Inpatient costs in the individual control patients

Patient	No. stay	Hospital	Reason	DRG	Relative weight	DRG costs [€]	Other costs [€]
B 1	1	University Bonn	Progression	E71B	0.597	1628.67	140.2
	2	„	Surgery	J11A	1.187	3238.24	153.97
	3	„	Not known	I65B	1.119	3052.73	-2057.08
	4	„	DRC	E73B	0.861	2348.89	-1340.11
	5	„	Not known	I65B	1.119	3052.73	-2057.08
					Total:	**8161.16**	
B 8	1	University Bonn	Progression	B15Z	3.866	10546.80	300.98
	2	„	Progression	B66B	1.360	3719.20	148.66
					Total:	**14706.64**	
B 9	1	Johanniter Bonn	Surgery	J11A	1.187	3092.22	77.94
					Total:	**3170.16**	
B 12	1	University Bonn	Toxicity	T62B	0.574	1565.92	189.75
					Total:	**1755.67**	
B 13	1	University Bonn	Toxicity	F71B	0.797	2174.29	189.75
					Total:	**2364.04**	
B 14	1	University Bonn	Surgery following neoadjuvant treatment	J23Z	1.545	4214.90	195.15
					Total:	**4410.05**	
B 15	1	University Bonn	Surgery following neoadjuvant treatment	J23Z	1.545	4214.90	195.15
					Total:	**4410.05**	
B 16	1	University Bonn	Surgery following neoadjuvant treatment	J16Z	2.369	6462.85	238.27
					Total:	**6701.12**	
C 1	1	Johanniter Bonn	Application of i.v. chemotherapy	G60B	0.421	1096.73	903.2
	2	„	Application of i.v. chemotherapy	G60B	0.421	1096.73	903.2
	3	„	Application of i.v. chemotherapy	G60B	0.421	1096.73	903.2
	4	„	Application of i.v. chemotherapy	G60B	0.421	1096.73	903.2

Patient	No. stay	Hospital	Reason	DRG	Relative weight	DRG costs [€]	Other costs [€]
	5	„	Application of i.v. chemotherapy	G60B	0.421	1096.73	903.2
	6	"	Application of i.v. chemotherapy	G60B	0.421	1096.73	903.2
					Total:	**11999.61**	
C 3	1	Johanniter Bonn	Toxicity	F74Z	0.405	1055.05	59.46
	2	St. Marien Bonn	Surgery	H01Z	4.577	11859.51	675.45
					Total:	**13649.47**	
C 4	1	Johanniter Bonn	Surgery	H61B	0.651	1695.90	40.17
					Total:	**1736.07**	
C 5	1	Johanniter Bonn	DRC	H41A	2.035	5301.32	114.43
					Total:	**5415.75**	
C 6	1	University Bonn	DRC	G67D	0.457	1246.74	167.65
					Total:	**1414.39**	
C 8	1	University Bonn	Surgery following neoadjuvant treatment	G17Z	3.077	8394.33	1242,69
	2	"	Surgery	G60B	0.421	1148.53	-424.56
					Total:	**10360,99**	
C 9	1	University Bonn	Progression	G18Z	2.652	7234.89	401.23
	2	St. Antonius Schleiden	Toxicity	G67B	0.580	1575.25	2571.81
					Total:	**11783.19**	
C 10	1	Johanniter Bonn	Diagnostic test	G46C	1.051	2737.93	1516.67
	2	"	DRC	G60A	0.654	1703.72	82.98
					Total:	**6041.29**	
C 11	1	St. Marien Bonn	Surgery	G07C	1.320	3420.27	664.85
					Total:	**4085.12**	
C 13	1	Johanniter Bonn	DRC	G60B	0.421	1096.73	1065.86
					Total:	**2162.59**	

DRC = Disease-related complication

Table D-16: Inpatient costs in the individual intervention patients

Patient	No. stay	Hospital	Reason	DRG	Relative weight	DRG costs [€]	Other costs [€]
BI 3	1	Johanniter Bonn	Progression	J18Z	1.771	4613.58	145.33
					Total:	**4758.91**	
BI 4	1	Johanniter Bonn	Diagnostic test	J62B	0.565	1471.86	135.42
					Total:	**1607.28**	
BI 5	1	Malteser Bonn	DRC	K62Z	0.685	1833.99	59,46
					Total:	**1893,45**	
BI 7	1	University Bonn	Toxicity	E75C	0.545	1486.81	1129.85
					Total:	**2616.66**	
BI 13	1	University Bonn	DRC	H61B	0.651	1775.99	946.02
	2	"	DRC	Z65Z	0.599	1634.13	121.36

Patient	No. stay	Hospital	Reason	DRG	Relative weight	DRG costs [€]	Other costs [€]
	3	"	DRC	J62B	0.565	1541.37	118.57
					Total:	**6137.43**	
BI 15	1	University Bonn	Progression	B66D	0.761	2076.08	123.71
					Total:	**2199.79**	
BI 18	1	University Bonn	DRC	E71A	1.230	3355.55	129.57
	2	"	DRC	A13B	10.309	28123.88	501.37
					Total:	**32110.37**	
BI 19	1	University Cologne	Progression	I65C	0.729	1947.96	-845.25
	2	University. Cologne	Progression	I08C	2.325	6212.63	348.34
					Total:	**7663.68**	
BI 23	1	Johanniter Bonn	Progression	J62A	1.251	3258.94	4456.61
	2	"	DRC	J62B	0.565	1471.86	104.42
					Total:	**9291.84**	
CI 3	1	University Bonn	Surgery following neoadjuvant treatment	G16B	3,969	10827,79	329,39
	2	"	Surgery following neoadjuvant treatment	H09A	3,753	10238,52	218,78
					Total:	**21614.48**	
CI 4	1	Johanniter Bonn	Diagnostic test	G60B	0.421	1096.73	73.27
					Total:	**1170.00**	
CI 5	1	Johanniter Bonn	Application of i.v. chemotherapy	G60B	0.421	1096.73	1969.17
	2	"	Diagnostic test	Z64B	0.394	1026.40	-376.83
					Total:	**3715.47**	
CI 8	1	Johanniter Bonn	DRC	G13Z	1.908	4970.47	1388.27
					Total:	**6358.74**	
CI 9	1	Johanniter Bonn	DRC	E64A	1.324	3449.11	627.36
	2	"	Diagnostic test	G46B	1.350	3516.84	262.38
	3	"	DRC	E64A	1.324	3449.11	-1524.78
					Total:	**9780.03**	
CI 12	1	Johanniter Bonn	Diagnostic test	G60B	0.421	1096.73	74.27
					Total:	**1171.00**	
CI 14	1	Johanniter Bonn	DRC	G65Z	0.520	1354.64	-922.03
	2	"	DRC	G18B	2.480	6460.5	-3519.74
					Total:	**3373.44**	
CI 19	1	University Bonn	DRC	G18B	2.480	6765.66	79.24
					Total:	**6844.90**	
CI 20	1	Waldkrankenhaus Bonn	Diagnostic test	G48C	0.796	2064.22	96.61
					Total:	**2160.83**	
CI 21	1	Johanniter Bonn	Progression	G07C	1.320	3438.69	138.09
	2	"	DRC	G02Z	3.423	8917.15	231.76
					Total:	**12725.7**	

DRC = Disease-related complication

Indirect costs

Table D-17: Indirect costs in the control and intervention group

Control patient	Days on sick leave [days]	Indirect costs [€]	Intervention patient	Days on sick leave [days]	Indirect costs [€]
B 1	missing	missing	BI 1	0	0.00
B 2	41	5827.74	BI 2	n. a.	0.00
B 3	n. a.	0.00	BI 3	n. a.	0.00
B 4	n. a.	0.00	BI 4	n. a.	0.00
B 5	missing	missing	BI 5	n. a.	0.00
B 6	n. a.	0.00	BI 6	n. a.	0.00
B 7	114	16203.96	BI 7	128	18193.92
B 8	n. a.	0.00	BI 8	15	2132.10
B 9	n. a.	0.00	BI 9	128	18193.92
B 10	44	6254.16	BI 10	n. a.	0.00
B 11	n. a.	0.00	BI 11	missing	missing
B 12	128	18193.92	BI 12	n. a.	0.00
B 13	n. a.	0.00	BI 13	n. a.	0.00
B 14	128	18193.92	BI 14	128	18193.92
B 15	128	18193.92	BI 15	43	6112.02
B 16	missing	missing	BI 16	93	13219.02
C 1	n. a.	0.00	BI 17	43	6112.02
C 2	n. a.	0.00	BI 18	n. a.	0.00
C 3	n. a.	0.00	BI 19	128	18193.92
C 4	n. a.	0.00	BI 20	n. a.	0.00
C 5	128	18193.92	BI 21	n. a.	0.00
C 6	n. a.	0.00	BI 22	128	18193.92
C 7	n. a.	0.00	BI 23	n. a.	0.00
C 8	88	12508.32	CI 1	n. a.	0.00
C 9	n. a.	0.00	CI 2	missing	missing
C 10	n. a.	0.00	CI 3	n. a.	0.00
C 11	n. a.	0.00	CI 4	missing	missing
C 12	n. a.	0.00	CI 5	n. a.	0.00
C 13	n. a.	0.00	CI 6	n. a.	0.00
C 14	n. a.	0.00	CI 7	18	2558.52
			CI 8	n. a.	0.00
			CI 9	n. a.	0.00
			CI 10	n. a.	0.00
			CI 11	n. a.	0.00
			CI 12	missing	missing
			CI 13	n. a.	0.00
			CI 14	128	18193.92
			CI 15	35	4974.90
			CI 16	73	10376.22
			CI 17	n. a.	0.00
			CI 18	missing	missing
			CI 19	n. a.	0.00
			CI 20	61	8670.54

Control patient	Days on sick leave [days]	Indirect costs [€]	Intervention patient	Days on sick leave [days]	Indirect costs [€]
			CI 21	missing	missing
			CI 22	128	18193.92
			CI 23	128	18193.92
Sum:		113569.86			199706.70
Median:		0.00			0.00
Mean:		4206.29			4992.67
SD:		7174.93			7371.50

n. a. = not applicable

Quality of life

Table D-18: EQ-5D frequency distribution during treatment with capecitabine

EQ-5D dimension	Control group				Intervention group			
	t_0	t_3	t_6	t_7	t_0	t_3	t_6	t_7
n	28	16	9	11	46	39	30	18
Mobility								
No problems %	57.1	56.2	77.8	72.7	54.3	46.1	63.3	61.1
Some problems %	42.9	43.8	22.2	27.3	45.7	33.3	36.7	38.9
Confined to bed %	0.0	0.0	0.0	0.0	0.0	2.6	0.0	0.0
Self-Care								
No problems %	82.1	93.7	100.0	90.9	87.0	89.7	90.0	88.9
Some problems %	14.3	6.3	0.0	9.1	10.9	10.3	10.0	11.1
Unable to %	3.6	0.0	0.0	0.0	2.1	0.0	0.0	0.0
Usual Activities								
No problems %	42.9	37.5	66.7	54.5	45.7	48.7	43.3	72.2
Some problems %	53.5	50.0	33.3	45.5	39.1	38.5	50.0	22.2
Unable to %	3.6	12.5	0.0	0.0	15.2	12.8	6.7	5.6
Pain / Discomfort								
None %	25.0	25.0	33.3	54.5	34.8	33.3	33.3	33.3
Moderate %	71.4	68.7	55.6	36.4	58.7	59.0	66.7	55.6
Extreme %	3.6	6.3	11.1	9.1	6.5	7.7	0.0	11.1
Anxiety / Depression								
None %	67.9	56.2	77.8	72.7	58.7	71.8	63.4	77.8
Moderate %	28.6	37.5	22.2	27.3	39.1	23.1	33.3	16.7
Extreme %	3.6	6.3	0.0	0.0	2.2	5.1	3.3	5.5

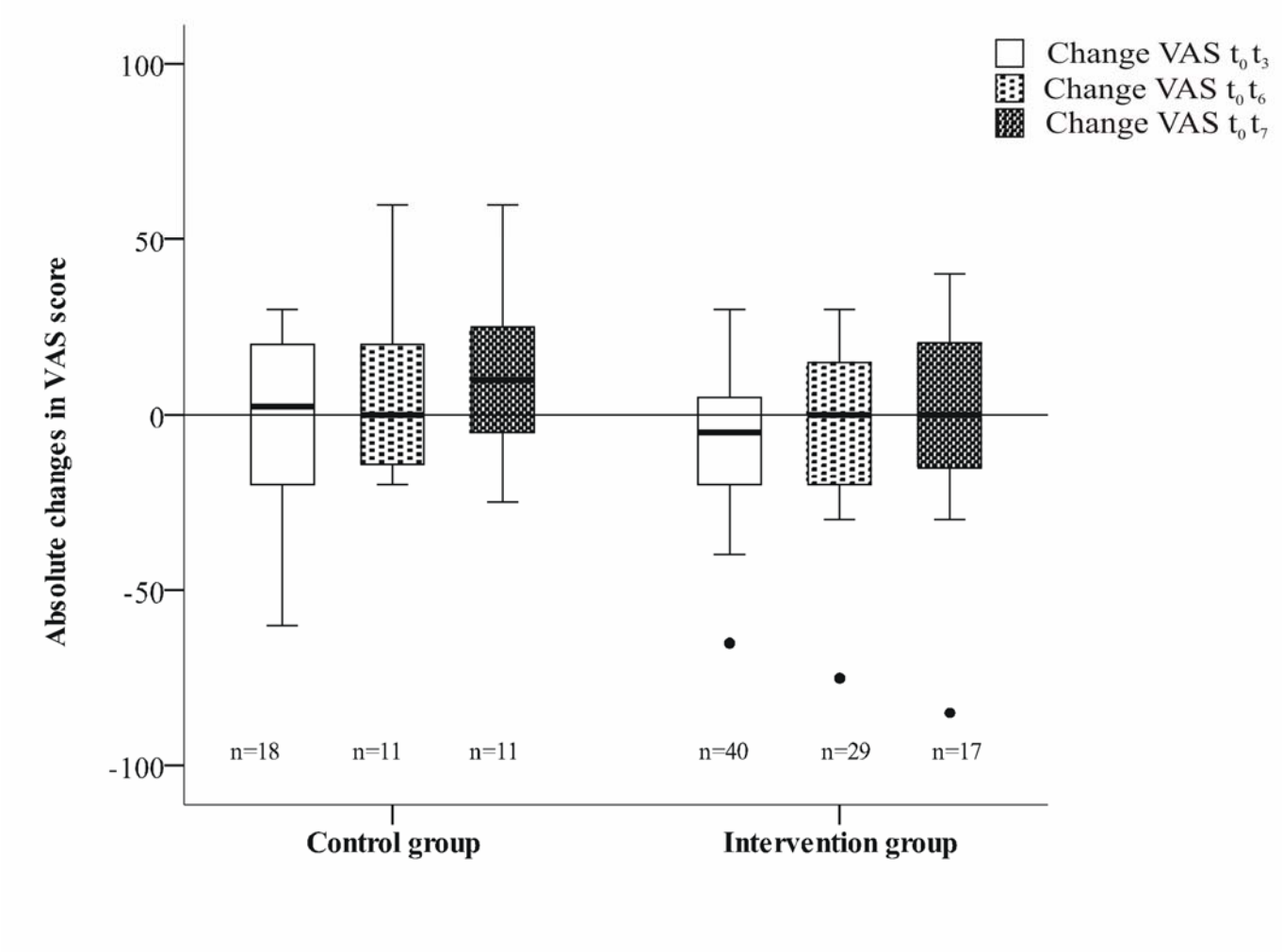


Figure D-1: Absolute changes in VAS scores

Hand-foot syndrome (HFS)

Table D-19: Median HFS and information on number of missing questionnaires, number of patients not treated with capecitabine and number of dead patients

		t_1	t_2	t_3	t_4	t_5	t_6	t_7
CG	n	29	23	18	17	11	11	11
	n missing	1	2	1	0	1	0	0
	n no Cap	0	5	9	10	14	14	13
	n dead	0	0	2	3	4	4	5
	median HFS	0.0	1.0	1.0	1.0	2.0	1.0	2.0
	IQR	0.0-1.0	0.0-1.0	0.75-2.0	1.0-2.0	1.0-2.0	1.0-2.0	1.0-2.0
IG	n	44	43	40	37	34	30	21
	n missing	2	0	0	1	0	2	1
	n no Cap	0	2	3	4	8	10	17
	n dead	0	1	3	4	4	4	7
	median HFS	0.0	1.0	1.0	1.0	1.0	1.0	0.5
	IQR	0.0-1.0	0.0-2.0	0.0-2.0	0.5-2.0	0.75-2.0	1.0-2.0	0.0-1.0
CG/IG	p-value*	0.440	0.607	0.646	0.383	0.023	0.592	0.019

*CG = control group, IG = intervention group, IQR = interquartile range, no Cap = no treatment with capecitabine, missing = missing questionnaire but patient treated with capecitabine, *Cochran-Armitage test for trend*

Willingness-to-pay (WTP)

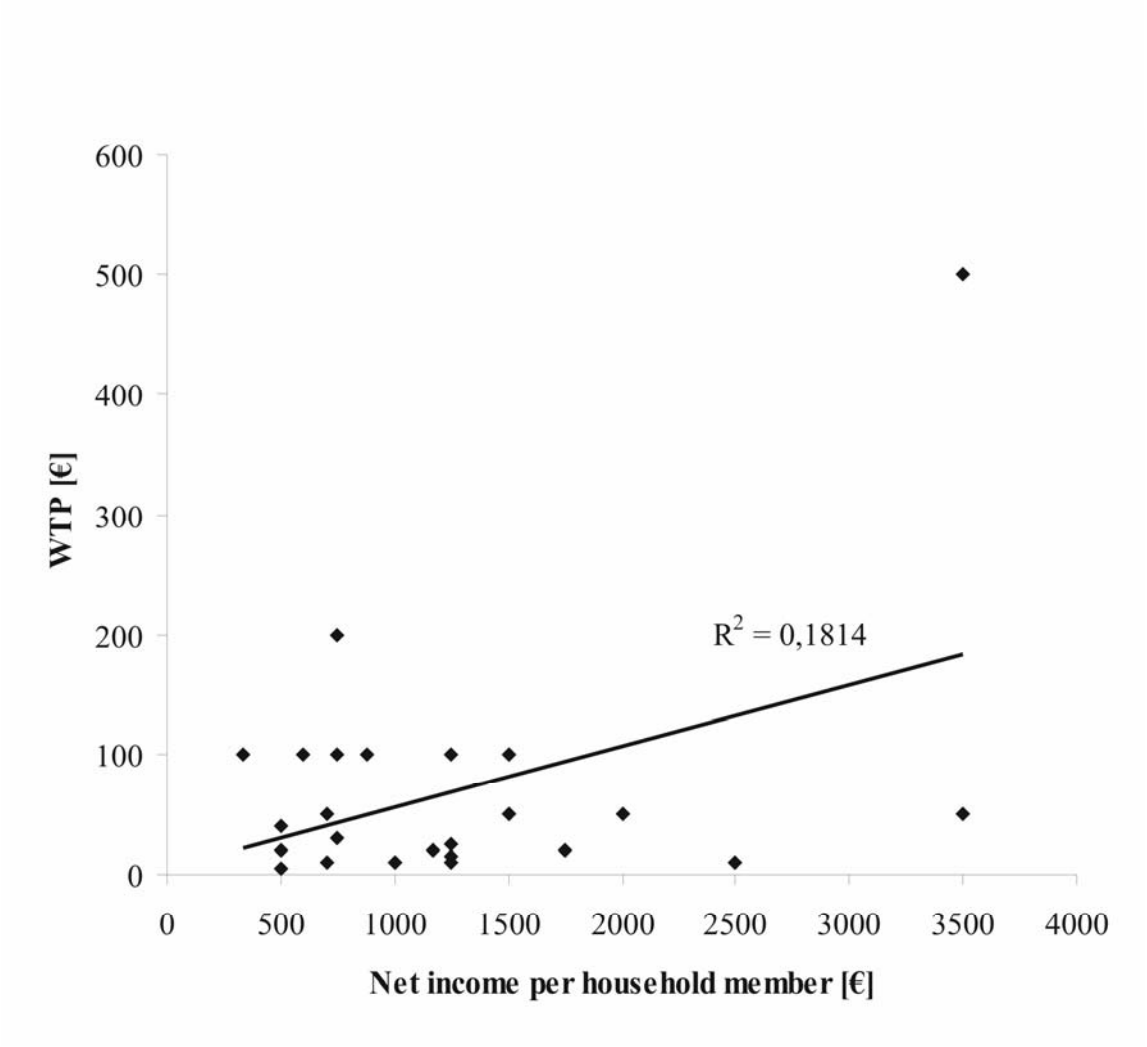


Figure D-2: WTP and net income per household member

Cost-utility analysis

Table D-20: Randomly selected matched patient pairs

Tumour entity	Treatment setting	Therapy regimen	Bis-phosphonate	Health insurance	IG	CG
Breast	Adjuvant	Cap Pac	No	Statutory	BI 16	B 12
Breast	Palliative	Cap	Yes	Statutory	BI 5 BI 8 BI 11 BI 17	B 4 B 6 B 11 B 8
Breast	Palliative	Cap	No	Statutory	BI 1	B 10
Breast	Palliative	Cap Tras	Yes	Private	BI 2	B 7
Colorectal	Neoadjuvant	Cap Ox	No	Statutory	CI 3	C 8
Colorectal	Palliative	Cap	No	Statutory	CI 1	C 7
Colorectal	Palliative	Cap Beva	No	Statutory	CI 16 CI 13	C 10 C 14

CG = control group, IG = intervention group, Therapy regimen: Cap = capecitabine monotherapy; Cap Beva = capecitabine + bevacizumab; Cap Ox = capecitabine + oxaliplatin; Cap Pac = capecitabine + paclitaxel; Cap Tras = capecitabine + trastuzumab

Table D-21: Best and worst selected matched patient pairs for sensitivity analysis

Tumour entity	Treatment setting	Therapy regimen	Bis-phososphonate	Health insurance	IG best case	IG worst case	CG
Breast	Adjuvant	Cap Pac	No	Statutory	BI 21	BI 16	B 12
Breast	Palliative	Cap	Yes	Statutory	BI 5 BI 8 BI 11 BI 17	BI 5 BI 8 BI 11 BI 17	B 4 B 6 B 11 B 8
Breast	Palliative	Cap	No	Statutory	BI 1	BI 1	B 10
Breast	Palliative	Cap Tras	Yes	Private	BI 2	BI 2	B 7
Colorectal	Neoadjuvant	Cap Ox	No	Statutory	CI 3	CI 3	C 8
Colorectal	Palliative	Cap	No	Statutory	CI 1	CI 20	C 7
Colorectal	Palliative	Cap Beva	No	Statutory	CI 13 CI 17	CI 16 CI 17	C 10 C 14

CG = control group, IG = intervention group, Therapy regimen: Cap = capecitabine monotherapy; Cap Beva = capecitabine + bevacizumab; Cap Ox = capecitabine + oxaliplatin; Cap Pac = capecitabine + paclitaxel; Cap Tras = capecitabine + trastuzumab

Table D-22: Socio-demographic patient characteristics of eleven randomly matched-pairs at the time of inclusion

Socio-demographic variable		**Control group**		**Intervention group**	
		n	**%**	**n**	**%**
Age	< 50 years old	1	9.1	2	18.2
	50-60 years old	4	36.4	3	27.3
	> 60 years old	5	54.5	6	54.6
Sex	Female	9	81.8	9	81.8
	Male	2	18.2	2	18.2
Marital status	Married / partner	9	81.8	9	81.8
	Single	1	9.1	1	9.1
	Widow	1	9.1	1	9.1
Current living situation	Living alone	2	18.2	1	9.1
	With family / partner	8	72.7	10	90.9
	Other	1	9.1	0	0.0
Education	Elementary school	4	36.4	4	36.4
	Secondary school	2	18.2	4	36.4
	O-levels	1	9.1	0	0.0
	Journeyman	1	9.1	2	18.2
	Master of a trade	1	9.1	0	0.0
	Bachelor	1	9.1	1	9.1
	No answer	1	9.1	0	0.0
Current employment situation	Full time job	1	9.1	1	9.1
	Part time job	0	0.0	2	18.2
	Unable to work	3	27.3	1	9.1
	Pensioner	6	54.5	4	36.4
	Housewife/ -man	1	9.1	3	27.3
Therapy setting	Oncology outpatient ward	7	63.6	6	54.5
	Oncology practice	4	36.4	5	45.5

It was tested for statistically significant differences between the selected control group and the selected intervention group (Fisher`s exact test):

age range: p = 1.000; sex: p = 1.000; marital status: p = 1.000, current living situation: p = 0.586, education: p = 0.852, current employment situation: p = 0.518, therapy setting: p = 1.000

Tables D-23 – D-47:

Tables D-23 – D-47 contain details on resource utilisation and cost calculation of the eleven randomly matched patient pairs and three additional patients (BI 21, CI 17, CI 20), separately for each patient. In case of a charge in euro [€] for an EBM or GOÄ digit or a medication, the amount of money was multiplied by the resource us (number of units) to calculate costs. In case of points for an EBM digit instead of a charge in euro [€] the points were multiplied by 3.72 cents and then by the resource use (number of units) to calculate costs.

Table D-23: *BI 1, study period 09.01.-09.07.2007*

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
1. Oncologist fee				
13500	540	2	40.18	
86503	25.56 €	2	51.12	91.30
2. Diagnostics				
2.1 Laboratory parameter				
32068	0.25 €	3	0.75	
32058	0.25 €	3	0.75	
32057	0.25 €	3	0.75	
32460	5.40 €	3	16.20	
32071	0.25 €	3	0.75	
32069	0.25 €	3	0.75	
32070	0.25 €	3	0.75	
32081	0.25 €	3	0.75	
32075	0.25 €	3	0.75	
32083	0.25 €	3	0.75	
32084	0.25 €	3	0.75	
32067	0.40 €	3	1.20	
32064	0.25 €	3	0.75	
32123	0.40 €	3	1.20	
32122	1.20 €	3	3.60	
32324	4.90 €	2	9.80	
32391	8.20 €	2	16.40	
32120	0.50 €	6	3.00	59.65
2.2 MRT/CT/PET				
34330	1865	1	69.38	69.38
2.3 Other				
33042	445	1	16.55	16.55
3. Administration				
01430	35	5	6.51	
32012	0	1	0.00	
01601	210	1	7.81	14.32
4. Drugs				
4.1 Antineoplastic				
Xeloda 500mg 120 St	534.55 €	7	3741.85	3741.85
				-70.00
Patient`s co-payment	10.00 €	7	70.00	3671.85
4.2 Supportive				
	0.00 €		0.00	0.00

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
4.3 Supportive (patient documentation)				
Hexobion 100 100St	14.21 €	5	71.05	
Imodium KAP 10St	11.41 €	1	11.41	
Equizym MCA	49.20 €	1	49.20	131.66
Patient`s co-payment	5.00 €	6	30.00	-79.20
Patient`s co-payment	49.20 €	1	49.20	52.46

Table D-24: BI 2, study period 17.01.-17.07.2007

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
1. Oncologist fee				
275	48.26 €	8	386.08	
78	24.13 €	1	24.13	
250	4.20 €	9	37.80	
272	24.13 €	1	24.13	472.14
2. Diagnostics				
2.1 Laboratory parameter				
3905	16.76 €	3	50.28	
3901	30.16 €	3	90.48	
3550	4.02 €	9	36.18	
3551	1.34 €	9	12.06	
3558	2.01 €	9	18.09	
3557	2.01 €	9	18.09	
3555	2.68 €	9	24.12	
3585	2.68 €	9	24.12	
3583	2.68 €	9	24.12	
3581	2.68 €	9	24.12	
3594	2.68 €	9	24.12	
3595	2.68 €	9	24.12	
3592	2.68 €	9	24.12	
3587	2.68 €	9	24.12	
3597	2.68 €	9	24.12	
3560	2.68 €	9	24.12	
3741	13.41 €	9	120.69	587.07
2.2 MRT/CT/PET				
5488	629.50 €	1	629.50	629.50
2.3 Other				
	0.00 €	0	0.00	0.00
3. Administration				
	0.00 €	0	0.00	0.00
4. Drugs				
4.1 Antineoplastic				
Xeloda 500mg 120 St	534.55 €	8	4276.40	
Trastuzumab Roche 612mg 500ml NaCl0.9%	4019.59 €	9	36176.31	41598.63
Aromasin 25mg 100 St	572.96 €	2	1145.92	-190.00
Patients Payment	10.00 €	19	190.00	41408.63
4.2 Supportive				
Hexobion 100 100St	14.21 €	4	56.84	
Remergil TAB 30mg N3	178.74 €	2	357.48	
Remergil TAB 30mg N2	94.37 €	1	94.37	

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
Perfalgan10mg/ml 12x100ml BristolMyers	43.11 €	1	43.11	
Pantozol 40mg 100 St	128.42 €	3	385.26	
Bondronat 6mg x 5 N1	1.652.08 €	2	3304.16	
Patient`s co-payment	10.00 €	7	70.00	4241.22
Patient`s co-payment	9.44 €	1	9.44	-104.44
Patient`s co-payment	5.00 €	5	25.00	4136.78
4.3 Supportive (patient documentation)				
Wobenzym N 800 St	129.95 €	1	129.95	
Selenase 300 100St	54.32 €	1	54.32	
Lektinol 0,5ml 25 AMP	235.73 €	1	235.73	
Equziym MCA 100St	49.20 €	4	196.80	
Patient`s co-payment	5.43 €	1	5.43	
Patient`s co-payment	129.95 €	1	129.95	616.80
Patient`s co-payment	10.00 €	1	10.00	-342.18
Patient`s co-payment	49.20 €	4	196.80	274.62

Table D-25: BI 5, study period: 08.02.–27.03.2007

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
1. Oncologist fee				
13215	50	5	9.30	
13220	235	2	17.48	
02100	160	2	11.90	38.69
2. Diagnostics				
2.1 Laboratory parameter				
32068	0.25 €	2	0.50	
32056	0.25 €	2	0.50	
32107	0.75 €	2	1.50	
32066	0.25 €	1	0.25	
32082	0.25 €	2	0.50	
32057	0.25 €	1	0.25	
32075	0.25 €	2	0.50	
32324	4.90 €	2	9.80	
32391	8.20 €	2	16.40	
32120	0.50 €	2	1.00	31.20
2.2 MRT/CT/PET				
	0	0	0.00	0.00
2.3 Other				
	0	0	0.00	0.00
3. Administration				
01600	110	2	8.18	8.18
4. Drugs				
4.1 Antineoplastic				
Xeloda 500mg 120 St	534.55 €	2	1069.10	1069.10
Patient`s co-payment	10.00 €	2	20.00	-20.00 1049.10
4.2 Supportive				
MCP AL Tropfen 100ml	12.25 €	1	12.25	
Bondronat 6mg N1	343.91 €	2	687.82	
Fraxiparin 0,3 x 10 FS	47.47 €	1	47.47	
Palladon 16mg RetKAP 20 St	129.07 €	1	129.07	

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
Palladon 2,6mg KAP 20 St	41.29 €	1	41.29	
Palladon 24mg RetKAP 20 St	187.89 €	1	187.89	
Ibuprofen 800 TAB 50St	14.77 €	1	14.77	1120.56
Patient`s co-payment	5.00 €	3	15.00	-65.00
Patient`s co-payment	10.00 €	5	50.00	1055.56
4.3 Supportive (patient documentation)				
MCP AL Tropfen 100ml	12.25 €	1	12.25	
Novalgin TRO 50ml	14.21 €	1	14.21	
Novaminsulfon TRO 100ml	16.72 €	1	16.72	
Ibu 800 CT 100St	21.11 €	1	21.11	
Celldolor 100/8mg 50St	43.98 €	1	43.98	
Omeprazol 20mg 60St	31.25 €	1	31.25	
MST 100mg 50St	140.42 €	1	140.42	
Movicol-Beutel 50St	34.86 €	1	34.86	
Laxoberal TRO	17.90 €	1	17.90	
Lactulose Sirup 500ml	9.44 €	1	9.44	
Furosemid 40mg 100St	13.55 €	1	13.55	355.69
Patient`s co-payment	10.00 €	1	10.00	-55.00
Patient`s co-payment	5.00 €	9	45.00	300.69

Table D-26: BI 8, study period 16.04.-16.10.2007

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
1. Oncologist fee				
13215	50	7	13.02	
13220	235	2	17.48	
02100	160	7	41.66	
13502	540	2	40.18	
13500	540	2	40.18	
86503	25.56 €	2	51.12	203.64
2. Diagnostics				
2.1 Laboratory parameter				
32068	0.25 €	5	1.25	
32058	0.25 €	5	1.25	
32065	0.25 €	5	1.25	
32057	0.25 €	5	1.25	
32082	0.25 €	5	1.25	
32066	0.25 €	5	1.25	
32071	0.25 €	5	1.25	
32069	0.25 €	5	1.25	
32070	0.25 €	5	1.25	
32081	0.25 €	5	1.25	
32075	0.25 €	5	1.25	
32083	0.25 €	5	1.25	
32056	0.25 €	5	1.25	
32072	0.40 €	5	2.00	
32064	0.25 €	5	1.25	
32324	4.90 €	5	24.50	
32391	8.20 €	5	41.00	
32460	5.40 €	5	27.00	
32120	0.50 €	4	2.00	114.00

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
2.2 MRT/CT/PET				
	0	0	0.00	0.00
2.3 Other				
33011	245	1	9.11	9.11
3. Administration				
01430	35	6	7.81	
01601	210	2	15.62	
40120	0.55 €	2	1.10	
90909	0.00 €	2	0.00	
90929	0.00 €	2	0.00	24.54
4. Drugs				
4.1 Antineoplastic				
Xeloda 500mg 120 St	534.55 €	9	4810.95	4810.95
				-90.00
Patient`s co-payment	10.00 €	9	90.00	4720.95
4.2 Supportive				
Bondronat 6mg/6ml N1 5x6ml	1.652.08 €	2	3304.16	
Omeprazol STADA 40mg 30St	38.38 €	1	38.38	
Pantozol 40mg 30St TMR	43.68 €	1	43.68	3386.22
Patient`s co-payment	5.00 €	1	5.00	-25.00
Patient`s co-payment	10.00 €	2	20.00	3361.22
4.3 Supportive (patient documentation)				
Equizym MCA	49.20 €	2	98.40	
Pantozol 40mg 30St TMR	43.68 €	2	87.36	
Lefax Kautabletten 20St	5.31 €	1	5.31	
Patient`s co-payment	49.20 €	2	98.40	191.07
Patient`s co-payment	3.80 €	1	3.80	-112.20
Patient`s co-payment	5.00 €	2	10.00	78.87

Table D-27: BI 11, study period: 27.06.-27.12.2007

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
1. Oncologist fee				
01311	175	2	13.02	
08220	235	4	34.97	
08345	540	2	40.18	
30420	265	10	98.58	186.74
2. Diagnostics				
2.1 Laboratory parameter				
32081	0.25 €	1	0.25	
32082	0.25 €	1	0.25	
32083	0.25 €	1	0.25	
32066	0.25 €	1	0.25	
32122	1.20 €	1	1.20	
32120	0.50 €	4	2.00	
32391	8.20 €	2	16.40	
32356	5.10 €	1	5.10	
32390	9.70 €	1	9.70	
32354	5.60 €	1	5.60	
32357	4.60 €	1	4.60	
32355	5.10 €	1	5.10	50.70

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
2.2 MRT/CT/PET				
	0	0	0.00	0.00
2.3 Other				
17311	1860	1	69.19	
17312	475	1	17.67	
17362	1900	1	70.68	157.54
3. Administration				
32019	0	0	0.00	0.00
4. Drugs				
4.1 Antineoplastic				
Xeloda 500mg 120St	534.55 €	5	2672.75	3245.71
Aromasin 25mg 100St	572.96 €	1	572.96	-60.00
Patient`s co-payment	10.00 €	6	60.00	3185.71
4.2 Supportive				
Bondronat 50mg 84St	1.101.00 €	2	2202.00	
Neuro ratio 100St	12.85 €	1	12.85	
Berberil N TRO	4.41 €	1	4.41	
Patient`s co-payment	5.00 €	1	5.00	2219.26
Patient`s co-payment	10.00 €	2	20.00	-29.38
Patient`s co-payment	4.38 €	1	4.38	2189.88
4.3 Supportive (patient documentation)				
Diclofenac 100mg 100St	16.80 €	1	16.80	24.45
Euphrasia AT 10ml	7.65 €	1	7.65	-10.00
Patient`s co-payment	5.00 €	2	10.00	14.45

Table D-28: BI 16, study period: 31.10.2007-01.05.2008

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
1. Oncologist fee				
08345	540	2	40.18	
08220	235	9	78.68	
01311	175	2	13.02	
02101	445	10	165.54	299.65
2. Diagnostics				
2.1 Laboratory parameter				
32120	0.50 €	2	1.00	
32122	1.20 €	9	10.80	
32058	0.25 €	5	1.25	
32064	0.25 €	3	0.75	
32065	0.25 €	3	0.75	
32066	0.25 €	6	1.50	
32069	0.25 €	5	1.25	
32070	0.25 €	5	1.25	
32071	0.25 €	4	1.00	
32081	0.25 €	6	1.50	
32082	0.25 €	6	1.50	
32083	0.25 €	6	1.50	
32068	0.25 €	3	0.75	
32391	8.20 €	1	8.20	
32460	5.40 €	1	5.40	
32392	9.20 €	1	9.20	

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
32324	4.90 €	1	4.90	
32086	0.40 €	1	0.40	
32248	1.40 €	1	1.40	
32073	0.40 €	2	0.80	
32072	0.40 €	1	0.40	
32075	0.25 €	2	0.50	
32074	0.25 €	1	0.25	
32057	0.25 €	1	0.25	
32085	0.25 €	1	0.25	
32325	4.90 €	1	4.90	
32056	0.25 €	1	0.25	
32113	0.60 €	1	0.60	
32112	0.60 €	1	0.60	
32115	0.75 €	1	0.75	
32116	0.75 €	1	0.75	
32390	9.70 €	1	9.70	74.30
2.2 MRT/CT/PET				
	0	0	0.00	0.00
2.3 Other				
33044	400	1	14.88	
34241	430	1	16.00	30.88
3. Administration				
40120	0.55 €	2	1.10	1.10
4. Drugs				
4.1 Antineoplastic				
Xeloda 500mg 120 St	534.55 €	3	1603.65	
Paclitaxel 99,23mg 250ml NaCl0.9%	677.66 €	10	6776.60	10582.25
Ibandronat 50mg 84St	1.101.00 €	2	2202.00	-150.00
Patient`s co-payment	10.00 €	15	150.00	10432.25
4.2 Supportive				
Tavegil 5AMP	11.50 €	2	23.00	
Granisetron 2mg 5TAB	100.29 €	2	200.58	
Ranitidin 50mg 5AMP	14.48 €	2	28.96	
Dexamethason 4mg 100ml NaCl0.9%	52.29 €	10	522.90	
Kevatril 1mg 100ml NaCl0.9%	69.91 €	10	699.10	
NaCl0.9% 250ml x10	23.40 €	1	23.40	
NaCl0.9% 10ml x20	10.22 €	1	10.22	
Heparin Calcium 7500 10 FS	25.50 €	1	25.50	
MCP Tropfen 100ml	12.25 €	1	12.25	
Aranesp 300µg 1 FS 0,6ml	856.49 €	1	856.49	
Vagiflor Zäpfchen 12St	22.90 €	1	22.90	
Ferrosanol duodenal KAP N3	26.58 €	1	26.58	
Patient`s co-payment	10.00 €	1	10.00	
Patient`s co-payment	5.00 €	10	50.00	2451.88
Patient`s co-payment	5.23 €	10	52.30	-182.20
Patient`s co-payment	6.99 €	10	69.90	2269.68
4.3 Supportive (patient documentation)				
Ferrosanol duodenal 100mg 100St	26.58 €	2	53.16	
Mar Meerwassernasenspray 20ml	4.85 €	1	4.85	
Vit B6 ratiopharm 40mg 100St	7.59 €	1	7.59	
Granisetron 2mg 5TAB	100.29 €	8	802.32	
Folsan 5mg 100St	18.31 €	1	18.31	
Vitasprint B12 Trinkampullen 10St	26.43 €	1	26.43	

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
Deumavan Salbe 20ml	14.48 €	1	14.48	
Multi-Gyn-Liquid Gel	9.95 €	1	9.95	
Patient`s co-payment	4.85 €	1	4.85	
Patient`s co-payment	26.43 €	1	26.43	
Patient`s co-payment	9.95 €	1	9.95	937.09
Patient`s co-payment	14.48 €	1	14.48	-75.71
Patient`s co-payment	5.00 €	4	20.00	861.38

Table D-29: BI 17, study period 30.11.2007-30.05.2008

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
1. Oncologist fee				
08345	540	3	60.26	
01311	175	2	13.02	
02100	160	6	35.71	109.00
2. Diagnostics				
2.1 Laboratory parameter				
32120	0.50 €	1	0.50	
32122	1.20 €	4	4.80	
32058	0.25 €	3	0.75	
32065	0.25 €	1	0.25	
32066	0.25 €	6	1.50	
32069	0.25 €	4	1.00	
32070	0.25 €	4	1.00	
32071	0.25 €	4	1.00	
32081	0.25 €	3	0.75	
32082	0.25 €	8	2.00	
32083	0.25 €	3	0.75	
32068	0.25 €	1	0.25	
32391	8.20 €	2	16.40	
32075	0.25 €	3	0.75	
32112	0.60 €	2	1.20	
32115	0.75 €	2	1.50	
32390	9.70 €	1	9.70	
32391	8.20 €	1	8.20	52.30
2.2 MRT/CT/PET				
34330	1865	1	69.38	
34340	1875	1	69.75	139.13
2.3 Other				
33042	445	2	33.11	33.11
3. Administration				
32019	0	0	0.00	0.00
4. Drugs				
4.1 Antineoplastic				
Xeloda 500mg 120 St	534.55 €	4	2138.20	
Navelbine 20mg KAP 4St	363.62 €	4	1454.48	
Navelbine 20mg KAP 1St	86.89 €	2	173.78	
Navelbine 30mg KAP 4St	547.73 €	4	2190.92	
Navelbine 30mg KAP 1St	133.01 €	1	133.01	6090.39
Patient`s co-payment	10.00 €	13	130.00	-147.38
Patient`s co-payment	8.69 €	2	17.38	5943.01

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
4.2 Supportive				
Bondronat 6mg/6ml Infusion 100ml NaCl0,9%	385.56 €	7	2698.92	
Sab simplex TRO 30ml	6.72 €	1	6.72	2705.64
Patient`s co-payment	10.00 €	7	70.00	-75.00
Patient`s co-payment	5.00 €	1	5.00	2630.64
4.3 Supportive (patient documentation)				
Pantozol 20mg 60St	56.16 €	1	56.16	
Imodium lingual 100St	16.60 €	1	16.60	
MCP Stada TRO 100ml	12.27 €	1	12.27	85.03
Patient`s co-payment	5.00 €	2	10.00	-15.62
Patient`s co-payment	5.62 €	1	5.62	69.41

Table D-30: BI 21, study period: 07.04.-07.10.2008

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
1. Oncologist fee				
01311	175	1	6.51	
02101	445	9	148.99	
08345	540	1	20.09	175.58
2. Diagnostics				
2.1 Laboratory parameter				
32068	0.25 €	6	1.50	
32058	0.25 €	5	1.25	
32071	0.25 €	4	1.00	
32069	0.25 €	5	1.25	
32070	0.25 €	5	1.25	
32081	0.25 €	6	1.50	
32082	0.25 €	6	1.50	
32083	0.25 €	6	1.50	
32073	0.40 €	2	0.80	
32064	0.25 €	2	0.50	
32065	0.25 €	3	0.75	
32066	0.25 €	5	1.25	
32122	1.20 €	8	9.60	
32120	0.50 €	1	0.50	24.15
2.2 MRT/CT/PET				
	0	0	0.00	0.00
2.3 Other				
	0	0	0.00	0.00
3. Administration				
40120	0.55 €	1	0.55	0.55
4. Drugs				
4.1 Antineoplastic				
Xeloda 500mg 120 St	534.55 €	3	1603.65	
Paclitaxel 130,2mg 250ml NaCl0.9%	975.19 €	1	975.19	
Paclitaxel 129,6mg 250ml NaCl0.9%	866.05 €	9	7794.45	
Tamoxifen 20mg 100St	21.47 €	1	21.47	10394.76
Patient`s co-payment	10.00 €	13	130.00	-135.00
Patient`s co-payment	5.00 €	1	5.00	10259.76
4.2 Supportive				
Tavegil 5AMP	11.50 €	2	23.00	

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
Granisetron beta 2mg 5St N1	100.29 €	3	300.87	
Ranitidin 50mg 5AMP	14.48 €	2	28.96	
Dexamethason 4mg 100ml NaCl0.9%	52.29 €	10	522.90	
Kevatril 1mg 100ml NaCl0.9%	69.91 €	10	699.10	
NaCl0.9% 250ml x10	23.40 €	1	23.40	
NaCl0.9% 10ml x20	10.22 €	1	10.22	
Heparin Calcium 7500 10 FS	25.50 €	1	25.50	
Bepanthen Augen-und Nasensalbe	3.24 €	1	3.24	
Pantozol 40mg 100St	128.42 €	1	128.42	
Berberil N AT	4.41 €	1	4.41	
Linocab direkt Kombipackung	16.78 €	1	16.78	
Clexane 60	172.20 €	1	172.20	
Tepilta	43.13 €	1	43.13	
Patient`s co-payment	4.38 €	1	4.38	
Patient`s co-payment	5.23 €	10	52.30	
Patient`s co-payment	6.99 €	10	69.90	
Patient`s co-payment	2.70 €	1	2.70	2002.13
Patient`s co-payment	10.00 €	2	20.00	-194.28
Patient`s co-payment	5.00 €	9	45.00	1807.85
4.3 Supportive (patient documentation)				
Ferrosanol duodenal 100St	26.58 €	1	26.58	58.88
Pantozol 20mg 30St	32.30 €	1	32.30	-10.00
Patient`s co-payment	5.00 €	2	10.00	48.88

Table D-31: CI 1, study period: 11.12.2006–11.06.2007

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
1. Oncologist fee				
13215	50	1	1.86	
80112	205	2	15.25	
13500	540	2	40.18	
86503	25.56 €	2	51.12	108.41
2. Diagnostics				
2.1 Laboratory parameter				
32068	0.25 €	2	0.50	
32058	0.25 €	2	0.50	
32057	0.25 €	2	0.50	
32460	5.40 €	2	10.80	
32071	0.25 €	2	0.50	
32069	0.25 €	2	0.50	
32070	0.25 €	2	0.50	
32081	0.25 €	2	0.50	
32075	0.25 €	2	0.50	
32083	0.25 €	2	0.50	
32084	0.25 €	2	0.50	
32067	0.40 €	2	0.80	
32064	0.25 €	2	0.50	
32123	0.40 €	2	0.80	
32122	1.20 €	2	2.40	
32324	4.90 €	1	4.90	
32392	9.20 €	1	9.20	34.40

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
2.2 MRT/CT/PET				
	0	0	0.00	0.00
2.3 Other				
	0	0	0.00	0.00
3. Administration				
01430	35	1	1.30	
01610	40	1	1.49	
01620	85	3	9.49	
01621	125	1	4.65	
01622	235	1	8.74	25.67
4. Drugs				
4.1 Antineoplastic				
Xeloda 500mg 120 St	534.55 €	5	2672.75	2672.75
				-50.00
Patient`s co-payment	10.00 €	5	50.00	2622.75
4.2 Supportive				
Omep 40mg N3	109.97 €	1	109.97	109.97
Patient`s co-payment	0.00 €	1	0.00	0.00
				109.97
4.3 Supportive (patient documentation)				
Hexobion 100 100St	14.21 €	1	14.21	28.01
Ibuprofen 600mg 50St	13.80 €	1	13.80	-10.00
Patient`s co-payment	5.00 €	2	10.00	18.01

Table D-32: CI 3, study period: 26.02.2007 - 26.08.2007

Digit / Medication	Points / €	Resource-use	Costs (€)	Sum (€)
1. Oncologist fee				
13215	50	11	20.46	
13220	235	8	69.94	
01510	1420	5	264.12	
02341	330	1	12.28	
02110	600	1	22.32	
02111	240	1	8.93	
13500	540	2	40.18	
13502	540	1	20.09	
86503	25.56 €	2	51.12	509.42
2. Diagnostics				
2.1 Laboratory parameter				
32068	0.25 €	6	1.50	
32058	0.25 €	6	1.50	
32065	0.25 €	6	1.50	
32057	0.25 €	6	1.50	
32082	0.25 €	6	1.50	
32066	0.25 €	6	1.50	
32460	5.40 €	6	32.40	
32071	0.25 €	7	1.75	
32069	0.25 €	7	1.75	
32070	0.25 €	7	1.75	
32081	0.25 €	6	1.50	
32075	0.25 €	6	1.50	

Digit / Medication	Points / €	Resource-use	Costs (€)	Sum (€)
32083	0.25 €	6	1.50	
32056	0.25 €	6	1.50	
32072	0.40 €	6	2.40	
32064	0.25 €	6	1.50	
32120	0.50 €	9	4.50	
32460	4.90 €	3	14.70	
32392	9.20 €	3	27.60	
32112	0.60 €	1	0.60	
32113	0.60 €	1	0.60	
32169	15.30 €	1	15.30	119.85
2.2 MRT/CT/PET				
34441	3430	1	127.60	127.60
2.3 Other				
33042	445	1	16.55	16.55
3. Administration				
01602	35	1	1.30	
01430	35	1	1.30	
32012	0	12	0.00	
01601	210	2	15.62	
40120	0.55 €	3	1.65	19.88
4. Drugs				
4.1 Antineoplastic				
Xeloda 500mg 120 St	534.55 €	2	1069.10	3464.26
Oxaliplatin 85mg Mayne 500ml Glu 5%	598.79 €	4	2395.16	-60.00
Patient`s co-payment	10.00 €	6	60.00	3404.26
4.2 Supportive				
Erythrozytenkonzentrat	81.00 €	2	162.00	
Voltaren 50 DRAG 50 St	19.83 €	1	19.83	199.79
Tilidin ratio plus TRO 50ml	17.96 €	1	17.96	-5.00
Patient`s co-payment	5.00 €	1	5.00	194.79
4.3 Supportive (patient documentation)				
Questionnaire cycle 4 missing				
Pantozol 20mg	88.37 €	2	176.74	
Locacorten Creme	18.94 €	1	18.94	195.68
Patient`s co-payment	8.84 €	2	17.68	-22.68
Patient`s co-payment	5.00 €	1	5.00	173.00

Table D-33: CI 13, study period: 24.07.2007-24.01.2008

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
1. Oncologist fee				
13215	50	7	13.02	
01510	1420	9	475.42	
80112	205	1	7.63	
13492	905	1	33.67	
13500	540	2	40.18	
13502	540	2	40.18	
86503	25.56 €	2	51.12	
86505	255.65 €	2	511.30	1172.50
2. Diagnostics				
2.1 Laboratory parameter				

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
32068	0.25 €	9	2.25	
32058	0.25 €	9	2.25	
32065	0.25 €	9	2.25	
32057	0.25 €	9	2.25	
32082	0.25 €	9	2.25	
32066	0.25 €	9	2.25	
32460	5.40 €	9	48.60	
32071	0.25 €	9	2.25	
32069	0.25 €	9	2.25	
32070	0.25 €	9	2.25	
32081	0.25 €	9	2.25	
32075	0.25 €	9	2.25	
32083	0.25 €	9	2.25	
32056	0.25 €	9	2.25	
32072	0.40 €	9	3.60	
32064	0.25 €	8	2.00	
32324	4.90 €	8	39.20	
32392	9.20 €	9	82.80	
32120	0.50 €	9	4.50	209.95
2.2 MRT/CT/PET				
	0	0	0.00	0.00
2.3 Other				
	0	0	0.00	0.00
3. Administration				
01430	35	3	3.91	
80032	0	1	0.00	
90909	0	1	0.00	
32012	0	2	0.00	
01601	210	1	7.81	
40120	0.55 €	1	0.55	12.27
4. Drugs				
4.1 Antineoplastic				
Xeloda 500mg 120 St	534.55 €	4	2138.20	
Avastin 300mg 250ml NaCl 0.9%	1.646.94 €	1	1646.94	20436.74
Avastin 470mg 250ml NaCl 0.9%	2.081.45 €	8	16651.60	-130.00
Patient`s co-payment	10.00 €	13	130.00	20306.74
4.2 Supportive				
Dexahexal 8mg/2ml 5x2 AMP N2	14.21 €	2	28.42	
Vitamin B Komplex Ratio 60 St KAP	8.38 €	1	8.38	36.80
Patient`s co-payment	8.38 €	1	8.38	-18.38
Patient`s co-payment	5.00 €	2	10.00	18.42
4.3 Supportive (patient documentation)				
	0.00 €	0	0.00	0.00

Table D-34: CI 16, study period: 20.08.2007-20.02.2008

Digit / Medication	Points / €	Resource-use	Costs (€)	Sum (€)
1. Oncologist fee				
13215	50	11	20.46	
13220	235	3	26.23	
01510	1420	6	316.94	

Digit / Medication	Points / €	Resource-use	Costs (€)	Sum (€)
01511	2700	1	100.44	
80111	175	1	6.51	
13491	865	1	32.18	
13500	540	2	40.18	
13502	540	2	40.18	
86503	25.56 €	2	51.12	
86505	255.65 €	2	511.30	1145.53
2. Diagnostics				
2.1 Laboratory parameter				
32068	0.25 €	9	2.25	
32058	0.25 €	9	2.25	
32065	0.25 €	9	2.25	
32057	0.25 €	9	2.25	
32082	0.25 €	9	2.25	
32066	0.25 €	9	2.25	
32460	5.40 €	9	48.60	
32071	0.25 €	9	2.25	
32069	0.25 €	9	2.25	
32070	0.25 €	9	2.25	
32081	0.25 €	9	2.25	
32075	0.25 €	9	2.25	
32083	0.25 €	9	2.25	
32056	0.25 €	9	2.25	
32072	0.40 €	9	3.60	
32064	0.25 €	9	2.25	
32324	4.90 €	9	44.10	
32392	9.20 €	9	82.80	
32120	0.50 €	9	4.50	215.10
2.2 MRT/CT/PET				
	0	0	0.00	0.00
2.3 Other				
	0	0	0.00	0.00
3. Administration				
01430	35	2	2.60	
80032	0	1	0.00	
90909	0	2	0.00	
32012	0	2	0.00	
32022	0	1	0.00	
01601	210	1	7.81	
01622	235	1	8.74	
40120	0.55 €	1	0.55	19.71
4. Drugs				
4.1 Antineoplastic				
Xeloda 500mg 120 St	534.55 €	9	4810.95	25464.31
Avastin 580mg 250ml NaCl	2.950.48 €	7	20653.36	-160.00
Patient`s co-payment	10.00 €	16	160.00	25304.31
4.2 Supportive				
Hexobion 100 20 St Dra N1	3.80 €	1	3.80	
Dexahexal 8mg/2ml 5x2 AMP N2	14.21 €	1	14.21	
Polyspectran 5g ASO N1	15.98 €	1	15.98	
Betaisodona Salbe 30g N1	5.07 €	1	5.07	39.06
Patient`s co-payment	5.00 €	3	15.00	-18.80
Patient`s co-payment	3.80 €	1	3.80	20.26

Digit / Medication	Points / €	Resource-use	Costs (€)	Sum (€)
4.3 Supportive (patient documentation)				
Orthomol immun Trinkfl 30 St	60.95 €	5	304.75	
Hexobion Vit B6 100mg 100 St	14.21 €	5	71.05	375.80
Patient`s co-payment	60.95 €	5	304.75	-309.75
Patient`s co-payment	5.00 €	1	5.00	66.05

Table D-35: CI 17, study period: 21.09.2007-21.03.2008

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
1. Oncologist fee				
13215	50	7	13.02	
01510	1420	8	422.59	
80112	205	1	7.63	
13492	905	1	33.67	
13500	540	2	40.18	
13502	540	2	40.18	
86503	25.56 €	2	51.12	
86505	255.65 €	2	511.30	1119.68
2. Diagnostics				
2.1 Laboratory parameter				
32068	0.25 €	9	2.25	
32058	0.25 €	9	2.25	
32065	0.25 €	9	2.25	
32057	0.25 €	9	2.25	
32082	0.25 €	9	2.25	
32066	0.25 €	9	2.25	
32460	5.40 €	9	48.60	
32071	0.25 €	9	2.25	
32069	0.25 €	9	2.25	
32070	0.25 €	9	2.25	
32081	0.25 €	9	2.25	
32075	0.25 €	9	2.25	
32083	0.25 €	9	2.25	
32056	0.25 €	9	2.25	
32072	0.40 €	9	3.60	
32064	0.25 €	9	2.25	
32324	4.90 €	9	44.10	
32392	9.20 €	9	82.80	
32120	0.50 €	9	4.50	
32248	1.40 €	1	1.40	216.50
2.2 MRT/CT/PET				
	0	0	0.00	0.00
2.3 Other				
33042	445	1	16.55	16.55
3. Administration				
01602	35	1	1.30	
90909	0	1	0.00	
32012	0	1	0.00	
01601	210	1	7.81	
40120	0.55 €	3	1.65	10.76
4. Drugs				

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
4.1 Antineoplastic				
Xeloda 500mg 120 St	534.55 €	6	3207.30	23335.06
Avastin 580mg 250ml NaCl	2.515.97 €	8	20127.76	-140.00
Patient`s co-payment	10.00 €	14	140.00	23195.06
4.2 Supportive				
Dexahexal 8mg/2ml 5x2 AMP N2	14.21 €	2	28.42	
Pantozol 40mg 60St TMR N3	79.55 €	1	79.55	
Omeprazol STADA 40mg 60St KMR N3	68.69 €	1	68.69	
Imodium 50St KAP N3	14.59 €	1	14.59	107.97
Patient`s co-payment	5.00 €	3	15.00	-22.96
Patient`s co-payment	7.96 €	1	7.96	85.01
4.3 Supportive (patient documentation)				
Equizym MCA	49.20 €	1	49.20	
Lachsöl Kapseln Omega 3 Fettsäuren 120 St	14.85 €	1	14.85	64.05
Patient`s co-payment	49.20 €	1	49.20	-64.05
Patient`s co-payment	14.85 €	1	14.85	0.00

Table D-36: CI 20, study period: 08.11.2007-08.05.2008

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
1. Oncologist fee				
13215	50	8	14.88	
01510	1420	3	158.47	
01511	2700	4	401.76	
02101	445	5	82.77	
02110	600	1	22.32	
02111	240	1	8.93	
13492	905	2	67.33	
13500	540	2	40.18	
13502	540	2	40.18	
86503	25.56 €	2	51.12	
86505	255.65 €	2	511.30	1399.23
2. Diagnostics				
2.1 Laboratory parameter				
32068	0.25 €	18	4.50	
32058	0.25 €	18	4.50	
32065	0.25 €	18	4.50	
32057	0.25 €	18	4.50	
32082	0.25 €	18	4.50	
32324	4.90 €	14	68.60	
32066	0.25 €	18	4.50	
32460	5.40 €	18	97.20	
32071	0.25 €	18	4.50	
32069	0.25 €	18	4.50	
32070	0.25 €	18	4.50	
32081	0.25 €	18	4.50	
32120	0.50 €	12	6.00	
32075	0.25 €	18	4.50	
32083	0.25 €	18	4.50	
32056	0.25 €	18	4.50	
32072	0.40 €	18	7.20	

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
32064	0.25 €	18	4.50	
32123	0.40 €	2	0.80	
32122	1.20 €	5	6.00	
32094	4.00 €	1	4.00	252.80
2.2 MRT/CT/PET				
/	0	0	0.00	0.00
2.3 Other				
33042	445	1	16.55	16.55
3. Administration				
01430	35	1	1.30	
01610	40	1	1.49	
01620	85	3	9.49	
01621	125	1	4.65	
01622	235	1	8.74	25.67
4. Drugs				
4.1 Antineoplastic				
Xeloda 500mg 120 St	534.55 €	4	2138.20	
Irinotecan 340mg in 250ml NaCl 0.9%	991.80 €	6	5950.80	
Folinsäure 800mg in 250ml NaCl 0.9%	441.99 €	6	2651.94	
5-FU 800mg in 250ml NaCl 0.9%	72.67 €	6	436.02	
5-FU 4500mg 46h Pumpe	192.03 €	6	1152.18	
Avastin 360mg in 250ml NaCl 0.9%	1.646.94 €	6	9881.64	22210.78
Patient`s co-payment	10.00 €	28	280.00	-323.62
Patient`s co-payment	7.27 €	6	43.62	21.887.16
4.2 Supportive				
Omeprazol 20mg 1A Pharma 60St KMR	31.25 €	5	156.25	
Erythrozytenkonzentrat	81.00 €	2	162.00	
Novaminsulfon Rat 500mg/ml 50ml Trp	13.60 €	1	13.60	
Prednisolon AL 20mg Tabl. 50St	15.98 €	2	31.96	
Movicol Beutel 50 St Pulver	34.86 €	2	69.72	
Spiro Comp Forte Rat 100/20 50St LTA	28.62 €	1	28.62	
Ondansetron STADA 8mg 5St Amp	79.80 €	2	159.60	
Dexahexal 8mg/2ml 5x2ml Amp	14.21 €	2	28.42	
Kalinor BTA 15St	7.59 €	1	7.59	657.76
Patient`s co-payment	5.00 €	9	45.00	-60.96
Patient`s co-payment	7.98 €	2	15.96	596.80
4.3 Supportive (patient documentation)				
MCP Hexal 100ml	12.27 €	1	12.27	
Imodium 10 St	11.41 €	1	11.41	
MAR Plus Pflegespray	5.15 €	1	5.15	23.68
Patient`s co-payment	5.00 €	2	10.00	-15.15
Patient`s co-payment	5.15 €	1	5.15	8.53

Table D-37: B 4, study period: 12.05.–31.07.2006

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
1. Oncologist fee				
08215	50	17	31.62	
08220	235	8	69.94	
01511	2700	4	401.76	
02343	725	3	80.90	

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
80112	205	1	7.63	
86503	25.56 €	1	25.56	
86505	255.65 €	1	255.65	
13500	540	1	20.09	
13502	540	1	20.09	913.23
2. Diagnostics				
2.1 Laboratory parameter				
32122	1.10 €	10	11.00	
32069	0.25 €	8	2.00	
32070	0.25 €	8	2.00	
32071	0.25 €	8	2.00	
32068	0.25 €	8	2.00	
32066	0.25 €	8	2.00	21.00
2.2 MRT/CT/PET				
	0	0	0.00	0.00
2.3 Other				
33041	465	4	69.19	69.19
3. Administration				
01430	35	5	6.51	
01600	110	1	4.09	
40120	0.55 €	1	0.55	11.15
4. Drugs				
4.1 Antineoplastic				
Xeloda 500 mg 120 FTA	534.55 €	2	1069.10	
Xeloda 150 mg 60 FTA	88.75 €	1	88.75	
Navelbine 55,2 mg in 250 ml NaCl	318.10 €	1	318.10	
Fareston Emra-Med 60 mg Tbl. 30 St.	55.07 €	1	55.07	
Avastin 6 mg/kg= 446,4 mg in 250 ml NaCl	2051.48 €	3	6154.44	
Patient`s co-payment	10.00 €	6	60.00	7685.46
Patient`s co-payment	8.88 €	1	8.88	-74.39
Patient`s co-payment	5.51 €	1	5.51	7.611.07
4.2 Supportive				
Zofran Zydis Lingual, 10St	113.67 €	1	113.67	
Pantozol 40mg, 30St	43.68 €	1	43.68	
Bondronat 6 mg in 250 ml NaCl	385.82 €	3	1157.46	
Kevatril 2mg, 5St	133.73 €	2	267.46	
Kevatril Amp. 1 mg 5 St.	100.59 €	1	100.59	
Neulasta 6 mg FS N1	1548.13 €	2	3096.26	
Oliclinomel 3,4% GF-E (1OP: 4x1500ml)	640,55	4	2562,20	
NaCl 0,9% Braun 20x10 ml	9,63	2	19,26	
Soluvit N 10AMP	155,07	2	310,14	
Vitalipid Adult 10AMP	112,63	2	225,26	
Addel N 20x 10ml	162,95	1	162,95	
Novalgin, Erw. Supp. 10St.	13,01	1	13,01	
NaCl 0,9% Braun 10x1000ml	17,11	2	34,22	
Sterofundin	15,14	2	30,28	8136.44
Patient`s co-payment	10,00	18	180,00	-210.00
Patient`s co-payment	5,00	6	30,00	7926.44
4.3 Supportive (patient documentation)				
Tromcardin forte, 100St	18.16 €	1	18.16	
Ibuprofen, 600mg 50St	13.80 €	1	13.80	
Pantozol, 40mg, 100St	128.42 €	1	128.42	160.38
Patient`s co-payment	5.00 €	2	10.00	-20.00

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
Patient`s co-payment	10.00 €	1	10.00	140.38

Table D-38: B 6, study period: 27.05.-27.11.2006

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
1. Oncologist fee				
08215	50	16	29.76	
08220	235	10	87.42	
01510	1420	3	158.47	
80112	205	2	15.25	
86503	25.56 €	2	51.12	
13500	540	2	40.18	
13502	540	2	40.18	
10215	50	1	1.86	
01511	2700	5	502.20	926.44
2. Diagnostics				
2.1 Laboratory parameter				
32122	1.10 €	9	9.90	
32069	0.25 €	9	2.25	
32071	0.25 €	9	2.25	
32068	0.25 €	9	2.25	
32070	0.25 €	9	2.25	
32066	0.25 €	9	2.25	21.15
2.2 MRT/CT/PET				
	0	0	0.00	0.00
2.3 Other				
32045	0.25 €	1	0.25	
32687	5.10 €	1	5.10	5.35
3. Administration				
01430	35	10	13.02	
01600	110	1	4.09	17.11
4. Drugs				
4.1 Antineoplastic				
Xeloda 150 mg Tbl. 60 St.	88.75 €	1	88.75	
Xeloda 500 mg Tbl. 120 St.	534.55 €	4	2138.20	
Ixoten 50 mg MTA 50 St.	325.36 €	7	2277.52	4415.72
Patient`s co-payment	8.88 €	1	8.88	-118.88
Patient`s co-payment	10.00 €	11	110.00	4.296.84
4.2 Supportive				
Zometa 4 mg in 250 ml NaCl	401.83 €	9	3616.47	
Neulasta 6 mg FS N1	1.548.13 €	4	6192.52	
Cosmofer 175 mg in 250 ml NaCl	141.00 €	5	705.00	
Tannolact Badezusatz 100 g	11.97 €	2	23.94	
Linola sept	5.85 €	3	17.55	
Hexobion 100 Drg 100 St.	14.21 €	1	14.21	
Cefasel 300 Tbl. 5x 20 St.	55.56 €	1	55.56	
Gabapentin 300mg, 50St	28.52 €	1	28.52	
Patient`s co-payment	10.00 €	18	180.00	10653.77
Patient`s co-payment	5.56 €	1	5.56	-215.56
Patient`s co-payment	5.00 €	6	30.00	10438.21
4.3 Supportive (patient documentation)				

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
Cefasel 300 Tbl. 5x 20 St.	55.56 €	1	55.56	
Orthomol immun, 30St, x4	223.80 €	1	223.80	279.36
Patient`s co-payment	223.80 €	1	223.80	-229.36
Patient`s co-payment	5.56 €	1	5.56	50.00

Table D-39: B 7, study period: 27.06.-27.12.2006

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
1. Oncologist fee				
271	16.09 €	9	144.81	
261	4.02 €	9	36.18	
250	4.20 €	7	29.40	
1	10.72 €	5	53.60	
60	16.09 €	1	16.09	
31	60.33 €	2	120.66	
Zusatz A	4.08 €	2	8.16	
297	6.03	1	6.03	
1103	24.08	1	24.08	439.01
2. Diagnostics				
2.1 Laboratory parameter				
3905	16.76 €	3	50.28	
3901	30.16 €	3	90.48	
3550	4.02 €	9	36.18	
3551	1.34 €	9	12.06	
3558	2.01 €	10	20.10	
3557	2.01 €	9	18.09	
3555	2.68 €	9	24.12	
3585	2.68 €	9	24.12	
3583	2.68 €	9	24.12	
3581	2.68 €	9	24.12	
3594	2.68 €	9	24.12	
3595	2.68 €	9	24.12	
3592	2.68 €	9	24.12	
3587	2.68 €	9	24.12	
3597	2.68 €	9	24.12	
3560	2.68 €	9	24.12	
3741	13.41 €	9	120.69	
4026	16.76 €	1	16.76	
4021	16.76 €	1	16.76	
4039	23.46 €	1	23.46	
4040	23.46 €	1	23.46	
4062	32.17 €	1	32.17	
3652	2.35 €	1	2.35	704.04
2.2 MRT/CT/PET:				
5700	461.64 €	1	461.64	461.64
2.3 Other:				
4851	13.64 €	1	13.64	
410	26.81 €	1	26.81	
420	10.72 €	3	32.16	
403	15.74 €	1	15.74	
11	8.04 €	1	8.04	

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
7	21.45 €	1	21.45	
401	23.31 €	1	23.31	
404	14.57 €	1	14.57	155.72
3. Administration:				
	0.00 €	0	0.00	0.00
4. Drugs				
4.1 Antineoplastic				
Xeloda 500 mg 120 FTA	534.55	9	4810.95	
Trastuzumab 680 mg in 250 ml NaCl	4019.59	1	4019.59	
Trastuzumab 510 mg in 250 ml NaCl	3229.08	6	19374.48	
Trastuzumab 504 mg in 250 ml NaCl	3229.08	1	3229.08	
Trastuzumab 495 mg in 250 ml NaCl	3229.08	1	3229.08	
Femara 100St	564.12	1	564.12	35772.82
Zoladex 3,6mg 3FS	545.52	1	545.52	-200.00
Patient`s co-payment	10.00 €	20	200.00	35572.82
4.2 Supportive				
Bondronat 6 mg in 500 ml NaCl 0.9%	386.16	9	3475.44	
NaCl0.9% 250mlx10	23.40	1	23.40	3498.84
Patient`s co-payment	5.00 €	1	5.00	-95.00
Patient`s co-payment	10.00 €	9	90.00	3403.84
4.3 Supportive (patient documentation)				
Pantozol 40mg, 60St	79.55	4	318.20	
Neuro ratio 100mg, 100St	12.85	2	25.70	343.90
Patient`s co-payment	5.00 €	2	10.00	-41.84
Patient`s co-payment	7.96 €	2	31.84	302.06

Table D -40: B 8, study period: 07.06.-12.09.2006

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
1. Oncologist fee				
08220	235	7	61.19	
01311	175	1	6.51	67.70
2. Diagnostics				
2.1 Laboratory parameter				
32122	1.10 €	1	1.10	
32058	0.25 €	1	0.25	
32064	0.25 €	1	0.25	
32065	0.25 €	3	0.75	
32066	0.25 €	1	0.25	
32069	0.25 €	1	0.25	
32070	0.25 €	1	0.25	
32071	0.25 €	1	0.25	
32435	6.90 €	1	6.90	
32083	0.25 €	3	0.75	
32081	0.25 €	3	0.75	
32082	0.25 €	3	0.75	
32068	0.25 €	1	0.25	
32120	0.50 €	1	0.50	13.25
2.2 MRT/CT/PET				
/	0		0.00	0.00
2.3 Other				

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
33040	360	1	13.39	
34231	400	1	14.88	28.27
3. Administration				
01601	210	1	7.81	
40120	0.55 €	1	0.55	8.36
4. Drugs				
4.1 Antineoplastic				
Xeloda 500 mg 120 FTA	534.55 €	2	1069.10	1069.10
				-20.00
Patient`s co-payment	10.00 €	2	20.00	1049.10
4.2 Supportive				
Kevatril 2mg TAB	133.73 €	1	133.73	
Vomex A 150mg 10 SUPP	8.95 €	1	8.95	
Riopan Gel 10St	7.69 €	1	7.69	
Capval Dragees	12.50 €	1	12.50	
Bondronat 6mg 250ml NaCl	385.82 €	3	1157.46	
Patient`s co-payment	4.57 €	1	4.57	1320.33
Patient`s co-payment	10.00 €	4	40.00	-54.57
Patient`s co-payment	5.00 €	2	10.00	1265.76
4.3 Supportive (patient documentation)				
Pantozol, 40mg, 60St	79.55 €	2	159.10	
Vomex A 150mg 10 SUPP	8.95 €	1	8.95	
Imbun retard 800mg 100St	30.37 €	1	30.37	
Novaminsulfon-ratio 500mg 50St	14.80 €	1	14.80	
Neuro-ratiopharm 50St	9.25 €	1	9.25	
Patient`s co-payment	15.00 €	1	15.00	222.47
Patient`s co-payment	5.00 €	3	15.00	-45.92
Patient`s co-payment	7.96 €	2	15.92	176.55

Table D-41: B 10, study period: 02.08.-02.11.2006

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
1. Oncologist fee				
80111	175	1	6.51	
13500	540	1	20.09	
86503	25.56 €	1	25.56	
13215	50	2	3.72	
13220	235	1	8.74	64.62
2. Diagnostics				
2.1 Laboratory parameter				
32120	0.50 €	1	0.50	
32066	0.25 €	1	0.25	
32064	0.25 €	1	0.25	
32057	0.25 €	1	0.25	
32071	0.25 €	1	0.25	
32068	0.25 €	1	0.25	
32075	0.25 €	1	0.25	
32324	4.90 €	1	4.90	
32391	8.20 €	1	8.20	15.10
2.2 MRT/CT/PET				
34330	1865	1	69.38	69.38

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
2.3 Other				
	0	0	0.00	0.00
3. Administration				
01601	210	1	7.81	
40120	0.55 €	1	0.55	8.36
4. Drugs				
4.1 Antineoplastic				
Xeloda 500 mg FTA 120 St.	534.55	2	1069.10	1069.10
Patient`s co-payment	10.00 €	2	20.00	-20.00
				1.049.10 €
4.2 Supportive				
Prednisolon 50 mg Tbl. 50 St.	29.99	1	29.99	41.84
Lorazepam ratio 1 mg Tbl. 20 St.	11.85	1	11.85	-10.00
Patient`s co-payment	5.00	2	10.00	31.84
4.3 Supportive (patient documentation)				
Nobilin Plus Kps., 4x60St	15.40	1	15.40	
Nobilin Lyco Kps., 4x60St	68.88	1	68.88	
Nobilin Q10 Multivitamin, 240St	73.90	1	73.90	
Patient`s co-payment	15.40	1	15.40	158.18
Patient`s co-payment	68.88	1	68.88	-158.18
Patient`s co-payment	73.90	1	73.90	0.00

Table D-42: B 11, study period: 11.07.2006-11.01.2007

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
1. Oncologist fee				
13215	50	20	37.20	
13220	235	4	34.97	
02100	160	3	17.86	
02101	445	13	215.20	
01312	205	1	7.63	
01510	1420	4	211.30	524.15
2. Diagnostics				
2.1 Laboratory parameter				
32120	0.50 €	17	8.50	
32066	0.25 €	7	1.75	
32064	0.25 €	1	0.25	
32068	0.25 €	2	0.50	
32069	0.25 €	1	0.25	
32071	0.25 €	5	1.25	
32058	0.25 €	1	0.25	
32083	0.25 €	7	1.75	
32081	0.25 €	7	1.75	
320	0.40 €	1	0.40	
32070	0.25 €	4	1.00	
32075	0.25 €	4	1.00	
32324	4.90 €	4	19.60	
32391	8.20 €	8	65.60	
32112	0.60 €	4	2.40	
32113	0.60 €	4	2.40	
32110	0.75 €	3	2.25	
32065	0.25 €	1	0.25	

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
32082	0.25 €	2	0.50	
32460	5.40 €	1	5.40	
32122	1.10 €	1	1.10	118.15
2.2 MRT/CT/PET				
34330	1865	1	69.38	
34341	2315	1	86.12	
34345	645	1	23.99	179.49
2.3 Other				
32760	4.10 €	4	16.40	
32722	7.70 €	3	23.10	
32749	12.80 €	1	12.80	
32750	2.60 €	9	23.40	75.70
3. Administration				
01600	110	2	8.18	
01601	210	3	23.44	
40120	0.55 €	1	0.55	
01430	35.00	10	13.02	45.19
4. Drugs				
4.1 Antineoplastic				
Xeloda 500 mg 120 FTA	534.55 €	4	2138.20	3861.24
Epirubicin 20mg in 250ml Glu 5%	156.64 €	11	1723.04	-150.00
Patient`s co-payment	10.00 €	15	150.00	3711.24
4.2 Supportive				
Bondronat 6 mg in 250 ml NaCl	385.82	8	3086.56	3086.56
Patient`s co-payment	10.00	8	80.00	-80.00
				3006.56
4.3 Supportive (patient documentation)				
Hexobion 100mg 100St	14.21	2	28.42	
Pantozol, 40mg, 30St	43.68	2	87.36	
Pantozol, 40mg, 60St	79.55	1	79.55	
MCP AL TRO	12.25	1	12.25	
Vomex A, 50mg, N1	6.40	2	12.80	
Perenterol 50mg	32.82	1	32.82	
Kalinor N3	45.59	1	45.59	
Imbun 800mg retard, N2	20.56	1	20.56	
Omeprazol STADA, 40mg, 60St	68.69	1	68.69	
Imodium (Janssen-cilag), 2mg, 50St	16.60	1	16.60	
Diclofenac 100 retard, 50St	13.17	1	13.17	
Kalinor Brause 30St	15.20	1	15.20	
Patient`s co-payment	10.00	2	20.00	
Patient`s co-payment	7.96	1	7.96	433.01
Patient`s co-payment	5.00	7	35.00	-72.40
Patient`s co-payment	9.44	1	9.44	360.61

Table D-433: B 12, study perspective: 27.09.2006-27.03.2007

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
1. Oncologist fee				
08220	235	9	78.68	
02101	445	9	148.99	
01311	175	1	6.51	234.17
2. Diagnostics				

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
2.1 Laboratory parameter				
32122	1.10 €	7	7.70	
32058	0.25 €	4	1.00	
32066	0.25 €	4	1.00	
32065	0.25 €	4	1.00	
32069	0.25 €	4	1.00	
32070	0.25 €	4	1.00	
32071	0.25 €	4	1.00	
32075	0.25 €	3	0.75	
32083	0.25 €	3	0.75	
32081	0.25 €	3	0.75	
32082	0.25 €	3	0.75	
32068	0.25 €	4	1.00	
32120	0.50 €	2	1.00	18.70
2.2 MRT/CT/PET				
	0	0	0.00	0.00
2.3 Other				
	0	0	0.00	0.00
3. Administration				
01601	210	3	23.44	
40120	0.55 €	3	1.65	25.09
4. Drugs				
4.1 Antineoplastic				
Xeloda 500 mg 120 FTA	534.55 €	3	1603.65	
Paclitaxel 105,9 mg	862.10 €	3	2586.30	
Paclitaxel 108 mg	862.10 €	1	862.10	
Paclitaxel 109 mg	862.10 €	1	862.10	
Paclitaxel 81,5 mg	677.66 €	1	677.66	
Paclitaxel 64,4 mg	677.66 €	1	677.66	
Paclitaxel 54,67 mg	677.66 €	1	677.66	
Paclitaxel 54,34 mg	677.66 €	1	677.66	9725.79
Bondronat 50 mg 84 Stück	1.101.00 €	1	1101.00	-140.00
Patient`s co-payment	10.00 €	14	140.00	9.585.79
4.2 Supportive				
Kevatril 1 mg in 100 ml NaCl	69.91 €	9	629.19	
Dexamethason 4 mg in 100 ml NaCl	52.08 €	9	468.72	
Aranesp 150 1 Amp. s.c.	486.53 €	3	1459.59	
Aranesp 300 1 Amp. s.c.	856.50 €	1	856.50	
Ferro sanol duodenal Kps. N3	26.58 €	1	26.58	
Bepanthen Salbe 100 g	10.02 €	1	10.02	
Sic-ophthal Trpf. N1	4.26 €	1	4.26	
Mundspüllösung	1.71 €	1	1.71	
Pantozol 40 N1	26.24 €	1	26.24	
Tavegil 5AMP	11.50 €	2	23.00	
Ranitidin 50mg 5AMP	14.48 €	2	28.96	
NaCl0.9% 250ml x10	23.40 €	1	23.40	
NaCl0.9% 10ml x20	10.22 €	1	10.22	
Heparin Calcium 7500 10 FS	25.50 €	1	25.50	
Patient`s co-payment	6.99 €	9	62.91	
Patient`s co-payment	5.21 €	9	46.89	
Patient`s co-payment	10.00 €	4	40.00	
Patient`s co-payment	5.00 €	7	35.00	
Patient`s co-payment	10.02 €	1	10.02	3593.89
Patient`s co-payment	4.05 €	1	4.05	-200.58

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
Patient`s co-payment	1.71 €	1	1.71	3393.31
4.3 Supportive (patient documentation)				
Pantozol, 40mg, 60St	79.55 €	2	159.10	
MCP-Tropfen, 100ml	12.25 €	1	12.25	
Juice plus, KAP	29.40 €	1	29.40	
Ferro sanol duodenal, 100St	26.58 €	1	26.58	
Unacid PD oral, 10St	28.73 €	1	28.73	
Ciprofloxacin, 500mg, 10St	16.68 €	1	16.68	
Patient`s co-payment	5.92 €	1	5.92	272.74
Patient`s co-payment	5.00 €	6	30.00	-65.32
Patient`s co-payment	29.40 €	1	29.40	207.42

Table D-44: C 7, study period: 24.07.2006-24.01.2007

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
1. Oncologist fee				
13215	50	6	11.16	
86503	25.56 €	2	51.12	
13500	500	1	18.60	
80112	205	2	15.25	96.13
2. Diagnostics				
2.1 Laboratory parameter				
32122	1.20 €	7	8.40	
32123	0.40 €	7	2.80	
32083	0.25 €	7	1.75	
32081	0.25 €	7	1.75	
32084	0.25 €	7	1.75	
32067	0.40 €	7	2.80	
32064	0.25 €	7	1.75	
32058	0.25 €	7	1.75	
32069	0.25 €	7	1.75	
32070	0.25 €	7	1.75	
32071	0.25 €	7	1.75	
32068	0.25 €	7	1.75	
32075	0.25 €	7	1.75	
32057	0.25 €	7	1.75	
32460	5.40 €	7	37.80	
32324	4.90 €	7	34.30	
32392	9.20 €	7	64.40	169.75
2.2 MRT/CT/PET				
34330	1865	1	69.38	69.38
2.3 Other				
34241	430	1	16.00	
33042	445	1	16.55	32.55
3. Administration				
01601	210	3	23.44	23.44
4. Drugs				
4.1 Antineoplastic				
Xeloda 500 FTA 120 St.	534.55 €	9	4810.95	4810.95
Patient`s co-payment	10.00 €	9	90.00	-90.00
				4720.95
4.2 Supportive				
Hexobion, 3x1, 100St	14.21 €	1	14.21	14.21

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
Patient`s co-payment	5.00 €	1	5.00	-5.00
				9.21
4.3 Supportive (patient documentation)				
Hexobion, 3x1, 100St	14.21	3	42.63	42.63
Patient`s co-payment	5.00 €	3	15.00	-15.00
				27.63

Table D-45: C 8, study period: 03.08.2006-03.02.2007

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
1. Oncologist fee				
13215	50	12	22.32	
02101	445	9	148.99	
01311	175	1	6.51	
13220	235	2	17.48	195.30
2. Diagnostics				
2.1 Laboratory parameter				
32120	0.50 €	13	6.50	
32066	0.25 €	1	0.25	
32070	0.25 €	1	0.25	
32071	0.25 €	1	0.25	
32075	0.25 €	1	0.25	
32324	4.90 €	1	4.90	
32395	19.90 €	1	19.90	32.30
2.2 MRT/CT/PET				
34330	1865	1	69.38	
34341	2315	2	172.24	
34345	545	1	20.27	261.89
2.3 Other				
	0	0	0.00	0.00
3. Administration				
	0	0	0.00	0.00
4. Drugs				
4.1 Antineoplastic				
Xeloda 500 mg 120 FTA	534.55 €	2	1069.10	
Oxaliplatin 100mg 500ml Glu 5%	700.19 €	4	2800.76	
Campto (Irinotecan) 250mg 500ml NaCl	865.68 €	4	3462.72	
5-FU 5200 mg in 240ml NaCl	91.53 €	4	366.12	
Avastin (Bevacizumab) 450mg 250ml NaCl	2.051.48 €	3	6154.44	
Oncofolic (Folinsäure) 1000mg 500ml NaCl	581.86 €	4	2327.44	16180.58
Patient`s co-payment	10.00 €	14	140.00	-167.45
Patient`s co-payment	9.15 €	3	27.45	16013.13
4.2 Supportive				
Zofran 8 mg 1 Amp. in 250 ml NaCl	71.37 €	4	285.48	
Zofran TAB 8mg, 10St	174.86 €	1	174.86	
Zofran 8mg 5AMP	108.74 €	1	108.74	
Calcium Braun 10, 20 Amp	10.40 €	1	10.40	
Magnesium Sulfat 10% , 5 Amp	7.08 €	2	14.16	
Imodium, 2mg, 20St	12.91 €	1	12.91	
MCP ratio 100ml	13.48 €	1	13.48	
Vomex A Dragees	6.40 €	1	6.40	
Zantic 5x5ml	15.93 €	1	15.93	

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
Tavegil 5AMP	11.50 €	1	11.50	
Buscopan 5x10ml Inj-Lsg	25.78 €	3	77.34	
Heparin 7500 10FS	25.50 €	1	25.50	
Pantozol, 40mg, 100St	128.42 €	2	256.84	
Patient`s co-payment	7.13 €	4	28.52	
Patient`s co-payment	39.15 €	1	39.15	1013.54
Patient`s co-payment	10.00 €	4	40.00	-167.67
Patient`s co-payment	5.00 €	12	60.00	845.87
4.3 Supportive (patient documentation)				
	0.00 €	0	0.00	0.00

Table D-46: C 10, study period: 25.08.-24.10.2006

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
1. Oncologist fee				
86503	25.56 €	1	25.56	
13500	500	1	18.60	
80112	205	1	7.63	51.79
2. Diagnostics				
2.1 Laboratory parameter				
32120	0.50 €	1	0.50	0.50
2.2 MRT/CT/PET				
34440	3430	1	127.60	127.60
2.3 Other				
01741	4325	1	160.89	160.89
3. Administration				
01601	210	2	15.62	15.62
4. Drugs				
4.1 Antineoplastic				
Xeloda 500 mg Tbl. 120 St.	534.55 €	1	534.55	534.55
Patient`s co-payment	10.00 €	1	10.00	-10.00
				524.55
4.2 Supportive				
Movicol Btl. N3	34.86 €	1	34.86	
Adumbran Tbl. N1 (Oxazepam)	10.40 €	1	10.40	
Metamizol, 100ml	16.71 €	1	16.71	
Pantozol, 40mg, 60St	79.55 €	1	79.55	
Iberogast, 50ml	16.70 €	1	16.70	158.22
Patient`s co-payment	5.00 €	4	20.00	-27.96
Patient`s co-payment	7.96 €	1	7.96	130.26
4.3 Supportive (patient documentation)				
	0.00 €	0	0.00	0.00

Table D-47: C 14, study period: 21.11.2006-21.05.2007

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
1. Oncologist fee				
13215	50	6	11.16	
01511	2700	1	100.44	
80112	205	2	15.25	

Digit / Medication	Points / €	Resource use	Costs (€)	Sum (€)
13500	540	2	40.18	
13502	540	2	40.18	
86503	25.56 €	2	51.12	
86505	255.56 €	2	511.12	
01510	1420	7	369.77	1139.21
2. Diagnostics				
2.1 Laboratory parameter				
32120	0.50 €	9	4.50	
32068	0.25 €	8	2.00	
32058	0.25 €	8	2.00	
32066	0.25 €	8	2.00	
32065	0.25 €	8	2.00	
32069	0.25 €	8	2.00	
32070	0.25 €	8	2.00	
32071	0.25 €	8	2.00	
32075	0.25 €	8	2.00	
32083	0.25 €	8	2.00	
32081	0.25 €	8	2.00	
32057	0.25 €	8	2.00	
32082	0.25 €	8	2.00	
32392	9.20 €	7	64.40	
32324	4.90 €	7	34.30	
32460	5.40 €	8	43.20	
32056	0.25 €	8	2.00	
32072	0.40 €	8	3.20	
32064	0.25 €	8	2.00	
32103	0.60 €	3	1.80	
32104	0.60 €	3	1.80	
32105	0.60 €	3	1.80	
32426	4.60 €	1	4.60	187.60
2.2 MRT/CT/PET				
	0	0	0.00	0.00
2.3 Other				
33042	445	1	16.55	16.55
3. Administration				
01601	210	2	15.62	
40120	0.55 €	2	1.10	16.72
4. Drugs				
4.1 Antineoplastic				
Xeloda 500 mg 120 FTA N3	534.55 €	6	3207.30	
Avastin 325 mg in 250 ml NaCl	1.631.95 €	3	4895.85	20412.03
Avastin 490 mg in 250 ml NaCl	2.051.48 €	6	12308.88	-150.00
Patient`s co-payment	10.00 €	15	150.00	20262.03
4.2 Supportive				
DexaHexal 8 mg/2 ml 5 Amp. N2	14.21 €	2	28.42	103.39
MCP AL Tropfen, 30ml, x3	10.78 €	3	32.34	-40.00
Novalgin Tropfen, 50ml, x3	14.21 €	3	42.63	63.39
Patient`s co-payment	5.00 €	8	40.00	
4.3 Supportive (patient documentation)				
	0.00 €	0	0.00	0.00