

Noémi Vártokné Hevér

**Economic evaluation of health technologies
in chronic conditions:
Challenges and opportunities for Hungary**

Department of Health Economics

Supervisor:

Márta Péntek Ph.D.

© Noémi Vártokné Hevér

CORVINUS UNIVERSITY OF BUDAPEST
Management and Business Administration
Doctoral School

Noémi Vártokné Hevér

**Economic evaluation of health technologies in chronic
conditions:**

Challenges and opportunities for Hungary

Ph.D. Dissertation

Budapest, 2014

Table of contents

I. INTRODUCTION	9
I.1. THE SCOPE OF THE DISSERTATION	9
I.2. BACKGROUND	11
<i>I.2.1. The challenge of health care financing</i>	<i>12</i>
<i>I.2.2. Three “crutches” for the easier interpretability of correspondence across the research topics of the dissertation</i>	<i>14</i>
I.2.3.1. Health technology	14
I.2.3.2. Quality-adjusted life-year (QALY)	16
I.2.3.3. Cost-effectiveness analysis (Cost-utility analysis)	17
I.3. RELEVANCE OF THE RESEARCH TOPICS	18
<i>I.3.1. The German approach to cost-effectiveness analysis in health care</i>	<i>18</i>
<i>I.3.2. Transferability of health economic evaluations in the European Union: challenges for Hungary</i>	<i>20</i>
<i>I.3.3. Challenges in the assessment of disease burden: case study in a chronic disease</i>	<i>21</i>
I.4. CORRESPONDING POINTS ACROSS THE THREE RESEARCH TOPICS	23
I.5. METHODOLOGY	24
I.6. THE RESEARCH QUESTIONS OF THE DISSERTATION	25
I.7. THE OUTLINE OF THE DISSERTATION	27
II. THE GERMAN APPROACH TO COST-EFFECTIVENESS ANALYSIS IN HEALTH CARE	29
II.1. BACKGROUND	29
II.2. LITERATURE SEARCH	30
II.3. HTA IN GERMANY	31
II.4. GERMAN HTA ORGANIZATIONS	33
II.4.1. DAHTA (DIMDI); HTA PROCESS	33
<i>II.4.2. IQWiG; HTA process</i>	<i>36</i>
II.4.2.1. Transferability of experiences and results	37
II.4.2.2. Quality of HTA	38
II.4.2.3. The efficiency frontier approach related to IQWiG	42
II.4.2.4. Often debated methodological issues of IQWiG	45
<i>II.4.3. Transparency of assessments</i>	<i>47</i>
II.5. HEALTH ECONOMICS (HE) AND HTA IN CENTRAL EASTERN EUROPEAN COUNTRIES	47
<i>II.5.1. HTA in Hungary</i>	<i>48</i>
II.6. LESSONS TO LEARN FROM GERMANY	49
II.7. CONCLUSIONS	50

III. TRANSFERABILITY OF HEALTH ECONOMIC EVALUATIONS IN THE EUROPEAN UNION: CHALLENGES FOR HUNGARY..... 53

III.1. BACKGROUND: RHEUMATOID ARTHRITIS AS A CHRONIC CONDITION	55
III.2. BIOLOGICAL THERAPIES FOR THE TREATMENT OF RA – SYSTEMATIC REVIEW OF THE HEALTH ECONOMIC LITERATURE COST-UTILITY OF BIOLOGIC DRUGS IN RHEUMATOID ARTHRITIS: SYSTEMATIC LITERATURE REVIEW AND ANALYSIS OF THE EVIDENCES	57
<i>III.2.1. Literature search</i>	57
<i>III.2.2. Results</i>	58
III.2.2.1. Systematic review by Velde et al. (2011)	59
III.2.2.2. Analysis of the articles revealed by the additional search	62
III.2.2.3. Summary of the main findings of the new literature search	80
III.2.2.4. Potentially useful articles with English abstract	82
III. 4 DISCUSSION, CONCLUSIONS	83

IV. CHALLENGES IN THE ASSESSMENT OF DISEASE BURDEN: CASE STUDY IN A CHRONIC DISEASE..... 88

IV.1. A BRIEF OVERVIEW ABOUT THE DISEASE OF BLADDER CANCER AND THERAPEUTIC GUIDELINES ...	89
IV.2. LITERATURE REVIEW	90
<i>IV.2.1. Review of the international literature</i>	91
IV.2.1.1. HRQoL of patients with BC	91
IV.2.1.2. The summary of studies about HRQoL of patients with BC – EQ-5D	91
IV.2.1.3. The summary of studies about HRQoL of patients with BC – SF-36	93
IV.2.1.4. HRQoL of patients with BC – SF-6D	102
IV.2.1.5. The summary of studies about HRQoL of patients with BC – FACT-BI	102
IV.2.1.6. BCI validation	108
IV.2.1.7. Cost of illness of patients with BC	110
<i>IV.2.2. Review of the Hungarian literature</i>	115
IV.3. THE EMPIRICAL STUDY – ELABORATION 1.	116
<i>IV.3.1. Background</i>	116
IV.3.2. MATERIAL AND METHODS	117
IV.3.2.1. Study design and patients	117
IV.3.2.2. Questionnaire survey and health related quality of life assessment	117
IV.3.2.3. The Bladder Cancer Index (BCI) questionnaire	118
IV.3.2.4. Translation of the BCI questionnaire into Hungarian	118
IV.3.2.5. Statistics and psychometric testing of the Hungarian BCI	119
<i>IV.3.3. Results</i>	120
IV.3.3.1. Patient characteristics and BC histology	120
IV.3.3.2. Health related quality of life of the BC patients	120
IV.3.3.3. Relationship between FACT-BI, SF-36, SF-6D and EQ-5D	123
IV.3.3.4. Psychometric results of the Hungarian BCI	124
IV.3.4. DISCUSSION	127
IV.4. THE EMPIRICAL STUDY – ELABORATION 2.	131

IV.4.1. <i>Epidemiology of BC</i>	132
IV.4.2. <i>Assessment of resource utilisations and costing</i>	134
IV.4.2.1. Direct medical costs.....	134
IV.4.2.2. Direct non-medical costs.....	135
IV.4.2.3. Indirect costs.....	137
IV.4.3. <i>Cost of illness in bladder cancer</i>	137
IV.4.3.1. Medicines within the category of direct costs.....	137
IV.4.3.2. Direct-non-medical costs.....	142
IV.4.3.3. Indirects costs.....	143
IV.5. CONCLUSIONS.....	143
V. SUMMARY AND CONTRIBUTIONS TO THE FIELD.....	144
VI. REFERENCES.....	150
VII. APPENDIX.....	169
VII.1. METHOTREXATE NAIVE EARLY RA PATIENTS – SUMMARY OF COST-UTILITY EVIDENCE IDENTIFIED.....	169
VII.2. RA PATIENTS WHO FAILED AT LEAST ONE SYNTHETIC DMARD THERAPY - SUMMARY OF COST-UTILITY EVIDENCE IDENTIFIED.....	175
VII.3. RA PATIENTS WHO FAILED AT LEAST ONE BIOLOGIC DMARD THERAPY - SUMMARY OF COST-UTILITY EVIDENCE IDENTIFIED.....	184
VII.4. DMARD NAIVE RA PATIENTS – QUALITY ASSESSMENT OF THE HEALTH ECONOMIC EVALUATIONS BY THE DRUMMOND CHECKLIST.....	194
VII.5. RA PATIENTS WHO FAILED AT LEAST ONE SYNTHETIC DMARD - QUALITY ASSESSMENT OF THE HEALTH ECONOMIC EVALUATIONS BY THE DRUMMOND CHECKLIST.....	202
VII.6. RA PATIENTS WHO FAILED AT LEAST ONE BIOLOGIC DMARD - QUALITY ASSESSMENT OF THE HEALTH ECONOMIC EVALUATIONS BY THE DRUMMOND CHECKLIST.....	213
VII.7. CLINICAL MANIFESTATIONS, EPIDEMIOLOGY AND MEASURES IN ADULT CROHN’S DISEASE. IN: PETRA BAJI: SYSTEMATIC REVIEW AND ANALYSIS OF EVIDENCES ON CLINICAL EFFICACY AND COST-EFFECTIVENESS OF BIOLOGICAL DRUGS FOR THE TREATMENT OF ADULT CROHN’S DISEASE. ISBN: 978-963-503-558-8, PP.1-12.....	223
VII.8. BIOLOGICALS FOR ADULT CROHN’ DISEASE – SYSTEMATIC REVIEW OF THE HEALTH ECONOMIC LITERATURE. IN: PETRA BAJI: SYSTEMATIC REVIEW AND ANALYSIS OF EVIDENCES ON CLINICAL EFFICACY AND COST-EFFECTIVENESS OF BIOLOGICAL DRUGS FOR THE TREATMENT OF ADULT CROHN’S DISEASE. ISBN: 978-963-503-558-8, PP.....	235
VII.9. THE ORIGINAL (ENGLISH) VERSION OF BLADDER CANCER INDEX (BCI).....	274
VII.10. THE HUNGARIAN VERSION OF THE BCI.....	281

List of Tables

TABLE 1 HEALTH CARE EXPENDITURES AS PERCENTAGE OF GDP	13
TABLE 2 HEALTH TECHNOLOGIES ACCORDING TO THEIR PHYSICAL NATURE	15
TABLE 3 HEALTH TECHNOLOGIES ACCORDING TO THEIR HEALTH CARE PURPOSE.....	16
TABLE 4 CURRENT TOPICS OF HTA IN GERMANY; 2012-2013.....	36
TABLE 5 HEALTH RELATED QUALITY OF LIFE OF PATIENTS WITH BLADDER CANCER	122
TABLE 6 COMPARISON BY TREATMENT SUBGROUPS	123
TABLE 7 CORRELATIONS BETWEEN THE DISEASE-SPECIFIC FACT-BL AND GENERIC HEALTH STATE MEASURES	124
TABLE 8 DOMAIN SPECIFIC SUMMARY AND SUBSCALE CHARACTERISTICS OF THE HUNGARIAN BCI QUESTIONNAIRE	125
TABLE 9 INTERSCALE CORRELATIONS BETWEEN BCI FUNCTION AND BOTHER SUBSCALES AND OTHER HEALTH RELATED QUALITY OF LIFE SCORES	126
TABLE 10 THE TRADE OF MEDICINES FOR INTRAVESICAL INSTILLATION SUPPORTED IN 100% BY THE NATIONAL HEALTH INSURANCE FUND IN LOW AND MEDIUM RISK CASES OF BC (2012).....	139
TABLE 11 THE TRADE OF MEDICINES FOR INTRAVESICAL INSTILLATION SUPPORTED IN 100% BY THE NATIONAL HEALTH INSURANCE FUND IN HIGH RISK CASES OF BC (2012).....	141
TABLE 12 AVERAGE DIRECT NON-MEDICAL COSTS PER PATIENT (2012).....	142

List of Figures

FIGURE 1 LEGAL FRAMEWORK AND ASSIGNMENT OF TASKS	32
FIGURE 2 THE HTA PROCESS AT DAHTA (DIMDI).....	34
FIGURE 3 PRODUCTION PROCESS FOR AN IQWiG ASSESSMENT	41
FIGURE 4 THE EFFICIENCY FRONTIER	44
FIGURE 5 EXPENDITURES OF THE DRUG BUDGET OF THE NATIONAL HEALTH INSURANCE FUND ADMINISTRATION (NHIFA) BETWEEN 2002 AND 2012	48
FIGURE 6 THE NUMBER OF NEW PATIENTS DIAGNOSED WITH BC (ICD C67) FROM 2001 TO 2011 ACCORDING TO THE DATA OF NATIONAL CANCER REGISTRY	133
FIGURE 7 INCIDENCE OF BC ACCORDING TO AGE GROUPS IN HUNGARY (2011).....	134

List of abbreviations

ABA: abatacept

ADA: adalimumab

BC: bladder cancer

BK-IC: Bricker's ileal conduit

BPT: bladder preservation therapy

CCD: continent cutaneous diversion

CEE: Central and Eastern Europe, Central and Eastern European

CoI: cost of illness

CR: continent reservoir

CTZ: certolizumab pegol

CUS: cutaneous ureterostomy

DDD: Daily defined dose

DMARD: disease-modifying antirheumatic drug

DOT: Days of treatment

EMA: European Medicines Agency

ETA: etanercept

EQ-5D – a generic health state measure (questionnaire)

EQ VAS – EQ Visual Analogue Scale

FACT-BI – Functional Assessment of Cancer Therapy for patients with bladder cancer

FFbH: Funktionsfragebogen Hannover

HAQ: Health Assessment Questionnaire

HAQ-DI: Health Assessment Questionnaire Disability Index

HE: Health Economics

HRQoL: health related quality of life

HTA: health technology assessment

GC: glucocorticoids

GOL: golimumab

IC: ileal conduit

ICD: International Classification of Diseases

ICUD: ileal conduit urinary diversion

INB: ileal neobladder

INBG: ileal neobladder group

INF: infliximab

LEF: leflunomide

LOS: length of stay

MoH: Ministry of Health

MTX: methotrexate

NHIFA: National Health Insurance Fund Administration

NMIBC: non-muscle-invasive bladder cancer

MIBC: muscle-invasive bladder cancer

NB: neobladder

NSAID: non-steroidal anti-inflammatory drug

OBS: orthotopic bladder substitution

OC: open radical cystectomy

OHTA: Office of Health Technology Assessment

ONB: orthotopic neobladder

QALY: quality-adjusted life-year

RA: rheumatoid arthritis

RARC: robot-assisted radical cystectomy

RC: radical cystectomy

RCT: randomized controlled trial

RTX: rituximab

SF-36: Short-Form-36 Health Survey

SF-6D: Short-Form-6D (health state utility measure derived from the SF-36)

SNBG: sigmoid neobladder group

TAHD: Technology Appraisal Head Department

TOC: tocilizumab

TS: Transparency Secretariat

TUR: transurethral resection

UUC: uretero-ureterocutaneostomy

I am most grateful to Péntek Márta, my Ph.D. thesis supervisor, not only for her professional support but conscientious mentoring and encouragement as well. I am indebted to my colleagues, László Gulácsi, Valentin Brodszky and Petra Baji for their constructive recommendations and insightful comments. I appreciate the friendly advice from my Ph.D. fellows, Ági, Bálint, Fanni, Irén, Mahshid and Orsolya. I am grateful to György Jenei for his support during my PhD studies. I would like to express my gratitude to Ágnes Zsóka, the program director of the Doctoral School, for her professional guidance and always helpful attitude.

I would like to thank my husband, Csaba Vártok, not only for his continuous assistance, but also for his endless love, kindness and support which has taken me to finalize this dissertation. I am grateful to our small daughter, Lelle, for her patience and smiles. Furthermore I would also like to thank my parents and grandparents for their love and endless support which has made possible to complete this work by now.

I. INTRODUCTION

I.1. The scope of the dissertation

The dissertation elaborates three autonomous research questions in the field of health economics.

First, the German approach to cost-effectiveness analysis in health care is introduced and analysed. The development of medical technologies has contributed to the growth of health care expenditures as a global tendency. Due to the scarcity of resources, health technologies like drugs, devices or medical interventions should not be reimbursed anymore solely according to the accessible benefit but economic considerations have become compelling in order to control cost rises. Accordingly, the criterion of cost-effectiveness has become crucial in reimbursement decisions in most of the countries of the European Union. For the evaluation of new drugs, the available ones are compared in terms of incremental costs and incremental benefits (quality-adjusted life-years, QALYs). In Germany, cost-effectiveness is interpreted in a distinct way, consequently, the approach to cost-effectiveness analysis differs to some extent from other European countries' practice.

Second, a systematic review and analysis of the available evidences are provided regarding the cost-effectiveness of biological drugs in a chronic rheumatic disease. Biological drugs revolutionized the treatment of numerous chronic conditions both in the field of rheumatology and oncology due to their high effectiveness. However, biologicals are costly drugs and their reimbursement is challenging even for economically developed countries. The introduction and continuous development of biologicals speeded up and extended health economic research worldwide.. The key questions in this rapidly evolving context are whether cost-effectiveness results can be transferred between jurisdictions of Europe and which lessons a country like Hungary with limited capacity for health economic analyses can learn from others.

Third, an assessment of health related quality of life (HRQoL) and disease-related costs the field of oncology, namely the cancer of the urinary bladder. Among the

urologic disorders bladder cancer (BC) plays outlying role both from medical and health economic perspective as it ranks 9th in overall cancer incidence. Cost-effectiveness analyses require input data both on effectiveness in terms of health gain (considering also the quality of the life years gained) and disease related costs on the social level. For that purpose, appropriate HRQoL measures are required and validated language versions are needed for cross country comparisons. In a cross-sectional survey, therefore, we performed the validation of a BC specific HRQoL measure into Hungarian. In health economic evaluations the link between disease-specific measures and health state utility tools is often used to calculate QALYs when preference based HRQoL data are not available. Nevertheless, this is an underexplored area in BC thus we focused secondarily on these crosswalks. Further key elements of cost-effectiveness analysis are health care utilisation and productivity loss related costs. However, whilst HRQoL data often present similarities and can be transferred across countries, costs data can hardly ‘travel’ between jurisdictions with different socio-economic conditions and health/social care. According to the review of the international literature I have performed in the field of BC, not only in Hungary but in the Central and Eastern European (CEE) region in general, there is a scarcity of data reflecting local features from the recent decades on which health economic models could be built. Thus, in Hungarian context the local data collection is an opportunity to support the criterion of cost-effectiveness, consequently reimbursement-related decision-making. Our cross-sectional survey in BC aimed to assess disease related expenditures in Hungary and results are interpreted in the light of the review of the international literature.

Regarding the structure of the dissertation, it differs from the usual design that consists of Background, Objectives, Methods, Results and Conclusions. The body of this dissertation comprises three autonomous publications in accordance with the three research questions introduced above. The first article was published in *Society and Economy* journal (Hevér and Balogh, [2013]); the second one is a book chapter (V. Hevér, [2014] In: Péntek, [2014]), whilst the third one is an original article which has been submitted for publication (target journal: *Pathology and Oncology Research*) (V. Hevér et al., [2014]). The latter is complemented by a literature review and a paper under submission.

Fundamentally, each research question has different nature regarding study objectives, methods as well as results, however, they correspond in applicability: they are for one goal, namely to provide inputs and support reimbursement and financing decisions in health care. Thus, I attribute an important role for this introductory part as it aims to reveal the coherent theoretical background and highlight the link between the three research topics.

Regarding the content of the Introduction (Part I.), after the research topics were introduced briefly at the beginning, taking a step back I stretch the horizon and stress the background of the dissertation. Afterwards, the relevance of the three research topics will be detailed with emphasizing the correspondence between them. Then methods of three researches will be specified briefly. Lastly, the structure of the dissertation will be presented.

I.2. Background

In the second part of the 20th century, in developed countries, welfare expenditures had been increasing considerably whereas in the context of health care, the supply of new medical technologies had been showing a growing tendency. With the strengthening conflict between the “available in term of medical issues” and “affordable”, a new discipline, namely Health Economics was established in the bound of health sciences and economics in the 1970-1980s (Gulácsi [2005]). In Hungary, like in the other post-socialist CEE countries, Health Economics (HE) has started to gain a more remarkable scope (Gulácsi et al., [2007]). Currently, it is an autonomous discipline as well as profession in Hungary, too (Boncz et al., [2006]).

In order to give a frame to the notion of the HE, I invoke the definition from Kobelt: “Health economics is the application of the theories, tools and concepts of the discipline of economics to the topics of health and health care. Economics as a science is concerned with the allocation of scarce resources; health economics is concerned with the allocation of scarce resources to improve health. This includes both resource

allocation within the economy to the health care system to different activities and individuals.” (Kobelt, [2013] p. 1.).

Since 1945, the ability to provide treatment for an increasingly wide range of diseases has grown with the introduction of new technologies in exponential way (Banta and Luce, [1993]). Demand for health care also has increased, partly giving responses to this tendency, but for other reasons as well. The resulting rise in health care costs has placed remarkable strain on scarce resources, furthermore, this situation has become even more challenging due to the past years’ global economic slowdown.

Nowadays, the economics of health care is a hot issue discussed in the context of scientific literature, public policy forums as well as the lay press. This can be interpreted as a symptom of a cardinal change in health care markets. Attention has shifted from the “passive” funding and administration of systems to active concern about the cost of care. The health economic thinking raises the following cardinal question: How much should we spend on health care and how do we ensure that it is spent efficiently? (Kobelt, [2013])

1.2.1. The challenge of health care financing

Total health care related spending as a proportion of gross domestic product (GDP) has showed an increase starting from different levels in all OECD countries. The rate of spending was between 7.5% and 12% of GDP in 2010 (9.5% to 12% in Western Europe, 7.5% to 9.5% in CEE) (Table 1).

Table 1 Health care expenditures as percentage of GDP

Country/Region	1970	1980	1990	2000	2010
OECD average	5.8%	7.3%	8.7%	8.4%	9.3%
US	6.9%	8.7%	11.9%	13.2%	17.7%
Japan	4.6%	6.5%	6.1%	7.7%	9.6%
Western Europe	4.7%	6.7%	7.1%	8.4%	9.5%
Central and Eastern Europe	NA*	NA	NA	6.1%	7.9%
Latin America	NA	NA	NA	NA	7.0%

*Data not available

Source: OECD (2013), WHO (2011)

The main cause contributing to the growth of health care expenditures is an increase in demand which can be due to various tendencies such as demographic change, i.e. aging of the industrialised world; rising incidence of chronic diseases; growing expectations of patients and spread of prevention programmes (Gulácsi, [2006]).

Concerns about the financing of health care are high on each government's agenda, particularly in countries where health care is predominantly funded with public money thorough taxes, social insurance or a combination of the two like in Hungary. Governments around the world, and particularly in Europe have attempted to contain costs applying various tools (e.g. reference pricing, positive or negative lists or volume contracts) aimed at both the demand for and the supply of health care. However, these tools for controlling costs has not proved successful than hoped (Gulácsi, [2012]). This can be attributed to the fact that growth in spending is driven primarily by the availability of new and improved technology to which cost-containment tools can be less easily applied (Banta, [1993]). The financial crises than began in the late 2000s has worsened the situation by making further increases in public spending on health care more cumbersome. Decisions about pricing and purchasing are now taking place in the context of cost and value rather than demand for innovation. Health care decision makers are focusing more narrowly in efficiency and within tighter budgets. New and

more costly therapies must prove a clear additional health benefit to be deemed worthy of an additional expenditure. Accordingly, decision-makers will increasingly require that innovative therapies including medicines and other interventions be assessed for relative effectiveness and cost-effectiveness rather than solely quality, efficacy and safety (Boncz [2006]).

In this subsection, based on foreign and Hungarian health economists' works I have attempted to collect those issues of Health Economics which are relevant from the point of view of this dissertation. In addition, I provided a theoretical background supporting the global understanding of the concept of this paper. In the I.3. and I.3. subsections the research questions of the dissertation can be deduced from this background highlighting their relevance as well as correspondence. However, firstly, it is important to define a few terms that are cardinal for the understanding of the dissertation, namely technology in health care context, QALY and cost-effectiveness (cost-utility) as so-called “crutches” since those will be central issues regarding each research question.

1.2.2. Three “crutches” for the easier interpretability of correspondence across the research topics of the dissertation

1.2.3.1. Health technology

Goodman introduces the term of health technology the following way: “Health technology is the practical application of knowledge to improve or maintain individual and population health. Health technology appears on its physical nature and its purpose as well” (Goodman, [2004, p.13.]). In Table 2 main categories of health technologies according to their physical nature are collected.

Table 2 Health technologies according to their physical nature

Health technologies	Examples
Drugs	aspirin, antibiotics, cancer chemotherapy
Biologics	drugs, vaccines, blood products
Devices, equipment and supplies	cardiac pacemaker, magnetic resonance imaging (MRI) scanner
Medical and surgical procedures	psychotherapy, bladder removal, cesarean section
Public health programs	water purification system, immunization program, smoking prevention program
Support systems	clinical laboratory, blood bank, electronic health record system
Organizational and managerial systems	prospective payment using diagnosis-related groups, alternative health care delivery configurations

If technologies are interpreted according to their health care purpose, categories presented in Table 3 can be designated:

Table 3 Health technologies according to their health care purpose

Health technologies	Examples
Prevention	immunization, hospital infection control program, fluoridated water supply
Screening	mammography, serum cholesterol testing
Diagnosis	electrocardiogram, x-ray for possible broken bone
Treatment	antiviral therapy, psychotherapy
Rehabilitation	exercise program for post-stroke patients, incontinence aid
Palliation	medication for depression or insomnia, caregiver support

1.2.3.2. Quality-adjusted life-year (QALY)

Outcome measurement in chronic diseases, as besides using survival as an outcome, a decline in physical and/or mental abilities over time should be also considered. Often such diseases affect several functions and produce a number of different symptoms, leading researchers to seek an outcome that encompasses all effects. The most frequently applied such measure in economic evaluation is QALY, which captures the overall effect of a disease on health related quality of life over a given period of time, and combines the quantity and quality of life gained from treatment. QALYs can be compared across diseases and thus support choices for resource allocation within an overall health care budget. Consequently, QALYs are the outcome measure preferred by many government bodies and other authorities that require economic evaluation before recommending that be provided utilizing public funds (Kobelt et al., [2013]).

1.2.3.3. Cost-effectiveness analysis (Cost-utility analysis)

The relevant question is often whether or not to replace an existing treatment with another which is more effective, but also more expensive. In such cases, an estimate is needed about the additional resources that must be spent in order to obtain the additional benefit. Hence, the relevant measure in economic evaluation is incremental cost-effectiveness ratio (ICER) which indicates the cost of producing one extra unit of benefit, for example a life year saved (Drummond, [1982]). The ICER is calculated by dividing the difference in cost of two treatments by the difference in their effects. If a treatment is both more effective and less costly, it is the dominant “alternative”, then, the decision is straightforward. When the choice is between treatments where one is more effective but more costly as well, the additional cost of achieving the additional outcome means the relevant information. The decision maker can then decide whether or not to opt for the more costly alternative based on a consideration of whether the extra cost is justified by the additional benefit obtained (Kobelt, [2013]).

Cost-effectiveness analyses provide information about the benefits, costs and the potential savings of a health product compared with other drugs and/or treatments (Drummond – Mooney [1982]). However, the health benefit must be expressed by a measure allowing comparisons across different disease so as to make the cost-effectiveness analysis useful for resource allocation related decisions. Cost-utility analysis expresses the incremental benefits of a treatment compared to others in QALY. The incremental cost-utility ratio (ICUR, but often called simply as incremental cost-effectiveness ratio - ICER) presents then the incremental expenditures needed to achieve 1 QALY gain. The lower the ratio of a cost per QALY, the most cost-effective the intervention is (Kobelt, [2013]). Cost-utility analysis has two major advantages compared to other types of economic evaluations: besides combining life expectancy and overall quality of life aspects, the use of a standard preference based outcome measure makes possible to compare treatments in different disease areas that may have quite distinctive clinical outcome measures (Drummond, [2008]).

I.3. Relevance of the research topics

I.3.1. The German approach to cost-effectiveness analysis in health care

According to the foreign and Hungarian health economists cited in subsection I.2., there have been various reasons behind the exponential growth of health care expenditures. Among them, the increasing supply of new and improved health technologies has been the most significant one resulting in the conflict of “available” and “affordable”. It has to be remarked that the proliferation of health care technologies and its expanding uses have been considered to contribute to burgeoning health care costs, and the former has been cited as “culprit” for the latter, however, this relationship between them is variable and complex. (Cutler, [2011]). Culprit or not, technologies can improve health outcomes, furthermore it encourages useful innovation. The development, adoption as well as diffusion of technologies are increasingly influenced by a widening group of policymakers in the health care sector. Health product makers, regulators, clinicians, patients, payers, government leaders and further affected entities, increasingly demand well-founded information to support decision-making about whether or how to develop technologies, to allow it on the market, to acquire it, to use it, to pay for its use, to ensure its appropriate use, and so on (Goodman, [2004]). The growth and development of health technology assessment (HTA) in government and the private sector is a response to this demand (Jönsson, [2008]). However, the extension of health economic research is a global tendency from the exploration of patients’ preferences regarding treatment goals to more and more sophisticated cost-effectiveness and budget impact analyses (Brodszky et al., [2013a]; Péntek et al; [2014]). HTA is quite a complex issue. The literature provides a range of definitions regarding the term of HTA. Here I invoke three definitions which complement each other:

- “Health technology assessment considers the effectiveness, appropriateness and cost of technologies. It does this by asking four fundamental questions: Does the technology work, for whom, at what cost, and how does it compare with alternatives?” (Goodman, [2004], p.12.)

- "HTA is a dynamic, rapidly evolving process embracing different types of assessments that inform real-world decisions about the value (i.e., benefits, risks and costs) of new and existing technologies”. The role of HTA is to support health policy decision-making and financing in health care (Drummond [2008], p.244).

- "HTA is a multidisciplinary field of policy analysis. It studies the medical, social, ethical and economic implications of development, diffusion, and use of health technology" (International Network of Agencies for Health Technology Assessment, www.inahta.org, [2002]).

The body of knowledge about HTA cannot be found in one place and is not static (Goodman, [2004]). Many countries have official or quasi-official specialised teams that assess the value of both current and new health technologies (Banta and Oortwijn, [2000]). These may be independent reimbursement agencies or specialised HTA agencies. Part II of the dissertation deals with the operational principles of the two HTA agencies in Germany, among them with an emphasis on the Institute for Quality and Efficiency in Health Care (IQWiG). There are two reasons behind the fact this topic constitutes one major part of the three ones in the concept of the dissertation. 1.) During my doctoral studies I had an opportunity to take part on a scholarship trip and study the German approach. 2.) The operational principles and methods of IQWiG are deemed being unique within Europe which has been worth studying from the point of view of applicability in the case of Hungary.

In the subsection I.1., the scope and relevance of HE, the conflict between the diffusion of new technologies and the financial limits has been already revealed (Boncz, [2006]; Banta, [2013]). The general purpose of all-time health policies is to gain as much health benefit as possible within tight budgets. In the last decades the continuous growth of health care expenditures is a global tendency. In several European countries, health care expenditures have been increased more rapidly than GDP (Stiglitz, [2000]). The consequence of the increasing of health care costs is that no longer resources are allocated solely according to the extent of achievable health benefit by a certain health technology but the cost associated with health benefits have to be taken into account as well (Boncz, [2006]). Accordingly, in financial decision-making, available but limited resources are allocated according to the requirement for cost-effectiveness of health technologies before reimbursement in European level (Gulácsi, 2004), however, the mechanism of resource allocation may vary among countries. The overwhelming majority of European countries apply the method established by the National Institute for Health and Care Excellence (NICE) (McCabe et al., [2008]). It means that a medicine can become financed if it fulfils a financial threshold expressed in cost/QALY. The index number of cost/QALY expresses cost-utility, in other words,

whether a therapy is utilized in an efficient way. The German approach to the assessment of cost-effectiveness without applying the QALY concept is considerably different. This unique approach is to be discussed as one research topic of the dissertation.

1.3.2. Transferability of health economic evaluations in the European Union: challenges for Hungary

In Western European context a relevant point is whether a country supports the QALY concept or does not opt for the application of it, however, in many CEE countries the hot issue is how to transfer foreign data so as to produce incremental cost/QALY ratios. Why is this difference so remarkable?

Subsection 1.2. revealed the various reasons behind the growth of health care expenditures in the last decades. We saw that the proliferation of new technologies contribute to the fact that it is time for cost-effectiveness (Gulácsi, [2008]). Further reasons like ageing and that life expectancy at birth has changed in positive way and it is showing a continuously increasing tendency in developed countries, resulted in the rising incidence of chronic diseases. Generally, the length of life of people has become longer, accordingly, people may spend more years with chronic disease(s) (Péntek, [2012]). Among chronic illnesses, inflammatory diseases affect a growing proportion of societies. In case of this kind of illnesses, a costly pharmaceutical group, called biologic drugs have become available. In Hungary, biologic drugs have been reimbursed since 2006. The amount financed by public resources regarding these drugs is tens of billions in HUF (Laki et al. [2013]) (Kozma et al., [2009]). Since local data are not always available, cost-effectiveness and cost-utility of new medicines are hard to be assessed in this way. Therefore, Hungary can apply for an alternative strategy: transferring data from foreign evaluations. The challenge is whether foreign cost-utility results can be adapted by neutralizing country-specific features. A phase of this constraint mechanism is demonstrated by the systematic review and analysis of evidences on cost-utility of biological drugs for the treatment of a chronic disease called rheumatoid arthritis (RA) in detail in Part III and another example (Crohn's Disease, CD) is summarized and presented in Appendix:

Diversity in methodological issues is one of the factors that contribute to the cumbersome transferability of HTA results across countries. Similarly to Hungary, in other CEE countries, HTAs based on national data are not always available (Gulácsi et al., [2014]). Therefore foreign HTAs are also applied, for instance, using demography, epidemiology, standard care, healthcare utilization, unit costs, and cost-effectiveness data from National Institute for Health and Clinical Excellence (NICE) analyses (Gulácsi et al., [2009]). For instance, before considering the development of a new economic evaluation, it is useful to assess whether any cost-effectiveness information exists and whether the results of the existing study or studies are relevant to the current decision problem. With the analysis of existing cost-effectiveness studies the question rises as to whether the results can be transferred to Hungary, and if not, which adjustments of these estimates are possible and/or necessary? Baseline characteristics of target population and clinical efficacy may be more generalizable, but epidemiology and costing data are often country-specific (Gulácsi, [2012]). In addition, differences in health and social care systems (e.g. home care, disability support pension) also might have an impact. Accordingly, it becomes clear that the available cost-effectiveness information is usually not directly transferable without adjustment for differences in treatment patterns, in unit costs or other aspects (e.g. discount rate). In order to target issues of transferability, investments need to be made in the collection of epidemiological and demographic data, plus data on clinical practice patterns, resource use, costs and health state valuations (Brodszky et al., [2010]).

1.3.3. Challenges in the assessment of disease burden: case study in a chronic disease

The empirical study presented in Part IV provides an example for the collection of data reflecting local characteristics. Besides inflammatory diseases, cancers as chronic illnesses affect a rising number of people as well. So as to make well-founded health policy decisions, cost-effectiveness (cost-utility) analysis based on local, good quality data should be conducted. However, in Hungary, data both on QALYs and costs are limited (Gulácsi et al., [2009]). Accordingly, another opportunity to produce QALY, i.e. information about health gains (including both the utility and the length of life years gained) and disease related costs, is conducting an analysis based on local data. The

empirical study about the disease burden of bladder cancer patients is an opportunity thorough which health policy decision-making can be supported. The importance of urologic diseases (incontinence, overactive bladder, prostate diseases) is increasing as these affect a substantial number of the population (Brodszky et al., [2013b]; Brodszky et al., [2013c]; Gulácsi et al., [2012]; Kovács et al., [2012]; Kovács et al., [2013]; Majoros et al., [2013]).

The empirical case study forming the main part of the dissertation has investigated the disease burden of a Hungarian bladder cancer (BC) population. I assessed HRQoL issues; and cost of illness (CoI) from different perspectives within the complex notion of disease burden. Below the relevance regarding these issues are stressed.

Mortality had been the most significant factor in judging health problems of the society before. In well-developed countries, however, life expectancy at birth has increased, accordingly, people may spend more years with chronic disease(s). Therefore, the following questions have gained relevance: Which is the point when people would sacrifice a few years in order to gain better HRQoL? At what expense are these benefits achievable? How much should be spend on certain interventions? It is no doubt about the fact that a year in perfect health is more valuable than a year not in perfect health. Consequently, it is worth conducting such interventions which do not lengthen the life but make it better, in other words improve HRQoL. Furthermore, some processes, that can lengthen the life but result a worse health state, are not necessarily desirable. In order to weigh the expenditures, it is necessary to express benefits in terms of length and quality of life, respectively, the way that distinctive diseases and interventions (e.g. RA and BC) are to be compared. Accountability has become a principal issue in health care: the processes have been performed, and the costs as well as results associated with processes have to be declared. The measurement of benefits achieved by different interventions has become the standard part of health care. It is more and more relevant to establish which technology results more health benefit on the money spent by taking into consideration benefits in the aspect of HRQoL besides mortality indices (Péntek, [2012]).

Different measures are available for assessing patients' HRQoL. One of the objectives of the case study was to evaluate HRQoL of the Hungarian patient population with BC. The Bladder Cancer Index (BCI) is a disease-specific instrument suitable for measuring HRQoL of BC patients, however, it was available only in English and French

at the period of data collection (Gilbert et al., [2007]; Gaunez et al., [2010]). Not only the translation but the validation of BCI questionnaire, too, as a crucial part of the empirical study has great relevance. Firstly, validation implies not just a usable but reliable instrument. Secondly, the development of the validated version of a questionnaire makes possible the participation in international studies (e.g. clinical trials in drug development) as results have become comparable. Thirdly, the link between BCI and health state utility instruments were assessed which is an alternative strategy to calculate QALYs in health economic evaluations. Among another reasons, the developing and broadening of health technologies contributed remarkably to the growth of health care expenditures, thusly, to make reimbursement decisions is a great challenge. In order to make well-funded decisions, cost of illness data have to be collected; the outgoings of the applied therapies as well as determining factors regarding cost-effectiveness should be assessed. Collection and analysis of cost of illness data support transferability issues across countries. Estimates of the costs associated with cancer care are essential both for the assessment of disease burden at societal level and for conducting economic evaluations of interventions to prevent, detect, or treat cancer. Comparisons of cancer costs between health systems and across countries can support understanding of the economic consequences of different health-care policies (Yabroff et al., [2013]).

In Hungary, little knowledge is available regarding the issues aimed by the case study.

I.4. Corresponding points across the three research topics

After stressing the relevance of the topics elaborated in the dissertation, it is crucial to point out those issues which connect the three research topics. These areas are connected at several points, among them the presumably most cardinal one, the principle of cost-effectiveness should be highlighted. Enforcing the criterion of cost-effectiveness means the meeting the requirements regarding cost as input as well as result as output (outcome). Accordingly, the mission of fulfilling this criterion is to support well-founded public decisions whereas the toolkit for it is health economic evaluations. Each research topic is a manifestation of this mission in distinctive dimensions and each topic represent a different level of this goal:

The assessment of the unique principles of the German approach in contrast with other Western European countries shows an alternative way toward providing information regarding cost-effectiveness, therefore supporting reimbursement related decision-making. This research question is answered within the scope of health technology assessment (HTA) as macro level.

The systematic literature review and analysis of the cost-utility evidences in a chronic disease demonstrate also an alternative way to support reimbursement related decision-making for those countries where data being necessary to produce QALYs are not available. These research issues constitute a phase of a health economic evaluation, so it can be interpreted as middle level. (The health economic evaluation is a tool for establishing the „value for money” of health care technology, thus forms an integral part of a HTA. It is the comparative analysis of alternative courses of action in terms of both their costs and consequences. (Drummond et al., [2005]).

The case study based on national data and conducted with the objectives to assess HRQoL, CoI among BC patients and to develop the Hungarian version of the BCI questionnaire, represents a way of supporting the criterion of cost-effectiveness, thusly, contribute to make well-founded reimbursement related decision-making in an indirect way. This research topic with the mission of producing data reflecting local features can be considered as the micro level of supporting decision-making.

In addition, below that part of the related literature is cited which reveals the embeddedness of the three research areas within one statement: “To make health-policy decisions related to utilizing resources allocated to health care, disease burdens, results expected from health technologies and preferences of people has to be known as well. To obtain these pieces of information, there is a need for available describing of diverse health statuses, measuring possibly health related benefits of interventions and knowing the value people attribute to these benefits” (Péntek, [2012], In: Gulácsi, [2012], p.96.).

I.5. Methodology

Each article has different methodology which is specified in detail in the related parts, therefore, in this introductory Part I. methods are introduced just briefly. „The German approach to cost-effectiveness analysis in health care” (Part II) is based on the

review of the related literature performed in PubMed database and relevant health economic journals.

The method of the material of “Cost-utility of biologic drugs in rheumatoid arthritis: systematic literature review and analysis of the evidences” within Part III (Transferability of health economic evaluations in the European Union: challenges for Hungary) is a systematic literature review conducted in the following databases: Ovid MEDLINE(R), Web of Knowledge and Centre for Reviews and Dissemination (CRD). The electronic search was performed using a standard and validated methodology and results were analysed in a systematic and standardised way. Besides analysing these evidences, the quality assessment of the studies according to a standardized procedure, called Drummond-checklist is provided (Drummond, [1996]).

In Part IV, first a systematic search of PubMed and review of the available literature was performed regarding HRQoL and costs in BC. “Challenges in the assessment of disease burden: case study in a chronic disease” (Part IV) is an empirical study applying both quantitative and qualitative methods. Patient data were collected by a cross-sectional survey. To validate the BCI questionnaire, a psychometric analysis was performed. The correlation between HRQoL measures was assessed by Pearson correlations. SPSS 20.0 programme package was used to record and analyse questionnaire data. Cost of illness (CoI) was calculated based on the cross-sectional survey in which a set of questions regarding disease related costs was compiled by members of our research group and data from the National Health Insurance Fund database were also included in the analysis.

I.6. The research questions of the dissertation

This dissertation focuses on three research questions in health economics which correspond based on the literature discussed in previous subsections.

(1) In this dissertation, based on the related literature, I attempt to synthetize the German approach to cost-effectiveness analysis in health care and HTA with focusing on points which make the German approach specific. A brief comparison is also made

with the HTA systems in CEE countries, among them concentrating mainly on Hungary and some lessons to learn are highlighted and discussed.

(2) Drug reimbursement decisions require health technology assessment (HTA) including economic evaluation in Hungary. I have participated in two HTAs in collaboration with colleagues and experts. These HTAs aimed to review systematically and analyse evidences both on clinical efficacy and cost-effectiveness of a costly pharmaceutical group, called biological drugs for the treatment of the chronic debilitating disease of rheumatoid arthritis (RA) and Crohn's disease (CD). My task was to systematically review and analyse the available health economic literature, focusing on cost-utility (cost/QALY) analyses that are the main drivers of reimbursement decisions. In this section I introduce the RA work in detail, and only reflect on the findings in CD which is presented in Appendix. I discuss also the importance, the challenges and opportunities of transferability of cost-utility results from other European countries to Hungary.

(3) Assessment of HRQoL and CoI provides evidences on disease burden, on the efficacy and effectiveness of a treatment and comparisons between of different treatment alternatives. Moreover, preference based HRQoL measures support reimbursement related decision making by providing utility results for cost-utility (cost/QALY) analyses. Lack of validated language versions of HRQoL measures in a country is a barrier for the participation in multicentre pharmaceutical studies, as well as for the comparison of outcomes of health care across countries and also for the assessment of transferability of international results.

The third objective of my thesis was to conduct an empirical study. We have designed this research aiming to develop and validate the Hungarian language version of a disease-specific HRQoL instrument (called BCI); and assess the disease burden (HRQoL and CoI) of a Hungarian urinary bladder cancer population. The unique feature of this research also from the international perspective, that it applied four diverse HRQoL measures simultaneously, namely a disease specific questionnaire (FACT-BI), a generic health state measure (SF-36) and two preference-based generic utility instruments (EQ-5D and SF-6D) alongside the BCI. These two latter are often used to calculate QALYs in health economic evaluations. Hence our results allow comparisons between the different measures and assessment of the relationship between disease specific HRQoL results and utility scores. These types of "cross walks" between

HRQoL measures are often used in the health economic literature when utility results in a specific disorder are not available. According to my knowledge and the literature review I performed in the field (see subsection IV.2.), no studies using these five measures within the same sample have been performed so far. The second main part of the empirical study deals with the estimation of disease burden in the financial sense consisting of the presentation of the number of patients affected by BC (epidemiology) and cost calculation in the Hungarian context.

I.7. The outline of the dissertation

Below I present the outline of the next parts of the dissertation.

In Part II, I describe and analyse the German perspective to conduct HTA and make a brief comparison with the Hungarian HTA system, too. Based on the existing literature, I synthesize the knowledge about the German principles of conducting HTA by examining the processes according to the two HTA agencies in Germany, namely the German Agency of Health Technology Assessment (DAHTA) and the Institute for Quality and Efficiency in Health Care (IQWiG) conduct HTAs. Next, the efficiency frontier as a core point of the German approach is explained. Regarding IQWiG, debated methodological issues should not be ignored, accordingly these divisive points of views are collected. Finally, a comparison with Hungarian HTA and lessons to be learned from Germany are discussed.

Part III starts with a wider acknowledging of the background of the topics discussed afterwards, namely the systematic review of the related literature as essential and integral parts of a HTA synthesizing evidences both on clinical efficacy and cost-effectiveness of biological drugs for the treatment of a chronic disease (RA). Regarding this HTA, I detail the method of systematic literature research performed in relevant databases, then hits of the literature search are listed, quality of the relevant studies are evaluated in a standardized, systematic way and the contents of these publications are extracted. Next, discussion and conclusions are drawn with a reference to the issue to transferability of HTA results and similarities with findings of the HTA (Crohn's Disease) I participated in are briefly pointed out.

In Part IV, I present an empirical study on HRQoL and CoI of Hungarian bladder cancer patients and the development and validation of the disease-specific Bladder Cancer Index (BCI) questionnaire. After revealing the relevance of this study, I introduce the discussed disease in focus. Then the summary of the international and Hungarian literature review regarding HRQoL; validation of the BCI questionnaire; and CoI in BC is provided. Afterwards the empirical study is presented in two steps. Firstly, the original article that has been submitted for publication about the validation of BCI and HRQoL of BC patients is presented. This paper includes the background of the study, the methods applied and the results with details about the demographics of the patient population, validation process and HRQoL issues. Moreover, in the discussion interpretations related to the results and limitations of the study are pointed out as well as areas for further research. Secondly, the paper under submission about the topic of CoI is stressed: epidemiology and methods of the calculation procedure is discussed, and then average costs are listed.

In part V, main findings and conclusions of the dissertation are summarised and I underline the surplus values achieved by the researches.

II. THE GERMAN APPROACH TO COST-EFFECTIVENESS ANALYSIS IN HEALTH CARE

Foreword

Previously, in resource allocation decision-making, health technologies were evaluated according to their safety, quality, and efficacy. The proliferation of new and improving technologies necessarily contributed higher costs. Concerns also about rising health care costs and pressures on health care policymakers to allocate resources resulted in that the dimension of cost has been considered as well when evaluating certain technologies. This demand for cost-effectiveness is reflected in a considerable increase in the number of HTA reports in the literature. These HTAs are conducted by specialised HTA agencies which may establish cost-effectiveness not necessarily the same way. In Europe, most countries follow the NICE approach which is based on explicit threshold expressed in cost/QALY. In UK, NICE has adopted a cost-effectiveness threshold range of £20 000 to £30 000/QALY gained (Nuijten and Dubois, [2011]). In contrast, with no supporting the use of QALY, IQWiG as one of the German HTA agencies represents a unique approach to cost-effectiveness analysis. However, the other German HTA organization, namely DAHTA establishes cost-effectiveness based on cost/QALY, the IQWiG's method is identified as the German approach in the literature. In this part I provide an overview about this German approach to conducting cost-effectiveness analysis.

II.1. Background

There is a need for more and better information for private and public decisions about financing health technologies. The development of health technology assessment (HTA) and economic evaluation is a response to this demand (Jönsson 2008). To define the HTA itself, three points have to be specified: (1) it describes the systematic evaluation of health-related procedures and methods such as vaccinations, medical treatments; (2) assesses the effectiveness, safety and economic viability of a health care intervention, as well as its social, ethical, legal and organisational effects; (3) serves as

the basis for decisions in the health system: e.g. in policy or in terms of treatment by a doctor (www.dimdi.de). The history of the HTA development was published by Gulácsi et al., 2009.

In Germany two institutes operate as HTA agencies, namely the German Agency of Health Technology Assessment (DAHTA) within the German Institute for Medical Documentation and Information (DIMDI) and the Institute for Quality and Efficiency in Health Care (IQWiG). The HTA methodology implemented by IQWiG is different compared to the international mainstream, thereby applying the efficiency frontier approach, adopting indication-specific thresholds and not using the QALY¹ concept (Weinstein, [2009]). This section focuses on the German approach with particular emphasis on the establishment, operation and main characteristics of the two German HTA agencies. The British HTA approach (NICE) is followed by certain Central-Eastern-European countries, including Hungary. However, as I point out in this paper that the German approach is methodologically sound and might be a very useful way in doing HTA in Hungary. The Hungarian HTA approach is described briefly, and some comparisons are made in order to see what can be learned from the German experiences.

II.2. Literature search

This article reviews HTA in Germany published to date in peer-reviewed biomedical journals. We studied the published literature for the past 10 years. The PubMed (database of life sciences and biomedical literature, <http://www.ncbi.nlm.nih.gov/pubmed/>) was searched systematically for articles dealing with HTA in Germany. The following search terms were used: "Technology Assessment, Biomedical"[Mesh] AND "Germany"[Mesh] AND ("2002/09/23"[PDat] : "2012/09/19"[PDat] AND English[lang]). The search resulted 45 hits. Articles in English dealing with HTA issues in Germany were selected by reviewing the titles and abstracts. Disease-specific studies and studies with no abstracts were excluded. Altogether three articles were included from the PubMed search (Drummond, [2007]); (Fricke and Dauben, [2009]); (Jönsson, [2007]). In order to capture further relevant

¹ A year of life is adjusted for its quality or its value. A year in perfect health is considered equal to 1.0 QALY.

articles on institutional framework and reimbursement process in Germany, and papers presenting HTA in Central- and Eastern-European countries three relevant journals were manually reviewed: Health Policy, The European Journal of Health Economics and Value in Health. Altogether six further studies were included, four of which dealt with Germany (Bekkering and Kleinen, [2008]); (Greiner and Schulenburg, [2010]); (Jönsson, [2008]); (Schulenburg et al., [2007]) and two with Central Eastern European countries (Gulácsi, [2007]); (Gulácsi et al., [2012]).

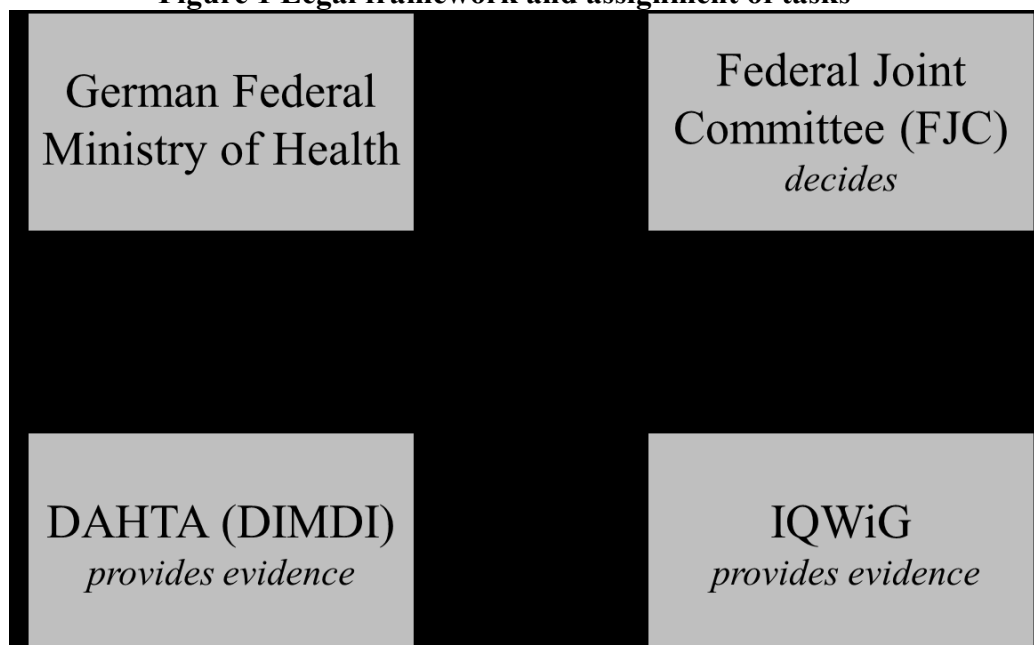
II.3. HTA in Germany

In Germany health care is regulated via sickness funds. The Federal Joint Committee (FJC) is responsible for determining which healthcare services (including medicines) are to be reimbursed by sickness funds and to formulate the cost consequences to be covered. The FJC is the supreme decision making body of the so-called self-governing system in Germany (Schulenburg et al., [2007]). It is supervised by the Federal Ministry of Health (FMH). To define a directive, the FJC is entitled to decide whether to commission or not a scientific institute to carry out benefit assessments or economic evaluations. The term “benefit assessment” refers to the whole process of the assessment of medical interventions with regard to their positive and negative causal effects compared with a clearly defined alternative treatment, a placebo (or a different type of sham intervention) or no treatment. In this context, beneficial and harmful aspects of an intervention are initially assessed on an outcome-specific basis and then presented. The conclusions drawn are always applied to groups of patients with certain characteristics (General methods 4.0.). These benefit assessments are sometimes referred to as “isolated benefit assessments”, to distinguish them from benefit assessments as part of a full economic evaluation (a study in which a comparison of two or more treatments or care alternatives is undertaken, and in which both the costs and outcomes of the alternatives are examined) (Bekkering and Kleijnen, [2008]). Such assessments provide an overview of the scientific evidence regarding the benefits of a health technology (e.g. a new drug). The term “benefit” can be defined here as health gain with its aspects of quantity (e.g. recovery, slowing disease progression, avoiding death) and quality (e.g. mobility, self-care, everyday activities, pain/discomfort, anxiety/depression, achieving better working capacity, improving functional role). The

term “benefit” refers to positive causal effects, and the term “harm” refers to negative causal effects of a medical intervention on patient-relevant outcomes. In this context “causal” means that it is sufficiently certain that the observed effects can be ascribed solely to the intervention to be tested. The terms “benefit” and “harm” refer to a comparison with a placebo (or another type of sham intervention) or no treatment (General Methods, 4.0.). Directives are formulated by the FJC regarding whether to reimburse or not for the medicine or other medical technology (the drugs, devices, medical and surgical procedures used in medical care, and the organizational and supportive systems within which such care is provided) in question. Assessments can be commissioned for any new licensed medicine. Decisions regarding what to commission are made by the FJC itself based on the work of internal working groups. Currently, the decision to commission is based on cost implication.

The FJC can entrust any agency with performing a benefit assessment. However, up to now the majority of the commissions have been addressed to the IQWiG (Bekkering and Kleinen, [2008]). In Germany the other HTA organization is the DAHTA within DIMDI. Relationships of the discussed health-economic German organizations, legal framework and assignment of tasks are illustrated on Figure 1.

Figure 1 Legal framework and assignment of tasks



Source: Siebert, [2010]

II.4. German HTA organizations

HTA has been discussed in Germany since the late 1990s, closely related to the implementation of evidence-based medicine (EBM). Evidence-based medicine is an approach of practicing medicine with the goal to improve and evaluate patient care. It requires the judicious integration of best research evidence with the patient's values to make decisions about medical care. This method is to help physicians make proper diagnosis, devise best testing plan, choose best treatment and methods of disease prevention, as well as develop guidelines for large groups of patients with the same disease (Torpy et al., [2006]). HTA was formally established with the German Health Care Reform at 2000 (Fricke and Dauben, [2009]). Two institutes operate as HTA agencies, namely the German Agency of Health Technology Assessment (DAHTA) and the Institute for Quality and Efficiency in Health Care (IQWiG). Below I concentrate particularly on IQWiG highlighting its processes for conducting HTA. To make its role clear I have to mention other institutions interacted with them such as FJC and FMH.

II.4.1. DAHTA (DIMDI); HTA process

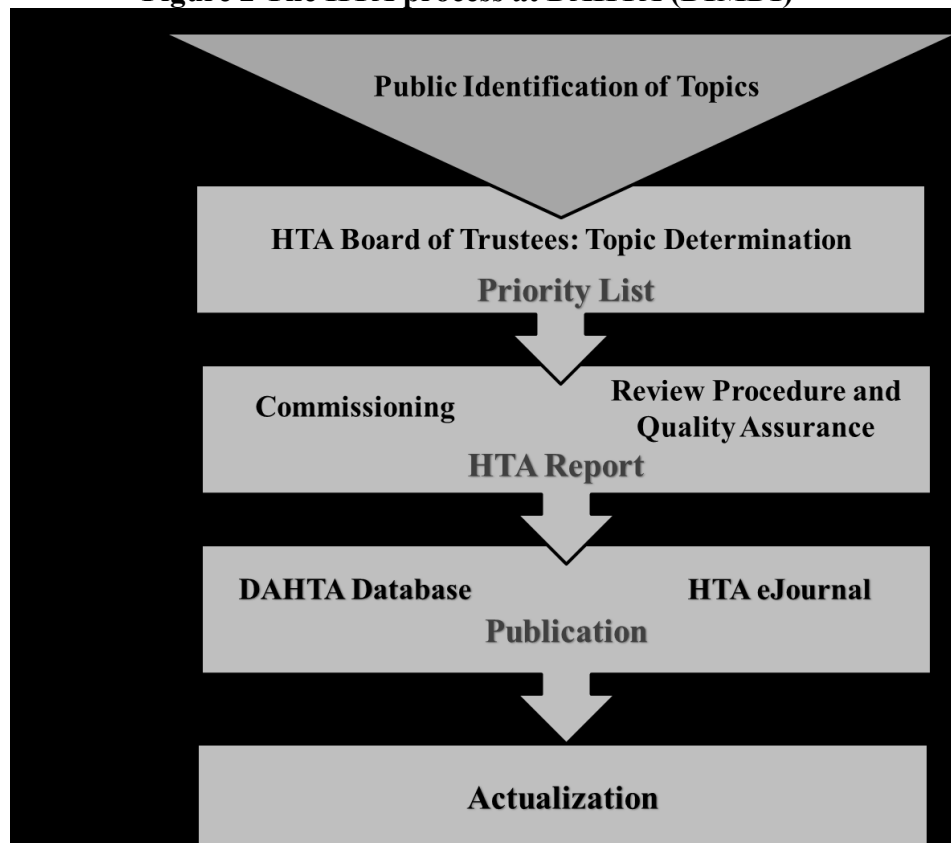
DIMDI, which belongs to the FMH, develops and operates database-supported information systems and specialized databases for drugs and medical devices. The DAHTA² as a part of DIMDI was established in 2000. It publishes HTA reports which are designed to inform health policy decisions (Fricke and Dauben, [2009]). These HTA reports cover different topics in the area of prevention, diagnosis, therapy, rehabilitation; nursing and methodology (see Table 4).

The DAHTA has two main functions: (1) Setup and maintenance of a database-supported information system for the assessment of the effectiveness and costs of medical procedures and technologies; (2) Granting research assignments for the assessment of procedures and technologies relevant to health in the form of HTA reports, and making the evaluation of these reports for acceptance into the information system (www.dimdi.de).

² The German Parliament established the German Agency for HTA (DAHTA) at the DIMDI as part of the Health Reform of 2000 (www.dimdi.de).

The DAHTA produces HTA reports according to a standardised procedure. The methodology in this regard is regularly adapted to the international standard. Because of the limited budget, scientific topics are selected and prioritized to be included in the HTA development program (Fricke and Dauben, [2009]). The procedure for identification of topics is outlined in Figure 2.

Figure 2 The HTA process at DAHTA (DIMDI)



Source: Fricke and Dauben, [2009]

The DAHTA accepts public suggestions for topics for HTA reports. Anyone may suggest online research questions in health-relevant areas.

The DAHTA produces scientific reports on topics suggested by the public. The following questions are answered in these publications: What is the topic (e.g. which disease)?; How many persons are affected?; Which procedures exist in this area (e.g. treatments)?; What are the associated costs?; Who carries these costs?; What are the current implications for health policy? (www.dimdi.de)

The HTA Board of Trustees³ (composed of insurance companies, hospitals and physicians, complemented by representatives of nursing, patients or consumers, as well as observer representatives from the IQWiG and the industry) receives the scientific texts, then sets priorities and determines the topics for future reports in a systematic multilevel procedure (Fricke and Dauben, [2009]). First, the HTA Board of Trustees prioritises the suggested topics online, and the DAHTA performs a literature search to investigate whether the assessment of the topics can be realised. Second, the members of the HTA Board of Trustees discuss the topics. Finally, the topics are prioritised online again.

As a rule, 10-12 topics are commissioned per year. The HTA reports are produced by expert researchers who work closely with the DAHTA. The members of the author group are derived from various specialist areas (e.g. medicine, health economics).

The DAHTA supports and coordinates the preparation of the individual work steps up to the final HTA report: (1) systematic literature search; (2) literature report; (3) interim report; (4) final report (preliminary); (5) final report (revised); (6) publication. This process takes one year. Every step is evaluated by two external and one internal experts. External opinions are provided by competent specialists who are familiar with the report topic (e.g. from universities or specialist associations). The evaluation process is anonymous, so., the author groups do not know the reviewers and vice versa.

Finally, publication completes the process of preparation of the HTA reports. Every HTA report which has been subjected to the individual quality steps is published in principle, regardless of the result. The reports can be read at no charge in the DAHTA database and in the German Medical Science e-journal as well, both of them are accessible at the website of DIMDI. In case it is necessary, the process ends with actualization of the reports.

The HTA reports prepared by DAHTA cover topics in the areas of prevention/screening, diagnosis, therapy, rehabilitation, nursing and methodology. In Table 4, I give a brief overview about the current topics of HTA in Germany.

³ Two committees support the DAHTA: the HTA Board of Trustees (professional) and the Scientific Advisory Board of HTA (methodology and strategy) (www.dimdi.de).

Table 4 Current topics of HTA in Germany; 2012-2013

Topic	Specific example for a HTA report	Provisional publication date
Prevention/ screening	Which options have primary prevention depending on different forms of eating disorders in practice? How effective are they? How is the cost-benefit-relation?	March 2013
Therapy/ rehabilitation	Which diets do support to lose weight and to keep it? How is the cost-effectiveness of different diets? Which ethical, social and juridical aspects have to be considered?	January, 2013
Methodology and others	In terms of out-patient care, can a continuous, retraceable, cost-neutral measurement be performed according to EU laws as to the extent to which the quality of care for out-patient rheumatism sufferers in a defined region (on a city, district, regional or provincial level) meets the care requirements as per §70 of the SGB V[1]? What indicators or criteria are important? What ethical, social and legal aspects must be taken into consideration?	September, 2012
Nursing	How can be realistically judged the individually required nursing? Are the resulting nursing investment and necessary services of the care givers and the providers appropriate and quality assured? Are the quality assurance systems appropriate to fulfil the demands of care in Germany? Which health economic, social and legal determining factors have to be considered?	February, 2013

Source: www.dimdi.de

II.4.2. IQWiG; HTA process

In 2004 the FJC established the IQWiG as an independent scientific unit according to a new law (Jönsson, [2007]). The FJC or the ministry can commission IQWiG for preparing an assessment of any particular research question which they want to resolve. Nevertheless, there is no explicit prioritization of topics. The IQWiG assesses effectiveness, quality, and efficiency of diagnostic and diverse therapeutic methods including pharmaceuticals. IQWiG's technology assessments are used to inform the

decision-making of the FJC. However, the IQWiG does not conduct assessments on its own. It gets commissions for assessments from its supplier base. The ultimate decision is taken by the FJC. Because IQWiG is a private institute established as an institution of the Foundation for Quality and Efficiency in Health Care to undertake commissions from the FJC and the FMH, it is responsible only to the foundation and its representatives (Fricke and Dauben, [2009]). The creation of the IQWiG in 2004 was welcome for several reasons. First, it was part of a new legislation aimed at improving the efficiency in the health care system. The purpose of the creation of IQWiG was to provide information for decisions about what should be funded within the statutory health insurance system. Second, IQWiG was created as an independent body which made possible to give unbiased advice to the decision makers. Third, the mandate covered all health technologies, not only drugs. However, according to the law drugs should be assessed for benefits only and not cost-benefit. The drawbacks of this exception became obvious with the publication of the first methods paper (IQWiG, [2006]), and the law was changed. The revised legislation, the German health care reform effective, 1 April 2007, also stated that the methods for cost-benefit analysis should be based on “international standards” (Jönsson, [2008]).

Regarding international standards for economic evaluation of health technologies and their relevance in the German context, it is important to emphasize the fact that Germany draws on experience, both good and bad, from those countries that have already implemented a requirement for economic evaluation of new health technologies. These include Australia, Canada and several European countries as well, for example Finland, Norway, Sweden, the Netherlands, Belgium, Portugal and the United Kingdom.

II.4.2.1. Transferability of experiences and results

According to Drummond, experience from abroad can be interpreted in two steps: methodologies and processes (Drummond, [2007]).

Currently, one of the most debated issues in Germany is the role of economic modelling. In some jurisdictions, for example in the UK, modelling is welcomed. In Germany there is some hesitation over the use of these techniques, because they require additional assumptions in extrapolating beyond the data observed in randomized

controlled trials (RCTs) for instance. (RCTs are often used to test the efficacy of various types of intervention within a patient population.)

As for processes, different jurisdictions employ different approaches with respect to: the perspective of the analysis, selection of technologies for appraisal; the involvement of stakeholders (e.g. manufacturers, professional groups and patient organisations) (Drummond, [2007]). I discuss the main methods and procedures of IQWiG for conducting HTA.

II.4.2.2. Quality of HTA

With the development of HTA, there is a need for ensuring the quality of it. An important way of improving quality is the continuous revision of the Methods papers on benefit assessment and on health economic evaluation. Both publications, the “General methods” and the “General Methods for evaluating the relation between cost and benefit” describe the scientific principles and methods that the IQWiG employs (www.iqwig.de). The newest edition of the General Methods is the version of 4.0. IQWiG assessments need to adhere to the “General methods” on benefit assessments and the “General Methods for evaluating the relation between cost and benefit” (Fricke and Dauben, [2009]). The methods must be followed by IQWiG and third parties working on behalf of it. Furthermore, any evidence submitted to the institute is assessed in the light of these methods.

Below I give a brief summary about the basic principles of IQWiG’s work, the institute’s products, process of product preparation and quality assurance of these products, which can be found more detailed in the General Methods 4.0 published in 2011.

Basic principles:

- *Independent:* (a) IQWiG carries out its scientific work in an independent manner. The contents of the reports cannot be influenced by those in industry, the statutory health insurance funds or politics. (b) Everyone being involved in working on a product of the institute must disclose all relationships which could influence the work and the result.

- *Evidence-based and objective*: (a) IQWiG reports are not based on personal opinions or convictions but on proof (evidence) which is documented using the most objective scientific methods; (b) Through its patient information the institute provides objective information on the latest scientific findings, thus enabling patients to make informed decisions.
- *Patient-oriented*: when assessing benefit, IQWiG applies criteria which are important to patients. The institute generally consults patient representatives in order to establish these criteria (patient-relevant outcomes) .
- *Transparent*: (a) IQWiG not only publishes the final reports on its projects but also the intermediate stages like the draft of the report plan and the preliminary results (preliminary report); (b) Scientists, industry, professional societies, doctors and patients have the opportunity to submit comments on the institute's work at different stages in the project.
- *Scientific*: as a scientific institute, IQWiG maintains a regular exchange with other research institutes and networks (IQWiG, [2011]).

Products of IQWiG

The IQWiG publishes its results in different forms. The products differ regarding scope, objective and target group:

- *Reports and rapid reports* are produced on the basis of a single commission awarded by the FJC or the FMH. The primary aim of reports is to make recommendations to the FJC for policy decisions. Rapid reports aim to provide up-to-date information on relevant topics, as well as on research questions not targeted towards policy decisions of the FJC. Detailed reports contain benefit assessments or evaluations of the cost-benefit relation of medical interventions.
- *Dossier assessments* are commissioned by the FJC within the early benefit assessment of drugs. Comprehensive dossiers submitted by pharmaceutical companies to the FJC form the basis of the assessments. IQWiG then examines whether the dossier proves an added benefit of a drug versus an appropriate comparator treatment. The result of such an assessment must be available three months after the relevant date for the submission of the dossier.

- *An addendum* can be commissioned by the FJC or FMH in case further need for work on the commission arises after completion of a report, rapid report or dossier assessment. For example, this might be relevant if the evidence base changes (e.g. new studies are published) during the consultations of the FJC.

- *Health information* provides easily understandable information for the public. It can be produced on the basis of a single commission from the FJC or FMH or in the form of accompanying information to a commission on a benefit assessment. Within the framework of the general legal duty to provide health information, IQWiG also addresses topics on its own initiative.

- *Working papers* are products prepared under the institute's own responsibility, without the need for a special commission from the FJC or FMH.

Process of product preparation

The most frequently products by IQWiG which also require the most effort are its reports. They contain recommendations on guideline decisions for the FJC. The simplified schedule for the production of reports is the following:

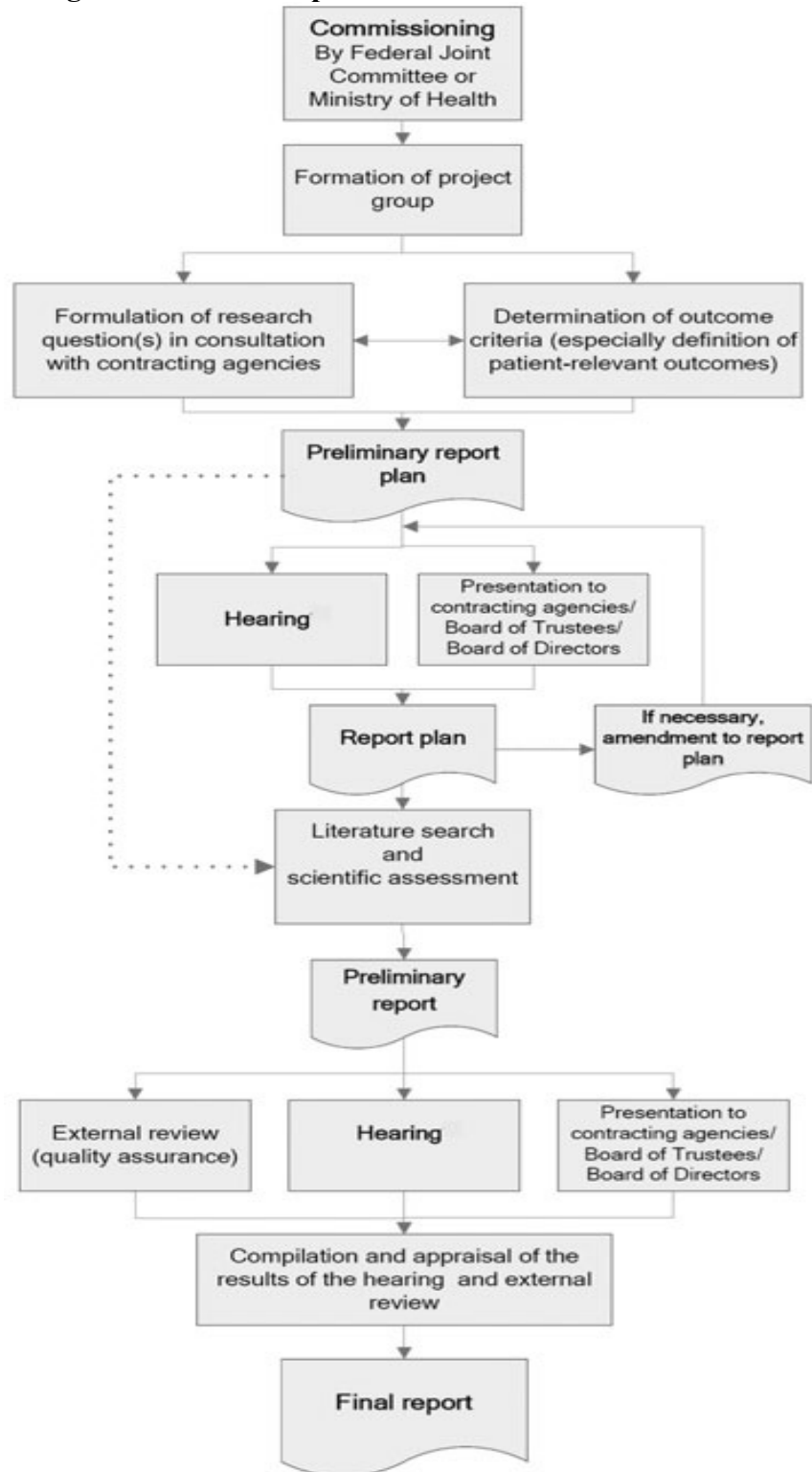
- *Selection of the topic:* A report is always initiated by a commission from the FJC or the FMH, depending on which establishes the research question.

- *Formation of a project group:* The project group formulates the scientific research question and the outcomes for the project in agreement with the contractor and external experts as well, if necessary.

- *Production of the report plan:* In this step a preliminary report plan is drawn up. This project outline provides a summary of the main planning stages for the rest of the project. The draft of the report plan is published, accordingly all interested parties have the opportunity to submit comments. Thereafter these comments are incorporated into the report plan version 1.0, which forms the basis of future work.

Publication of the results: The results of the search and the scientific evaluation are initially published as a preliminary report (preliminary result), and comments can again be submitted. Then the preliminary report is revised taking the comments into consideration and is published as a final report together with the documentation of the comments (IQWiG, [2011]). Figure 3 shows the production process used by IQWiG.

Figure 3 Production process for an IQWiG assessment



Source: IQWiG, [2011]

As Figure 3 shows, assessments on behalf of the IQWiG are subjected to internal reviews. IQWiG conducts hearings after publication of the draft report plan and after publication of the draft report itself. The fact that these hearings may have an impact on the final version of the assessment, increases the transparency of the process (Fricke and Dauben, [2009]).

Quality assurance of IQWiG products

The evaluation of the advantages and disadvantages of medical interventions may have an impact on many areas of medicine, so IQWiG's reports must meet high scientific quality standards. IQWiG ensures the quality of its products by:

- *Guaranteeing independence:* IQWiG closely monitors both staff members and external experts to make sure they have no conflicts of interest that could give rise to prejudice.
- *Multi-stage internal quality assurance (review):* All products, including intermediate products such as the report plan, undergo several internal reviews. In addition to a content and biometry review, this also includes a review of information acquisition.
- *External review, external expertise:* External experts are involved at an early stage of project planning in almost all commissions. Additional external experts are invited to review the products. Scientists, industry and patients are also given the opportunity to offer their expertise by submitting comments (www.iqwig.de).
- *Regular monitoring and updating of the work methods:* The methods, recorded in the institute's Methods Papers, are updated and revised annually to accommodate current requirements and developments in health-care research and the health-care system (Fricke and Dauben, [2009]).

II.4.2.3. The efficiency frontier approach related to IQWiG

Before the presentation of the efficiency frontier approach itself, it is worth providing a short description about its theoretical background. The efficiency frontier was first defined by Harry Markowitz who launched portfolio theory as one cornerstone of mainstream economics (Markowitz, [1952]).

The portfolio theory considers a universe of risky investments and explores what might be an optimal portfolio based upon those possible investments. The notion of "optimal" portfolio can be defined in one of two ways: definition 1: For any level of volatility, all the portfolios having that volatility have to be taken into consideration. From among them all, the one having the highest expected return has to be selected; definition 2: For any expected return, all the portfolios having that expected return have to be taken into account. From among them all, the one having the lowest volatility has to be selected.

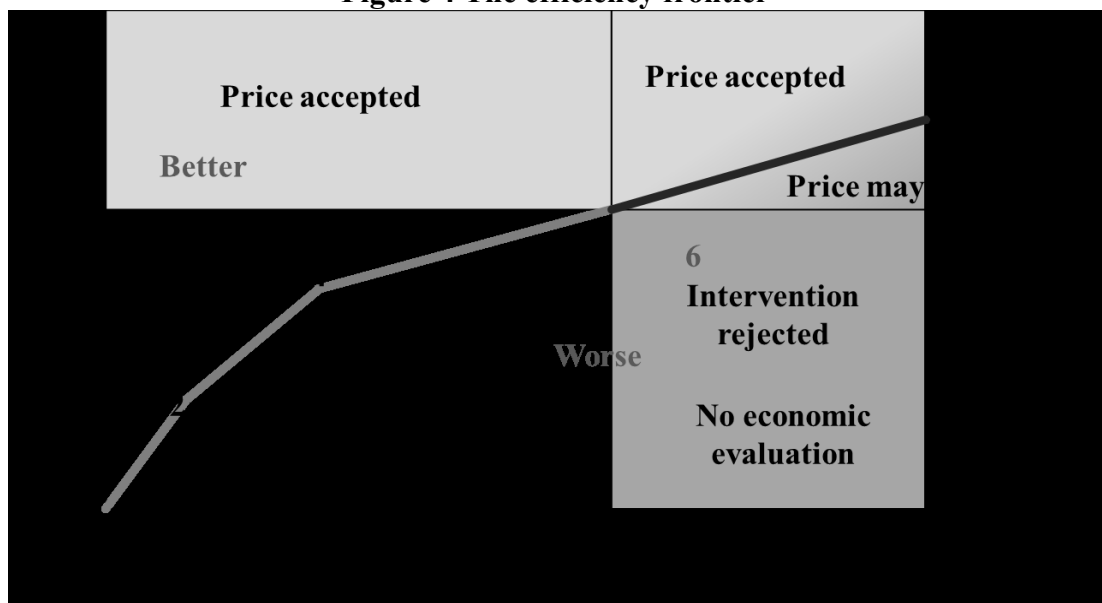
Each definition results a set of optimal portfolios. Definition 1 gives an optimal portfolio for each possible level of risk. Definition 2 provides an optimal portfolio for each expected return. Actually, the two definitions are equivalent. The set of optimal portfolios obtained using one definition is exactly the same set which is obtained from the other. That set of optimal portfolios is called the efficient frontier itself (Markowitz, [1952]).

In health economics, the efficiency frontier concept is an extension of the standard approach of incremental cost-effectiveness ratios. The cardinal point of the approach in the context of health care is the following: "*An efficiency frontier is constructed for each therapeutic area as the basis for health economic evaluation of relevant health technologies*" (IQWiG, [2009]). The efficiency frontier provides information which can serve as guidance for decision makers with regard to setting maximum reimbursable prices. Without employing a universal threshold, the efficiency frontier method is based on the determination of the prevailing efficiency in a given therapeutic area in Germany. The specification of the therapeutic area includes the specific disease, the conditions of treatment (e.g. inpatient care), target population, ranking of therapy (first, second choice, etc.), and whether it is a mono-therapy or combination therapy. In order to construct the frontier there are three major steps to take: (1) Defining the vertical axis, quantifying the benefit for the chosen interventions and ensuring an approximately cardinal scale to be used which reflects the benefit in the therapeutic area in question. (2) Defining the horizontal axis and quantifying the total net costs per patient for each of the selected therapies. (3) Plotting the interventions and drawing the efficiency frontier.

The concept of the efficiency frontier can be seen graphically in Figure 4. The theoretical efficiency frontier plot shows options increasing in efficiency from left to

right. The gradient of the line segment connecting any two options represents the incremental benefit per incremental net costs. The efficiency frontier itself is comprised of the most efficient therapeutic alternatives within the particular therapeutic area. The efficiency frontier plot compares the therapeutic benefit of available interventions within a given therapeutic area with the outcome-related net costs of these interventions. Interventions on the frontier denote the net cost for any given benefit that is consistent with the efficiency that can be achieved by the package of interventions on the current market (IQWiG, [2009]).

Figure 4 The efficiency frontier



Source: Siebert, [2010]

Prices can lead to health technologies being positioned on an already existing segment of the efficiency frontier, showing thereby consistent efficiency with already existing interventions. If a price results in an intervention being positioned below the efficiency frontier (e.g. intervention 1 in Figure 4), this indicates a lower efficiency. This price is deemed too high and needs to be adjusted, or at least justified. Interventions above the efficiency frontier indicate improved efficiency and thus redefine the frontier as Figure 4 shows. But the interpretation of the value of interventions does not depend just on the positions referenced to the line of the efficiency frontier but on the comparison of the relative positions of interventions to

each other as well. For example, positive gradients (e.g. between points 2 and 4) reflect additional benefit for increased cost while negative gradients (e.g. between points 4 and 5) indicate less benefit yet more costs, accordingly intervention 5 reflects negative efficiency. The positions of Interventions such as intervention 3 in Figure 4 require further interpretation as they do not reflect negative efficiency with respect to any existing intervention (e.g. intervention 2).

Recommended actions for the decision maker can be derived from the last plotted point on the efficiency frontier (i.e. technology showing the highest benefit) which currently is the intervention 4 in Figure 4 (Siebert, [2010]).

II.4.2.4. Often debated methodological issues of IQWiG

For the revision of the first Methods paper (IQWiG, [2006]) IQWiG commissioned an international group of experts⁴, under leadership of US consultants. Taking into consideration the number of qualified health economists that can be found in Germany, it was a surprising step according to Jönsson. In spite of the international support by the experts, the new version of Methods paper, namely General Methods 4.0 (IQWiG, [2011]) did not reflect the international standard in the field (Jönsson, [2008]).

Below I present the main debated issues regarding the Methods paper.

On the one hand, the document fails to give any guidance for the use of economic evaluation to support health policy decisions in Germany, on the other hand, it pictures health economics and economic evaluation in particular, as a subject totally void of theory and method.

Another problematic point in the guideline is that it states that the purpose is to set “ceiling prices” for drugs. If economic evaluation were used for setting prices, it should be done for all inputs in the production of health, hospital stays, doctors’ fees, etc., and not only drugs. But there is great confusion about what is meant by ceiling prices. One interpretation is that they are reference prices, over which the patients have to pay extra cost. This would create great inequalities, for example for access to new cancer drugs. Another interpretation is that the ceiling price represents the willingness to pay (WTP) by the Statutory Health Insurance for a specific treatment. But the WTP varies with the

⁴ Prof. Dr. Vincenzo Atella (Italy), Prof. Dr. Jaime Caro (Canada), Prof. Dr. Gérard de Pourvoirielle (France). Prof. Dr. David Henry (Australia), Prof. Dr. Maurice McGregor (Canada), Prof. Dr. Alistair McGuire (England), Dr. Erik Nord (Norway), Prof. Dr. Uwe Siebert (Austria)

quantity (indication). Different prices will give different distributions of consumer and producer surplus; i.e. the value above the price paid and the difference between price and cost, respectively. A lower price increases the consumer surplus, but at the same time reduces the producer surplus. The price will therefore also impact incentives for innovation. The producer gets only a small part of the total consumer surplus generated by pharmaceutical innovation.

Furthermore, Jönsson underlines the fact that economic evaluation is neither sufficient nor necessary for setting prices. Economic evaluations can provide information about value for money, and thus effect how resources are allocated. This may have an influence on prices, but more importantly, also on quantities (Jönsson, [2008]).

IQWiG's approach to economic evaluation is heavily criticized by different authors like Brouwer, Claxton, Jönsson, Rutten and Sculpher regarding the scope of assessments conducted (Pauly et al., [2012]). Although IQWiG recommends cost-effectiveness analysis in its general form, it rejects comparisons across clinical areas and the use of an explicit threshold that is applied across specialties and clinical programs. In contrast to other HTA agencies applying cost-effectiveness analysis such as NICE in the United Kingdom, IQWiG does not support the use of QALYs. IQWiG's approach is to assess the value of a new technology in the context of its specific clinical indication. All relevant comparators within this are selected and incremental cost-effectiveness methods are employed (both of these are consistent with other agencies' preferred methods) (Pauly et al., [2012]). The main difference is in defining value in this context. While in other organizations' practice a generic cost-effectiveness threshold is used (e.g. in terms of cost per QALY), IQWiG defines a disease/indication-specific threshold which is inferred from previous decisions made in Germany in that area. Consequently, it is not clear how IQWiG's methods can inform resource allocation decisions given that costs and effects inevitably extend beyond individual disease areas (Pauly et al., [2012]). At this point it is quite important to emphasize the fact that a drug or other health technology can never be cost-effective in itself; only within a specific indication in relation to a specific alternative.

There are several other confusing components of the guidelines, for instance the definition of indirect costs and the absence of a clear standpoint on the important issue that a social perspective is relevant in Germany where the statutory health insurance covers both health care and income losses (Jönsson, [2008]).

The IQWiG turned into a full HTA agency assessing not only the benefits but also the costs of drugs and therapies. The institute definitely started with a number of cost-effectiveness assessments in 2010 to support decision-making on reimbursement of drugs for the German sickness funds. This was an important change of emphasis for the German health care market. Previously, reimbursement decisions had been made solely on the basis of benefit (Greiner and Schulenburg, [2010]).

II.4.3. Transparency of assessments

The transparency of assessments is one of the most important issues of HTA. There are different aspects of transparency. One is the transparency of the assessment itself. Guidelines are aiming to secure transparency of assessments as much as possible, meaning that there is a plausible link between the evidence depicted and the conclusions drawn. Furthermore, the use of HTA in health-care decision-making should be transparent, i.e. the link between the assessment and related decisions is plausible. If an assessment should have any impact on decision-making, transparency is required with regard to both aspects of the process (Fricke and Dauben, [2009]).

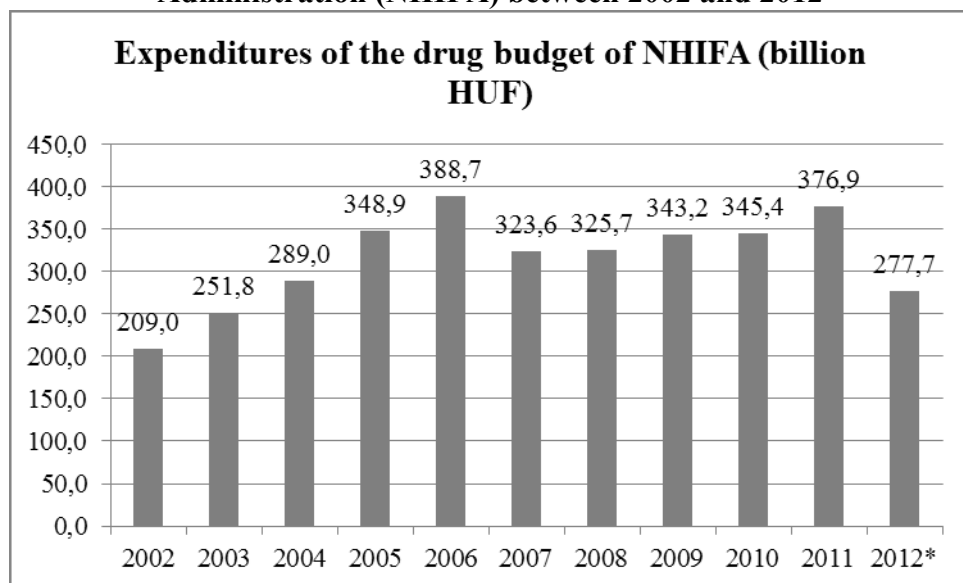
II.5. Health Economics (HE) and HTA in Central Eastern European countries

At the end of the 1990s, after the change of regime in Eastern Europe, in spite of the expectations only two countries started to introduce HE and HTA, Hungary and Poland. In these countries HTA offices and some university departments of HE have been established to get a better view on the health care system (Gulácsi et al., [2012]). Other countries also have tried to put greater emphasis on HE and HTA such as Croatia (Vártokné Hevér, [2012]), Romania, Slovak Republic and Serbia with partial success. Below I discuss the case of Hungary briefly.

II.5.1. HTA in Hungary

As regards the institutional framework related to HTA in Hungary⁵, in 2004 the Transparency Secretariat (TS) was formed at the National Health Insurance Fund Administration (NHIFA) and Ministry of Health to assess the therapeutic value or clinical benefits of drugs and to compare the results with already existing therapies so as to prepare decisions on reimbursement applications (Gulácsi et al., [2009]). The Office of Health Technology Assessment (OHTA) has the task of providing an organizational framework for technology assessment that serves as the basis for the medicine subsidy approval policy of the NHIFA. Regarding the expenditures of NHIFA between 2002 and 2012, there is a significant drop in 2007 after the growing tendency since 2002. Figure 5 indicates the absolute value of the expenditures of NHIFA.

Figure 5 Expenditures of the drug budget of the National Health Insurance Fund Administration (NHIFA) between 2002 and 2012



*planned expenditures

Source: www.eski.hu

In 2012 due to the saving measures, the planned amount of expenditures drops with almost 36%.

⁵ In the Hungarian context an important role of HTA is to order drugs to the existing reimbursement categories (see these categories in Baji et al. 2012a and Baji et al. 2012b).

In 2010, OHTA was renamed to Technology Appraisal Head Department (TAHD). TAHD is responsible for evaluating the submitted economic dossiers that is a legally required part of each company submission (Gulácsi et al., [2012]).

In 2002, the Ministry of Health (MoH) released guidelines for conducting health economic analyses that determine the methodological issues of health economic evaluations. The guidelines expired in 2004, but were extended until 2006 (Gulácsi, [2007]). Since then no new guidelines have been issued. During 2007-2008, a professional team made a checklist for the evaluation of the methodological quality of the company submissions for reimbursement (Inotai et al., [2012]). The HTA community was not involved in this process. The checklist is used for internal TAHD evaluation of the submitted dossiers. TAHD staff is responsible for preparing the evaluation report itself. In the Hungarian HTA process it is an important feature that neither recommendations, nor reimbursement decision details are available to the general public. Due to the fact that reports are not public, it is difficult to judge the value of these materials and the principle of transparency is damaged.

To mention a methodological issue related to the Hungarian HTA process as well, I would highlight the fact that epidemiology of various diseases, disease severity, mortality and costs of diseases and treatments are crucial for health economic analysis (Péntek et al., [2008]). In Hungary (and other Central-Eastern-European countries, too) valid data are rarely available. The same is true for the standard practice of different diseases (Minier et al., [2010]). This is important because identifying treatment comparators is one of the first steps in health economic analysis.

In the past decade several HE and HTA studies were conducted in Hungary (Boncz et al., [2006]; Péntek et al., [2007]; Betlehem et al., [2008]; Péntek et al., [2008]; Sebestyén et al., [2009]; Boncz et al., [2010]; Inotai et al., [2012]). This tendency should be continue parallel with eliminating the problematic issues of the HTA process.

II.6. Lessons to learn from Germany

I discussed the operational principles and processes related to one of the German HTA agencies, namely IQWiG.

Regarding the key points at DAHTA, it produces HTA reports according to a standardised procedure. The methodology in this regard harmonizes with the international standard. Due to the limited budget, scientific topics are selected and prioritized to be included in the HTA development program.

The HTA process of DAHTA is transparent from the identification of topics to the implementation. For instance, at the beginning of the process DAHTA accepts public suggestions for topics for HTA reports; and the last element of the process is the actualization of reports if it is necessary. Regarding the content of reports, it is predictable since future studies are indicated in the website of DIMDI (see Table 1).

As for IQWiG's process, its independence within the health care system makes possible to give unbiased advice to the decision makers. On the one hand, assessments on behalf of the IQWiG are subjected to internal reviews, and on the other hand, external expertise is involved as well, i.e. scientists, industry and patients are also given the opportunity to offer their expertise by submitting comments. All these practices increase the transparency of the HTA process.

While at DAHTA and IQWiG the process of HTA is open to the broad public, the same cannot be said for the Hungarian context, where the process and details are unavailable not only for the public but stakeholders as well.

As regards processes related to the institutes (DAHTA, IQWiG) in Germany and Hungary (TAHD), different jurisdictions employ different approaches with respect to the selection of technologies for appraisal; the use of independent assessors; the involvement of stakeholders (e.g. manufacturers, professional groups and patient organisations); and the transparency of the process.

II.7. Conclusions

I have studied HTA in the German setting and described briefly the Hungarian HTA system among other Central-Eastern-European examples based on the published literature. There are two HTA agencies in Germany: the DAHTA as a part of DIMDI and IQWiG. Both of them produce HTA reports but the operation of these organizations differs in several aspects. The key distinction between them is that DAHTA informs the

public on benefit, risks and cost-effectiveness, while IQWiG provides information for the FJC regarding maximum reimbursement rates. In addition, there are further differences concerning the following aspects:

Structure of HTA: while at DAHTA the prioritization is open to the public and is done by the Board of Trustees; in case of IQWiG, FJC is responsible for collection and prioritization and these steps are not open to the public

Methods: (a) DAHTA conducts assessments of both benefits and costs, IQWiG applies a 2-step approach for benefit and efficiency assessment and primarily compares efficiency within diseases (using same benefit measure); (b) DAHTA's approach depends on research question, based on international and national standards, IQWiG's method is based on the efficiency frontier approach; (c) while DAHTA makes comparisons across health care system, IQWiG compares technologies within specific indications; (d) CEA conducted by DAHTA is based on cost/QALY, while IQWiG uses cost/clinical benefit in CEA

Processes for conduct of HTA: at DAHTA stakeholders are involved regularly in topic selection; at IQWiG the practice of hearings or written comments are typical

Use of HTA in decision-making: while DAHTA is a supportive information provider, i.e. it makes recommendations and other parties decide; IQWiG has direct link to reimbursement decisions as it recommends and FJC makes a decision

Accordingly, IQWiG's approach has several key points in which it differs not only from DAHTA but the practice of other organizations all around the world. Among them the aim of setting "ceiling prices" and applying a disease/indication-specific threshold instead of an explicit one in terms of cost/QALY is still heavily debated.

With the change regarding IQWiG's profile in 2010, assessments are based on the examination not only of benefits but costs as well. Therefore, these assessments support decision-making taking into consideration two dimensions of technologies instead of only one.

The Hungarian HTA system is somewhat different from the German setting, it is less developed and transparent. However, the differences might be even more significant if I compare Hungary to the UK, US or Canada. The Hungarian health care system, financing principles and incentives, the process of decision making and the role of the HTA are different in Hungary compared to these countries.

Future research is needed to evaluate whether the German HTA approach or the UK (US, Canada) HTA approach is more transferable and useful to the Hungarian settings. According to our best knowledge this issue has not been raised and evaluated yet.

As regards next steps, in order to broaden the horizon of the recent article and to synthesize the knowledge in this field, it is worth examining other HTA organizations of different countries, even continents and making direct comparisons of them.

III. TRANSFERABILITY OF HEALTH ECONOMIC EVALUATIONS IN THE EUROPEAN UNION: CHALLENGES FOR HUNGARY

Foreword

Several countries have already introduced the “fourth hurdle”, namely a requirement for cost-effectiveness evidence before reimbursement of new drugs (Gulácsi et al., [2004]). Within Europe most cost-effectiveness and cost-utility studies have been performed in United Kingdom, Northern European countries, The Netherlands, Germany, and France. These countries differ considerably from Central and Eastern European countries (CEE), among them Hungary in several aspects such as GDP per capita, health and social care systems, demography, morbidity, health status of the population in question, comparator medications, standard practice, reimbursement mechanisms of medications and financing of health care institutions, price level or unit costs. Accordingly, transferability of these health-economic results to jurisdictions of CEE is rather limited (Gulácsi et al., [2014]). Moreover, there are significant shortcomings in terms of Health Technology Assessment (HTA) capacity (number of professionals and budget to generate new country-specific HTA results) in the CEE region (Vártokné Hevér, [2012]). In the developed countries sophisticated methodology and research centres of health economics and health technology assessment were established over the past 35 years whereas CEE member states of the European Union have lagged behind. Due to methodological diversification, results of locally performed health economics studies are constrained in international utility. CEE countries are absolutely dependent on cost-effectiveness results from abroad, and this seems to persist in the long-term. Transferability and adaptability of the results of health economics studies carried out elsewhere through European collaboration is vital for these countries (Noorani et al., [2007]). Hence it is a great challenge for Hungary as well to find out how the published results can be made more transferable and more useful. So as to fulfil this purpose, the following steps should be taken:

- In principle, HTA, including economic evaluation requires data on epidemiology and other characteristics of target population, disease progression, treatment impact, preferences, resource utilizations and unit prices. In Hungary

similar to other CEE countries, valid data on these issues are rarely available (Gulácsi [2007]). Treatment effect/relative risk reduction and clinical practice patterns (resource use) may be more generalizable, whereas prices and baseline risk need to be country specific. So as to address issues of transferability, investments need to be made in the collection of epidemiological and demographic data, plus data on clinical practice patterns, resource use, costs and health state valuations (health related quality of life – HRQoL) (Brodzky et al., [2010]).

- Good epidemiology data, HRQoL and cost data are needed of course, but until we have such data we should at least try to be coherent, using the same data and the same concept of analysis in different HTA materials submitted by companies. The opportunity to learn from previous HE and HTAs would speed up the learning cycle of Health Economics (HE) and HTA professionals, and more and better materials would be created. Appraisal would be easier and quicker for the same reason. However, it is still a challenge for Hungary, as it is difficult to judge the value of these materials due to the fact that reports are not available for the public (Gulácsi et al., [2012]).

- Making studies transferable from other countries needs a high level of coordination and cooperation among key players. The fact that reports are not publicly available in Hungary creates an obstacle for them. Clear incentives from policy makers and funders would assist in the transfer of company knowledge to other jurisdictions, in this case to CEE countries. Incentives and motivation is the key to transferability (Gulácsi et al., [2012]).

On the whole, the main challenges for HTA in Hungarian context are partly similar to the ones in countries with a developed economy; no question it is time for cost-effectiveness (Gulácsi et al. [2009]). The reason why the “fourth hurdle” is very relevant in Hungary is that many existing drugs are unevaluated and many new, expensive drugs are becoming available (Gulácsi et al. [2004]). However, there are very important differences as well, that is why transferability and adaptability issues have to be taken into consideration (Kolasa et al., [2012]).

The first step of the mechanism of transferring data is the review of the available material. For Hungary, it is a rational strategy to review whether there are analyses from CEE countries as similar settings. If cost-effectiveness studies from the Czech Republic, Poland, Romania, Bulgaria or further countries of the region were found, comparing and analysing results regarding costs, treatment effects etc. might provide an approximate estimation of the Hungarian cost-effectiveness ratio.

The literature review (subsection III.2.) constitutes a chapter of a HTA book with the title of Biological therapies for the treatment of RA – systematic review of the health economic literature (V. Hevér [2014], In: Péntek, [2014]). Several parts of the book are explained by the content of previous chapters. So as to facilitate the understanding of this Part III, the Background as a short extract from the first chapter of the book is provided below.

III.1. Background: rheumatoid arthritis as a chronic condition

Rheumatoid arthritis (RA) is a chronic inflammatory arthropathy associated with articular damage, attendant comorbidities, particularly in the cardiovascular system, and with increasing disability and socioeconomic decline. RA causes pain, swelling and stiffness of affected joints, patients commonly experience fatigue. Productivity loss and work disability is a major problem in RA even today.

Several validated measures are available to assess disease activity on RA. The DAS28 can be used to assess whether an individual patient has a significant improvement of the disease activity, compared to baseline. It is also possible to choose a baseline independent absolute level of disease activity as goal for your therapeutic intervention.

The American College of Rheumatology (ACR) developed a core set for of disease activity measures for RA clinical trials. ACR 20, ACR 50, and ACR 70 reflect 20%, 50%, or 70% relative improvement compared to baseline. Clinical trials report the percentage of study participants who achieve ACR20, ACR50, and ACR70.

The Health Assessment Questionnaire Disability Index (HAQ-DI or briefly HAQ) is a valuable, effective, and sensitive tool for measurement of functional status in RA. HAQ correlates with disease duration, disease progression and moreover, with disease related costs in RA.

EQ-5D is a standardised instrument for use as a measure of health outcome. An EQ-5D health state may be converted to a single summary index, so called utility that is used to calculate the Q of the QALY. The EQ-5D is one of the most extensively studied instruments and shows validity and responsiveness for use in RA. Furthermore, a strong relationship has been proved between HAQ and EQ-5D in RA, thus HAQ has been widely used in RA health economic studies to model disease progression, related costs and utilities.

Drug treatment of RA comprises three main modalities: disease-modifying antirheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GCs). A significant proportion of RA patients can attain a state of very low disease activity or remission with traditional DMARDs (also called synthetic DMARDs) such as methotrexate (MTX) and leflunomide (LEF).

New and highly effective DMARDs have continued to emerge, in particular, biological agents (also called biological DMARDs or Biological Response Modifier Drugs – BRMD) which target tumour necrosis factor alpha (TNF-alpha or TNF- α), the interleukin 1 (IL-1) receptor, the IL-6 receptor, B lymphocytes and T-cell costimulation. Currently eight biological drugs are registered by the European Medicines Agency (EMA) for the treatment of RA: abatacept (ABA), adalimumab (ADA), certolizumab pegol (CTZ), etanercept (ETA), golimumab (GOL), infliximab (INF), tocilizumab (TOC) and rituximab (RTX). Randomized controlled trials (RCTs) have demonstrated the efficacy of biologic agents in treatment of RA. (Péntek – Gulácsi, [2014]).

The objective of this part is to review and analyse the literature regarding cost-utility results of biological treatments for RA.

III.2. Biological therapies for the treatment of rheumatoid arthritis – systematic review of the health economic literature Cost-utility of biologic drugs in rheumatoid arthritis: systematic literature review and analysis of the evidences

III.2.1. Literature search

We performed a systematic literature search for health economic evaluations of abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab and tocilizumab for the treatment of RA. The search included the time period between 2008 and April 2012 and ran in the following databases: Ovid MEDLINE(R) 1946 to Present with Daily Update, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Web of Knowledge and Centre for Reviews and Dissemination (CRD).

Original articles of full economic evaluations presenting cost-utility data (cost/QALY) of biological therapies (abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab) for RA were retrieved by two independent reviewers.

Articles with full text in English or German were analysed. Data were extracted using a standard collection form and are presented in a table format but also short descriptive summary of each is provided. Quality of the economic evaluations was assessed using the checklist developed by Drummond et al. (Drummond and Jefferson, [1996]).

Articles written in other language than English or German (but fulfilling our inclusion criteria based on their title and English abstract) are listed as potentially relevant publications.

Cost-utility analyses form before 2008 were captured by a review article (van der Velde et al., [2011]). Van der Velde et al. performed a systematic literature search for cost-effectiveness studies of biological drugs (etanercept, infliximab, adalimumab, anakinra, abatacept, rituximab, natalizumab, golimumab, and efalizumab) compared to

any DMARD⁶ for RA (van der Velde et al., [2011]). The electronic literature search was closed in the 3rd quarter of 2008. Altogether 18 health economic evaluations were selected, 16 of them were cost-utility analyses which were included in our current report.

III.2.2. Results

The search resulted 450 hits, 23 articles fulfilled our inclusion criteria.

The number of hits and included articles were as follows (articles overlapping between databases are listed only where first appeared):

- Ovid MEDLINE(R) 1946 to Present with Daily Update – 85 hits / 17 articles included (Belevitin et al., [2010]), (Benucci et al., [2011]), (Brodszky et al., [2010]), (Davies et al., [2009]), (Hallinen et al., [2010]), (Kielhorn et al., [2008]), (Kobelt et al., [2011]), (Lindgren et al., [2011]), (Merkesdal et al., [2010]), (Prokes, [2009]), (Sany et al., [2009]) (Schulze-Koops et al., [2009]), (van den Hout et al., [2009]), (Vera-Llonch et al., [2008]), (Virkki et al., [2008]).

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations – 15 hits / 2 articles included (Diamantopoulos et al., [2012]), (Soini et al., [2012]).

- Web of Knowledge – 250 hits / 3 articles included (Benucci et al., [2009]), (Kobelt et al., [2009]), (Malottki et al., [2011]).

- Centre for Reviews and Dissemination (CRD) -100 / 1 included article (Schipper et al., [2011]).

⁶ disease-modifying antirheumatic drugs

The list of hits and reasons of exclusion are available at **webpage:** <http://hecon.uni-corvinus.hu> : *Péntek (ed.): Biologicals in rheumatoid Arthritis – Appendix 8.8*

Among the 23 articles 1 was in Czech and 1 in Russian and the full text was not available for 1, thus we performed detailed analysis of 20 publications and provide only abstract for the other three.

The systematic review by Velde et al. included 16 articles analysing the cost-utility of adalimumab, etanercept or infliximab, no studies on rituximab or abatacept were identified (van der Velde et al., [2011]).

In the next sections first we give a summary of the 16 cost-utility studies (time period: - 2008) discussed by Velde et al. (van der Velde et al., [2011]). Then a short description of the 20 articles from our additional search (2008-2012) is provided. Main data (characteristics and results) of the analysis are presented also in tables using a standardized extraction format (Appendix VII.1., VII.2., VII.3) Quality assessment of the economic evaluations according to the Drummond checklist is presented separately (Appendix VII.4., VII.5., VII.6.).

III.2.2.1. Systematic review by Velde et al. (2011)

In this systematic review (van der Velde et al., [2011]) incremental cost-effectiveness ratios (ICERs) were stratified by biologic agent and indications for the use of biologics in RA patients.

Sixteen cost-utility studies were involved (Bansback et al., [2011]), (Barbieri et al., [2011]), (Barton et al., [2004]), (Brennan et al., [2007]), (Chen et al., [2006]), (Coyle et al., [2006]), (Jobanputra et al., [2002]), (Kobelt et al., [2004]), (Kobelt et al., [2003]),

(Kobelt et al., [2005]), Marra et al., [2007]), (Spalding and Hay, [2006]), (Tanno et al., [2006]), (Welsing et al., [2004]), (Wong et al., [2002]).

- DMARD naive patients: five studies evaluated a DMARD sequence containing a biologic agent compared to a DMARD sequence without biologics in patients with no previous DMARD experience (one study focused on early RA patients).

- Patients with MTX failure: three studies evaluated biologic combination therapy in methotrexate-resistant patients.

- Patients with min. 2 DMARD failures: eight evaluations analysed the cost-utility of inserting a biologic monotherapy or combination therapy into a DMARD sequence compared to a DMARD sequence in patients who failed at least 2 DMARDs.

Biologic agents evaluated included adalimumab, etanercept, and infliximab, either as monotherapies or combination therapies and one study evaluated biologics as a class (tumour necrosis factor-alpha antagonists). Authors did not identify evaluations of the interleukin-1 receptor antagonist anakinra, second-generation biologics (e.g., abatacept, rituximab) or the lately registered agents (golimumab or certolizumab pegol).

Biologics were compared to DMARD monotherapies, combination therapies, DMARD sequences and mixed drug treatments that included DMARDs and other drugs. There was extensive heterogeneity across the selected evaluations in terms of characteristics of the patient population and methods applied. Most evaluations were conducted in the US (n=5), UK (n=4), Sweden (n=3), Canada (n=2), The Netherlands (n=1) and Japan (n=1). Economic perspectives included societal (n=8) and payer (n=11). Most evaluations considered a lifetime time horizon (n=10). All of the studies considered direct costs, 9 incorporated indirect costs as well. All cost-utility studies used model-based analytic approaches. Efficacy data from the Anti-Tumour Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) were used in all of the studies that evaluated infliximab, except 3 studies that used registry or other data. Similarly RCT data for etanercept and adalimumab were the most frequently applied.

The quality of life weight most often used to calculate QALYs was a score derived from the EQ-5D Index (and one missed to identify the utility used), weights were mainly (n=10) derived by transforming HAQ⁷ scores using linear regression.

ICERs were converted and presented in 2009 Canadian dollars by the authors.

In patients with no previous DMARD experience (biologic DMARD sequence vs. traditional DMARD sequence) no studies were conducted from the societal perspective. The median ICER from the payer's perspective varied between \$270 000 and \$77 000 per QALY depending on the position of the biologic drug within the sequence (the later the more beneficial), and the overall median ICER was \$130 000/QALY. (The median ICER of infliximab + MTX was \$142,000/QALY [range \$100 000 –\$169 000/QALY].)

In patients who failed methotrexate monotherapy (biologic combination therapy versus methotrexate monotherapy) 3 studies evaluated biologic combination therapy (infliximab+MTX), all the three took the societal perspective and 2 studies also took a payer perspective (Kobelt et al., [2003]), (Marra et al., [2007]), (Wong et al., [2002]). Efficacy data were retrieved from the ATTRACT trial. ICER values ranged from \$6 000–\$92 000/QALY.

In patients who failed at least 2 DMARDs eight evaluations estimated the cost-utility of inserting a biologic monotherapy or combination therapy into a DMARD sequence compared to a DMARD sequence. All of them took the societal perspective (one performed the analysis from the payer perspective as well). ICER values varied highly within a range of \$45 000–\$612 000/QALY. Median ICERs by biologic drug were \$81 000/QALY for adalimumab, \$79 000/ QALY for adalimumab+MTX, \$127 000/QALY for etanercept, \$75 000/QALY for etanercept+MTX, and \$133 000/QALY for infliximab+MTX. There were no consistent trends across the results.

Authors conclude that at a willingness to pay threshold of \$50 000 per QALY gain (Canada 2009), biologics were not cost effective in patients with no previous DMARD

⁷ Health Assessment Questionnaire

exposure and patients who failed MTX combination therapy or sequential DMARD administration. Evidences suggest cost-effectiveness in patients who failed MTX monotherapy, nevertheless, this might be partly due to the choice of comparator, where methotrexate-resistant patients continued to receive methotrexate.

III.2.2.2. Analysis of the articles revealed by the additional search

The 20 articles were stratified by patient groups:

- DMARD naive patients: 4 articles (Davies et al., [2009]), (Kobelt et al., [2011]), (Schipper et al., [2011]), (van den Hout et al., [2009]).
- RA patients with synthetic DMARD failure: 8 articles (Diamantopoulos et al., [2012]), (Kobelt et al., [2009]), (Lekander et al., [2010]), (Sany et al., [2009]), (Schulze-Koops et al., [2009]), (Soini et al., [2012]), (Vera-Llonch et al., [2008]), (Virkki et al., [2008]).
- RA patients with biologic DMARD failure: 8 articles (Benucci et al., [2011]), (Brodzky et al., [2010]), (Hallinen et al., [2010]), (Kielhorn et al., [2008]), (Lindgren et al., [2009]), (Malottki et al., [2011]), (Merkesdal et al., [2010]), (Vera-Llonch et al., [2008]).

Methotrexate naive RA patients

Davies et al., United States (2009) – TNF- α antagonists

The objective of this study was to estimate the comparative lifetime cost-effectiveness of sequenced therapy with TNF- α antagonists as the initial therapeutic intervention for patients with early RA (Davies et al., [2009]). The model following a structure described by Bansback et al. examined costs and clinical outcomes over a course of five competing sequential regimens, rather than by comparing single agents against another:

- a reference sequence without biologic therapy

- 3 sequences with a single biologic followed by traditional DMARD
- a dual biologic sequence in which treatment was initiated with adalimumab+MTX followed by etanercept monotherapy (within a supplementary analysis)

In the base case analysis the adalimumab-plus-MTX-initiated sequence resulted in the greatest number of QALY (3.24 QALYs). When the adalimumab-plus-MTX-initiated sequence was followed by etanercept before switching to other DMARD, the number of QALY was increased by one-third over the course of therapy (4.22 QALY vs 3.24 QALY). Regarding the ICERs, the sequences of etanercept and infliximab+MTX were extendedly dominated by the adalimumab-plus-MTX-initiated sequence. Comparing DMARD and single TNF-sequences, the adalimumab-plus-MTX-sequence provided the greatest ICER of US \$47 157 per QALY. When productivity costs included, the infliximab-plus-MTX-sequence was dominated by the etanercept sequence, although both remain extendedly dominated by the adalimumab-plus-MTX-sequence for which ICER was US \$23 377 per QALY compared with the etanercept sequence.

According to the supplementary analysis, the strategy of treating with etanercept as a second-line TNF-antagonist subsequent to first-line adalimumab could yield an additional QALY compared with adalimumab and extendedly dominated all single TNF-strategies, at a cost of US \$42 727 per QALY and US \$19 663 per QALY if productivity was included. At US \$50 000 considered a minimum cost-effectiveness threshold in the US adalimumab-plus-MTX therapy was found to have a 70% probability of being cost-effective.

The results of sensitivity analyses demonstrated how the cost-effectiveness of adalimumab versus DMARD changed with varying assumptions:

- applying a EQ-5D utility regression by Kobelt, et al increased the cost per QALY of adalimumab to US \$65 000

- when the HAQ progression was assumed to be twice or when the withdrawal rate from DMARD therapy was half both that applied in the base case, cost per QALY was also between US \$60 000 and US \$70 000
- radiographic progression evidence suggests that TNF-antagonists may arrest disease progression to the extent that the HAQ score remains stable during periods of continued response. This scenario produced the lower ICER for adalimumab of US \$36 000.
- other sensitivity analyses produced cost per QALY for adalimumab versus etanercept of between US \$42 000 and US \$54 000.

The analysis outlined above had 3 primary limitations:

- ERA trial data were used to model responses to etanercept monotherapy as combination therapy with MTX was not studied in the ERA
- the model did not consider the influence of delays in treatment initiation for early ERA
- the study suffered from a paucity of evidence on the effectiveness of traditional DMARD

This model based analysis showed that of the 3 TNF-antagonists, adalimumab had the most favourable cost-effectiveness, whether used as initial therapy followed by DMARD or followed sequentially by another TNF-antagonist (Davies et al., [2009]).

Van den Hout et al., The Netherlands (2009) – infliximab

The objective of this study was to evaluate societal costs and QALYs of four treatment strategies for patients recent-onset active RA (sequential monotherapy, step-up combination therapy, initial combination therapy with prednisone, or initial combination therapy with infliximab – BeST trial) (Van den Hout et al., [2009]).

The study differs from previous ones at certain points:

- the article based on the observational data of Bet study while previous ones were all modelling studies, combining different types of data from different sources
- previous studies all compared fixed medication therapies, whereas the study of Van den Hout et al. compared dynamic strategies, intensifying or tapering medication based on the patient's status
- the study contained exclusively cost-utility analysis

As for the results, in the primary analysis based on the British EQ-5D, with societal costs, according to the friction cost method, the QALYs and costs for strategy 1 were less favourable than for strategies 2 and 3. Strategy 4 resulted in the highest number of QALYs, but at considerably higher costs: the cost-utility ratio of strategy 4 compared with the best alternative, strategy 3, was €130 000 per QALY, which is generally considered too high.

In the secondary analysis based on the Dutch EQ-5D, SF-6D and time trade-off (TTO), the QALY differences between strategies were smaller than for the British EQ-5D, therefore the cost-utility ratios of strategy 4 compared with strategy 3 were higher: €140 000; €250 000 and €320 000 per QALY, respectively.

Restricting costs to only health care (with QALYs based on the British EQ-5D), the cost-utility ratio of strategy 4 compared with strategy 3 was €190 000 per QALY.

The most crucial factor in the secondary analyses was the method used to value productivity costs. If productivity was valued according to the human capital method, then the costs and QALYs for strategies 1 and 2 were less favourable than for strategies 3 and 4. The cost-utility ratio of strategy 4 compared with strategy 3 was €22 000 per QALY, which was generally considered highly acceptable. It is an important establishment of the article that using the human capital method, the more favourable productivity costs almost completely compensated for the higher costs of the initial combination therapy with infliximab.

The study showed that initial combination therapy with infliximab resulted in significantly better quality of life than the other treatment strategies. Considering only health care costs, this improvement is obtained at costs that are generally considered too

high, and initial combination therapy with prednisone would be preferred. Depending to the extent to which productivity was valued, the costs of infliximab could be largely compensated by saving on productivity costs (Van den Hout et al., [2009]).

Kobelt et al., Sweden (2011) – etanercept

In this article the cost-effectiveness of early biologic treatment, followed by dose-reduction in the case of remission is compared with standard treatment (Kobelt et al., [2011]). The economic model adapted was based on the combined effect of function and disease activity to estimate costs and utility of different treatment options and radiographic progression was incorporated as an effect on function. Regarding the results, the ICER for etanercept/MTX was €13 500 compared with MTX alone. As for sensitivity analyses, it was performed for the time horizon, the perspective, the discontinuation rate, the proportion of patients switching or returning to full dose and the utility adjustment in the biologics group. As for the results of sensitivity analyses, costs for the etanercept/MTX strategy were slightly higher, but associated with a QALY gain of 1 to 2.3. Results were most sensitive to the drop-out rate, the duration of treatment with reduced etanercept dose, time horizon and the perspective of the analysis. The utility adjustment did not change the results significantly. ICERs changed with varying certain assumptions:

- when 75 percent instead of 50 percent of drop-outs are switching to a biologic, the cost per QALY gained with etanercept/MTX decreases to €10 400 as costs in the MTX strategy increased proportionally more due to the higher underlying drop-out rate
- if the drop-out rate increased in both groups, the cost per QALY for etanercept/MTX decreased, again due to a larger cost increase in the MTX strategy: with a double drop-out rate, the ICER decreased to €2 200.
- if failure to maintain remission was double, or if dose reduction was only possible during the clinical trial period, the ICER for etanercept/MTX increased to €19 400.
- including only medical costs, the ICER increased to €34 000
- a longer time perspective (20 years) reduced the ICER to €8 200

The core point of the study was that the dose-reduction in the early RA may influence positively the cost-effectiveness of biologic treatment. The results indicated that a situation where a considerable proportion of patients achieved remission, dose-adjustments will increase the cost-effectiveness of treatment (Kobelt et al., [2011]).

Schipper et al., The Netherlands (2011) – TNF- α inhibitors

A Markov model was used to evaluate the cost-effectiveness of the following three strategies on 5-year horizon: starting MTX monotherapy, followed by the addition of leflunomide (LEF), followed by MTX with addition of anti-TNF; Strategy 2: start with MTX and LEF combination followed by MTX with anti-TNF; and Strategy 3: immediate start with MTX and anti-TNF (Schipper et al., [2011]). The analysis was performed following both a health care and societal perspective. Starting with a combination (MTX plus LEF or anti-TNF) was more costly than starting with MTX alone, the ICER for starting on anti-TNF vs. initially MTX was from the health-care perspective €138 028/QALY and from a societal perspective of €136 150/QALY over 5 years (Schipper et al., [2011]).

RA patients who failed synthetic DMARD therapy

Vera-Llonch et al., US (2008) – abatacept

The cost-utility of abatacept treatment in women aged 55–64 years with moderately to severely active RA and inadequate response to MTX was analysed on a 10-year and lifetime horizon (Vera-Llonch et al., [2008]). Abatacept plus methotrexate therapy was compared to methotrexate treatment, no other biological drugs were considered as alternative strategies. Efficacy data were retrieved from the abatacept phase III clinical trial (AIM). Abatacept therapy was assumed to result an improvement in the HAQ-DI in comparison with MTX alone. Patients with HAQ-DI improvements of 0.5 or greater at 6 months were assumed to continue to receive abatacept; those failing to achieve this

level were assumed to discontinue treatment with a HAQ returning to a value equal to what it would have been in the absence of such treatment. All patients discontinuing abatacept (irrespective of reason) were assumed to continue to receive MTX. For patients receiving MTX only the HAQ-DI was assumed to increase by 0.065 annually to reflect disease progression. For patients receiving abatacept plus MTX the estimated mean (SD) percentage HAQ-DI change at 3 months following therapy initiation was -30.2% ($\pm 36.1\%$); at 6 months, it was -35.2% ($\pm 37.6\%$). This clinical benefit was assumed to remain constant in those who continued abatacept, nevertheless an annual disease progression of 0.015 was applied. Only medical treatment costs were considered and both costs and utilities were estimated on predicted values of the HAQ. A discount rate of 3% was applied. Mortality risk was estimated based on age and the expected value of the HAQ-DI.

Over 10 yrs., the non-discounted QALY gain with abatacept was 1.2 per patient (4.6 vs. 3.4 for MTX) at an incremental (discounted) cost of \$51 426 (\$103 601 vs. \$52 175, respectively); over a lifetime, corresponding figures were 2.0 QALYS (6.8 vs. 4.8) and \$67 757 (\$147 853 vs. \$80 096). Cost-effectiveness was [mean (95% CI)] \$47 910 (\$44 641; \$52 136) per QALY gained over 10 years and \$43 041 (\$39 070; \$46 725) per QALY gained over a lifetime. The probability that abatacept would be cost-effective at a threshold of \$50 000 per QALY was 0.80 over a 10 year time horizon, and 0.99 when a lifetime perspective was employed.

Sensitivity analysis was performed for different scenarios (e. g. no therapy discontinuation for lack of efficacy or other reasons; therapy discontinuation for lack of efficacy occurs at 3 months; variation of mortality related to HAQ; no mortality benefit with abatacept therapy; variation of annual HAQ increase; variation of the threshold for clinically meaningful improvement) confirming the robustness of the results (10-year: \$40 190 to \$70 209, lifetime: \$37 551 to \$60 106 per QALY) (Vera-Llonch et al., [2008]).

Virkki et al., Finland (2008) – infliximab

Cost-utility of infliximab was estimated in Finnish RA patients in a real-life clinical setting (n=297) (Virkki et al., [2008]). The median ICER of infliximab versus synthetic DMARD treatment was 51 884 €/QALY. The strength of this analysis is that real-life data were extensively used nevertheless methodological weaknesses hampers the results (e.g. no alternative biologicals were considered for the analysis) (Virkki et al., [2008]).

Kobelt et al., Sweden (2009) - TNF- α inhibitors

Kobelt used patient level data from a registry to feed a discrete event simulation model. They analysed the cost-utility of TNF inhibitor treatments in Sweden (Kobelt et al., [2009]). The 10-year costs in the base case amounted to USD336 000 (S.D.=USD 64 000) or €223 000, with a total of 4.4 QALYs. Over 5 years, the costs amounted to USD 208 000 or EUR 138 000 and QALYs to 2.5. The results were most sensitive to HAQ level at treatment start, but also to underlying disease progression, age, and disease duration. Starting treatment at a lower HAQ level (0.85) reduces costs by 10% and increases QALYs by 20% (Kobelt et al., [2009]).

Sany et al., France (2009) – infliximab

A cost–utility analysis of the annual costs was done with a comparison between the previous and the following year under infliximab treatment based on registry data, involving a cohort of 635 RA patients (Sany et al., [2009]). The analysis was performed from the health insurance coverage point of view however indirect costs were also considered. Before the use of infliximab, after 1 and 2 years, the mean annual cost per patient for the care of RA was €9 832, €27 723 and €46 704, respectively. In this analysis the incremental net benefit (INB) was used instead of ICER. INB is an indicator equivalent to the cost–effectiveness ratio. It is defined for a willingness to pay λ by the formula $INB(\lambda) = \lambda \Delta \text{Effectiveness} - \Delta \text{Costs}$. $INB(\lambda) > 0$ means that, for the willingness to pay λ , the cost–effectiveness ratio is perhaps acceptable by the society and will be so if the 95% CI is positive and lower than the acceptable threshold λ (€45 000 in France). According to the analysis when it was expressed in QALYs, also for severe HAQ, $\lambda > €100 000$ (Sany et al., [2009]).

Lekander et al., Sweden (2010) – infliximab

The main feature of this study is that the assessment of cost-effectiveness of infliximab compared to nonbiological treatment based on real-world patient-level data (Lekander et al., [2010]). These patient-level data were derived from the SRQ (Swedish Rheumatology Quality) Register. Such patient registries have several advantages:

- enable important complementary analyses of cost-effectiveness of TNF-use in RA
- represent real-world use compared with the more selective and controlled nature of the trial-based data
- using large patient cohorts from clinical practice ensures high external validity of the assessments
- disease-progression while on treatment can also be tracked over longer time compared with data from clinical trials which generally have shorter follow-up
- using registry data enable incorporation of real-world data on drug discontinuation patterns in the economic evaluation

On the other hand, where it was necessary, the data have been complemented with published data, including rate of natural disease progression, costs and utilities. For example, the comparator arm (natural progression without biological treatment) was based on published results from the ERAS study and not on STURE registry data which reflects the most important limitation to cost-effectiveness assessments based on real-world data.

Another particular characteristic of the model applied is that data on adverse events were included.

According to the STURE registry data, there was a change in treatment patterns over time, identifying a change to infliximab use earlier in the course of the disease in more recent years which was reflected both in shorter disease duration and lower baseline

HAQ values. Based on disease duration at start of infliximab therapy, subgroups of patients in the data set with earlier stage RA and later stage RA were, therefore, analysed separately and compared with the base case, enabling a reflection of how the cost-effectiveness have been affected by this shift in treatment strategy.

Regarding the results, the base case analyses showed that the gain in QALYs associated with infliximab treatment was 1.019. Infliximab was also associated with an incremental cost of €23 264, resulting in an ICER of €22 830. According to the analyses of earlier- and later-stage RA, the ICER was lower for patients with earlier-stage RA and higher for patients with later-stage RA compared with the base case.

The sensitivity analyses conducted estimated the effects of a range of variables: adverse events, age at start of treatment, costs, discount rate, disease progression, drug costs, and mortality. In addition, both best- and worst-case scenario were performed. As for results, age at start of treatment initiation and the rate of natural disease progression had the largest effect on the ICER. The results ranged from €18 000 to €47 000. The best-case scenario resulted in an ICERs of €8 360 and the worst-case scenario €67 237.

The main surplus value of this analysis was the assessment based on real-world data. The ICERs of infliximab compared with natural progression and ICERs in all sensitivity analyses fell well below €65 000 per QALY which is a commonly referred threshold for cost-effectiveness in Sweden. A further important interpretation of the results is that treating patients with earlier- than later- stage RA was potentially most cost-effective (Lekander et al., [2010]).

Schulze et al., Germany (2009) – etanercept

This article based on the TEMPO study which had shown that the combination of etanercept and MTX in the treatment of RA is superior to monotherapy (Schulze et al., [2009]). It further suggested that remission of RA is a realistic treatment goal. Taking into consideration these establishments, the objective of the study was to demonstrate the sustainability of the combination for daily clinical practice taking economic aspects into account.

The main characteristics of the study in which it differs from the most ones:

- containing both cost-effectiveness (CEA) and cost utility (CUA) analyses
- besides HAQ applying a German instrument, namely Funktionsfragebogen Hannover (FFbH) to measure the functionality of patients

As for the results, the incremental cost-effectiveness ratio of the combination was €21 300 per life year in remission as compared with MTX alone. The incremental cost-utility ratio of the combination was €38 700 per QALY.

These results indicate that both health-economic parameters suggest adopting the combination therapy into daily clinical practice of RA patients (Schulze et al., [2009]).

Soini et al., Finland (2012)– adalimumab, etanercept, tocilizumab

Different treatment sequences were compared in a hypothetical Finnish moderate to severe RA patients using a probabilistic microsimulation model in a lifetime scenario (Soini et al., 2012)]. Adalimumab + MTX, etanercept + MTX, or tocilizumab + MTX were used as first biologics followed by rituximab + MTX and infliximab + MTX and MTX alone was added as a further comparator. (The first-line biologic DMARD comparators included were the two established and reimbursed TNF inhibitors – the most used (adalimumab, ADA) and most affordable (etanercept, ETA) – and a new option (tocilizumab, TOC). Important note: infliximab + MTX and rituximab + MTX were considered as second line biological therapies.).The resources were valued with Finnish unit costs (year 2010) from the healthcare payer perspective but additional analyses were carried out, including productivity losses. Biologic DMARDs significantly increase the QALYs gained when compared to MTX alone. Tocilizumab + MTX was more cost-effective than adalimumab + MTX or etanercept + MTX in comparison with MTX alone, and adalimumab + MTX was dominated by etanercept + MTX. The ICER with tocilizumab + MTX methotrexate was €18 957 (€17 057) compared to MTX alone. According to the cost-effectiveness efficiency frontier and cost-effectiveness acceptability frontier in Finland, tocilizumab + MTX should be considered before rituximab + MTX, infliximab + MTX, and basic supportive care (Soini et al., 2012)].

Diamantopoulous et al., Italy (2012) – tocilizumab

An individual patient simulation model was used to assess the cost-utility of treatment sequences starting with tocilizumab or the most commonly prescribed biologics (etanercept - ETA, adalimumab - ADA, or infliximab) in Italy (Diamantopoulous et al., [2012]). In the analysis strategy ETA – ADA – RTX -ABA – palliative was compared to TOC – ADA – RTX – ABA – palliative care strategy. Alternative analysis replaced etanercept with adalimumab or infliximab: ADA – ETA – RTX – ABA – palliative; INF – ETA – RTX ABA – palliative. Authors also analysed the cost-utility of adding TOC to standard-of-care: TOC – ETA – ADA – RTX – ABA – palliative. Other TNF- α blockers such as golimumab or certolizumab pegol were not considered in the analysis. The model applied lifetime horizon. Patient characteristics, treatment efficacy, and quality of life data were based on three phase 3 tocilizumab clinical trials (OPTION, TOWARD, LITHE). Only direct costs were considered. In the base-case analysis tocilizumab dominated standard of care. In the basecase analysis replacement of etanercept with tocilizumab reduces costs and realized more QALYs. Similar results were found if adalimumab was replaced, the ICER in case of infliximab replacement was €2 655/QALY. Adding tocilizumab to standard-of-care sequence resulted an ICER of €17 119/QALY. Tocilizumab was dominant in sensitivity analyses (Diamantopoulous et al., [2012]).

RA patients who failed at least one biologic DMARD therapy

Kielhorn et al., UK (2008) – rituximab

Incremental cost-effectiveness of rituximab treatment was modelled on the lifetime horizon using a Markov model of 6-months cycles (Kielhorn et al., [2008]). The analysis compared cost and outcomes of two treatment sequences, representing the current UK standard both with and without rituximab. The population characteristics matched those of the Randomised Evaluation of Long-term Efficacy of rituximab in RA (REFLEX) phase III randomised control trial. Five HAQ categories were established in

the model and average cost for each category was estimated from the UK registry. Only direct medical costs were considered for the analysis. Utility data (health gain) were mapped from HAQ.

The model assumed that patients receive etanercept prior to entering the simulated treatment sequence, thus no further data on etanercept were presented.

In the primary analysis patients either follow the current standard treatment sequence of synthetic DMARDs reflecting real life clinical practice in the UK or an alternative sequence, which is identical, except for the introduction of rituximab:

- leflunomide, gold, cyclosporin, palliative care/methotrexate vs.
- rituximab+methotrexate, leflunomide, gold, cyclosporin, palliative care-methotrexate.

In the secondary analysis, switch between TNF α blocking agents is included:

- adalimumab+methotrexate, infliximab+methotrexate, leflunomide, gold, cyclosporin, palliative care/methotrexate vs.
- rituximab+methotrexate, adalimumab+methotrexate, infliximab+methotrexate, leflunomide, gold, cyclosporin, palliative care/methotrexate

Repeated courses of 2x1000 mg rituximab at every 9 months were considered, for all other drugs licences dose as per the EU label was used. (Infliximab: 3 mg/kg, average patient weight: 75 kg, no drug wastage or increase in dose was included in the calculation; adalimumab 40 mg every second week).

Patients enter the model and are allocated to either of the two treatment sequences. They are then exposed to the first treatment in the sequence and are allocated to one of the three responder groups (ACR 20–49, 50–69, 70+) or to the non-responder group. The mean drop in HAQ for each of these groups was calculated from the rituximab phase III trial (REFLEX). The HAQ score is assumed to drop by 0.1 for non-responders, 0.45 for ACR20–49, 0.85 for ACR50–69 and 1.11 for ACR70+ responders. While on treatment, patient HAQ scores are assumed to progress by 0.017 during each model cycle. For patients on palliative care a HAQ progression of 0.065 was assumed. Once treatment stops, the entire initial gain in HAQ is assumed to be lost instantly

(100% rebound effect). Time on treatment was applied from a study by Barton et al. assuming 4.25 years for all DMARDs (including rituximab) apart from infliximab where a higher drop-out was assumed (2.46 years). Regarding the non-biological DMARDs treatments, duration was 1.7 years for cyclosporin, 3.85 years for gold and 4.1 years for leflunomide. Mortalities derived from the life-table were adjusted to the individual's HAQ score (1.33 / unit HAQ). A discount rate of 3.5% was applied. Total discounted QALYs were 3.051 and 2.324 for the rituximab arm and the standard of care arm, respectively, resulting in an incremental QALY gain of 0.727 in the primary analysis. In the secondary analysis a lower QALY gain was observed (0.526). The incremental cost-effectiveness ratio (ICER) was £11 749 and £6 103 per QALY in the primary and secondary analysis, respectively. In the sensitivity analysis significant variability was observed in changes to rituximab dosing re-treatment (from 9 months to 6 months) and when changing the HAQ long-term progression. Variability was also observed when baseline age is increased. However when measuring the cost-effectiveness acceptability, the model estimates that there is an 89% probability of rituximab being cost-effective at a threshold of £30 000 (Kielhorn et al., [2008]).

Vera-Llonch et al., US (2008) – abatacept

Cost-utility of abatacept compared to synthetic DMARD treatment was assessed using a simulation model to depict progression of disability (HAQ) in women with moderately to severely active RA and inadequate response to anti-TNF (Vera-Llonch et al., [2008]). Outcomes and costs were simulated alternatively over 10 years and a lifetime for a hypothetical cohort of 1,000 women between the ages of 55 and 64 years. At model entry, patients were assumed to receive either oral disease modifying antirheumatic drugs (DMARD) only or oral DMARD plus abatacept. (At the time the study was conducted, efficacy data in this patient population were available for abatacept only.) Efficacy data were retrieved from the ATTAIN clinical trial. For patients receiving oral DMARD only, the HAQ-DI was assumed to increase by 0.065 annually to reflect disease progression. Patients with HAQ improvements of -0.50 or greater at 6 months were assumed to continue to receive abatacept; those failing to achieve this level of clinical benefit were assumed to discontinue treatment. Patients also were assumed to possibly discontinue abatacept for other reasons (adverse events).

All patients discontinuing abatacept were assumed to continue to receive stable doses of oral synthetic DMARD. Authors did not consider switching from abatacept to another biologic DMARD as there are no data on the efficacy of the latter agents given prior failure with abatacept. For patients discontinuing abatacept, the HAQDI was assumed to return to a value equal to what it would have been in the absence of such treatment. The QALY gain with abatacept compared to synthetic DMARD was 1.0 QALY (undiscounted) per patient over 10 years and 1.6 QALY over a lifetime. Incremental cost-effectiveness of abatacept (2 006 US\$) over a 10-year time horizon was estimated to be [mean (95% CI)] \$50 576 (\$47 056, \$54 944) per QALY gained (3% discount rate used for both costs and effectiveness). On a lifetime basis, cost-effectiveness was \$45 979 (\$42 678, \$49 932) per QALY gained. Findings were robust in sensitivity analyses (Vera-Llonch et al., [2008]).

Lindgren et al., Sweden (2009) – rituximab

Lindgren et al. estimated the cost-effectiveness of rituximab in RA patients not responding adequately to the first TNF- α inhibitor using a model constructed to predict resource consumption and health outcomes in a population-based registry of biological treatments in Southern Sweden (Lindgren et al., [2009]). Resource consumption was based on a regular population-based survey of patients in Southern Sweden. Rituximab was incorporated as second line treatment, using effectiveness from a clinical trial (REFLEX and it was thus compared to the mix of second line biologics used in SSATG. Total costs in the rituximab strategy are estimated at €401 100 compared with €403 000 in the TNF-inhibitor arm. Total QALYs are 5.98 and 5.78, respectively. In terms of ICER rituximab therapy was dominant strategy and findings were found to be robust in extensive sensitivity analysis (Lindgren et al., [2009]).

Brodzky et al., Hungary (2010) – rituximab

Cost-utility of rituximab (RTX) versus palliative care (synthetic DMARD) was modelled on a lifetime horizon in Hungary (Brodzky et al., [2010]). Two scenarios

were applied: 1 course of RTX treatment (2 infusions) and 3-year RTX therapy. Baseline patient characteristics were equivalent to the patient population of the REFLEX rituximab trial (moderate and severe RA, who have failed DMARDs and at least one TNF- α inhibitor) and efficacy data were retrieved from this same trial. Linear regression between HAQ and EQ-5D from a previous Hungarian survey was used to generate utility inputs. Official price lists were used for cost calculation and costs not directly connected with RTX treatment were estimated according to HAQ level, based on a Hungarian survey. Additionally a cost-minimization analysis was also performed to compare RTX treatment with switching from one TNF- α inhibitor to another. One course of rituximab treatment resulted an ICER of -31 140 €/QALY from societal perspective and 38 763 €/QALY from health care payer perspective. Results for repeated courses of rituximab were 11 234 €/QALY and 13 400 €/QALY, respectively (Brodszky et al., [2010]).

Hallinen et al., Finland (2010)

The aim of this study was to evaluate the cost-utility of different treatment strategies after treatment failure with one TNF-inhibitor in a Finnish setting (Hallinen et al., [2010]). Initially, the patients received either best supportive care (BSC) or one of the following treatments before BSC: adalimumab (ADA), abatacept (ABA), etanercept (ETA), infliximab (INF) or rituximab (RTX). Further treatments were added to the most cost-effective strategy in a stepwise manner. Rituximab and abatacept was considered as an option for those RA patients who did not tolerate or who did not get an adequate response to other treatments, including at least one TNF-inhibitor therapy. Regarding the results, the most efficient strategy is to use RTX+MTX→BSC or, if the WTP of €37 013 per QALY gained is not too much, RTX+MTX→INFL+MTX→BSC treatment strategies after TNF-inhibitor failure. In detail:

- adding a second biologic treatment after TNF-inhibitor failure increased the average treatment failure costs by €16 843-41 866 and gave 0.46-0.70 additional QALYs compared with BSC alone, depending on which biologic treatment was chosen. The most cost-effective choice was RTX+MTX with an ICER of €30 248 per QALY gained, which was lower than those of either INF+MTX (€36 121), ETA+MTX (€50 372), ADA+MTX (€50 941) or ABA+MTX (€67 003). Treatment with RTX+MTX

dominated ETA+MTX, ADA+MTX and ABA+MTX, as it was less costly and more effective. Compared with INF+MTX, the cost of an additional QALY with RTX+MTX was €18 585.

- when a third biologic treatment was added after RTX+MTX, the average treatment costs increased further by €14 024-35 414 and resulted in 0.38-0.52 additional QALYs, depending on which biologic treatment came next. Compared with treatment with RTX+MTX (→BSC), the ICERs of adding biologic treatment ranged from €37 013 (INF+MTX) to €68 100 (ABA+MTX) per QALY gained. Compared with giving INF+MTX as the third biologic treatment, an additional QALY with ADA+MTX, ETA+MTX and ABA+MTX cost €260 197, €145 658 and €151 562, respectively.

- in case of a fourth biologic treatment was added after INF+MTX, the average treatment costs increased further by €20 595-34 547 and 0.38-0.49 additional QALYs were gained. Compared with treatment with RTX+MTX→INF+MTX→BSC, the additional QALY with ETA+MTX cost €54 836, with ADA+MTX €54 701 and with ABA+MTX €70 616. Compared with ETA+MTX and ADA+MTX, an additional QALY with ABA+MTX costs €158 411 and €123 755, respectively.

The study showed that treatment with rituximab was a cost-effective treatment strategy in Finland (Hallinen et al., [2010]).

Merkesdal et al., Germany (2010) – TNF- α inhibitors, rituximab

This study investigated the cost-effectiveness ratios of either (1) rituximab or (2) a TNF- α inhibiting agent as second line biological treatment in patients with active RA and an inadequate response to etanercept therapy (Merkesdal et al., [2010]). The study differs from most of the cost-effectiveness analyses related to RA in several points.

- objective: while most economic evaluations focus on the cost effectiveness of TNF-inhibitors as (1) first line biological therapy after failure of DMARDs, or (2) first line therapy in early RA in comparison with MTX therapy, this cost-effectiveness analysis focused on second-line biological therapy comparing biological options after failure of TNF-inhibitors

- sensitivity analysis: uncertainties addressed by extensive sensitivity analysis, included not only the important input parameters for the model but also the methods used to derive these key parameters
- effectiveness evidence: the treatment sequence applied for the German treatment line was based on expert opinion. The employment of expert opinions in fields where superior evidence is missing is a common and accepted tool for the development of economic models

Regarding the results, the ICER of rituximab compared to the standard sequence amounted to €24 517 per QALY focussing on direct medical costs.

The inclusion of indirect costs in both treatment sequences showed higher cost estimates of €266 063 and €274 901. The incremental QALY gain was 0.57. This gave an ICER of €15 565 per QALY.

The inclusion of indirect costs reflects the cost-saving potential of highly effective drugs on long-term outcomes such as work-productivity or work-disability rates. This is an important issue for the demonstration of the real value for money of an expensive but effective treatment option. The economic impact of these positive long-term effects in rituximab treatment became obvious when comparing the ICERs when productivity costs are either included or not (€13 922 vs €8 836), indicating a drop of incremental costs of about 40% due to effects on indirect costs (Merkesdal et al., [2010]).

Malottki et al., UK (2011) - adalimumab, etanercept, infliximab, rituximab and abatacept

Malottki et al. conducted a systematic literature search in 2009 for RCTs, cost-effectiveness and cost-utility studies of adalimumab, etanercept, infliximab, rituximab and abatacept treatment in RA patients who failed at least one biological therapy (Malottki et al., [2011]). They identified three cost-utility studies which were identical

to literature search was closed at those captured by our search (Kielhorn et al., [2008], (Lindgren et al., [2009]), (Vera-Llonch et al., [2009])). They performed an independent economic assessment as well.

One course of RTX results in 0.144 QALY gain compared with palliative treatment (non-biological DMARD) in lifetime horizon, incremental direct and total costs are 5 582 € and 4 494 €, respectively, resulting an ICER of – 31 140 €/QALY from societal perspective and 38 763 € from health care payer perspective. Three-year treatment with RTX provided a gain of 0.511 QALY at an incremental direct and total costs of 13 400 € and 11 234 €, respectively, the ICER was 26 223 €/QALY from societal and 21 980 €/QALY from health care payer perspective. Cost-minimization proved that that RTX dominates TNF- α inhibitor for patients who have failed 1 previous TNF- α inhibitor therapy (Malottki et al., [2011]).

Benucci et al., Italy (2011)

This study focused on the cost-effectiveness of rituximab treatment based on follow-up data of 32 RA patients in Italy (Benucci et al., [2011]). Only direct costs were considered in the analysis. After 1 year of treatment the observed ICER on 28 patients was €23 696/QALY. The ICER was more favourable if rituximab was applied as second line compared to third line treatment (Benucci et al., [2011]).

III.2.2.3. Summary of the main findings of the new literature search

DMARD naive RA patients

The summary of the evidences are summed in Appendix VII.1. The four articles involving DMARD naive RA patients assessed the cost-utility of etanercept, infliximab

and adalimumab as first line therapies. Two of them were performed in The Netherlands, one in the US and one in Sweden. Among the studies 1 applied payers', 2 societal perspective and 1 both. All of them applied discount rates (3% n=3; 4% n=1) both for the effects and costs. Efficacy data were derived from different sources including registry and RCT data (e.g. BeSt trial, COMET trial) but also assumptions were made i.e. efficacy of TNF- α inhibitors was considered from patients with DMARD experience in one of the Dutch analysis. All the four were modelling studies (2 individual sampling, 2 Markov models), the time horizon was 2 years (n=1), 5 years (n=1) and lifetime (n=2). Utilities were obtained by the EQ-5D (n=3) and HUI (n=1) and one study performed sensitivity analysis for other utility measurements as well. In the US, the ICER of adalimumab sequence dominated the etanercept and infliximab sequences. In The Netherlands the ICER of strategy 4 (initial combination with infliximab) compared with strategy 3 (initial combination with prednison) was €130 000/QALY, and in the other Dutch study the ICER of anti-TNF strategy compared with the MTX strategy was €136 207/QALY from the societal perspective. In Sweden early etanercept therapy was compared to MTX alone, no other biologicals were considered in the analysis. The ICER for the biologic strategy was €13 518/QALY if dose adjustment was allowed for patients in remission.

RA patients who failed at least one traditional DMARD therapy

The summary of the evidences is given in Appendix VII.2. Eight analyses estimated the cost-utility of biologicals in RA patients who failed at least one traditional DMARD therapy. The studies were performed in Sweden (n=2), Finland (n=2) US, (n=1), France (n=1), Italy (n=1) and Germany (n=1). The health care payer's perspective was used in the majority of the studies (n=5). Besides the TNF- α inhibitors abatacept and tocilizumab were also analysed. Six models and two observational studies were applied and data sources of efficacy were not restricted only to RCTs but real life data were also incorporated in many analyses. Seven studies derived EQ-5D utilities from HAQ (regression) and only one in Sweden used survey results of a registry. Most studies used lifetime horizon but alternative assessments were often performed in sensitivity analyses. In general, the ICER for TNF- α inhibitors was within the acceptable range.

Studies suggest that tocilizumab might be beneficial as well, abatacept resulted an ICER \$47 910 on 10-year horizon when compared to MTX therapy (no other alternatives were considered).

RA patients who failed at least one biological DMARD

The summary of evidences is presented in Appendix VII.3. Eight studies analysed the cost-utility of biologicals for RA patients whom has already failed at least one biological DMARD therapy. The studies were performed in the UK (n=2), US (n=1), Sweden (n=1), Finland (n=1), Germany (n=1), Italy (n=1), Hungary (n=1). Rituximab and abatacept treatments were compared to traditional DMARD and TNF- α inhibitor sequences. With the exception of a 1-year observational study in Italy, all evaluations applied modelling approach on a lifetime horizon, data for effectiveness were retrieved from RCTs. Societal perspective was used only in three studies. Rituximab seems to be dominant strategy compared to TNF- α inhibitor sequences. The ICER of abatacept compared to MTX therapy was \$50 576/QALY on a 10-year horizon and \$45 979/QALY on lifetime horizon in the US.

III.2.2.4. Potentially useful articles with English abstract

Prokes M., Czeh Republic (2009) [Article in Czech]– adalimumab, infliximab, etanercept

A comparison of effectiveness of adalimumab, infliximab and etanercept in the treatment of RA was made and cost-effectiveness of each TNF antagonist for Czech Republic was performed (Prokes M., [2009]). The prices of therapy of all three TNF antagonists are similar in the first year of treatment of patients with average weight, in

the second year the price of infliximab is lower, but only in the case of patients where the doses do not reach 4 amp. of infliximab. Clinical effectiveness was evaluated in DAS28 and HAQ units. Cost-effectiveness of all TNF antagonists was similar, when 2 amp. of infliximab per dose physician considered sufficient, but when patients were given higher doses of infliximab the trend to lower cost-effectiveness of infliximab compared to adalimumab and etanercept was observed (Prokes M., [2009]).

Belevitin AB et al, Russia (2010) [Article in Russian]

According to Medline parameters of the article authors discuss the costs and benefits of adalimumab in RA and the methods of economic assessment of advisability of modern biological medication usage in military medicine (Belevitin et al., [2010]).

Benucci et al., Italy (2009) [full text not available]

The objective of this study is to perform a cost-effective analysis of 86 patients with RA in therapy with adalimumab 40 mg every other week and etanercept 50 mg/week for two years in a population of patients observed in clinical practice (Benucci et al., [2009]). Incremental costs and QALYs gains are calculated compared with baseline, assuming that without biologic treatment patients would remain at the baseline level through the year. The results after two years showed an ICER for the adalimumab group €42 521.13/QALY and for the etanercept group €39 171.76/QALY (Benucci et al., [2009]).

III. 3. Discussion, conclusions

There is an increasing demand for cost-effectiveness data in the decision making process across Europe. Cost-effectiveness analyses are always comparative and incremental, that is, they permit an insight to the benefits, costs and the potential savings of a product compared with other pharmaceuticals and/or treatment, optimally in a reliable, reproducible, and verifiable way. However, to make the cost-effectiveness analysis useful for decisions on resource allocation, the health benefit must be expressed

with a measure that is comparable across diseases. Cost-utility analysis expresses the incremental benefits of a treatment compared to others in "quality-adjusted life-year" (QALY) where the "Q" includes information on the utility of a health status from a societal point of view. The incremental cost-utility ratio (ICUR, but often called simply as incremental cost-effectiveness ratio - ICER) presents then the incremental expenditures needed to achieve 1 QALY gain. The lower the ratio of a cost per QALY, the most cost-effective the intervention is said to be.

Even though there is no theoretical or empirical basis for it, ICER values ranging from \$50 000 to \$100 000 / QALY are sometimes used as a threshold in the United States, where as in the UK, NICE has adopted a cost-effectiveness threshold range of £20 000 to £30 000 / QALY gained (Nuijten and Dubois, [2011]). Although in several European countries (including Hungary and many others from the Eastern and Central region) there is not a well-defined threshold for reimbursement decisions, the ICER ratio is often used as basis for the evaluation of new technologies.

Therefore, in our current report we focussed on cost-utility analyses of biological therapies in RA. Our systematic literature review revealed 36 cost-utility studies. The majority (n=19) evaluated biological treatment for RA patients who have already failed at least one traditional DMARD therapy, eight considered those who have failed at least one biological drug. However the number of studies involving DMARD naive RA patients was rather substantial as well (n=9).

There are several key steps when performing and interpreting health economic reports. These include (1) defining perspective and time horizon, (2) collecting data on healthcare utilization, (3) costing healthcare resources,(4) analysing data on utilization and cost, (5) defining and measuring health effects, (6) adjusting costs and effects for inflation and discounting, (7) and evaluating uncertainty (Nuijten and Dubois, [2011]). There was extensive methodological heterogeneity across the 36 selected health economic evaluations. Economic perspectives included societal and payer, some studies presented results for both. The majority applied model-based analytic approach but some relied on short (1 or 2 years) observational data. All of the studies considered direct costs but indirect costs were ignored by many evaluations. Data from randomized controlled trials were used the most frequently to assess effectiveness but in some cases (especially in the latest analysis) findings from registries were also incorporated. Real-

world data might refine the results of RCT based economic evaluations and be more generalizable to the field. However at the same time their outputs are more difficult to interpret and the internal validity of the findings is more limited.

The quality of reporting is crucial in health economic publications since usually neither the model itself nor the inputs (e.g. patient level data from RCTs or cohorts) are available. Hence the analysis is not reproducible for outsiders and critical appraisals have to rely on the reported data. The checklist developed by Drummond et al. is widely used for the quality assessment of health economic papers (Drummond and Jefferson, [1996]). Applying these criteria on the 36 selected publications we found that reporting practices often failed to present key data appropriately. Authors commonly missed to describe methods for identifying, selecting, and synthesizing data for key model parameters and also study design was not clearly described in many publications. Important details which might have significant impact on the results (e.g. dose escalation) were frequently missing from the description.

Considering the above mentioned variability and weaknesses of the methods definitive conclusions are difficult to make regarding the cost-utility of biologicals in RA. There is mixed evidence of cost-effectiveness in selected populations. For instance, the ICER of infliximab+methotrexate therapy for RA patients who failed methotrexate monotherapy varied between 6 451 – 91 484 CAN\$/QALY in a Canadian review (Van der Velde et al., [2011]). Not only the time horizon and discounting were deterministic but also different utility measures (EQ-5D, HUI-2, HUI-3, SF-6D) resulted quite diverse ICERs (37 209 – 80 620 CAN\$/QALY) even if the same perspective was applied (Marra et al., [2007]).

However for the current health technology assessment the basic questions are whether the available literature results are relevant to CEE countries (namely Bulgaria, Czech Republic, Hungary, Poland, Romania and Slovak Republic), and how to transfer them to support local policy making, financing and reimbursement decisions and professional guidelines.

Most of the cost-utility analyses were performed in the US (n=8) and Northern Europe (Sweden n=7, Finland n=3), but countries from Western Europe also contributed

with numerous evaluations (UK n=6, The Netherlands n=3, Germany n=2, Italy n=2, France n=1). Canada and Japan had 2 and 1, respectively. Only one publication from Hungary was available in English.

These countries differ considerably from CEE countries in GDP per capita, health and social care systems, demography, morbidity, health status of the given population in question (RA), comparator medications, standard practice, prescription behaviours of the doctors, reimbursement mechanisms of medications and financing of health care institutions, price level, unit costs, direct and indirect costs. Thus the transferability of these health economic results to jurisdictions of CEE is rather limited. Furthermore, there are noticeable limitations in terms of HTA capacity (number of professionals and budget to generate new country specific HTA results) in the CEE region. Hence it is essential to find out how these published results could be made more transferable and more useful. Managed transferability is crucial for sustainable financing of biological medications.

For that purpose a wide spectrum of deterministic factors has to be analysed, such as country-specific RA guidelines (both professional and financing), financing mechanisms, patient data, financing incentives, access to health care facilities where biologicals provided to RA patients. Some important questions will be answered by this HTA report. However, we will presumably face the problem of lack or at least shortage of information. To bridge this gap and to achieve reliable data we have to collect as many reliable local data as possible and develop a model which is able to represent the environment where it is used (country-specific characteristics) and which also allows investigating the effect of different hypotheses and scenarios on a number of outcomes. Conference abstracts reflect an increasing activity in many countries and it is highly probable that further studies can be captured by reviewing local papers and submission dossiers. For instance in Hungary, several cost-of-illness studies, partial and full HTA reports are available in Hungarian often with short English abstract (Brodszky et al., [2009]; Brodszky et al., [2007a]; Brodszky et al., [2007b]; Brodszky et al., [2007c]; Gulácsi and Lepp-Gazdag, [2002]; Májer et al., [2006]; Péntek et al., [2011]; Péntek et al., [2007]). These sources might offer important inputs for country-specific health economic modelling and provide relevant information about the reimbursement practice in a specific country.

I find important to note that the heterogeneity of the cost-effectiveness literature and the scarcity of studies from the CEE region seems to be not specific only for RA. I found similar results in the evaluation of the cost-effectiveness literature for biological drugs in Crohn's disease (CD), another chronic inflammatory disease (V.Hevér, Brodsky, Gulácsi, [2014], In: Baji [2014]; V.Hevér, Péntek [2014], In: Baji [2014]). (See Appendix) Our systematic review in CD revealed twelve cost-utility analysis of adalimumab and/or infliximab treatment for CD from the UK (n=5), US (n=4), Canada (n=2) and France (n=1). Studies were performed from the third party payer perspective and regardless of the chronic character of CD, most of the models included a short time horizon (1-year n=7, 5-year n=2). Differences in comparators, methods, data, modelling approach prevent reliable interpretation of the results. Nevertheless, available cost-utility suggest that adalimumab treatment is likely to dominate infliximab. Sensitivity analyses revealed that with a sufficiently large price reduction infliximab treatment may have become cost-effective. There were no cost-utility studies from Central Eastern European (CEE) countries according to our international literature search.

IV. CHALLENGES IN THE ASSESSMENT OF DISEASE BURDEN: CASE STUDY IN A CHRONIC DISEASE

Foreword

Health economic evaluation requires data on health related quality of life (HRQoL) and costs. HRQoL related data may differ among countries. It is crucial to develop valid versions of HRQoL measures for each country in order to make data comparable across different jurisdictions. The transferring of cost data is quite limited between countries due to their different socio-economic conditions. Consequently, in order to conduct health economic evaluation in a reliable way, there is a need for local data. Based on this background, we designed an empirical study in the field of oncology, namely in bladder cancer (BC). The purpose of this study was to develop and validate the Hungarian Version of a BC-specific questionnaire, to assess the HRQoL of a Hungarian BC patient population and to estimate the CoI.

This part of the dissertation consists of four subsections. The key element of this part is the empirical study involving patients with bladder cancer (BC). This original article targets an oncology journal, thus it just introduces the disease only very briefly and does not contain the review of the related literature in detail. Therefore, the BC is described in the first subsection (IV.1.) so as to support understanding of the study. Then I provide the summary of the international and Hungarian literature review regarding HRQoL; validation of the Bladder Cancer Index (BCI) questionnaire; and cost of illness (CoI) in BC (IV.2.). Afterwards the original article under publication is inserted (title: Health related quality of life in patients with bladder cancer: A cross-sectional survey and validation study of the Hungarian version of the Bladder Cancer Index; submitted to: Pathology and Oncology Research) (IV.3.). Lastly, the third subsection including a material prepared for submission specifies the volume and consistence of Hungarian population affected by BC (i.e. epidemiology) and cost of illness (CoI) (IV.4.).

IV.1. A brief overview about the disease of bladder cancer and therapeutic guidelines

By definition bladder cancer (BC) is a cancer that forms in tissues of the urinary bladder, the organ that stores urine (<http://www.cancer.gov/cancertopics/types/bladder>). Based on a histology result, BC can be divided into two specific groups: so-called non-muscle-invasive (restricted solely to the mucous membrane of the bladder) and muscle-invasive bladder tumours. Regarding these two groups, there is a significant difference between the prognosis and treatment. The treatment is regulated through professional and financing guidelines (Protocol about the treatment of bladder tumours by the Ministry of Health Care, 2008; Protocol about the finance of diagnostics and treatment of bladder cancer, 2010).

In diagnostics of the non-muscle-invasive BC (NMIBC), the most important examination is the cystoscopy making possible to analyse the urethra and the whole surface of bladder but in addition laboratory and imaging technologies have an important role as well. Each bladder tumour has to be removed by a technique performed through the urethra, namely transurethral resection (TUR), in the NMIBC case the diagnostics and surgical intervention may coincide. In order to hamper the recurrence of cancer, intravesical therapy is applied locally, chemotherapy of the bladder (bladder instillation) should be performed once in case of non-invasive tumour 6 hours after the intervention. Mitomycin C, epirubicin and doxorubicin are the available agents. In case of low and middle risk non-invasive tumours adjuvant chemotherapy (bladder instillation) should be performed for 6 months which is equivalent with 9 catheter interventions (once a week for 4 weeks, once a month for 6 months). In case of high risk NMIBC, local immunotherapy in the form of BCG catheter instillation is suggested at least for a year (once a week for 6 weeks, afterwards, monthly) which means 16 catheterisations per year. Urine-cytology test should be performed in every third months, and depending on the risk of tumour bladder cystoscopy is necessary to follow the disease for 5 years or more, in case of high risk urography is suggested to be performed once a year. If recurrence and progression are observed, the therapy should be modified.

In the diagnostics of muscle-invasive bladder cancer (MIBC) or metastatic tumours, cystoscopy and histology biopsy are key elements as well. In case of muscle-invasive tumour, the bladder should be removed (radical cystectomy). Urinary diversion due to bladder removal has various methods: 1) creation of a stoma on the abdomen (uretero-ileocutaneostomia) when urine is voided into the stoma fixed to the abdomen; 2) catheterizable pouch, when this pouch has to be voided by the catheter 4-5 times a day; 3) orthotop neobladder which is connected to the urethra, urine is voided thorough the urethra, its control can be learnt; 4) ureter diverted into the intestine, without the need of stoma creation (ureterosigmoidostomia). From the point of the view of the patient, it should be underlined that in case of the first two surgical solutions, he/she has to live with a stoma on the abdominal wall after the intervention. In case of the third alternative the urine is voided thorough the urethra as in healthy people, but the control of it have to be learnt. The fourth method without stoma is the oldest, the urine is voided thorough the rectum. In case of well-defined muscle-invasive tumours the bladder can be spared and TUR, radio- and chemotherapy can be applied. Radical cystectomy can be complemented by chemotherapy and radiotherapy can be performed in certain cases.

Staging of cancer is a key issue in oncology. It is used in order “to describe the severity of a person’s cancer based on the size and/or extent (reach) of the original (primary) tumour and whether or not cancer has spread in the body. The TNM system is one of the most widely used cancer staging systems. The TNM system is based on the size and/or extent (reach) of the primary tumour (T), the amount of spread to nearby lymph nodes (N), and the presence of metastasis (M) or secondary tumours formed by the spread of cancer cells to other parts of the body. Grade (G) is an indicator of how quickly a tumour is likely to grow and spread. A number is added to each letter to indicate the size and/or extent of the primary tumour, the grade of growing of a tumour and the degree of cancer spread”.

(<http://www.cancer.gov/cancertopics/factsheet/detection/staging>)

IV.2. Literature review

The objective of this subsection is to review and analyse the literature regarding the overall disease burden in bladder cancer. Disease burden might be manifested in non-

material (social, emotional, psychological) and material issues as well. To capture both manifestations, HRQoL and CoI related publications were searched. The literature search was performed in an international medical literature database, PubMed (the database of life sciences and biomedical literature, available at <http://www.ncbi.nlm.nih.gov/pubmed/>). Within the topic of HRQoL the focus was on articles dealing with measuring HRQoL with the questionnaires applied in the empirical study (EQ-5D; Short-Form-36 Health Survey, SF-36; Short-Form-6D, SF-6D; Functional Assessment of Cancer Therapy for patients with bladder cancer, FACT-BI) and validation of BCI, respectively. Regarding the material sense, all studies which assessed the economic burden of BC and published data on distinctive therapies were captured. Articles in English were selected by reviewing the titles and abstracts, studies with no abstracts were excluded. Below each search strategy is introduced and I provide a brief overview about the content of the relevant articles.

IV.2.1. Review of the international literature

IV.2.1.1. HRQoL of patients with BC

The aim of the literature search was to review studies dealing with HRQoL in BC which applied EQ-5D, SF-36, SF-6D, and FACT-BI instruments. An electronic search was performed between the period of 01.01.2003 and 04.30.2014 in PubMed database.

IV.2.1.2. The summary of studies about HRQoL of patients with BC – EQ-5D

Before the presentation of the searching method and the summary of studies, a short description is provided about the tool of EQ-5D health survey.

The EQ-5D is self-report questionnaire consisting of two parts, the EQ-5D-3L descriptive system and a health thermometer, namely EQ Visual Analogue Scale (EQ VAS) (Rabin [2001]). The first covers five health dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Within a dimension the patients can chose from three options (no problems, some problems, extreme problems), consequently, 243 different health states can be described. An EQ-5D-3L health state can be converted to a single summary index by using a formula that vitally attaches

weights to each of the levels in each dimension. This formula is based on the valuation of EQ-5D health states from general population samples. For instance, the value range of the score is between -0.594 and 1 (totally health) in the UK. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale with endpoints labelled "Best imaginable health state" and "Worst imaginable health state". In case of both EQ-5D and EQ VAS, higher scores indicate better health states.

In order to capture studies applying the EQ-5D preference-based measure in BC, the following search strategy was performed in PubMed: ("urinary bladder neoplasms"[MeSH Terms] OR ("urinary"[All Fields] AND "bladder"[All Fields] AND "neoplasms"[All Fields]) OR "urinary bladder neoplasms"[All Fields] OR ("bladder"[All Fields] AND "cancer"[All Fields]) OR "bladder cancer"[All Fields]) AND (eq-5d[All Fields] OR eq5d[All Fields] OR euroqol[All Fields]) AND ("2003/01/01"[PDAT] : "2014/06/30"[PDAT])

(Note: The search can be reproduced by inserting the above specified search strategy in the search box of PubMed, see <http://www.ncbi.nlm.nih.gov/pubmed/>)

The search resulted in 4 hits (articles). Inclusion criteria referred to the period of publication of articles (from 01.01.2013 to 06.30.2014) and the language of both the abstract and the article itself (English). Publications studying specifically not BC were excluded.

The 2 following studies met the inclusion criteria:

Tejido-Sanchez et al., 2014 (Spain)

The aim of the article was to determine the variables that affect HRQoL of patients treated by radical cystectomy with ileal conduit. The authors analysed HRQoL using the EQ-5D questionnaire and compared the result with demographic variables (gender, age, work situation, studies, income, partner) and clinical variables (tumour stage, time since cystectomy was performed, adjuvant chemotherapy, recurrent and complications of the stoma). Regarding results, a total of 59 patients participated in the study, with a mean

age of 69 years (47-84). Mean time from cystectomy was 43 months (12-83), with 61% complications related to the stoma. Stoma complications were associated with limitations in personal care, pain/discomfort, anxiety, depression and HRQoL in general. Female gender was connected with limitations in daily activities and adjuvant chemotherapy with anxiety/depression and HRQoL in general. The rest of the variables proved not statistically significant (Tejido-Sanchez et al., [2014]).

Li et al., 2013 (China)

The purpose of this study was to evaluate the clinical value of the use of urostomy bags in the management of urine leakage in patients with bladder cancer after radical cystectomy. Urine leakage was retrospectively analysed in 483 patients with BC who underwent radical cystectomy between the period of 2004 and 2010. Two patient groups were compared: before 2008, all patients with urine leakages were treated by routine dressing changes (group A); after 2008, the leakages were managed with urostomy bags (group B). HRQoL (EQ-5D) and cost for urine leakage for both groups were assessed. As for results, patients in group B had an overall better life quality compared with group A. The score for pain/discomfort was significantly higher in group A. The average cost in management of urine leakage was significantly higher in group A than in group B as well. The surplus value of this study is that early use of urostomy bag is a good choice for urine leakage in patients with bladder cancer after radical cystectomy and neobladder reconstruction (Li et al., [2013]).

IV.2.1.3. The summary of studies about HRQoL of patients with BC – SF-36

Before the presentation of the searching method and the summary of studies, a short description is provided about the SF-36 questionnaire.

The SF-36 health survey is a 36-item Likert-scaled self-report instrument measures health status in the following eight dimensions: Physical Functioning (PF); Role limitations – Physical (RP); Bodily Pain (BP); General Medical Health (GH); Vitality (VT); Social Functioning (SF); Role limitations – Emotional (RE); Mental Health (MH) (McHorney, [1994]). These eight profile scales can be directly transformed into a scale

ranged from 0 to 100 by the assumption, that each question has the same weight. The SF-36 provides psychometrically-based physical component summary (PCS) and mental component summary (MCS) scores. Higher scores correspond to better health states. In our survey the validated Hungarian version of the SF-36v1 (hereinafter SF-36) was applied. Besides providing a description of health the SF-36 has the capability to conduct an economic evaluation through the SF-6D utility index (see next section).

To find studies applying the SF-36 questionnaire the following search strategy was applied in PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>): ("urinary bladder neoplasms"[MeSH Terms] OR ("urinary"[All Fields] AND "bladder"[All Fields] AND "neoplasms"[All Fields]) OR "urinary bladder neoplasms"[All Fields] OR ("bladder"[All Fields] AND "cancer"[All Fields]) OR "bladder cancer"[All Fields]) AND (sf-36[All Fields] OR sf36[All Fields] OR SF-36[All Fields] OR SF36[All Fields]) AND ("2003/01/01"[PDAT] : "2014/04/30"[PDAT]).

The search resulted in 26 hits. Inclusion criteria referred to the language of both the abstract and the article (English). Publications studying specifically not BC were excluded.

Among 26 hits, 16 studies met inclusion criteria. Taking into consideration the length-related-limits, below I extract those publications on a more detailed way which are directly connected with the empirical study among BC patients and just mention briefly the rest of the relevant articles. Furthermore, I concentrate on and summarize those materials of the extracted studies which are specifically discussing topics related to the empirical study of Hungarian BC population.

Yang et al., 2013 (China)

The objective of the study is to assess the functional results and HRQoL in bladder cancer patients with an orthotopic neobladder (ONB). SF-36 questionnaire was applied. The functional results between patients with an ONB and those with other types of urinary diversion were compared at 6, 12 and 24 months after surgery. Data

from 82 participants (54 with orthotropic and 28 with non-orthotropic urinary diversion) were included in the analysis. The SF-36 scores following orthotropic urinary diversion were significantly superior to those following non-orthotropic urinary diversion. The scores of patients with orthotropic urinary diversion about total health were higher compared to patients with non-orthotropic urinary diversion. Although, no differences were observed in the scores of physical functioning between patients with orthotropic and those with non-orthotropic urinary diversion. Further results regarding HRQoL were similar, however, the mental health of patients with orthotropic urinary diversion was more easily restored in comparison with that of patients with non-orthotropic urinary diversion, which reduced their overall recovery time (Yang et al., [2013]).

Colombo et al., 2012 (Italy)

The aim of the article is to assess both the feasibility and the efficacy of a short-term intensive schedule of neoadjuvant intravesical chemotherapy in patients with recurrent non-muscle invasive bladder cancer (NMIBC). A randomised phase 2 clinical study involved 54 patients with recurrent NMIBC who were submitted to neoadjuvant chemotherapy intravesical instillations according to two different timing schedules. Regarding intervention, intravesical mitomycin C (40 mg/40 ml was administered according to a schedule of either one instillation per week for 6 wk (group 1) or three instillations per week for 2 wk (group 2) prior to transurethral resection (TUR). SF-36 questionnaire was used at randomisation and before TUR. No statistically significant difference in SF-36 domain score was detected pre- and post-treatment between groups (Colombo et al., [2012]).

Miyake et al., 2012 (Japan)

This study compares the HRQoL of patients with sigmoid and ileal neobladders following radical cystectomy. HRQoL of all patients with an ONB was evaluated applying the SF-36 survey 12 months after surgery. The study involved 212 patients, among them 88 with sigmoid neobladder and 124 with ileal neobladder. There were no significant differences in all eight scores derived from SF-36 between sigmoid (SNBG) and ileal neobladder groups (INBG), respectively; however, in comparison with the

scores of an age-matched control in Japan, one and two scores in SNBG and INBG, respectively, were significantly lower, whereas one score in INBG was significantly favourable. In spite of the lack of any significant differences in all scores between male SNBG and INBG, three scores in female SNBG were significantly superior to those in female INBG. Multivariate analyses were performed to evaluate the contribution of several factors on each scale score of the SF-36 questionnaire, and they revealed that HRQOL, particularly that associated with physical and social functions, appeared to be significantly deteriorated in elderly patients and/or those not able to spontaneously void (Miyake et al., [2012a]).

Miyake et al., 2012 (Japan)

The objective of this study was to retrospectively compare the clinical outcomes of sigmoid and ileal NB among women. Altogether 18 and 14 women participated in the study who underwent orthotropic NB reconstruction using sigmoid and ileal segment, respectively, after radical cystectomy, and clinical outcomes between the SNBG and INBG were compared. The rate of patients who could void spontaneously in SNBG (94.4%) was significantly greater than that in INBG (64.3%). SF-36 questionnaire for HRQoL did not show any significant differences in 7 of the 8 scores between the 32 women with NB and an age-matched control population; however, 3 of the 8 scores in SNBG were significantly higher than those in INBG. Taking into account the better voiding function and QOL in SNBG, the outcomes of sigmoid neobladder proved to be more favourable rather than outcomes associated with ileal NB in women following radical cystectomy (Miyake et al., [2012b]).

Takenaka et al., 2011 (Japan)

This article is dealing with the assessment of general health, urinary and sexual related quality of life in patients with orthotropic neobladder. These segments of HRQoL of 88 patients (78 male and 8 female) undergone orthotropic neobladder and followed for more than 5 years were surveyed by SF-36 and further instruments. Satisfaction with urinary and sexual function was evaluated by visual analogue scale (VAS). As for results by SF-36, 2 categories (Role-limitations - physical and Role

limitations - Emotional) showed significantly lower scores, however, Bodily Pain resulted a better than average score for Japanese people of the same age. Patients who had daytime incontinence presented worse scores in several categories on SF-36, while enuresis did not affect SF-36 score. As for sexual function, 88% of the patients had lost sexual function. On VAS, satisfaction with urinary and sexual function was 5.63 and 0.98, respectively. The main conclusions of the study are that general HRQoL was well maintained, although the presence daytime incontinence impaired it. Most patients were not pleased with their level of sexual function 5 years after orthotropic neobladder construction (Takenaka et al., [2011]).

Vakalopoulos et al., 2011 (Greece)

The aim of the article is to compare HRQoL of patients with orthotropic neobladder (ONB) and uretero-ureterocutaneostomy (UUC). Four questionnaires, among them SF-36 and FACT-G were applied in the study and patients were interviewed face-to-face 7-84 months after the operation. Thirty-nine patients (35 men and 4 women) with a mean age of 66.95 underwent radical cystectomy due to invasive bladder cancer and urinary diversion. Patients were randomized to ileal ONB and UUC groups. Comparing the two groups there were statistically significant differences regarding neither the scores of FACT-G, nor the scores of SF-36 subgroups, except Role limitations - Emotional subgroup on behalf of UUC ($P = 0.022$). To conclude, patients with UUC surprisingly presented at least equal HRQoL than the presumably less debilitating and more recent ONB. Accordingly, UUC is a considerable option for urinary diversion after radical cystectomy in the era of HRQoL for selected patients (Vakalopoulos et al., [2011]).

Miyake et al., 2010 (Japan)

This study reviews the long-term outcomes of orthotropic neobladder (ONB) creation. Altogether 235 Japanese men who underwent ONB reconstruction after radical cystectomy were followed for at least 3 years. The types of ONB used were Studer, Reddy, Hautmann and Mainz NB in 136, 51, 32 and 16 patients, respectively. Regarding results, 210 of the 235 men could void spontaneously, and day- and night-time continence was achieved in 189 and 149, respectively. According to SF-36 survey,

no significant differences were found in 7 of the 8 scale scores between the sample and an age-matched control population in Japan. Any parameters examined among the four groups with distinctive neobladder did not show significant differences, except post-void residual, which was significantly smaller in the Reddy group than in the other three groups. To sum up, the ONB resulted satisfactory outcomes on long-term follow-up, irrespective of the types of ONB (Miyake et al., [2010]).

Philip et al., 2009 (United Kingdom)

HRQoL of patients undergone orthotrophic substitution (OBS) or ileal conduit urinary diversion (ICD) following radical cystectomy was compared in the study. Both interventions are the types of radical cystectomy which is the gold standard in treatment of muscle invasive bladder cancer. Among the total of 57 patients, 52 (28 with OBS and 24 with ICD) responded to SF-36 survey and a functional index questionnaire were included. Patients with a median age of 70 years had similar points with SF-36. All eight scales of it were favourable in both groups. OBS patients were associated with significantly better physical functioning. In the sample, 42% of men with OBS and 25% of diversions could maintain an erection to varying degrees. Of the OBS patients, 85% were continent with two patients indicating reduced HRQoL due to pad usage. Among OBS patients, 96% had significant relationships and a more active life-style. On the whole, results demonstrate a better HRQoL and a more active lifestyle among OBS patients compared to ICD group in a similar age-group population (Philip et al., [2009]).

Autorino et al., 2009 (Italy)

The purpose of this paper is to compare health HRQoL between patients with two different types of urinary diversion, IC and ONB, and between them and an age-matched population included healthy persons. Eighty eight patients treated with radical cystectomy had a follow-up of more than 12 months. The SF-36 questionnaire was provided to each patient, 79 of them (90%) returned the questionnaire and were included in this analysis. They were divided into two groups: group 1 included 44 patients with an IC diversion, and group 2 comprised 35 patients with an ONB. Normative values of an age-matched healthy Italian population were considered as a

control. No significant difference was apparent in any scale score between the ONB and IC groups. Scores for the scales of Role limitations – Physical, Social Functioning and Role limitations - Emotional in both the ONB and IC groups were significantly below the Italian population norm. Patients with an ONB 65 years old or older (n=18) reached significantly lower scores for Role limitations - Physical and Role-limitations Emotional scales than those younger than 65 years (n=17; $p < 0.05$). The conclusion of the study is that in line with the existing literature, few differences between IC and ONB substitution have been found, suggesting that patients adapt to whatever is required for them. Consequently, the assumption that continent reconstruction provides better HRQoL than IC diversion is not supported (Autorino et al., [2009]).

Hashine et al., 2008 (Japan)

The aim of this study is to assess HRQoL of bladder cancer patients following bladder preservation therapy (BPT). Between January 1992 and July 2005 eighty patients with muscle-invasive bladder cancer had been treated with BPT consisting of TUR, intra-arterial chemotherapy and radiotherapy. Among them, 48 who were alive and free from recurrence at the time of survey were asked to participate in the study. A total of 168 patients who had been treated for superficial bladder cancer in the same period were used as a control group. Three questionnaires, among them the SF-36 were applied. No significant difference was detected in age, gender and other clinical factors among the two groups. Regarding results by SF-36, scores of the total of 8 scales were lower in patients with BPT compared to values reached by the control group, however, except Bodily Pain ($p = 0.047$) there was no significant difference. A tendency was manifested toward a diminished Physical Functioning ($P = 0.053$) and Role limitations - Physical ($P = 0.064$) in BPT. The authors conclude that despite certain HRQoL-related outcome parameters after BPT were lower than those of control group, these differences were not significant. Based on this study, patients preserving native bladder had an acceptable HRQoL (Hashine et al., [2008]).

Harano et al., 2007 (Japan)

This study provides an assessment about the functional results, HRQOL outcomes, and complications in patients with an INB in comparison to those with cutaneous diversion (ileal conduit and cutaneostomy). Between 1992 and 2003, INB (type Studer) was created in 30 patients and cutaneous diversion in 38 patients. In 2004, 54 patients were asked to fill the SF-36 questionnaire. The functional results in patients with an INB and the postoperative complications in patients with both urinary diversions were evaluated as well. Altogether 41 patients (21 with INB and 20 with cutaneous diversions) provided data for the analysis. There were no differences in the overall QOL between the two groups. Complete daytime and night-time urinary continence was achieved in the 21 patients (100%) and 13 patients (61.9%), respectively. Overall 19 early complications in 18 patients (60.0%) and seven late complications in six patients (20.0%) with an INB were recorded. However, among those with cutaneous diversion there were 15 early complications in 14 patients (36.8%) and eight late complications in six patients. HRQOL related results and the frequency of complications in the INB group and those in the cutaneous diversion group were similar. However, the functional results of the INB patients were satisfactory (Harano et al., [2007]).

Ohrström et al., 2006 (Sweden)

One of the objectives of this article was to assess the changes in functional status during physical activity, and assess the well-being in patients undergone radical cystectomy and continent urinary diversion, and a control group. Eleven patients with continent cutaneous diversion were involved in the study. The control group included 12 men, matched for age and activity level. So as to evaluate the participants' functional status and well-being, the SF-36 survey was applied. Regarding results, differences were not detected by SF-36 between the groups. HRQoL was similar with the norms for the general Swedish population aged 65 to 74 (Ohrström et al., [2006]).

Yoshimura et al., 2005 (Japan)

The authors in this study assess the general HRQoL of patients with superficial bladder cancer who underwent multiple TURs. The SF-36 survey was applied. Altogether 93 of 133 patients answered the questionnaire at the first TUR, 34 at the second TUR, 17 at the third TUR, and 34 at the fourth or later TUR. In comparison with age- and sex-matched Japanese norms, the general health perception was severely impaired in patients with superficial bladder cancer. Their mental health was also severely deteriorated at the first TUR, but gradually improved to normal as TUR was repeated. The scores of Physical Functioning, Social Functioning, and Role limitations - Emotional demonstrated decreased at the second or third TUR, and increased afterwards if TUR was repeated four or more times. Only two scales of Bodily Pain and Vitality had no negative impact from this disease. Although superficial bladder cancer is not frequently lethal, patients with this disease reported that their general health was much deteriorated (Yoshimura et al., [2005]).

Porserud et al., 2014 (Sweden)

The feasibility and effects of an exercise training programme were assessed in patients undergone cystectomy due to urinary bladder cancer. A 12-week group exercise training programme proved not feasible for most cystectomy patients. However, functional capacity and the Role limitations - Physical scale score of SF-36 increased in the short and long term for patients in the intervention group compared with controls (Porserud et al., [2014]).

Cookson et al., 2003 (USA)

The authors published results of the validation of FACT-VCI questionnaire designed specifically to measure HRQoL in patients undergone radical cystectomy (RC) and urinary diversion (UD). The FACT-VCI had adequate internal consistency (Cronbach's alpha >0.70). Intraclass correlation of the questionnaire was 0.79. There was good correlation between the validated SF-36 and FACT-VCI ($r = 0.81$). The result was

initial validation of this survey for the assessment of HRQoL in patients following RC and UD (Cookson et al., [2003]).

IV.2.1.4. HRQoL of patients with BC – SF-6D

Before the presentation of the searching method, a short description is provided about the SF-6D instrument.

The SF-6D is a generic preference-based single index measure of health (Brazier et al., [2004]). SF-6D scores were calculated based on the results gained from SF-36 questionnaire. We provide SF-6D values of all the four suggested methods, namely ordinal health state valuation model, standard gamble health state valuation model, Bayesian parametric mean and Bayesian posterior mean (Brazier, [2008]). The value range of SF-6D is between 0.0 (worst health state) and 1.0 (best health state) when it is counted from the SF-36v1. SF-6D score can be used in the assessment of the quality-adjusted life-years (QALYs) and the cost-effectiveness of various healthcare interventions.

So as to find studies applying the SF-6D preference-based measure (see more detailed in section of Methods), the following search strategy was conducted in PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>): ("urinary bladder neoplasms"[MeSH Terms] OR ("urinary"[All Fields] AND "bladder"[All Fields] AND "neoplasms"[All Fields]) OR "urinary bladder neoplasms"[All Fields] OR ("bladder"[All Fields] AND "cancer"[All Fields]) OR "bladder cancer"[All Fields]) AND (sf-6d[All Fields] OR sf6d[All Fields] OR SF-6D[All Fields] OR SF6D[All Fields])

The search resulted no hits.

IV.2.1.5. The summary of studies about HRQoL of patients with BC – FACT-BI

Before the presentation of searching method and the summary of studies, a short description is provided about the FACT-BI questionnaire.

The FACT-BI is Likert-scaled self-report instrument which was developed specifically for measuring HRQoL of bladder cancer patients. The FACT-BI includes the FACT-G which is a 27-item compilation of general questions divided into four primary HRQoL domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being (Cella, [1993]). These four domains are completed with the Bladder Cancer Subscale, forming the FACT-BI disease-specific questionnaire (Botteman et al., [2003]). The following scores were calculated from the FACT-BI health survey: physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), functional well-being (FWB), total FACT-G, overall bladder-specific subscale and total FACT-BI score. Higher scores indicate better HRQoL.

To capture articles using the FACT-BI disease-specific questionnaire, the following search strategy was applied in PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>): ("urinary bladder neoplasms"[MeSH Terms] OR ("urinary"[All Fields] AND "bladder"[All Fields] AND "neoplasms"[All Fields]) OR "urinary bladder neoplasms"[All Fields] OR ("bladder"[All Fields] AND "cancer"[All Fields]) OR "bladder cancer"[All Fields]) AND (fact-bl[All Fields] OR ("Focus Altern Complement Ther"[Journal] OR "fact"[All Fields]) AND I[All Fields]) OR fact-bl[All Fields] OR ("Focus Altern Complement Ther"[Journal] OR "fact"[All Fields]) AND I[All Fields])) AND ("2003/01/01"[PDAT] : "2014/04/30"[PDAT])

The search resulted in 15 hits. Inclusion criteria referred to the language of both the abstract and the article itself (English). Publications studying specifically not BC were excluded.

The following 7 articles met the inclusion criteria.

Gacci et al., 2013 (Italy)

The objective of this multicentre study is to assess differences in HRQoL among recurrence-free women undergoing cutaneous ureterostomy (CUS), Bricker's ileal conduit (BK-IC) and Orthotropic neobladder VIP (ONB-VIP) in disease-free females treated with radical cystectomy (RC), with long-term follow up (range 36-122 months;

mean 60.1 months). Patients filled in 3 questionnaires, among them FACT-BI. The sample consisted of 37 females (median age: 68), including 12 who underwent CUS, 16 with underwent BK-IC, and 9 who underwent ONB-VIP. Women undergoing CUS had worse FACT-BL scores compared with BK-IC and ONB-VIP patients, worse HRQoL regarding physical and emotional well-being ($p=0.008$ and $p=0.02$, respectively). The conclusion of the study is that long-term disease-free females treated with CUS resulted worse HRQoL compared with women who underwent BK-IC or ONB-VIP (Gacci et al., [2013]).

Yuh et al., 2009 (USA)

The study aims to prospectively determine the effect of robot-assisted radical cystectomy (RARC) on HRQoL after surgery. HRQoL of 34 patients was assessed by Functional Assessment of Cancer Therapy-Bladder (FACT-BI) questionnaire which were administered before and then over a 6-month period after RARC. Follow-up FACT-BI and domain scores for physical, social, emotional and functional well-being were subscales compared with those obtained before RARC. The mean time after RARC for the 1-, 3- and 6-month assessments was 29, 90 and 193 days, respectively. Initially, significant decreases were detected in the physical and functional domains, with improvements in the emotional domain ($p<0.001$). Total FACT-General (FACT-G) and FACT-BI scores decreased in the initial period after RARC and then progressively improved. No statistically significant difference was found in total scores at 3 months after surgery; at the 6-month follow-up the total FACT-BI scores exceeded those before RARC ($p=0.048$). HRQoL appears to return promptly to, or exceed, baseline levels by 6 months after RARC. Based on these results, authors established that by 6 months after RARC, HRQoL returns promptly to, or exceeds, baseline levels. Improvement in the short term might cause quicker initiation of adjuvant chemotherapy (Yuh et al., [2009]).

Kikuchi et al., 2006 (Japan)

The objective of this paper is to evaluate and compare HRQoL of patients with ileal conduit (IC), continent reservoir (CR) or ileal neobladder (NB), followed from 1987 to 2002. FACT-BI questionnaire was applied in the study, forty-nine patients (20 IC, 14

CR and 15 NB) responded to it. In these 3 patients groups the physical, social/familial, emotional and functional well-being subscales of FACT-G were equally favourable. Patients with IC had less difficulty with controlling urine but had a worse body image compared with NB patients. Interest in sex was extremely low in all patients. There were no significant difference in mean total value of FACT-BI in patients with IC, CR and NB (106.3+/-16.4, 104.0+/-14.2, and 110.9+/-18.0, respectively). The conclusion of the study is that general HRQoL does not vary regardless of the type of urinary diversion. The method used to reconstruct the urinary system has an impact on urinary function and body image (Kikuchi et al., [2006]).

Allareddy et al., 2006 (USA)

The article is dealing with evaluating HRQoL of long-term survivors of BC. The FACT-BL instrument was applied. Regarding results, HRQoL scores were compared between patients undergoing radical cystectomy or those with an intact bladder and between continent and conduit urinary diversion groups. The impact of current age and time since diagnosis of cancer on HRQoL were also assessed. A total of 259 patients (82 undergoing radical cystectomy and 177 undergoing other therapy, respectively) were involved in the study. No differences in general HRQoL scores were detected between radical cystectomy and intact bladder groups and between the 2 urinary diversion groups, however, patients undergoing RC resulted worse sexual function scores. HRQoL of BC patients appeared to decrease with increasing age ($p=.01$). Results suggest that treatment does not influence general HRQoL of long-term bladder cancer survivors, but sexual functioning can be adversely affected in those undergoing cystectomy. Long-term HRQoL declines even in patients with intact bladders (Allareddy et al., [2006]).

Mansson et al., 2007 (Sweden)

The goal of the study is to compare two patient populations with supposed cultural differences undergoing radical cystectomy and orthotopic bladder substitution to determine whether these show differences in the answers to self-report instruments. The FACT-BI questionnaire was completed by 29 and 32 Swedish and Egyptian male

patients, respectively. As for results, there were significant differences between the two native groups. Better health outcomes by FACT-G were obtained in the Swedish patients. Differences were also found by the disease-specific FACT-BI subscale. To sum up, these results indicate that different sociocultural backgrounds have an effect on patient-assessed outcomes. When analysing results from comparative studies, this should be taken into account (Mansson et al., [2007]).

Herman et al., 2004 (USA)

The objective of this phase I study is to assess whether bladder preservation with concurrent gemcitabine and radiotherapy influenced patient-reported HRQoL. Overall 23 patients underwent TUR of bladder tumour, followed by twice-weekly gemcitabine with concurrent radiotherapy. The initial dose was 10 mg/m² given twice weekly and increased afterwards as tolerated. There was no statistically significant difference in the FACT-G or FACT-BI or the combination before, during, or after treatment. The FACT-BI values were lower in patients who received higher doses of gemcitabine (greater than 20 mg/m² versus 20 mg/m² or less). The results of this study indicate that concurrent gemcitabine with conformal radiotherapy is a tolerable treatment regimen for bladder preservation (Herman et al., [2004]).

Matsuda et al., 2003 (France)

The study aims to assess HRQoL among BC survivors at least five years after diagnosis, detect the long term effects of therapies, and important pathological and socio-demographic factors influencing the HRQoL of such survivors. Overall 78 males and 17 females, with a median age of 72 years filled in the FACT-BI questionnaire. Among the 95 patients (76 with a superficial tumour, 17 with an invasive tumour), 20 had undergone total cystectomy. Total cystectomy definitely had a negative impact on the autonomy of survivors, and it was reflected in low scores on the BC-specific subscale in questions related to sexuality. Candidates reported impotency and loss of sexual interest after the cystectomy. However, neither the type of therapy, nor the time from the most recent major treatment had an impact on scores. There were no negative psychological effects of treatments in the long-term. Survivors' HRQoL was influenced by their

autonomy in daily life and by old age. Moreover, familial situation affected Emotional and Familial/Social Well-being critically. These results highlighted the long-term negative effect of total cystectomy on BC-survivors. HRQoL was also determined by patient autonomy and other socio-demographic backgrounds. The maintenance of good health, sexual function and active family relationships should be promoted in order that patient's HRQoL is not deteriorated significantly after treatment (Matsuda et al., [2003]).

Conclusions

Altogether 21 studies assessed the impact of various therapies applied in BC on HRQoL and outcomes associated with therapies with different measures: a.) radical cystectomy: EQ-5D 1, SF-36 10 and FACT-BI 6 studies; b.) bladder preservation therapies (TUR, gemcitabine and radiotherapy): SF-36 3 and FACT-BI 1 study.

Based on the results of SF-36, there is no significant difference in terms of HRQoL between the distinct therapies, nevertheless, in Physical Functioning, Social Functioning and Role Emotional scales differences in scores can be observed. According to the results measured by FACT-BI, cystectomy deteriorates HRQoL, especially sexual function is affected negatively.

On international level, the amount of available data about HRQoL of BC patients is limited. By reviewing the related literature, I have found not any Hungarian studies applied these 5 HRQoL questionnaires. The introduction of measuring HRQoL outcomes in clinical practice is necessary so as to evaluate Hungarian therapeutic results and to make cross-country comparisons. Validated Hungarian versions of FACT-BI, EQ-5D, SF-36 and SF-6D are available.

From the point of view of our research aim I find important to highlight in the one hand, that no studies were published from Hungary. On the other hand, the relationship of these four HRQoL measures has not been studied yet.

IV.2.1.6. BCI validation

The BCI questionnaire is introduced in the IV.3.2.3. subsection.

The objective of the literature search was to review studies dealing with the validation of BCI questionnaire. An electronic search was performed in the period of 01.01.2003. and 04.30.2014. in PubMed (MEDLINE) database.

In order to capture studies dealing with Bladder Cancer Index, the following search strategy was performed in PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>): ("urinary bladder neoplasms"[MeSH Terms] OR ("urinary"[All Fields] AND "bladder"[All Fields] AND "neoplasms"[All Fields]) OR "urinary bladder neoplasms"[All Fields] OR ("bladder"[All Fields] AND "cancer"[All Fields]) OR "bladder cancer"[All Fields]) AND "bladder cancer index"[All Fields] AND ("2003/01/01"[PDAT] : "2014/04/30"[PDAT]).

The search resulted in 8 hits (articles). Inclusion criteria referred to the language of the abstract (English). Publications studying specifically not the validation of BCI were excluded.

The following 3 studies met the inclusion criteria:

Gaunez et al., 2010 (France)

The objective of this study was the translation and linguistic validation of the French version of BCI. As for methods, double-back translation of the original BCI was conducted. At first, two urologists translated the English version into French. Afterwards, a first consensus between the translators and a group consisting of urologists and nurses was achieved. Then professional translators performed the back-translation of this version in order to ensure that no distortion was observed between the two questionnaires. Lastly, a pilot study followed by an interview was carried out among one woman and five men with BC. Regarding results, no difficulties were reported by the pilot group in comprehension or completion of the French version of the BCI. The main conclusion of the study is that impact of various bladder cancer treatments on HRQoL could hence be assessed as well as compared (Gaunez et al., [2010]).

Gilbert et al., 2010 (USA)

The article deals with the development and validation of a reliable, responsive multidimensional instrument to measure disease specific HRQoL in BC patients. Regarding methods, the content of the instrument based on qualitative information from a panel of BC providers and from patient focus groups as well. Draft items were piloted and revised, resulting in the 36-item Bladder Cancer Index consisting of urinary, bowel and sexual health related domains. In psychometric analysis the authors assessed internal consistency, test-retest reliability, convergent validity, concurrent validity and criterion validity. As for results, internal consistency and test-retest reliability was high at 0.77 to 0.91 and at 0.73 to 0.95, respectively. Correlations among the 3 domains were low ($r \leq 0.39$), showing interscale independence. Health outcome differed significantly between clinically distinct treatment groups. The BCI showed moderate correlation with existing external measures, suggesting that it captures aspects of HRQoL that are not detected by general measures. The main conclusion of this study is that the BCI is the first available validated instrument to evaluate health outcomes across a range of local treatments used for bladder cancer (Gilbert et al., [2010]).

Schmidt et al., 2014 (Spain)

The aim of the authors is to develop the Spanish version of the BCI, and assessed its acceptability and psychometric properties. So as to adapt the BCI into Spanish, the forward and back-translation method was applied, expert panels, and cognitive debriefing patient interviews were performed. The Spanish BCI and the SF-36 Health Survey were self-administered by 197 patients. Regarding results, of psychometric analysis, reliability coefficients ranged between 0.75 and 0.97. The validity analysis showed Moderate associations between the BCI function and both subscales for urinary ($r=0.61$) and bowel ($r=0.53$) domains; conceptual independence among all BCI domains ($r \leq 0.3$); and low correlation coefficients with the SF-36 scores, ranging 0.14-0.48 were showed by the validation analysis. To conclude, the Spanish BCI proved to be a well-accepted, reliable, valid, responsive instrument. Regarding performance it is similar compared to the original questionnaire. These findings support its use as a

valuable and comprehensive tool for assessing HRQoL across a wide range of BC patients (Schmidt et al., [2014]).

Conclusions

Altogether 3 studies have published specifically about the validation of BCI. It has been validated in 3 countries (USA, France and Spain) so far. The BCI questionnaire developed in 2007 in the USA (Gilbert et al., [2007]) is applied more frequently, especially for evaluating the efficiency regarding cystectomy. Therefore, the development and validation of its Hungarian version is a relevant issue.

IV.2.1.7. Cost of illness of patients with BC

The goal of the literature search was to review studies dealing with CoI in BC. Regarding the method, an electronic search was performed between the period of 01.01.2003 and 04.30.2014 in PubMed (MEDLINE) database.

So as to capture studies dealing with CoI in BC, the following search strategy was used in PubMed database (<http://www.ncbi.nlm.nih.gov/pubmed/>): "Urinary Bladder Neoplasms"[Mesh] AND "Cost of Illness"[Mesh]

The search resulted in 22 hits. Inclusion criteria referred to the period of publication of articles (from 01.01.2013 to 04.30.2014) and the language of both the abstract and the article itself (English). Publications studying specifically not BC were excluded.

The following 9 articles met the inclusion criteria.

James-Gore et al., 2013 (USA)

The authors attempted to estimate the cost of NMIBC. Bladder cancer affects 70000 Americans each year. Since the diagnosis, management, and long-term follow-up of NMIBC requires advanced imaging and invasive testing, according to economic evaluations BC is the costliest cancer to treat in the US on a per capita basis. In spite of adjunctive tests for surveillance, there is a need for cystoscopy and cytology. Indirect

costs include loss of work, decreased productivity, and worse HRQoL associated with diagnosis, treatment, and surveillance. Improvement may be achieved with better compliance with evidence-based practices for NMIBC (James-Gore et al., [2013]).

Lee et al., 2012 (USA)

The background of the study is that intravesical chemotherapy following TUR of bladder tumour has been underused despite the good scientific evidences (level 1) supporting its performance. The primary goal was to estimate the economic and humanistic consequences related to preventable recurrences in patients with NMIBC. A 2-year model was developed to estimate the number of preventable recurrences in patients untreated with perioperative intravesical chemotherapy. Therapy utilization data were gained from a retrospective database analysis and a review study of 1,010 patients with NMIBC. Recurrence rates of NMIBC were transferred from a randomized controlled trial (RCT) comparing TUR of bladder tumour with or without perioperative mitomycin C. Costs were estimated applying Medicare reimbursement rates. QALY estimates were collected from the available literature. Regarding results, if all patients received immediate intravesical chemotherapy, 7 827 bladder recurrences could be avoided. An economic savings of \$3 847 per avoidable recurrence were estimated, resulting in an aggregate savings of \$30.1 million. In addition, 1.025 QALYs are lost every 2 years due to preventable recurrences, resulting in 0.13 QALYs lost per avoidable recurrence. This means 0.02 QALYs lost per patient not receiving immediate intravesical chemotherapy (Lee et al., [2012]).

Lee et al., 2011 (USA)

The objective of the paper was to compare the financial burden of open radical cystectomy (OC) versus robotic-assisted laparoscopic radical cystectomy (RC) with pelvic lymph node. Altogether 103 and 83 patients undergoing OC and RC, respectively, were involved. Data were collected on patient demographics, perioperative parameters and length of stay (LOS) in hospital. Cohorts were divided into the following subgroups: ileal conduit (IC), continent cutaneous diversion (CCD) and ONB subgroups. Authors used a linear cost model so as to simulate treatment with OC vs RC.

Procedural costs were obtained from the Medicare Resource Based Relative Value Scale. Materials costs were derived from the respective suppliers. Despite a higher cost of materials, RC was less expensive than OC for IC and CCD, although the cost advantage decreased for ONB. The costs per case in RC with IC, CCD and ONB were \$20 659, \$22 102 and \$22 685, respectively, compared to \$25 505, \$22 697 and \$20 719 in case of OC. LOS in hospital was the most significant cost item; RC resulted a shorter LOS in comparison with OC, although this effect was inadequate to compensate the higher cost of robotic surgery. In spite of contributing to a higher cost of materials, RC can be more cost efficient than OC as a treatment for BC, particularly with IC (Lee et al., [2011]).

Sievert et al., 2009 (Germany)

The aim of this study was to utilize the recent literature to identify opportunities for improving the benefits and costs of BC care. Regarding the method, the authors reviewed the recent literature in PubMed database; the focus was on cost-effectiveness analyses. Results suggest that the financial burden of BC is well-characterized in the literature. New technologies like urine-based tests, photodynamic diagnostic tool (PDD) and therapeutic regimes (intravesical chemotherapy, adjuvant immunotherapy) can improve the diagnosis, treatment and on-going monitoring of BC patients, accordingly, with potential improvements in clinical outcomes and concurrent cost-savings as well (Sievert et al., [2009]).

Grossman et al., 2008 (USA)

The background of the study is that BC results from complex and only partially understood host-environmental interactions. As for risk factors for BC, tobacco smoking is the greatest one. Lifestyle may have a significant impact on the incidence of this disease. The forms of chemoprevention and their relevance to BC, the influence of lifestyle and complementary medicine, and the costs regarding diagnosing and treating the disease might provide a base for improvement in diminishing the incidence, recurrence and costs of this disease as well (Grossman et al., [2008]).

Uchida et al., 2007 (Japan)

The background of the study is that frequent recurrence of superficial BC means a significant problem. The aim of the authors was to review the accessible treatment of superficial BC, concentrating on the economic aspects of intravesical instillation. The costs associated with intravesical instillation of bacille Calmette-Guérin (BCG) and its side effects were analysed by performing a cost-effectiveness analysis. Among 139 patients with BC, grade 1 (G1) in 21 lesions, grade 2 (G2) in 60 lesions, grade 3 (G3) in 40 lesions, and unclassified in 17 lesions occurred. The disease stage was Stage Ta in 85 lesions, T1 in 47 lesions, and Tis in 6 lesions. According to statistical analyses, intravesical instillation of BCG was the most important factor preventing recurrence, and intravesical chemotherapy did not influence recurrence. Regarding the 5-year recurrence-free survival rate, it was 78% and 28% for tumours with and without BCG instillation, respectively. The cost-effectiveness ratio of BCG instillation was about \$3 900 per 5-year recurrence-free period (Uchida et al., [2007]).

Avritscher et al., 2006 (USA)

The goal of the paper was to estimate the lifetime cost of BC and the contribution of complications to the total costs. As for methods, the number of resources used during management of BC was multiplied by their unit charges. The authors estimated future costs by creating two hypothetical scenarios. In the best-case scenario, they assumed patients with superficial disease developed recurrences at the cohort's mean rate and that patients with MIBC were disease free after definitive therapy. In the worst-case scenario, they supposed patients with superficial disease developed MIBC and that all patients subsequently died of BC. The average cost of BC was \$65 158. Sixty percent of this cost (\$39 393) was attributable to surveillance and treatment of recurrences, and 30% (\$19 811) was associated with complications. The lifetime cost of BC was lower for the worst-case scenario (\$99 270) than for the best-case scenario (\$120 684) (Avritscher et al., [2006]).

Hollenbeck et al. 2009 (USA)

There is an absence of evidence to guide the optimal management of BC, urologists disagree in how aggressively they treat early-stage disease. The objective of the study is to examine associations between initial treatment intensity and subsequent outcomes. Regarding methods, the authors ranked the providers based on the intensity of treatment they administered to their patients (as measured by their average BC expenditures reported to Medicare in the first 2 years after diagnosis) and then grouped them into quartiles that contained approximately equal numbers of patients. Associations between treatment intensity and outcomes of survival as well as subsequent major interventions were assessed, too. As for results, the average Medicare expenditure per patient for providers in the highest quartile of treatment intensity was more than twice that for providers in the lowest quartile of treatment intensity (\$7 131 vs. \$2 830, respectively). High-treatment intensity providers more commonly applied endoscopic surveillance and conducted more intravesical therapy and imaging studies than low-treatment intensity providers. However, neither the intensity of initial treatment corresponded with a lower risk of mortality, nor initial intensive management obviated the need for later interventions. To sum up, patients treated by high-treatment intensity providers did not appear to benefit in terms of the assessed outcomes (Hollenbeck et al. [2009]).

Hong et al. 2008 (USA)

The background of the study is that BC contributes to the highest cost per patient from diagnosis to death and is the fifth most expensive cancer to treat (exceeding \$3.4 billion annually in the USA). Current surveillance regimens require intense follow-up causing high cost and emotional burden. Bladder tumour markers hold the promise to reduce these costs, however they not have been widely adopted in oncological practice so far. MEDLINE search of all available literature concerning bladder tumour markers and cost-effectiveness was performed. Authors reviewed retrospective and prospective studies, reviews, decision analyses, cost-effectiveness analyses and opinion papers. Cost-effectiveness of bladder tumour markers in surveillance routines was assessed. Regarding results, tumour markers are associated with a higher sensitivity and lower specificity than urine cytology. According to several cost-effectiveness analyses tumour markers significantly lower the cost of BC surveillance. To conclude, bladder tumour

markers cannot definitively replace cystoscopy in surveillance regimens. Recent reports suggest potential for tumour markers to control the financial and emotional cost of BC care and improve HRQoL. Until prospective analyses applying HRQoL outcomes are performed, wider adoption of bladder tumour markers will be impeded (Hong et al. [2008]).

Conclusions

Most CoI studies were performed in the USA and one study was conducted in Germany. There is a great variability among CoI studies regarding study objectives. Four and two papers estimate the costs regarding therapies applied in NMIBC and MIBC, respectively. Results of 3 studies are associated with cost savings due to the implementation of intravesical therapy. No CoI studies from Hungary or the CEE region has been published so far in PubMed. Since BC contributes to the highest cost per patient from diagnosis to death and is the fifth most expensive cancer to treat; it might be an important goal to estimate the CoI in Hungary in order to provide local data for decisions on resource allocation.

IV.2.2. Review of the Hungarian literature

According to my best knowledge and review of the database of Hungarian journals (www.matarka.hu), Hungarian data is available regarding neither the HRQoL and CoI of BC patients; nor the cost-effectiveness of the applied therapies. Hungarian authors have published studies dealing with the therapies in BC, however, those were principally associated with diagnostic issues, risk assessment, survival, recurrence; and a few studies evaluated functional outcomes Kondás et al., [1996]; Samodai et al., [1996]; Romics et al., [2006]; Keszthelyi et al., [2009]; Szűcs et al., [2012]).

IV.3. The empirical study – elaboration 1.

IV.3.1. Background

BC ranks 9th in worldwide cancer incidence as it is the 7th most common cancer in men and the 17th most common cancer in women (Ploeg, Aben and Kiemeney, [2009]). Both the disease itself and the therapies applied (e.g. transurethral surgery, intravesical chemotherapy, radical cystectomy with urinary diversion) might have influence on health related quality of life (HRQoL) of individuals with BC. However, not much is known in the international medical literature regarding the burden imposed by BC cancer upon patients [Botteman et al., [2003]]. Evidences on the HRQoL effects of different urinary diversions are weak (Ali et al., [2014]). Moreover, there are only a few BC-specific instruments to explore and measure HRQoL outcomes in depth [3]. For the Central and Eastern European (CEE) countries, lack of validated language versions is an additional obstacle for the comparison of outcomes of care and participation in international multicentre trials. The Bladder Cancer Index (BCI) questionnaire was developed and validated in the US to assess HRQoL of patients with BC (Gilbert et al, [2010]). It has been applied in an increasing number of studies (Hedgepeth et al., [2010]; Bartsch et al., [2014]; Poch et al., [2014]; Abourmohamed et al., [2014]) and was validated for a few languages (US English, Spanish and partially in French) but not for the CEE countries (Gilbert et al, [2010]; Gaunez et al., [2010]; Schmidt et al., [2014]).

Due to this large financial impact of managing BC, economic considerations have come into focus in the past decades (Yeung et al, [2011]). HRQoL measures that provide utility scores for quality-adjusted life-year (QALY) calculations in cost-effectiveness analyses gained special importance (Torrance, [1986]; Svatek et al., [2014]). However, epidemiological cohorts and clinical trials that generate evidence on disease-specific HRQoL changes rarely incorporate utility measures. In health economic analyses, therefore, disease-specific HRQoL data of cancer patients are often converted to utility scores or used as a proxy to calculate QALYs (McTaggart et al., [2013]). According to our knowledge, the most widely used utility measure, the EQ-5D questionnaire has been reported only in two BC studies so far (Tejido-Sanchez et al., [2014]; Li et al, [2014]). Extrapolated utility scores from other conditions with similar health states have been used to estimate QALY gains as little is known on the link

between disease-specific HRQoL and preference based health state measures in the field of BC (Kulkarni et al., [2009]; Wong et al., [2003]).

The objectives of the study were, therefore, to assess the HRQoL of patients with BC and analyse the relations between diverse HRQoL tools, including utility measures. We aimed to validate the Hungarian language version of the BCI questionnaire as well. The unique feature of this study is that we applied four instruments alongside the BCI, namely the disease-specific Functional Assessment of Cancer Therapy for patients with bladder cancer (FACT-BI), the Short-Form-36 (SF-36) generic health state measure and the EQ-5D and Short-Form-6D (SF-6D) utility assessments. In this paper we report results of a multicentre cross-sectional survey in a convenience sample patients with BC in Hungary.

IV.3.2. Material and Methods

IV.3.2.1. Study design and patients

Patients' data were collected through a cross-sectional survey at three hospital based urology centres in Hungary. Consecutive patients diagnosed with BC and aged 18 or over who attended routine medical care were invited to participate in the study. The target number of participants was 150. The recruitment was pursued between May 2012 and September 2013. All participants provided informed consent prior to their inclusion in the study. The study was approved by the appropriate ethics committee (Scientific and Research Ethics Committee of the Medical Research Council, Hungary; 7794-112012/EKU) and have therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

IV.3.2.2. Questionnaire survey and health related quality of life assessment

Main clinical parameters including disease history, type of urinary diversion, type and stage of cancer, the distinct interventions applied and co-morbidities were provided by the urologists. Patients filled in a set of questions regarding their demographics and completed the validated Hungarian versions of BC-specific FACT-BI questionnaire, and of two generic health state measures, namely the EQ-5D and SF-36 (Cella et al., [1993]; Rabin and de Charro, [2001]; McHorney et al., [1994]). SF-6D utility scores were

derived from SF-36 by ordinal, standard gamble, Bayesian and parametric approach (Brazier et al., [1998]). Due to lack of local value sets in Hungary, the UK tariffs were used to calculate EQ-5D and SF-6D utility scores. The Hungarian language version of the BCI was developed and applied also in the survey (details are provided below). Higher scores indicate better HRQoL regarding each of the applied instruments.

IV.3.2.3. The Bladder Cancer Index (BCI) questionnaire

The BCI is a disease-specific HRQoL questionnaire that involves two introductory questions and 3 primary domains, namely urinary, bowel and sexual functions, containing 14, 10 and 12 items, respectively (Gilbert et al., [2010]). Each primary domain consists of two subdomains (function and bother). Item responses are based on four and five-point Likert scales. To calculate domain summary and subscale scores, items are standardized to a 0-100 point scale and an average is calculated for each. Higher values indicate better HRQoL. The minimum number of non-missing items needed to compute the score is defined for each score.

IV.3.2.4. Translation of the BCI questionnaire into Hungarian

The language of the original BCI is United States English (Gilbert et al., [2010]). Three Hungarian translations of the questionnaire were carried out independently by three researchers, qualified in health economics, native speakers of Hungarian who were fluent in English. Subsequently, the forward Hungarian translations were reconciled and a blind back-translation into English was performed by an independent professional translator. The backward translation was compared to the original BCI and discussed, involving two urologists and a Hungarian consensus version was formed. Cognitive debriefing interviews and pilot testing were performed involving five patients with BC (age: 56-74; males: 2; 3 patients with native bladder, 1-1 with neobladder and ileal conduit). Based on the experiences of the pilot the final consensus version was shaped and formatted as the original BCI.

IV.3.2.5. Statistics and psychometric testing of the Hungarian BCI

SPSS 20.0 programme package was used to record and analyse questionnaire data. Descriptive statistics of the variables were calculated. Correlations (Pearson coefficients) between the FACT-BI, SF-36 Physical / Mental Component Summary score, SF-6D, EQ-5D score and EQ VAS were analysed. Correlations of >0.5, 0.30–0.49, and 0.1–0.29 were considered as strong, moderate, and weak relationships, respectively. Comparison across treatment subgroups (transurethral resection - TUR, TUR with intravesical therapy, cystectomy with ileal conduit, cystectomy with neobladder) was analysed by Kruskal-Wallis test. Level of significance was set at $p < 0.05$.

Psychometric analysis of the Hungarian BCI was performed following the quality criteria proposed by Terwee and colleagues (Terwee et al., [2014]). Internal consistency (the extent to which items of a questionnaire are correlated) was estimated applying Cronbach's alpha coefficient for each domain and subdomain of the Hungarian BCI. To determine dimensionality, an exploratory factor analysis was used. Our predefined hypothesis was that data related to the Hungarian BCI fit to the 3 primary and 6 subdomains of the original BCI. A scale is usually considered consistent if factor analysis is performed (confirms dimensionality of the questionnaire) and the value of Cronbach's alpha is between 0.70-0.95 (Terwee et al., [2014]). Criterion validity was not feasible due to lack of a well-established gold standard measure in BC. To assess construct validity, interscale correlations (Pearson coefficients) between BCI domains and subscales were analysed, as well as with FACT-BI, EQ-5D, SF-36 and SF-6D scores. Our pre-specified hypothesis were that: 1) correlations between urinary, sexual, and bowel BCI domains are weak as these three are supposed to measure different impacts; 2) correlations between function and both subscales within each domain are moderate as the alteration of a function can, but not necessarily bothers the patient; 3) correlations are moderate or strong with the disease-specific FACT-BI but weaker correlations are expected with the generic instruments (EQ-5D, SF-36 and SF-6D). Correlations of >0.5, 0.30–0.49, and 0.1–0.29 were regarded as strong, moderate, and weak, respectively (Cohen, [1992]). To qualify construct validity as appropriate, usually $\geq 75\%$ of the results should be in accordance with the predefined hypotheses (Terwee et al., [2014]). Discriminating ability between four treatment subgroups (TUR without and with intravesical therapy, cystectomy with ileal conduit or with neobladder) was

analysed by Kruskal-Wallis test. To assess reproducibility (reliability) 50 patients were asked at the end of the visit to fill in a second piece of BCI at home and mail back. Relations between the results of the two rounds were analysed by Pearson correlation considering a correlation ≥ 0.70 between (sub)domains as sufficient level of reliability. Floor or ceiling effects were considered if more than 15% of the respondents had the lowest or highest possible score, respectively.

IV.3.3. Results

IV.3.3.1. Patient characteristics and BC histology

Altogether 151 patients (males N=98, 65%) were involved in the study with a mean age of 66.3 (SD 9.6) years and disease duration of 4.2 (SD 3.8) years (<1 yr.: 4%, 1-5 yrs.: 66%, >5 yrs.: 30%). The majority (N=114, 76%) was married while the others were living alone. The average Body Mass Index (BMI) was 27.8 (SD 5.1). Urothelial carcinoma was the most frequent BC type (N=89, 82%) other types occurred in 7 (7%) patients and the specific type of malignancy was not available in 12 (11%) cases at the time of the survey.

Non-invasive tumour was more common than muscle invasive disease. Distribution by cancer stages was as follows — T1: N=48 (33%), T2: N=17 (12%), T3: N=6 (4%), T4: N=1 (1%), Ta: N=60 (41%), Tis: N=4 (3%), missing data N=4 (3%); and by cancer grades as G1: N=33 (22%), G2: N=55 (36%), G3: N=33 (22%), missing data N=2 (1%) patients TUR with intravesical therapy was applied in 68 (45%) patients, 60 (40%) had solely TUR and 20 (13%) underwent cystectomy (among them 14 patients had ileal conduit diversion and 6 had neobladder). Three patients (2%) with muscle invasive tumour received palliative therapy but did not undergo cystectomy.

IV.3.3.2. Health related quality of life of the BC patients

Main results on HRQoL scores are presented in Table 5. The mean EQ-5D score of the sample did not differ significantly from the age-matched general population norm (by age groups 45-54 years: 0.751 vs. 0.808; 55-64 years: 0.794 vs. 0.765; 65-74 years 0.808 vs. 0.756; 74-85 years: 0.728 vs. 0.634; , $p > 0.05$) (Szende and Németh, [2003]). The SF-36 domain scores were (mean, SD): Physical Functioning 67.8 (27.0); Role

Physical 56.8 (42.8); Bodily Pain 73.4 (27.6); General Health 50.9 (23.2); Vitality 65.4 (25.3); Social Functioning 78.6 (25.1); Role Emotional 63.4 (44.1) and Mental Health 69.6 (24.2). These average scores are comparable to the Hungarian population norm of age-group >65 years (Czimbalmos et al., [1999]). In the age-group of 45-54 BC patients had lower (worse) average scores in the Physical Functioning, Role Physical and Role Emotional domains than the respective population norm in Hungary (72 vs. 85, 56 vs. 71, and 53 vs. 73, respectively). Deterioration in Physical Functioning was detectable also in age-group 55-64 (69 vs. 79). BC patients aged ≥ 65 years had similar SF-36 scores as the general Hungarian population of the same age. (Levels of significance cannot be calculated as S.D. was not provided in the publication of SF-36 population norms (Czimbalmos et al., [1999])). Results of SF-6D scored by the four distinctive methods did not differ considerably.

Table 5 Health related quality of life of patients with bladder cancer

Summary scores, score range (Number of respondents, %)	Mean (S.D.)
FACT-BI Physical well-being (PWB), 0-28 (N=146, 96.7%)	23.1 (5.4)
FACT-BI Social/family well-being (SWB), 0-28 (N=148, 98.0%)	21.6 (5.5)
FACT-BI Emotional well-being (EWB), 0-24 (N=150, 99.3%)	17.9 (4.9)
FACT-BI Functional well-being (FWB), 0-28 (N=149, 98.7%)	19.2 (6.6)
FACT-BI Bladder Cancer Subscale (BICS), 0-48 (N=150, 99.3%)	32.9 (7.1)
FACT-BI Trial Outcome Index (TOI), 0-104 (N=150, 99.3%)	74.1 (17.8)
FACT-BI, 0-156 (N=150, 99.3%)	113.3 (25.1)
FACT-G, 0-108 (N=150, 99.3%)	80.6 (19.5)
EQ-5D score, -0.594 - 1 (N=148, 98.0%)	0.784 (0.242)
EQ VAS, 0-100 (N=141, 93.4%)	67.8 (19.3)
SF-36 Physical component summary (PCS)*, 0-100 (N=149, 98.7%)	45.6 (10.4)
SF-36 Mental component summary (MCS)*, 0-100 (N=148, 98.0%)	48.4 (12.7)
SF-6D Ordinal v2 – SG health state valuation, 0-1 (N=121, 80.1%)	0.717 (0.141)
SF-6D Ordinal v2 – Ordinal health state valuation, 0-1 (N=125, 82.8%)	0.738 (0.155)
SF-6D Bayesian v2 – Parametric Mean, 0-1 (N=121, 80.1%)	0.717 (0.141)
SF-6D Bayesian v2 – Posterior Mean, 0-1 (N=125, 82.8%)	0.683 (0.136)

Source: Own table based on data from the cross-sectional survey

SG=standard gamble *QualityMetric Health Outcomes Scoring Software was used applying maximum data recovery method for missing data estimation. Number of respondents with no missing responses for the 36 items was 116 (77%).

Note: The FACT-BI Trial Outcome Index (TOI) comprises the sum of scores of PWB, FWB and BICS; FACT-G is calculated by adding the scores PWB, SWB, EWB, FWB; while FACT-BI includes the sum of the scores of FACT-G and BICS.

The difference of FACT-BI, EQ-5D, SF-36 and SF-6D scores across the four treatment subgroups was not significant (Table 6). We find important to note, however, that the sample size was small in the cystectomy with neobladder subgroup (N=6) that hampers the reliability of this result.

Table 6 Comparison by treatment subgroups

Domains	Native bladder		Cystectomy		Comparison of the four subgroups*, p value
	TUR (N=63) Mean (S.D.)	TUR with intravesical therapy (N=68) Mean (S.D.)	Ileal conduit (N=14) Mean (S.D.)	Neobladder (N=6) Mean (S.D.)	
Age, years	66.4 (10.0)	66.9 (9.9)	64.1 (7.5)	63.7 (7.2)	0.591
Disease duration, years	3.8 (4.4)	4.3 (2.9)	5.2 (3.4)	6.5 (4.6)	0.032
FACT-BI	112.1 (28.7)	115.8 (21.8)	108.6 (24.7)	109.2 (22.2)	0.648
EQ-5D	0.788 (0.264)	0.815 (0.179)	0.617 (0.354)	0.810 (0.193)	0.229
EQ VAS	68.5 (20.3)	68.7 (16.2)	62.4 (26.9)	64.2 (21.7)	0.858
SF-36 Physical Component score	46.6 (10.4)	45.4 (10.3)	43.3 (11.0)	40.9 (10.7)	0.496
SF-36 Mental Component score	49.0 (12.7)	48.5 (12.1)	40.5 (12.5)	63.2 (4.4)	0.002
SF-6D [†]	0.739 (0.137)	0.720 (0.143)	0.623 (0.113)	0.702 (0.193)	0.101
BCI Urinary:	80.1 (20.7)	85.9 (16.5)	74.1 (17.0)	52.2 (23.6)	0.006*
– function	72.6 (28.3)	77.8 (27.4)	64.4 (32.5)	20.8 (10.9)	0.005
– bother	86.3 (19.8)	89.8 (14.6)	76.9 (16.9)	68.9 (22.0)	0.007
BCI Bowel:	84.6 (16.2)	85.0 (14.5)	75.5 (19.1)	65.8 (23.6)	0.046
– function	84.9 (15.1)	84.1 (18.3)	82.9 (15.6)	56.3 (29.4)	0.257
– bother	84.4 (19.4)	85.7 (15.8)	71.1 (24.4)	72.2 (15.8)	0.043
BCI Sexual:	50.9 (26.3)	52.7 (21.0)	39.9 (21.0)	37.3 (41.1)	0.343
– function	35.9 (32.5)	40.1 (27.3)	24.0 (27.6)	28.2 (39.9)	0.448
– bother	73.5 (30.6)	70.0 (26.9)	62.3 (29.8)	50.0 (43.6)	0.442

Source: Own table based on data from the cross-sectional survey

*Kruskal-Wallis test was performed. TUR=transurethral resection. [†]Results with SF-6D Bayesian parametric mean scores are presented.

IV.3.3.3. Relationship between FACT-BI, SF-36, SF-6D and EQ-5D

Results are presented in Table 7. Correlations between FACT-BI, EQ-5D, EQ Visual Analogue Scale (EQ VAS), SF-36 and SF-6D were moderate or strong ($r \geq 0.467$). The association of the FACT-BI and the two utility measures, namely the EQ-5D score and SF-6D, was strong. SF-36 Physical component summary score correlated weakly with SF-36 Mental component summary score.

Table 7 Correlations between the disease-specific FACT-BI and generic health state measures

	FACT-BI	SF-36 physical component summary score	SF-36 mental component summary score	SF-6D score [†]	EQ-5D score	EQ-VAS
FACT-BI	1	0.590*	0.578*	0.643*	0.693*	0.620*
SF-36 physical component summary score	-	1	0.263*	0.695*	0.643*	0.567*
SF-36 mental component summary score	-	-	1	0.730*	0.592*	0.467*
SF-6D score ^a	-	-	-	1	0.676*	0.572*
EQ-5D score	-	-	-	-	1	0.634*
EQ-VAS	-	-	-	-	-	1

Source: Own table based on data from the cross-sectional survey

*Correlation is significant at the 0.01 level. [†]Results with SF-6D Bayesian parametric mean scores are presented. Results with the other three SF-6D scores variants were similar (data not shown).

IV.3.3.4. Psychometric results of the Hungarian BCI

In Table 8, descriptive statistics of the Hungarian BCI are presented. Cronbach's alpha was in the required range of 0.70-0.95 indicating high internal consistency, only the sexual function was slightly higher (0.97). In factor analysis (applying principal axis factoring method) when 3 factors were fixed in accordance with the 3 primary domains of the BCI, data did not fit. In case of 6 factors analogue with the 6 subdomains, responses to the 36 items fit to the 6 subdomains with the exception of 5 items. (The outlier items were item number 24, 25 in urinary function; 36, 42 in bowel bother; and 52 in sexual bother subdomains.)

Table 8 Domain specific summary and subscale characteristics of the Hungarian BCI questionnaire

BCI domains	Number of items	Missing items ^a	Missing score ^b	Observed range	Mean (SD)	Cronbach's alpha	Test-retest correlation ^c
Urinary:	14	44 (28.5)	18 (11.9)	31.6 - 100	81.1 (19.7)	0.86	0.85*
- function	6	23 (15.2)	24 (15.9)	8.3 - 100	72.6 (29.5)	0.79	0.84*
- bother	8	35 (23.2)	23 (15.2)	39.3 - 100	86.4 (17.9)	0.85	0.70*
Bowel:	10	24 (15.9)	21 (13.9)	28.3 - 100	83.4 (16.2)	0.82	0.67*
- function	4	22 (14.6)	22 (14.6)	25.0 - 100	83.6 (17.4)	0.79	0.81*
- bother	6	23 (15.2)	21 (13.9)	16.7 - 100	83.3 (18.8)	0.75	0.69*
Sexual:	12	43 (28.5)	34 (22.5)	4.6 - 100	50.5 (23.9)	0.91	0.78*
- function	7	38 (25.2)	30 (19.9)	0.0 - 100	36.7 (29.9)	0.97	0.87*
- bother	5	38 (25.2)	28 (18.5)	10.0 - 100	97.4 (9.5)	0.88	0.67 *

Source: Own table based on data from the cross-sectional survey

^a Number and percentage of patients with any missing item; ^b Number and percentage of patients with missing score; ^c N=50 patients; *p<0.01

Interscale correlations between urinary and bowel/sexual domains were moderate ($r=0.489$ and $r=0.311$, respectively) and between bowel and sexual domains was weak ($r=0.289$). Interscale correlations between BCI domain subscales are presented in Table 9. Correlations between urinary, sexual, and bowel BCI subdomains were low or moderate but bordering to low, in accordance with our hypothesis, only the urinary bother and bowel bother scores presented moderate but bordering to strong correlation ($r=0.484$). Strong correlations were found between function and bother scores within the urinary and bowel domains ($r=0.499$ and 0.547 , respectively), as expected, however, it was low but bordering to moderate in the sexual domain ($r=0.263$).

Table 9 Interscale correlations between BCI function and bother subscales and other health related quality of life scores

Measures	BCI Urinary		BCI Bowel		BCI Sexual	
	function	bother	function	bother	function	bother
BCI urinary function	1	--	--	--	---	---
BCI urinary bother	0.499*	1	---	---	---	---
BCI bowel function	0.276*	0.383*	1	---	---	---
BCI bowel bother	0.343*	0.484*	0.547*	1	---	---
BCI sexual function	0.290*	0.349*	0.188**	0.258*	1	---
BCI sexual bother	-0.130	0.133	0.132	0.162	0.263*	1
FACT-BI	0.423*	0.719*	0.363*	0.521*	0.467*	0.126
EQ-5D score	0.251*	0.569*	0.307*	0.584*	0.327*	0.084
EQ VAS	0.276*	0.469*	0.234*	0.364*	0.439*	0.163
SF-36 Physical Component score	0.317*	0.488*	0.280*	0.354*	0.417*	0.096
SF-36 Mental Component score	0.222**	0.495*	0.317*	0.435*	0.282*	0.138
SF-6D	0.286*	0.570*	0.297*	0.368*	0.319*	0.153

Source: Own table based on data from the cross-sectional survey

*Correlation is significant at the 0.01 level; **Correlation is significant at the 0.05 level.

Note: Numbers in bold are the interscale correlation coefficients comparing function and bother scores within each domain of the Hungarian BCI.

Correlations with other HRQoL measures applied in the study are indicated in Table 9. Correlations of the BCI subscales and the other disease-specific measure, the FACT-BI were moderate or strong, only the sexual bother subdomain presented weak relationship ($r=0.126$). Regarding the correlations between the BCI and generic HRQoL measures, these were weaker than with the FACT-BI (except one: bowel bother and EQ-5D score) which is in line with our predefined hypothesis. In the urinary and bowel domains, correlations of the generic HRQoL measures with the bother subdomains were stronger than with the functional subdomains. Correlations with the sexual bother subdomain were not significant.

An analysis of the Hungarian BCI by treatment subgroups is presented in Table 6. Mean scores across the four subgroups differed significantly in five domains. Although results in sexual summary, sexual function, sexual bother and bowel bother were not significant, differences in scores manifested among groups undergone cystectomy and without cystectomy, respectively. Accordingly, urinary, bowel and sexual scores were

consistently lower in cystectomy groups than in native bladder, i.e. endoscopically managed (TUR) groups of BC patients. Mean scores by disease stages (Ta, T1/Tis, T2, T3 and T4) did not indicate statistically significant differences ($p>0.05$).

Among the subdomains of urinary, bowel and sexual function the test-retest correlation was strong (between 0.805 and 0.871) while in the bother subdomains the coefficient was strong but slightly under the required 0.70 cut-off (between 0.665 and 0.698). Rate of participants reporting maximum score was the highest in both urinary and bowel primary domains (28.6% and 13.1%, respectively), consequently, ceiling effects were relatively strong regarding these domains. Minimal ceiling effect was observed in the sexual domain (0.9%). Floor effects were no relevant at all since none of the patients had minimum score.

IV.3.4. Discussion

In this cross-sectional study we assessed the HRQoL of patients with BC in three hospital based urology centres in Hungary. Among the domains of the SF-36 questionnaire, the lowest mean scores were found in the General Health and Role Physical areas (51 and 57, respectively). The average SF-36 domain scores of the BC patient sample were similar to the mean scores of the general Hungarian population aged 65 years and over (Czimbalmos et al., [1999]). Nevertheless, analysis by age-groups revealed deterioration in Physical Functioning younger BC patients (45-64 years), furthermore, Role Physical and Role Emotional were also affected in age-group 45-54 years. The difference between BC patients' results and population norms was not statistically significant with the other generic health state measure, the EQ-5D score. The rate of patients with native bladder was dominant (87%) in our sample, that can account for the rather favourable results with the general health state tools. Furthermore, general health state measures are usually less sensitive for smaller changes. According to a recent systematic literature review by Ali and colleagues, the difference between patients with ileal conduit and neobladder was not significant with the SF-36 in most of the studies (Ali et al., [2014]). Their overall conclusion was, based on the available results including studies with disease-specific tools as well, that neobladder urinary diversion shows only marginally better HRQoL compared to ileal conduit diversion,

especially when considering younger and fitter patients. In our survey, comparison of generic HRQoL measures across treatment groups did not result significant differences, with the exception of SF-36 Mental Component Score (Table 5). The FACT-BI did not present significant difference, either. We find important to point out, however, that our results by treatment types might be biased by the small sample sizes in the cystectomy subgroups (Table 6). Further studies involving larger samples with cystectomy are needed.

Mean utility scores assessed by the EQ-5D and SF-6D were comparable in our patient sample and their correlation was strong, indicating that the two instruments perform similarly in BC. Comparison of QALY results of cost-utility studies based on the EQ-5D and SF-6D seems to be reliable, nevertheless, further research investigating their equivalency especially in terms of responsiveness to changes in BC, is encouraged. Estimation of EQ-5D and SF-6D utility scores from FACT-BI seems to be promising as well. Mapping studies across various settings of patients with BC might provide clear evidences.

The Hungarian BCI proved to be satisfactory regarding survey characteristics in validation analysis involving 151 patients with BC. Internal consistency was excellent as marked by Cronbach's alpha (Terwee et al., [2007]) (Table 8). Psychometric experts disagree on the minimum number of subjects needed for assessment of internal consistency of a questionnaire by factor analysis (Terwee et al., [2007]; Sousa and Rojjanasrirat, [2011]). Rules-of-thumb vary from four to 10 candidates per variable, with a minimum number of 100 subjects, accordingly, our sample including 151 participants fulfilled these criteria. Factor analysis revealed that responses given to the Hungarian BCI questionnaire, with the exception of five outlier items of the 36, fit to the six subdomains of the original BCI, but not to the three primary domains. This result indicates that the relations between subdomains (function and bother) within each primary domain are not stronger than relations between primary domains themselves. Respectively, function and bother subdomains are closer to each other than function and bother pairs within a primary domain. Interscale correlations between BCI subdomains revealed good construct validity, referring adequate measurement independence among urinary, bowel and sexual domains (Table 9). The association between BCI and the other disease-specific measure (FACT-BI) was stronger than with the generic health state measures, that supports the disease-specific character of the questionnaire.

Response rate across BCI domains (78% and 88%) was comparable to the generic SF-36 and SF-6D measures indicating good feasibility of the Hungarian BCI, although not as excellent as the EQ-5D and FACT-BI questionnaires had (Table 5 and 6).

Alongside the advances in urology surgery reconstructive aspects gained greater importance and the need to assess and compare the HRQoL impact of different treatment strategies is increasing (Hedgepeth et al., [2010]). In contrast with the generic health state measures and the FACT-BI as presented above, the difference across treatment subgroups was significant in the urinary and bowel summary scores and also in the urinary function and bother subdomains of the BCI (Table 6). Seems that the BCI is more sensitive to capture treatment effects, nevertheless the discriminating capacity of the Hungarian BCI between therapeutic subgroups have to be confirmed in larger studies involving more patients with cystectomy.

Comparison of our results with the original BCI validation study by Gilbert and colleagues revealed similarities that support the appropriateness of the Hungarian version of the BCI questionnaire (Gilbert et al., [2010]). As in our study, Cronbach's alpha was higher in the sexual domain than in the other two domains and reproducibility was the weakest in the sexual bother subdomain. We found somewhat stronger correlations between BCI and FACT-BI than the original BCI study, nevertheless, the pattern was similar as bother subdomains presented stronger correlation than function subdomains in the urinary and bowel domains but not in the sexual domain. BCI presented stronger correlation with FACT-BI than with generic health state measure (SF-12 and SF-36, respectively) in both surveys. Feasibility is not comparable as Gilbert and colleagues did not report response rates among the 693 BCI patients contacted, but analysed only data of 315 patients (45%) who completed the questionnaire (Gilbert et al., [2010]).

A minor difference to note is that the relationship between sexual function and bother was weak in our survey whilst it was moderate in the original BCI study. Thus the sexual domain of the Hungarian BCI seems to be slightly an outlier compared to the original BCI. There might be, in the background, cultural differences between populations towards reporting about sexual life, including the ability to be sexually aroused, to have intercourse or to reach orgasm. Certainly, we cannot exclude translation bias either, although we did not experience notable difficulties with the perception of these items during cognitive debriefing interviews. Patients who did not respond the sexuality related items during the pilot were asked for the reasons and they

said that those questions were ‘irrelevant’ as they had no sexual life. Actually the BCI questionnaire does not offer shortcuts. For instance, item number 51 asks "Over the past 4 weeks, how often did you have any sexual activity?" ; and the next item, number 52 asks: "Over the past 4 weeks, how often have you had pain related to intercourse?". In our survey patients who responded ‘Not at all’ for question 51 either skipped the next one or responded ‘Never’. Obviously in their case the response ‘Never’ does not mean a painless intercourse but simply the lack of activity. This shortcoming of the original BCI questionnaire may weaken its feasibility and sensibility to demonstrate HRQoL effects. Another point to consider is that only participants who completed the questionnaire were included in the original BCI analyses. This patient selection can also have positive impact on psychometric results and be a reason for the differences in the sexual domain. Nevertheless, findings by Schmidt and colleagues seem to strengthen our observations regarding the BCI sexual domain as they also found weak correlation between sexual function and bother subdomains in the validation study of the Spanish version of the BCI (Schmidt et al., [2014]). The relationship between BCI subdomains and SF-36 was comparable to ours and the weakest correlation was observed with sexual bother subdomain. By contrast, response rates were somewhat higher in their study with follow-up design (N=197) but higher ceiling effect was observed. Only few patients have had cystectomy (N=6, 3.2%) thus comparison across treatment groups was not investigated. Overall, we encourage new multi-country studies to get a better insight into cross-cultural differences, as well as on the impact of age, gender and disease stage on the performance of the BCI, with special focus on the sexual domain.

Relations between the BCI and generic health state and utility measures deserve further attention. The moderate and weak association between BCI and EQ-5D, SF-36 and SF-6D indicates, on the one hand, that the BCI captures HRQoL aspects that are not detectable with generic questionnaires, particularly in urinary and bowel functioning and sexual areas. On the other hand, estimation of EQ-5D or SF-6D utility scores from BCI results is very limited. Thus, we suggest applying preference-based measures alongside the condition-specific BCI questionnaire in studies that aim to provide QALYs for economic evaluations.

Some limitations of our study have to be taken into account. The sample was not representative as the survey was performed in three hospital based urology centres. The rate of patients with cystectomy was quite low thus the generalizability of our results to

this subgroup of patients is limited. For the same reason, evidences on discriminating ability of the Hungarian BCI between treatment groups are promising but have to be confirmed in further studies. Responsiveness to changes was not assessed due to the cross-sectional design of our study. We encourage further studies to focus specifically on these points. Among the pros, we find important to highlight that according to our knowledge we were the first to analyse the relations between BCI, FACT-BI and the EQ-5D and SF-6D preference-based measures in parallel.

In summary, understanding disease-related quality of life issues is crucial in the management of BC both for clinical and financial decision making as well as for informing patients about the expected outcomes. Comparison across studies and cumulative analysis of different experiments require validated language versions of HRQoL instruments. The Hungarian version of the Bladder Cancer Index questionnaire proved to be a reliable and valid disease-specific instrument in our study to assess HRQoL of patients with BC. Further prospective studies involving larger patient samples are suggested to provide additional understanding of HRQoL measures' responsiveness to changes, performance across treatment groups and the impact of sex-specific concerns. Relations between BCI and the two preference-based utility measures, namely the EQ-5D and SF-6D, were weak, therefore, estimation of utility scores from the BCI is not supported by our results. However, modelling utility scores from the FACT-BI seems to be a fruitful area for further research.

We believe that health technologies for the treatment of BC will successively improve and the significance of measuring HRQoL outcomes both in clinical trials and health economic evaluations will increase as well. This study aimed to contribute to that goal.

IV.4. The empirical study – elaboration 2.

A further research aim of the BC study was to estimate and analyse the cost of illness of BC patients in Hungary.

To evaluate disease burden, there is a need for two kinds of inputs: data associated with the number as well as constitution of patient population (i.e. epidemiology); and

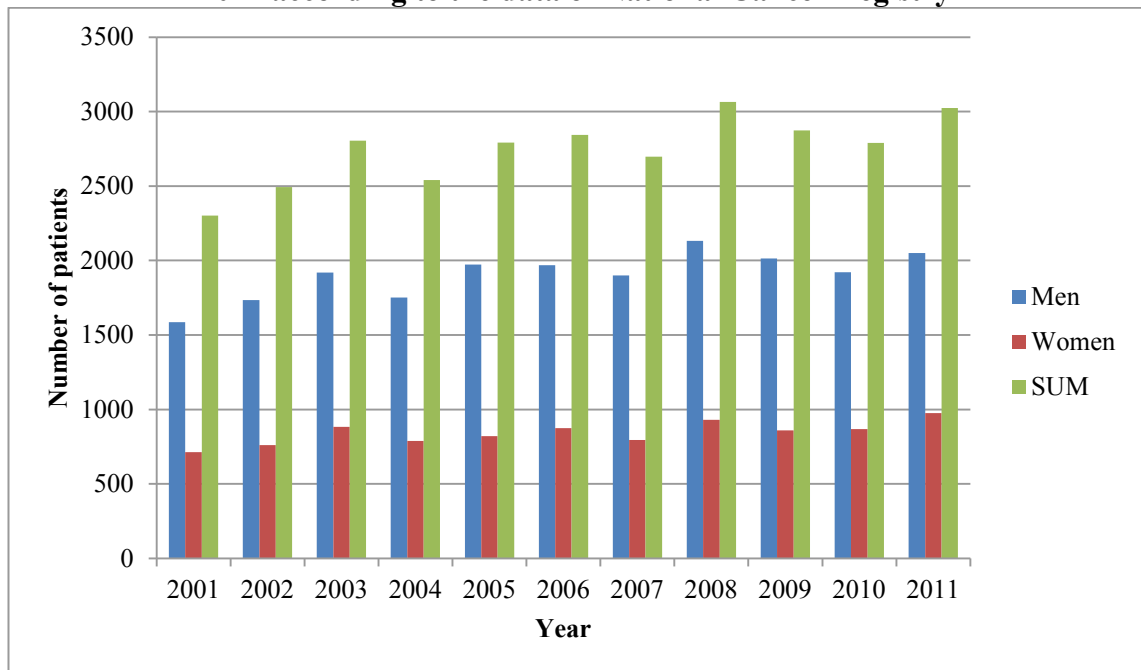
data regarding cost, respectively. Epidemiology data were obtained from the National Cancer Registry in Hungary and Eurostat database. Data regarding direct medical, direct non-medical and indirect costs were derived from the cross-sectional survey. In these cost categories, currently we focus on the following elements: some specific medicines gained from the databases of the National Health Insurance Fund Administration (NHIFA); those elements of direct non-medical and indirect costs which are not available in the insurant databases.

IV.4.1. Epidemiology of BC

According to the International Classification of Diseases (ICD), the code of BC cancers is C67 (subgroups of 01, 02, 03, 04, 05, 06, 07, 08 and 09).

In Hungary, data related to patients with bladder tumour are collected by the National Cancer Registry. Figure 6 demonstrates the evolution of number of new patients diagnosed with BC according to gender-based division between 2001 and 2011. Each year in the period considered BC was diagnosed in case of twice men in comparison with women. However, there is a significant variation in the number of new cases diagnosed with BC in the 11-year period (Figure 6).

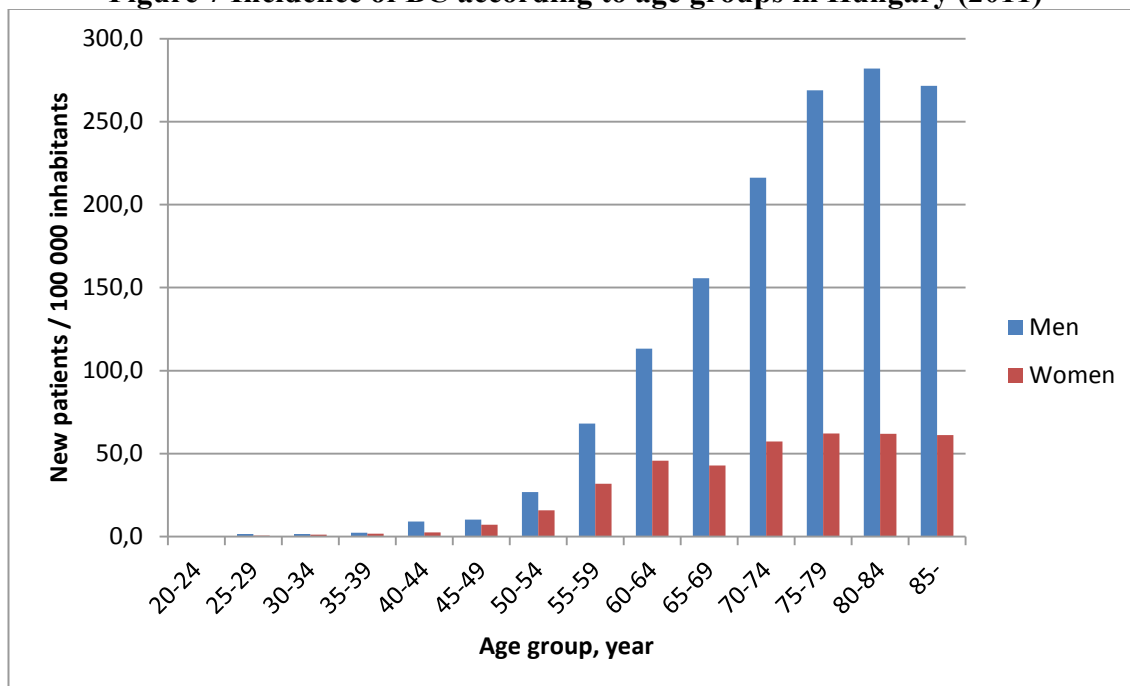
Figure 6 The number of new patients diagnosed with BC (ICD C67) from 2001 to 2011 according to the data of National Cancer Registry



Source: National Cancer Registry C67 data

In 2011 the incidence of BC had been increasing till the age of 84 years in case of men (Figure 7). In age group 50-54 the prompt increase of incidence can be observed, then, it is continuously growing by age till age-group 80-84. In case of women, the incidence stagnates above 70 years, accordingly, new cases among men are responsible for the growth of incidence. The highest incidence is associated with the age group 80-84 and above 85 years, In childhood, teenage and early young age the incidence is neglectable (overall 4 cases reported in age group 0-24); then from 25 years it is gradually increasing (altogether 130 cases reported in age group 25-49).

Figure 7 Incidence of BC according to age groups in Hungary (2011)



Source: National Cancer Registry C67 data, 2011; population: Eurostat database

IV.4.2. Assessment of resource utilisations and costing

Data regarding cost of illness have been collected by the cross-sectional survey as well. In addition, unit costs were derived from the databases of Central Statistics Office, National Health Insurance Fund and National Institute for Quality-and Organisational Development in Healthcare and Medicines. The method of cost calculation was the following: at first, unit charges of selected cost items were calculated, then these values were multiplied with the number of resource uses indicated in the cross-sectional survey, and finally, based on these values the average cost per patient referred to 2012 was calculated. (The reason why year 2012 was considered is that two-third part of the data was collected during that period.)

Below the types of costs and the method of calculation of unit costs are described.

IV.4.2.1. Direct medical costs

Costs associated with outpatient care, inpatient care and medicines are included in this category. In our study, data related to drug trade were calculated within this group,

those were transferred from the database of NHIFA. Medicines that can be prescribed with reimbursement of 100% only for BC by the NHIFA and for preventing the recurrence of tumour locally in the BC were considered for the current cost analysis. However, these drugs cover only one segment of the therapies applicable for BC and do not contain other medicines, e.g. systemic chemotherapy, painkillers, antibiotics and other drugs applied during inpatient care.

IV.4.2.2. Direct non-medical costs

This category includes such not typically health-related means which are necessary for interventions. In this dissertation costs associated with travelling to health care (different vehicles; ambulance; healthcare-related traveling voucher) and informal care were calculated within the group of direct non-medical costs. Data regarding non-medical costs were derived from the responses of the cross-sectional survey.

Costs related to transport

The survey about the use health care services within the cross-sectional survey inquired about the frequency of traveling, the vehicle used (public transport, train, bus, car) and the distance of the clinic from patient's home. Participants travelled to one of the 3 Hungarian hospital-based urology centres situated in Budapest, Nyíregyháza and Pécs. Based on responses, patients with BC visit the doctor 4 times per year on the average. Therefore, I multiplied the average cost per way per patient with this value in order to get the average annual cost of transport per patient. Below I present briefly the methods which were applied in calculating unit costs regarding the different vehicles used to get to the clinic.

Public transport

Public transport was relevant not only when patients definitely indicated that they used public transport so as to get to the clinic but the tariffs of it were taken into account as well when candidates reported about traveling by train/bus. The three research centres were found in Budapest, Nyíregyháza and Pécs. Regarding Budapest, prices established by the Centre of Transport of Budapest (Budapesti Közlekedési Központ,

BKK) in 2012 were used in costing, and taking into account the size of the capital, 2 tickets were considered per way to the clinic, and overall 4 tickets due to the way back per patient (980 HUF). Considering 1 ticket there and back, the average cost of using public transport per patient in Nyíregyháza and Pécs is 612.5 and 640 HUF, respectively.

Bus/Train

Costs associated with traveling by bus/train were calculated from survey data provided by patients and tariffs of Volán in 2012, respectively. From the point of view of cost, it was irrelevant whether patients used train or bus since tariffs of these vehicles are equal. Three parameters, namely, the distance between patients' place of living and the clinic they belong to; the average bus prices according to km ranges; and the frequency of clinician's visits were considered in order to calculate the average cost of transport per patient due to BC in 2012. In case of using bus/train, so as to get to the certain clinic, the average cost of traveling by bus/train per patient had to be complemented by the average cost of using public transport regarding the relevant city per patient.

Car

To calculate the costs emerged due to transport by car to the clinic, data were derived from the database of Hungarian Tax and Financial Control Administration. The average price of fuel in 2012 (427 HUF); the average fuel consumption (10.5 l/100 km) and the cost of amortization per km (9 HUF) were taken into account so as to get the average cost per km (50.9 HUF).

Ambulance and health related transport voucher

Costs due to the use of ambulance and health-related transport voucher have to be counted in the category of non-medical direct costs, too. The unit cost of ambulance was 888.0 HUF/km in 2012 (Balogh et al., [2014]). The analogue of the calculation of unit cost of health related transport voucher and transport by bus/train is equivalent.

Costs related to informal care and social services

Informal care related cost emerges in the following cases: the patient gets help from a family member; the patient pays an official person for helping in daily activities; the patient pays for social care. None of the respondents reported about paying an official person for help. The cost of providing help by family members based on the average wage per hour (1 832.7 HUF) which was derived from the unit cost of productivity loss (293 231.9 HUF/month); and the hours spent for help.

Twenty-five percent of the monthly wage of the user was considered as the fee of social service (http://www.efoesz.hu/download/teritesi_dij.pdf) which was equivalent with 10 687.5 HUF/month. (Only 1 patient reported that he had used social service. He did not indicate the number of average days of use per month, hence, I made an assumption that social care was provided 15 days in a month.)

IV.4.2.3. Indirect costs

This category involves productivity loss related costs that are derived from the changed capacity in payed work of patients due to the disease.

Cost of productivity loss

The cost of productivity loss was calculated in case of disabled pension, half-time work, sick-pay and leave of absence without payment due to BC. The relevant time units were considered in each form of work loss: disabled pension and half-time work – month, sick-pay and leave of absence – day. The unit cost of productivity loss in 2012 was 293 231.9 HUF/month.

IV.4.3. Cost of illness in bladder cancer

IV.4.3.1. Medicines within the category of direct costs

Table 10 presents the trade of medicines for intravesical instillation supported in 100% by the National Health Insurance Fund in low and medium risk cases of BC in 2012. There are four brands traded with two agents: epirubicin and mitomicin. According to

indicators of trade like the volume of packs sold, days of treatment (DOT), financial support by the National Health Insurance Fund, fee payment by patients, the trade of medicines with epirubicin agent was the greatest. The Farmorubicin PFS/RTU 50 mg tinctured injection ran to the 96.3% of the all medicines with epirubicin agent, while among medicines with mitomicin agent the Mitomycin-C Kyowa 20 mg was associated with the greatest volume of trade (88.1%).

Table 10 The trade of medicines for intravesical instillation supported in 100% by the National Health Insurance Fund in low and medium risk cases of BC (2012)

Year	Brand	Medicine	Packing	ATC-code	Agent	Packs sold (pieces)	Days of treatment (DOT)	Support by the social insurance fund (HUF)	Trade (gross consumer price, HUF)	Patient's charge fee (HUF)
2012	EPIRUBICIN ACCORD	EPIRUBICIN ACCORD 2 MG/ML OLDATOS INJEKCIÓ VAGY INFÚZIÓ	1x25ml	L01DB03	epirubicin	65	3250	541515	561015	1950
2012	EPIRUBICIN-TEVA	EPIRUBICIN-TEVA 2 MG/ML OLDATOS INJEKCIÓ VAGY INFÚZIÓ	1x5 ml in injection flask	L01DB03	epirubicin	20	200	46500	52500	6000
2012	EPIRUBICIN-TEVA	EPIRUBICIN-TEVA 2 MG/ML OLDATOS INJEKCIÓ VAGY INFÚZIÓ	1x25 ml in injection flask	L01DB03	epirubicin	34	1700	296215	306415	10200
2012	FARMORUBICIN	FARMORUBICIN RD 50 MG POR OLDATOS INJEKCIÓHOZ	1x in injection flask	L01DB03	epirubicin	6	300	98622	100422	1800
2012	FARMORUBICIN	FARMORUBICIN PFS/RTU 10 MG OLDATOS INJEKCIÓ	1x in injection flask	L01DB03	epirubicin	64	640	245832	265032	19200
2012	FARMORUBICIN	FARMORUBICIN PFS/RTU 50 MG OLDATOS INJEKCIÓ	1x in injection flask	L01DB03	epirubicin	4906	245300	83504934	84976734	1471800
					Epirubicin, SUM	5095	251390	84733618	86262118	1528500
2012	MITOMYCIN	MITOMYCIN-C KYOWA 10 MG POR OLDATOS INJEKCIÓHOZ	5x in injection flask	L01DC03	mitomicin	287	7180	5870005	5956165	86160
2012	MITOMYCIN	MITOMYCIN-C KYOWA 20 MG POR OLDATOS INJEKCIÓHOZ	5x in injection flask	L01DC03	mitomicin	102	5080	3588053	3618533	30480
2012	MITOMYCIN	MITOMYCIN-C KYOWA 20 MG POR OLDATOS INJEKCIÓHOZ	1x in injection flask	L01DC03	mitomicin	2890	28900	21784820	22651820	867000
					Mitomicin, SUM	3279	41160	31242877	32226517	983640
					Sum of the two agents (HUF)	8374	292550	115976495	118488635	2522140

Source: National Health Insurance Fund

Note: DOT: Days of Treatment (DOT) value is calculated according to Defined Daily Dose (DDD) by WHO. WHO has not defined DDD regarding these medicines since they can be applied in various types of cancers. However, in Hungary these ones can be provided by special financial support solely in BC (ICD C67) in BC.

high risk cases of BC, four medicines for intravesical instillation supported in 100% by the National Health Insurance Fund were traded in 2012. The agent of each of the four medicines was bcg vaccine, among them the Bcg-Medac powder and solvent to intravesical suspension 1x50 ml was responsible for the greatest part of trade (87.0%) (Table 11).

Table 11 The trade of medicines for intravesical instillation supported in 100% by the National Health Insurance Fund in high risk cases of BC (2012)

Year	Brand	Medicine	Packing	ATC-code	Agent	Packs sold (pieces)	Days of treatment (DOT)	Support by the social insurance fund (HUF)	Trade (gross consumer price, HUF)	Patient's charge fee (HUF)
2012	BCG-MEDAC	BCG-MEDAC POR ÉS OLDÓSZER INTRAVEZIKÁLIS SZUSZPENZIÓHOZ	1x powder ampul +1x50 ml solvent pouch+catheter fitment	L03AX03	bcg vaccine	4079	183555	87486481	88710181	1223700
2012	BCG-MEDAC	BCG-MEDAC POR ÉS OLDÓSZER INTRAVEZIKÁLIS SZUSZPENZIÓHOZ	1x powder ampul +1x50 ml solvent pouch+catheter fitment	L03AX03	bcg vaccine	11	495	235841	239141	0
2012	IMMUCYST	IMMUCYST POR ÉS OLDÓSZER INTRAVEZIKÁLIS SZUSZPENZIÓHOZ	1x81mg powder ampul +1x3 ml solvent ampul	L03AX03	bcg vaccine	334	15030	7525688	7625888	100200
2012	IMMUCYST	IMMUCYST POR INTRAVEZIKÁLIS SZUSZPENZIÓHOZ	1x injektion flask	L03AX03	bcg vaccine	266	11970	5994898	6074698	79800
				Sum	4690	211050	101242908	102649908	1403700	1403700

Source: National Health Insurance Fund

The overall financial support by the National Health Insurance Fund for the 3 agents was 219.7 million HUF in 2012.

Two relevance studies from the international literature reported about the results achieved by intravesical chemotherapy (mytomicin C) and intravesical instillation (BCG), respectively, which therapeutic methods were applied in our survey, too. The two studies establish that these therapies are associated with preventable recurrences and cost savings. In the Hungarian BC population, 130 patients (86.8%) received intravesical therapy.

IV.4.3.2. Direct-non-medical costs

Table 12 Average direct non-medical costs per patient (2012)

DIRECT, NON-MEDICAL COSTS, HUF/year		
Annual average costs per patients	Mean	SD
Transport	9 213.5	17 435
Ambulance	2 646.4	24 173.4
Health-related transport voucher	1 319.9	5 273.2
Providing help by family members (informal care)	179 871.5	631 052.7
Social care	849.3	10 436.8

Source: Own table based on data from the cross-sectional survey

Table 12 lists direct-non-medical costs. Average cost related to transport was 9 213.5 HUF/patient/year. Health related transport voucher was used by 15 of 151 patients (0.099%); the average cost associated with this item was 1 319.9 HUF/patient/year. Ambulance was used by solely 1 patient (0.0066%); the average cost was 2 646.4 HUF/patient/year regarding this component.

Although only 24 of 151 patients (15.9%) got help from family members for self-care or everyday activities, the average cost was relatively high (179 871.5

HUF/patient/year). Solely 1 patient demanded social care in the sample (0.007%), so the average cost associated with this factor of non-medical costs was marginal (849.3 HUF/patient/year).

IV.4.3.3. Indirects costs

The component calculated within the category of indirect costs is productivity loss which was associated with mean 267 007.3 HUF/patient/year (S.D.=893 110.8 HUF/patient/year).

IV.5. Conclusions

Understanding disease-related quality of life issues are crucial in the management of BC both for clinical decision making and informing patients about the expected outcomes. Comparison across studies and cumulative analysis of different experiments require validated language versions of HRQoL instruments. Moreover, most clinical studies use disease-specific instruments whilst cost-effectiveness analyses require preference based utility scores. Thus there has been an increasing use of estimating utilities from disease-specific instruments in health economic analyses but it is an underexplored area in BC. In our study the Hungarian version of the BCI questionnaire proved to be a reliable and valid disease-specific instrument to assess HRQoL of patients with BC. Further prospective studies involving larger patient samples are suggested to provide additional understanding of its responsiveness to changes, performance across treatment groups and the impact of sex-specific concerns. Relations between BCI and the two preference based utility measures, namely the EQ-5D and SF-6D, were weak, therefore, estimation of these utility scores from the BCI is not supported by our results. The estimation of disease burden is crucial in order to make well-founded reimbursement decisions.

V. SUMMARY AND CONTRIBUTIONS TO THE FIELD

In this dissertation a comprehensive picture about different mechanisms and different levels of supporting reimbursement related decision-making is provided. Three separate but interrelated issues regarding economic evaluation of health technologies with an emphasis on challenges and opportunities for Hungary were assessed. In part II, within the context of HTA as macro level, a unique approach of conducting cost-effectiveness analysis in health care was analysed. In part III, a systematic literature review of cost-utility evidences of biologic health technologies in two chronic conditions (RA in detail and CD in brief) were presented as parts of completed HTAs interpreted as middle level. In part IV, an empirical study about the validation of BCI questionnaire as well as assessing HRQoL and CoI of patients with BC as another chronic condition was presented in the context of data producing for health economic evaluation as micro level. Each of the three research question is corresponded by the issue of cost-effectiveness and transferability of health economic results, especially from the point of view of Hungary.

The proliferation of new and improving health technologies has led to the exponential growth of health care expenditures. The growing tension between ‘technologically available’ and affordable has brought the demand for cost-effectiveness. This demand is reflected by the growth and development of HTA. Although HTA in itself is a common tool for promoting the selection of cost-effective health technologies, the process and principles of conducting HTAs may show diversity. Different jurisdictions apply different approaches with respect to the perspective of the analysis, selection of technologies for appraisal; the involvement of stakeholders. The majority of Western-European countries follow the methods established by NICE whereas in Germany the IQWiG represents a unique approach to cost-effectiveness analysis. Besides analysing the most cardinal principles which make the German approach specific, the surplus value of this research is that lessons can be learnt from Germany are discussed as well in the case of Hungary where the capacity is limited in both professional and institutional sense.

Two HTA agencies operate in Germany. Among them, DAHTA employs operational principles which are consistent with other HTA agencies in Europe whereas IQWiG’s

approach differs in several key points from the practice of other HTA organizations. Among them the most significant as well as debated ones are applying a disease/indication-specific threshold instead of an explicit one in terms of cost/QALY; and the efficiency frontier approach.

In contrast to other European HTA agencies applying cost-utility (cost/QALY) analysis, IQWiG does not support the use of QALYs. The point of IQWiG's approach is to assess the value of a new technology in its specific clinical indication. The main difference is manifested in defining value in this context. While in other organizations' practice a generic cost-effectiveness threshold is applied, mainly in terms of cost per QALY, IQWiG establishes a disease/indication-specific threshold which is inferred from previous decisions made in Germany in that area. Accordingly, it is not clear how IQWiG's methods can inform resource allocation decision-making given that costs and effects inevitably extend beyond individual disease areas.

The efficiency frontier which is an extension of the standard approach of incremental cost-effectiveness ratios is organically connected with the previous debated issue. The point of the approach is that an efficiency frontier is constructed for each therapeutic area as the basis for health economic evaluation of relevant health technologies. Without applying a universal threshold, the method is based on the determination of the prevailing efficiency in a given therapeutic area in Germany. The efficiency frontier consisting of the most efficient therapeutic alternatives within the particular therapeutic area compares the therapeutic benefit of available interventions with the outcome-related net costs of them. Interventions on the frontier denote the net cost for any given benefit that is consistent with the efficiency that can be achieved by the package of interventions on the current market.

Despite the German approach to cost-effectiveness analysis is heavily debated by several health economists, it represents such elements which might serve as examples especially for Hungary. The most important one is the high extent of transparency of the whole HTA process including external and internal control as well. Although HTA in Hungarian context is still far from the German HTA, in Hungary the transparency of process is available neither for the public nor for stakeholders. On the whole, challenges for HTA in Hungary are partly similar to the ones in countries with a developed economy; it is obvious that it is time for cost-effectiveness. However, there are very

important differences as well, that is why transferability and adaptability issues have to be taken into consideration.

Regarding further research orientations, it would be useful to assess whether the German or the UK HTA approach is more transferable and useful to the Hungarian settings. According to my best knowledge this issue has not been raised and evaluated yet in depth. In addition, it would be interesting to investigate the causes behind the reluctance of applying the QALY concept in Germany and follow the changes.

Whereas in Germany the use of QALY is not supported, CEE countries apply QALY but in case of this setting data being necessary to produce QALY are slightly available similarly to other post-socialist countries. Due to the scarcity of local data based on national studies, CEE countries are highly dependent on cost-effectiveness results from abroad. Accordingly, the context regarding Western Europe and CEE region is differing. That is why transferability and adaptability of the results of health economic studies carried out in different settings is vital for these countries.

A segment of the mechanism is presented in Part III. The systematic review of the available literature of cost-utility results in a chronic inflammatory disease (RA) was a crucial step in the process of adaptability of foreign data. Altogether 36 studies were captured by the systematic literature search in RA. The quality of reporting is quite an important issue in health economic publications since usually neither the model itself nor the inputs are provided. Thusly the analysis is not reproducible and critical appraisals have to rely on the reported data. Therefore, besides synthesizing the results of the selected cost-utility studies, the quality assessment of the published data was performed based on the criteria established by Drummond and Jefferson. According to this checklist, it could be established that the 36 publications frequently failed to demonstrate key data (mainly methods for identifying selecting, and synthesizing data for key model parameters; study design) appropriately which might have significant impact on the cost per QALY results.

Regarding the results, the comparison of cost-effectiveness results across studies was problematical. Differences in comparators, methods, data, modelling approach prevent reliable interpretation of the results of such comparisons thus it is not possible to draw definitive conclusions. Our findings in the HTA of biological therapies in Crohn's Disease (CD) confirmed the generalizability of our observations in RA.

From the point of view of Hungary, it was important to review whether results from similar settings are available. In case of RA, there was solely one study conducted in Hungary. Most of the analyses were performed in Western-European countries. However, these nations differ significantly from CEE countries in a range of features, among them GDP per capita, health and social care systems, demography, morbidity, health status of the given population in question (RA), reimbursement mechanisms of medications and financing of health care institutions or costs and so on. Hence the transferability of these health economic results to jurisdictions of CEE is limited.

So what are the opportunities for Hungary regarding economic evaluation? In RA and other chronic diseases with expensive therapies, valuable cost-effectiveness studies have been already conducted and models have been built mainly in Western European countries. However, some extent of this professional knowledge can be transferred among different jurisdictions. For instance, literature revealed that certain models (Bansback et al., [2005]; Kobelt et al.; [2003]) are transferred by several countries instead of constructing new ones. However, these countries adapt the cost-effectiveness models with a respect of local features: they do not only apply country-specific input data but alter the structure of models according to the local clinical and financing practice. Accordingly, opportunities are given but what are the challenges for Hungary?

In CEE countries data about clinical practice, HRQoL, costs are limited hence those should be explored. Considering the time constrains to produce health economic evaluations for the increasing number of new health technologies, quick cross-sectional surveys might offer good proxies about the characteristics of local settings. However, in the long term, so as not to face with the same problem, follow-up studies and well-designed patient registries should be established as well as systematic data collection should be introduced particularly in areas associated with costly therapies. In other words, performance of health care (both in terms of inputs and outputs) should be measured, however, it requires not only financial resources but education, training and highly qualified professionals as well.

Thus, currently there is a gap between the two parts of Europe regarding opportunities. So as to bridge this gap or at least to take steps toward it, data collection in local setting might be a viable opportunity for Hungary. However this strategy is

associated with substantial transaction and other costs, this is a possible way for conducting health economic evaluation in a reliable way.

The empirical study about the validation of the BCI questionnaire; HRQoL; and CoI of patients with BC is the implementation of this opportunity.

As for BC-specific instruments, there are only a few ones available to measure HRQoL outcomes in depth. Regarding CEE countries, lack of validated language versions is an additional obstacle for the comparison between results of multicentre trials. The BCI questionnaire developed and validated in the US to assess HRQoL of patients with BC has been applied in an increasing number of studies, however, it was validated for a few languages (US English, Spanish and partially in French) but not for the CEE countries. Accordingly, the translation and validation of the Hungarian version of BCI questionnaire was a significant surplus value of the empirical study. By validation not just a usable but reliable instrument has been produced which is applicable in further HRQoL studies. In addition, the development of the validated Hungarian version of BCI includes an opportunity for Hungary to participate in international studies as national results have become comparable in international context.

During the elaboration of the translation, an important shortcoming of the original version has been explored. The BCI questionnaire cannot treat such scenarios when certain items are not relevant for respondents. Accordingly, participants are constrained to give answers to each question within a domain, for example, even though someone did not have any sexual activity over the past 4 weeks, the questionnaire makes him/her to answer to the question about the frequency of pain related to intercourse over the past 4 weeks as well. Consequently, in the scoring process BCI is not able to differentiate the following scenarios: (A) somebody did not have any sexual activity over the past 4 weeks and that is why he/she had never pain related to intercourse; (B) the patient had sexual activity over the past 4 weeks but he/she had no pain related to intercourse. This shortcoming of the questionnaire might weaken its sensibility to demonstrate HRQoL related effects and might be responsible for the differences observed regarding the sexual domain. Hence this methodological issue being relevant in international context as well is a new scientific result.

Another surplus value of the empirical study is that it is the first assessment in international level which applies four HRQoL questionnaires, among them a disease-specific instrument (FACT-BI), a general health state questionnaire (SF-36) and two preference-based utility measures (EQ-5D, SF-6D).

Understanding disease related quality of life issues are crucial in the management of BC both for clinical decision making and informing patients about the expected outcomes. Comparison across studies and cumulative analysis of different experiments require validated language versions of HRQoL instruments. Moreover, most clinical studies use disease-specific instruments whilst cost-effectiveness analyses require preference based utility scores. Thus there has been an increasing use of estimating utilities from disease-specific instruments in health economic analyses but it is an underexplored area in BC. Our study assessed relations between disease-specific and utility measures firstly in international context. Relations between BCI and the two preference-based utility measures, namely the EQ-5D and SF-6D, were weak, therefore, estimation of these utility scores from the BCI is not supported by our results.

Another important conclusion of the empirical study is that the Hungarian version of the BCI questionnaire proved to be a reliable and valid disease-specific instrument to assess HRQoL of patients with BC. Further prospective studies involving larger patient samples are suggested to provide additional understanding of its responsiveness to changes, performance across treatment groups and the impact of sex-specific concerns.

BC related researches with the aim of serving data for health economic evaluations should use preference-based utility measures. With applying the EQ-5D and SF-6D utility instruments, our study is the first which provides data for health economic evaluations. Based on the HRQoL and cost data calculated by the empirical study, a further research direction can be the producing of cost/QALY as a common measure by which absolutely different chronic diseases like RA and BC is becoming comparable for the financing decisions. This is the key for supporting resource allocation decision-making based on information of good quality.

VI. REFERENCES

Aboumohamed A.A. et al. [2014]: Health-related Quality of Life Outcomes After Robot-assisted and Open Radical Cystectomy Using a Validated Bladder-specific Instrument: A Multi-institutional Study. *Urology.*, 83(6): pp.1300-1308., doi: 10.1016/j.urology.2014.02.024.

A húgyhólyagrák diagnosztikájának és kezelésének finanszírozási protokollja. „Finanszírozási protokoll - háttéranyag”, [2010]. Országos Egészségbiztosítási Pénztár, Elemzési, Orvosszakértői és Szakmai Ellenőrzési Főosztály, Budapest. Available at : http://site.oep.hu/prot2/32_A_hugyholyagrak_finanszirozasi_protokoll_hatteranyag_a.pdf. Date of download: 07.28.2014.

Ali, A.S., Hayes, M.C., Birch, B., Dudderidge, T., Somani, B.K. [2014]: Health related quality of life (HRQoL) after cystectomy: Comparison between orthotopic neobladder and ileal conduit diversion. *European Journal of Surgical Oncology*, doi: 10.1016/j.ejso.2014.05.006. [Epub ahead of print]

Az Egészségügyi Minisztérium Szakmai Protokollja a húgyhólyag daganatok ellátásáról, 2008. Készítette: A Sugárterápiás és Onkológiai Szakmai Kollégium, a témában érintett Urológiai, Radiológia és Nucleáris Medicina Szakmai Kollégiumok jóváhagyásával. Available at: www.eum.hu/download.php?docID=2895. Date of download: 08.04.2013

Baji, P., Boncz, I., Jenei, Gy., Gulácsi L. [2012]: Comparing cost-sharing practices for pharmaceuticals and health care services among four Central-European countries. *Society and Economy* 34(2) pp.221–240.

Baji, P., Pavlova, M., Gulácsi, L., Groot, W. [2012]: Changes in Equity in Out-of-pocket Payments during the Period of Health Care Reforms: Evidence from Hungary. *International Journal for Equity in Health* 11(36) pp.1-11., doi: 10.1186/1475-9276-11-36.

- Balogh, O. et al. [2014]: Cost-of-illness in patients with moderate to severe psoriasis: a cross-sectional survey in Hungarian dermatological centres. *European Journal of Health Economics*. 15 (Suppl 1) :pp.S101-9., doi: 10.1007/s10198-014-0599-z
- Bansback, N. J., Brennan, A., Ghatnekar, O. [2005]: Cost effectiveness of adalimumab in the treatment of patients with moderate to severe rheumatoid arthritis in Sweden. *Annals of the Rheumatic Diseases*; 64(7), pp.995-1002., doi: 10.1136/ard.2004.027565
- Barbieri, M., Wong, J. B., Drummond, M. [2005]: The cost effectiveness of infliximab for severe treatment-resistant rheumatoid arthritis in the UK. *Pharmacoeconomics*. 23(6), pp.607-618., doi: 1170-7690/05/0006-0607/\$34.95/0
- Barton, P., Jobanputra, P., Wilson, J. [2004]: The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis. *Health Technology Assessment*.; 8(11), pp. 1-91.
- Bartsch, G., Daneshmand, S., Skinner, E.C., Syan, S., Skinner, D.G., Penson, D.F. [2014]: Urinary functional outcomes in female neobladder patients. *World Journal of Urology*, 32(1): pp.221-228., doi: 10.1007/s00345-013-1219-8.
- Bekkering, G. E., Kleijnen, J. [2008]: Procedures and methods of benefit assessments for medicines in Germany. *European Journal of Health Economics* 9(Suppl 1): pp.5-29., doi: 10.1007/s10198-008-0122-5.
- Belevitin, A. B., Tyrenko, V. V., Grigor'eva, O. A., Bologov, S. G. [2010]: Economic assessment of the use of biological medications in military medicine. *Voenna Medit Sinskii Zhurnal*. 331(12), pp.4-8.
- Benucci, M., Gobbi, F., Sabadini, L., Saviola, G., Baiardi P., Manfredi, M. [2009]: The economic burden of biological therapy in rheumatoid arthritis in clinical practice: cost-effectiveness analysis of sub-cutaneous anti-TNF alpha treatment in Italian patients. *International Journal of Immunopathology and Pharmacology*. 22(4), pp.1147-1152.

- Benucci, M., Saviola, G., Baiardi, P., Manfredi, M. [2011]: Cost-effectiveness treatment with Rituximab in patients with rheumatoid arthritis in real life. *Rheumatology International*. 31(11), pp.1465-1469., doi: 10.1007/s00296-010-1502-6.
- Betlehem, J., Kriszbacher, I., Oláh, A., Boncz, I., Sebestyén, A., Marton, J., Nagy, G., Gulácsi, L., Bódis, J., Veres, R. [2008]: The patients safety standards of acute stroke management in Hungary. *Value in Health*, 11(3), p.A217.
- Boncz, I. [2006]: Népegészségügyi programok egészség-gazdaságtani elemzése. Pécsi Tudományegyetem Egészségtudományi Kar, Pécs. Available at: http://doktoriiskola.etk.pte.hu/dok/doktoriiskola/ertekezesek/BonczI_ertekezes.pdf.
Date of download: 02.15.2014
- Boncz, I., Brodszky, V., Péntek, M., Ágoston, I., Nagy, Zs., Kárpáti, K., Kriszbacher, I., Fuszek, P., Gulácsi, L. [2010]: The disease burden of colorectal cancer in Hungary. *European Journal of Health Economics* 10(Suppl 1). pp.35-40.
- Boncz, I., Dózsa, Cs., Kaló, Z., Nagy, L., Borcsek, B., Brandtmüller, Á., Bethlehem, J., Sebestyén, A., Gulácsi, L. (2006): Development of health economics in Hungary between 1990-2006. *European Journal of Health Economics* 7(Suppl 1.), pp.4-6., doi: 10.1007/s10198-006-0364-z
- Botteman, M. F., Pashos, C. L., Hauser, R. S., Laskin, B. L., Redaelli, A. [2003]: Quality of life aspects of bladder cancer: a review of the literature. *Quality of Life Research*. 12(6), pp.675-88
- Brazier, J. E., Roberts, J. R. [2004]: The estimation of a preference-based index from the SF-12. *Medical Care*, 42(9), pp.851-859
- Brazier, J. E., Rowen, D., Hanmer, J. [2008] *Revised SF-6D scoring programmes: a summary of improvements*. PRO newsletter, The Voice for Patient Centered Outcomes Reserach Professionals Worldwide (40)pp.14-15. Available at: http://www.pro-newsletter.com/images/PDF_articles/sf-6d.pdf, date of download: 05.03.2014
- Brennan, A. et al. [2007]: Modelling the cost effectiveness of TNF-alpha antagonists in the management of rheumatoid arthritis: results from the British Society for Rheumatology Biologics Registry. *Rheumatology (Oxford)*.46(8), pp.1345-1354.

- Brazier, J., Usherwood, T., Harper, R., Thomas, K. [1998]: Deriving a preference-based single index from the UK SF-36 Health Survey. *Journal of Clinical Epidemiology*, 51(11): pp.1115-1128. doi:S0895-4356(98)00103-6 [pii]
- Brodzky, V., Érsek, K., Gulácsi, L. et al. [2009]: *Certolizumab pegol in patients with rheumatoid arthritis: systematic review and health economic evaluation (A certolizumab pegol kezelés rheumatoid arthritisben, irodalmi áttekintés és egészség-gazdaságtani elemzés)*. Discussion Paper, Health Economics and Health Technology Assessment Research Centre, Hungarian Office for Health Technology Assessment, Corvinus University of Budapest; ISBN 978-963-503-448-2.
- Brodzky, V., Gulácsi, L., Kárpáti, K et al [2007a]: *Parenteral methotrexate in patients with rheumatoid arthritis: systematic review, crosssectional study and economic evaluation (A parenteralis methotrexat szerepe a rheumatoid arthritis terápiájában: a szakirodalom áttekintése, keresztmetszeti vizsgálat és egészség-gazdaságtani elemzés.)* English abstract available. Discussion Paper, Health Economics and Health Technology Assessment Research Centre, Hungarian Office for Health Technology Assessment, Corvinus University of Budapest; ISBN 978-963-503-421-5.
- Brodzky, V., Orlewska, E., Péntek, M., Kárpáti, K., Skoupa, J., Gulácsi, L.[2010]: Challenges in economic evaluation of new drugs: experience with rituximab in Hungary. *Medical Science Monitor*. 16(1), pp.1-5.
- Brodzky V, Péntek M, Kovács Á, Rencz F, V. Hevér N, Gulácsi L [2013]: Frequency of lower urinary tract symptoms in men and women in Hungary – results of an open label questionnaire study from 2012. *Value In Health*, 16(7): p.A635.
- Brodzky, V., Péntek, M., Májer, I. et al. [2007b]: *Abatacept in the treatment of rheumatoid arthritis; systematic review and economic evaluation (Az abatacept szerepe a rheumatoid arthritis terápiájában; a szakirodalom szisztematikus áttekintése és egészség-gazdaságtani értékelés)*. English abstract available. Discussion Paper, Health Economics and Health Technology Assessment Research Centre, Hungarian Office for Health Technology Assessment, Corvinus University of Budapest. Available at: <http://hecon.uni->

corvinus.hu/download/english/publ/hecon_research_22_hun.pdf. Date of download: 08.08.2013.

Brodzky, V., Péntek, M., Májer, I., és mtsai [2007c]:. *Economic evaluation of the first TNF-alpha inhibitor therapy in patients with rheumatoid arthritis (A rheumatoid arthritis terápiájában alkalmazott első TNF-alfa gátló kezelés egészség-gazdaságtani elemzése)*. Discussion Paper, Health Economics and Health Technology Assessment Research Centre, Hungarian Office for Health Technology Assessment, Corvinus University of Budapest. 2007.

Brodzky V, Péntek M, Baji P, Balogh O, V. Hevér N, Gulacsi L [2013]: Budget impact analysis of biosimilar infliximab treatment for rheumatoid arthritis in six central European countries. *Value In Health*, 16(7): A558.

Cella, D.F. et al. [1993]: The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *Journal of Clinical Oncology.*, 11(3) pp.570-579.

Chen, Y. F. et al. [2006]. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. *Health Technology Assessment*, 10(42) pp.1-229.

Cohen, J. [1992]: A power primer. *Psychological Bulletin*, 112(1): pp.155-159., doi: 10.1037/0033-2909.112.1.155.

Coyle, D. et al. [2006]: *Infliximab and etanercept in patients with rheumatoid arthritis: a systematic review and economic evaluation*. Ottawa: Canadian Coordinating Office for Health Technology Assessment. Available at: <http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?LinkFrom=OAI&ID=3200600221#.VARXF01O7wo>. Date of download: 02.08.2013

Czimbalmos, Á., Nagy, Z., Varga, Z., Hustik, P. [1999]: Páciens megelégedettségi vizsgálat SF-36 kérdőívvel, a magyarországi normálértékek meghatározása. *Népegészségügy* 80 (1): pp.4-19.

Davies, A., Cifaldi, M. A., Segurado, O. G., Weisman, M. H. [2009]:. Cost-effectiveness of sequential therapy with tumor necrosis factor antagonists in early rheumatoid arthritis. *The Journal of Rheumatology*, 36(1), pp.16-26., doi: 10.3899/jrheum.080257.

x

Diamantopoulos, A. et al.[2012]: Economic evaluation of tocilizumab combination in the treatment of moderate-to-severe rheumatoid arthritis in Italy. *Journal of Medical Economics*. 15(3), pp.576-585., doi: 10.3111/13696998.2012.665110.

Drummond, M. [2007]: Technology assessment in the German Context. *European Journal of Health Economics* 8(Suppl 1), p.S3, doi: 10.1007/s10198-007-0067-0.

Drummond et al. [2008]: Key principles for the improved conduct of health technology assessments for resource allocation decisions. *International Journal of Technology Assessment Health Care*, 24(3): pp.244-58., doi: doi: 10.1017/S0266462308080343.

Drummond, M. F., Jefferson, T. O. [1996]: Guidelines for authors and peer reviewers of economic submissions to the BMJ. *The British Medical Journal Economic Evaluation Working Party*, 313(7052): pp.275-283.

Drummond, M. F. et al. [2005]: *Methods for the economic evaluation of health care programmes*. Third edition. New York: Oxford University Press.

Fricke, F. U., Dauben, H. P. [2009]: Health Technology Assessment: A Perspective from Germany. *Value in Health* 12(Suppl 2), pp.S20-27., doi: 10.1111/j.1524-4733.2009.00555.x.

Gacci, M., Saleh, O., Cai, T., Gore, J. L., D'Elia, C., Minervini, A., Masieri, L., Giannessi, C., Lanciotti, M., Varca, V., Simonato, A., Serni, S., Carmignani, G., Carini, M. [2013]: Quality of life in women undergoing urinary diversion for bladder cancer: results of a multicenter study among long-term disease-free survivors. *Health and Quality of Life Outcomes*. 11(43), pp.1-6., doi: 10.1186/1477-7525-11-43.

- Gaunez, N. et al [2010]: [French translation and linguistic validation of the questionnaire Bladder Cancer Index (BCI)]. *Progrés en Urologie*, 22(6): pp.350-353., doi: 10.1016/j.purol.2011.12.004.
- Gilbert, S. M., Dunn, R. L., Hollenbeck, B. K., Montie, J. E., Lee, C. T., Wood, D. P., Wei, J. T. [2010]: Development and validation of the Bladder Cancer Index: a comprehensive, disease specific measure of health related quality of life in patients with localized bladder cancer. *The Journal of Urology*. 183(5): pp.1764-1769., doi: 10.1016/j.juro.2010.01.013.
- Gilbert, S.M., Wood, D. P., Dunn, R. L., Weizer, A. Z., Lee, C. T., Montie, J. E., Wei, J. T. [2007]: Measuring health-related quality of life outcomes in bladder cancer patients using the Bladder Cancer Index (BCI). *Cancer*, 109(9), pp.1756-1762., doi: 10.1002/cncr.22556
- Goodman, C. S. [2004]: *Introduction of Health Economic Assessment*. The Lewin Group, Falls Church, Virginia, USA. Available at: https://www.nlm.nih.gov/nichsr/hta101/ta101_c1.html., date of download: 02.08.2014.
- Greiner, W., Schulenburg, J-M. [2010]: HTA in Germany: very special and specific. *European Journal of Health Economics*, 11(1), pp.1-3., doi: 10.1007/s10198-009-0216-8.
- Gulácsi, L. [2007]: The time for cost-effectiveness in the new European Union member states: the development and role of health economics and technology assessment in the mirror of the Hungarian experience. *European Journal of Health Economics*, 8(2): pp.83-8., doi: 10.1007/s10198-007-0046-5
- Gulácsi, L. [2005]: *Egészség-gazdaságtan*. Medicina Könyvkiadó Rt., Budapest.
- Gulácsi, L. [2012]: *Egészség-gazdaságtan és technológiaelemzés*. Medicina Könyvkiadó Zrt., Budapest
- Gulácsi, L., Boncz, I., Drummond, M. [2004]: Issues for countries considering introducing the "fourth hurdle": the case of Hungary. *International Journal of Technology Assessment in Health Care*, 20(3): pp.337-341.

- Gulácsi, L., Brodszky, V., Majoros, A., Piróth, C., Böszörményi-Nagy, G., Baji, P., V. Hevér, N., Balogh, O. Péntek, M. [2012]: Cost of illness of overactive bladder syndrome in Hungary. *Value in Health*, 15(7): p.A456.
- Gulácsi, L. - Brodszky, V. - Péntek, M. - Varga, S.- Vas G. - Boncz, I. [2009]: History of health technology assessment in Hungary. *International Journal of Technology Assessment in Health Care* 25(Suppl): 120-126
- Gulácsi, L., Kovács, E., Oesterle, A., Boncz, I. [2007]: Verseny az egészségügyben. Egyesült államokbeli és nyugat-európai példák. *Közgazdasági Szemle*, 54(5): pp.480-498.
- Gulácsi, L., Lepp-Gazdag, A. [2002]: *Leflunomide, etanercept és inflixmab terápia és a rheumatoid arthritis megbetegedés magyarországi morbiditási prevalenciája a kórhái-, járóbeteg és az alapellátás területén*. Discussion Paper, Health Economics and Health Technology Assessment Research Centre, Hungarian Office for Health Technology Assessment, Corvinus University of Budapest.
- Gulácsi, L.,- Orlewska, E., Péntek, M. [2012]: Health economics and health technology assessment in Central and Eastern Europe: a dose of reality. *European Journal of Health Economics*, 13(5): pp.25-31.
- Gulácsi, L., Rencz, F., Péntek, M., Brodszky, V., Lopert, R., Hevér, N. V., Baji, P. [2014]: Transferability of results of cost utility analyses for biologicals in inflammatory conditions for Central and Eastern European countries. *European Journal of Health Economics*, 15(Suppl 1): pp.27-34., doi: 10.1007/s10198-014-0591-7.
- Gulácsi, L. [2007]: The time for cost-effectiveness in the new European Union member states, the development and role of health economics and technology assessment in the mirror of the Hungarian experience. *European Journal of Health Economics* 8(2): pp.83-88., doi: 10.1007/s10198-007-0046-5.
- Hallinen, T. A. et al. [2010]: . Cost-utility of different treatment strategies after the failure of tumour necrosis factor inhibitor in rheumatoid arthritis in the Finnish setting. *Rheumatology* (Oxford), 49(4): pp.767-777., doi: 10.1093/rheumatology/kep425.

Hedgepeth, R.C. et al. [2010]: Body image and bladder cancer specific quality of life in patients with ileal conduit and neobladder urinary diversions. *Urology*, 76(3): pp.671-675., doi: 10.1016/j.urology.2010.01.087. Holton, G. A.: Risk Encyclopedia. Available at: http://riskencyclopedia.com/articles/efficient_frontier/

Homepage of EuroQol: <http://www.euroqol.org>

Homepage of Functional Assessment of Chronic Illness Therapy. Available at: <http://www.facit.org>

Homepage of SF-36. Available at: <http://www.sf-36.org/>.

Homepage of Szabolcs Volán Zrt. Available at: http://www.szabolcsvolan.hu/szforg/ellenor/nyiregyhaza_dijak_20130301.htm?1.

Homepage of the German Institute of Medical Documentation and Information. Available at: <http://www.dimdi.de/static/en/>.

Homepage of the Institute for Quality and Efficiency in Health Care. Available at: <https://www.iqwig.de/institute-for-quality-and-efficiency-in-health.2.en.html>

Homepage of the National Cancer Institute at the National Institutes of Health. available at: (<http://www.cancer.gov/cancertopics/factsheet/detection/staging>)

Homepage of the University of Sheffield. Available at: <http://www.shef.ac.uk/scharr/sections/heds/mvh/sf-6d>.

Homepage of Tükebusz. Available at: <http://www.tukebusz.hu/tartalmak/Jegyek>
http://www.efoesz.hu/download/teritesi_dij.pdf. Date of download: 08.11.2014.

http://www.rheumatology.org/practice/clinical/patients/diseases_and_conditions/rheumatoid_arthritis/

Inotai, A., Pékli, M., Jóna, G., Nagy, O., Remák, E., Kaló, Z. [2012]: Attempt to increase the transparency of fourth hurdle implementation in Central-Eastern European middle income countries: publication of the critical appraisal methodology. *BioMed Central Health Services Research* 12:332., doi: 10.1186/1472-6963-12-332.

IQWiG (2006): *General Methods 2.0.*, Available at: <https://www.iqwig.de/index.925.en.html> Downloaded on 01.08.2012

IQWiG (2011): *General Methods 4.0.*, Available at: <https://www.iqwig.de/index.428.en.html>. Downloaded on 02.08.2012

International Network of Agencies for Health Technology Assessment (INAHTA). Available at: <http://www.inahta.org>. Date of download: 01.28.2014

Jobanputra, P. et al. [2002]: The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation. *Health Technology Assessment*. 6(21): pp.1-110., doi: 10.3310/hta6210.

Jönsson, B. [2007]: Economic evaluation for pharmaceuticals in Germany. *European Journal of Health Economics*, 8(Suppl 1): pp.S1-2., doi: 10.1007/s10198-007-0066-1.

Jönsson, B. [2008]: IQWiG: an opportunity lost? *European Journal of Health Economics*, 9(3): pp.205-207, doi: 10.1007/s10198-008-0109-2.

Keszthelyi, A., Majoros, A., Nyirády, P., Mayer, P., Bach, D., Romics, I. [2009]: Voiding symptoms and urodynamic findings in patients with modified ileal neobladder. *Pathology and Oncology Research*, 15(3): pp.307-313., doi: 10.1007/s12253-008-9099-8.

Kielhorn, A. et al. [2008]: UK cost-utility analysis of rituximab in patients with rheumatoid arthritis that failed to respond adequately to a biologic disease-modifying antirheumatic drug. *Current Medical Research and Opininion*, 24(9): pp.2639-2650., doi: 10.1185/03007990802321683.

Kikuchi, E. et al. [2006]: Assessment of Long-Term Quality of Life Using the FACT-BL Questionnaire in Patients with an Ileal Conduit, Continent Reservoir, or Orthotopic Neobladder. *Japanese Journal of Clinical Oncology*, 36(11): pp.712-716., doi: 10.1093/jjco/hyl094.

Kobelt, G. [2013]: *Health Economics: An Introduction to Health Economic evaluation*. Third Edition. Office of Health Economics, London, United Kingdom

- Kobelt, G., Eberhardt, K., Geborek, P. [2004]: TNF inhibitors in the treatment of rheumatoid arthritis in clinical practice: costs and outcomes in a follow up study of patients with RA treated with etanercept or infliximab in southern Sweden. *Annals of the Rheumatic Diseases*. 63(1): pp.4-10.
- Kobelt, G. et al. [2003]: The cost-effectiveness of infliximab (Remicade) in the treatment of rheumatoid arthritis in Sweden and the United Kingdom based on the ATTRACT study. *Rheumatology* (Oxford), 42(2): pp.326-335, doi: 10.1093/rheumatology/keg107.
- Kobelt, G. et al. [2011]: Cost-effectiveness of etanercept treatment in early active rheumatoid arthritis followed by dose adjustment. *International Journal of Technology Assessment in Health Care*, 27(3): pp.193-200., doi: 10.1017/S0266462311000195.
- Kobelt, G., Lindgren, P., Geborek, P. [2009]: Costs and outcomes for patients with rheumatoid arthritis treated with biological drugs in Sweden: a model based on registry data. *Scandinavian Journal of Rheumatology*, 38(6): pp.409-418., doi: 10.3109/03009740902865464.
- Kobelt, G. et al. [2005]: Cost effectiveness of etanercept (Enbrel) in combination with methotrexate in the treatment of active rheumatoid arthritis based on the TEMPO trial. *Annals of the Rheumatic Diseases*, 64(8): pp.1174-1179., doi:10.1136/ard.2004.032789.
- Kolasa, K., Kaló, Z., Zah, V., Dolezal, T. [2012]: Role of health technology assessment in the process of implementation of the EU Transparency Directive: relevant experience from Central Eastern European countries. *Expert Review Pharmacoeconomics and Outcomes Research*, 12(3): pp.283-287., doi: 10.1586/erp.12.12.
- Kondás, J., Engloner, L., Váczi, L., Kondér, G. [1996]: Transurethral resection and intra-arterial chemotherapy for muscle-invasive bladder cancer. *International Urology and Nephrology*, 28(2): pp.181-187.

- Kovács, Á., V. Hevér, N., Tóth, A., Pálffi, B. [2012]: A női vizeletinkontinencia epidemiológiája Magyarországon; kérdőíves vizsgálat 2011. *Magyar Urológia*, 24(4): pp.159-166.
- Kovács, Á., V. Hevér, N., Tóth, A., Pálffi, B. [2013]: Férfiak alsó húgyúti tüneteinek gyakorisága Magyarországon – egy nyílt kérdőíves vizsgálat eredményei. *Magyar Urológia*, 25(1): pp.22-26.
- Kozma, P. O. et al. [2009]: *Az autoimmun gyulladós kórképek biológiai terápiái az ártámogatási rendszerben*. Országos Egészségbiztosítási Pénztár, Ártámogatási Főosztály. Available at: http://www.oep.hu/pls/portal/docs/PAGE/SZAKMA/OEPHUSZAK_EUSZOLG/GYOGYSZER/SZAKMAI%20ELEMZ%C3%89SEK/20091209.PDF. Date of download: 08.12.2014
- Kulkarni, G.S., [2009]: Cost-effectiveness analysis of immediate radical cystectomy versus intravesical Bacillus Calmette-Guerin therapy for high-risk, high-grade (T1G3) bladder cancer. *Cancer*, 115(23): pp.5450-5459., doi:10.1002/cncr.24634.
- Laki, J. et al. [2013]: Economical aspect of biological therapy in inflammatory conditions in Hungary. *Expert Opinion on Biological Therapy*, 13(3): pp.327-337., doi: 10.1517/14712598.2013.735654.
- Lekander, I. et al. [2010]: Cost-effectiveness of real-world infliximab use in patients with rheumatoid arthritis in Sweden. *International Journal of Technology Assessment in Health Care*, 26(1): pp.54-61., doi: 10.1017/S0266462309990596.
- Li, X. et al. [2014]: Use of urostomy bags in the management of perioperative urine leakage after radical cystectomy. *Cancer Nursing*, 37(3): pp.170-174., doi: 10.1097/NCC.0b013e318277db29.
- Lindgren, P., Geborek, P., Kobelt, G. [2009]: Modeling the cost-effectiveness of treatment of rheumatoid arthritis with rituximab using registry data from Southern Sweden. *International Journal of Technology Assessment in Health Care*, 25(2): pp.181-189., doi: 10.1017/S0266462309090230.

- Májér, I., Péntek, M., Broszky, V. et al. [2006]: *Egészség-gazdaságtani modellezés: a biológiai szerek eredményessége, költsége és költség-hatékonysága a rheumatoid arthritis gyógykezelésében, különös tekintettel az infliximab (REMICADE®) terápiára*. Discussion Paper, Health Economics and Health Technology Assessment Research Centre, Hungarian Office for Health Technology Assessment, Corvinus University of Budapest.
- Majoros Attila, Rencz Fanni, Vártokné, Hevér Noémi, Tóth Attila: *Férfiak és nők alsó húgyúti tüneteinek gyakorisága Magyarországon – egy nyílt kérdőíves vizsgálat eredményei*. A Nemzetközi Kontinencia Társaság továbbképző konferenciája és a Magyar Kontinencia Társaság IV. Kongresszusa, 2013. október 11-12., 54. o.
- Malotki, K. et al [2011]: Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation. *Health Technology Assessment*, 15(14): pp.1-278., doi: 10.3310/hta15140.
- Markowitz, H. [1952]: Portfolio Selection. *The Journal of Finance* 7(1): pp.77-91.
- Marra, C. A. et al. [2007]: Not all "quality-adjusted life years" are equal. *Journal of Clinical Epidemiology*, 60(6): pp.616-624., doi:10.1016/j.jclinepi.2006.09.006.
- McHorney C. A. et al [1994]: The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Medical Care*, 32(1): pp.40-66.
- McInnes, I. B., O'Dell, J. R. [2010]: State-of-the-art: rheumatoid arthritis. *Annals of the Rheumatic Diseases*, 69(11): pp.1898-1906., doi: 10.1136/ard.2010.134684.
- McTaggart-Cowan, H., Teckle, P., Peacock, S. [2013]: Mapping utilities from cancer-specific health-related quality of life instruments: a review of the literature. *Expert Review of Pharmacoeconomics Outcomes and Research*, 13(6): pp.753-765., doi:10.1586/14737167.2013.850420.
- Merkesdal, S. et al. [2010]: Cost-effectiveness analysis of rituximab treatment in patients in Germany with rheumatoid arthritis after etanercept-failure. *European Journal of Health Economics*, 11(1): pp.95-104., doi: 10.1007/s10198-009-0205-y.

- Minier, T. et al. [2010]: Cost-of-illness of patients with systemic sclerosis. *Rheumatology* (Oxford), 49(10): pp.1920-1928., doi: 10.1093/rheumatology/keq165.
- Noorani, H. Z. et al. [2007]: Priority setting for health technology assessments: a systematic review of current practical approaches. *International Journal of Technology Assessment in Health Care*, 23(3): pp.310-315., doi: <http://dx.doi.org/10.1017/S026646230707050X>
- Nuijten, M. J., Dubois, D. J. [2011]: Cost-utility analysis: current methodological issues and future perspectives. *Frontiers in Pharmacology*, 2: 29., doi: 10.3389/fphar.2011.00029.
- Pauly, M. V., McGuire, T. G., Barros, P. P. [2012]: *Health Economics – Handbooks in Economics*, Oxford. Available at: http://books.google.hu/books?id=Pia95cLN84cC&pg=PA487&lpg=PA487&dq=IQWIQ+guideline+Germany&source=bl&ots=KCbWnIqWin&sig=eUIO_q9RkwnZKtO8T0G0RxHRIZM&hl=en&sa=X&ei=1MwpUKzIN5CMswbOjIDIBw&redir_esc=y#v=onepage&q=IQWIQ%20guideline%20Germany&f=false. Downloaded on 07.08.2012
- Péntek, M., Brodszky, V., Czirják, L. et al. [2011]: Biológikumok alkalmazása reumatoid arthritisben – terápiafelmérés (BARAT vizsgálat): biológiai terápiát kezdő betegek klinikai jellemzői és egészségügyi szolgáltatások igénybevételének jellemzői. *Immunológiai Szemle*, 3(4): pp.36-48.
- Péntek, M., Horváth, C., Boncz, I., Falusi, Z., Tóth, E., Sebestyén, A., Majer, I., Brodszky, V., Gulácsi, L. [2008]: Epidemiology of osteoporosis related fractures in Hungary from the nationwide health insurance database, 1999-2003. *Osteoporosis International* 19(2): pp.243-249., doi: 10.1007/s00198-007-0453-6
- Péntek, M., Gulácsi, L. [2014]: *Epidemiology, quality of life and costs in rheumatoid arthritis. In: Systematic review and analysis of evidences on clinical efficacy and cost-effectiveness of biological drugs for the treatment of rheumatoid arthritis.* Editor: Péntek, M., Corvinus University of Budapest, Department of Health Economics, Budapest. ISBN: 978-963-503-575-5

- Péntek, M., Kobelt, M., Czirják, L., Szekanecz, Z., Poór, Gy., Rojkovich, B., Polgár, A., Genti, Gy., György Kiss, Cs., Brodszky, V., Májer, I., Gulácsi, L. [2007]: Costs of rheumatoid arthritis in Hungary. *Journal of Rheumatology*, 34(6): pp.1437-1439.
- Péntek, M., Rojkovich, B., Czirják, L., Géher, P., Keszthelyi, P., Kovács, A., Kovács, L., Szabó, Z., Szekanecz, Z., Tamási, L., Tóth, A. E., Ujfalussy, I., Hevér, N. V., Strbák, B., Baji, P., Brodszky, V., Gulácsi, L. [2014]: Acceptability of less than perfect health states in rheumatoid arthritis: the patients' perspective. *European Journal of Health Economics*, 15(Suppl 1): pp.101-109., doi: 10.1007/s10198-014-0596-2.
- Ploeg, M., Aben, K. K., Kiemeney, L. A. [2009]: The present and future burden of urinary bladder cancer in the world. *World Journal of Urology*, 27(3): pp.289-293., doi:10.1007/s00345-009-0383-3.
- Poch, M. A. et al. [2014]: Short-term patient reported health-related quality of life (HRQL) outcomes after robot-assisted radical cystectomy (RARC). *British Journal of Urology International*, 113(2): pp.260-265., doi: 10.1111/bju.12162.
- Prokes, M. [2009]: Effectiveness of TNF antagonists in routine clinical practice and costs. *Vnitřní Lékarství*, 55(1): pp.45-53.
- Rabin, R., de Charro, F. [2001]: EQ-5D: a measure of health status from the EuroQol Group. *Annals of Medicine*, 33(5): pp.337-343.
- Romics, I. et al. [2006]: Experiences with radical cystectomy combined with urinary diversion by ureteral sigmoidpouch (Mainz-pouch II) in bladder cancer patients. *Orvosi Hetilap*, 147(35): pp.1691-1696.
- Samodai, L. et al. [1996]: Continent urinary diversion after radical cystectomy: 3 years' experience. *International Urology and Nephrology*, 28(4): pp.511-516.
- Sany, J. et al. [2009]: Medico-economic evaluation of infliximab in rheumatoid arthritis--prospective French study of a cohort of 635 patients monitored for two years. *Rheumatology (Oxford)*, 48(10): pp.1236-1241., doi: 10.1093/rheumatology/kep198.

- Schipper, L. G. et al. [2011]: Treatment strategies aiming at remission in early rheumatoid arthritis patients: starting with methotrexate monotherapy is cost-effective. *Rheumatology* (Oxford), 50(7): pp.1320-1330., doi: 10.1093/rheumatology/ker084.
- Schulenburg, J-M. et al. [2007]: Methods for determining cost-benefit ratios for pharmaceuticals in Germany. *European Journal of Health Economics* 8(S1): pp.S5-S31., doi: 10.1007/s10198-007-0063-4.
- Schulze-Koops, H. et al. [2009]: Health-economic assessment of combination therapy for rheumatoid arthritis with methotrexat and etanercept based on the TEMPO Study. *Zeitschrift für Rheumatologie*, 68(10): pp.836-841., doi: 10.1007/s00393-009-0506-7.
- Schmidt, S. et al. [2014]: Bladder cancer index: cross-cultural adaptation into Spanish and psychometric evaluation. *Health and Quality of Life Outcomes* 12:20., doi: 10.1186/1477-7525-12-20.
- Sebestyén, A. et al. [2009]: The relationship between between surgical delay over 24 hours and 30 days mortality following femoral neck fracture in the presence of different co-morbidities. ISPOR Fourteenth Annual International Meeting Research Abstracts, *Value in Health*, 12(3): PMS14, A66
- Siebert, U. [2010]: *Approaches to Economic Evaluation at German Agencies for HTA*. [oral presentation]. Workshop on Economic Analysis of Nutrition Interventions, February 23-24. Bethesda, Maryland, United States.
- Soini, E. J. et al. [2012]: Cost-effectiveness of adalimumab, etanercept, and tocilizumab as first-line treatments for moderate-to-severe rheumatoid arthritis. *Journal of Medical Economics*, 15(2): pp.340-351., doi: 10.3111/13696998.2011.649327.
- Sokka, T. et al. [2010]: Work disability remains a major problem in rheumatoid arthritis in the 2000s: data from 32 countries in the QUEST-RA study. *Arthritis Research and Therapy*, 12(2): p.R42., doi: 10.1186/ar2951.
- Sousa V. D., Rojjanasrirat, W. [2011]: Translation, adaptation and validation of instruments or scales for use in cross-cultural health care research: a clear and user-

- friendly guideline. *Journal of Evaluation in Clinical Practice*. 17(2): pp.268-274., doi: 10.1111/j.1365-2753.2010.01434.x.
- Spalding, J. R., Hay, J. [2006]: Cost effectiveness of tumour necrosis factor-alpha inhibitors as first-line agents in rheumatoid arthritis. *PharmacoEconomics*, 24(12): pp.1221-1232.
- Stiglitz, J. E. [2000]: *A kormányzati szektor gazdaságtana*. KJK-KERSZÖV Jogi és Üzleti Kiadó Kft., Budapest
- Svatek, R. S. et al. [2014]: The Economics of Bladder Cancer: Costs and Considerations of Caring for This Disease. *European Urology*., doi: 10.1016/j.eururo.2014.01.006. [Epub ahead of print].
- Szende, Á., Németh, R. [2003]: Health-related quality of life of the Hungarian population. *Orvosi Hetilap*, 144(34): pp.1667-1674.
- Szűcs, M. et al. [2012]: Investigation of anal sphincter function following Mainz pouch type II urinary diversion after radical cystectomy. *International Urology and Nephrology*, 44(4): pp.1013-1020., doi: 10.1007/s11255-012-0142-z.
- Tanno, M. et al. [2006]: Modeling and cost-effectiveness analysis of etanercept in adults with rheumatoid arthritis in Japan: a preliminary analysis. *Modern Rheumatology*, 16(2): pp.77-84.
- Tejido-Sanchez, A. et al. [2014]: Quality of life in patients with ileal conduit cystectomy due to bladder cancer. *Actas Urológicas Españolas*, 38(2): pp.90-95., doi: 10.1016/j.acuro.2013.04.006.
- Terwee, C. B. et al. [2007]: Quality criteria were proposed for measurement properties of health status questionnaires. *Journal of Clinical Epidemiology*. 60(1): pp.34-42., doi:10.1016/j.jclinepi.2006.03.012.
- Torpy, J. M., Lynm, C., Glass, R. M. [2006]: JAMA patient page. Evidence-based medicine. *Journal of the American Medical Association*, 296(9): p.1192.
- Torrance, G. W. [1986]: Measurement of health state utilities for economic appraisal. *Journal of Health Economics*, 5(1): pp.1-30.

- Van den Hout, W. B. et al. [2009]: Cost-utility analysis of treatment strategies in patients with recent-onset rheumatoid arthritis. *Arthritis and Rheumatology*. 61(3): pp.291-299., doi: 10.1002/art.24169.
- Van der Velde, G. et al. [2011]: Cost-effectiveness of biologic response modifiers compared to disease-modifying antirheumatic drugs for rheumatoid arthritis: a systematic review. *Arthritis Care and Research* (Hoboken), 63(1): pp.65-78., doi: 10.1002/acr.20338.
- Vártokné Hevér, N: [2012]: Egészségügyi reform Horvátországban. *Köz-Gazdaság* 7(3): pp.177-190.
- Vera-Llonch, M., Massarotti, E., Wolfe, F. [2008]: Cost-effectiveness of abatacept in patients with moderately to severely active rheumatoid arthritis and inadequate response to tumor necrosis factor-alpha antagonists. *The Journal of Rheumatology*, 35(9): pp.1745-1753.
- V. Hevér, N. [2014]: Biological therapies for the treatment of RA – *systematic review of the health economic literature*. In: Péntek, M. [2014]: *Systematic review and analysis of evidences on clinical efficacy and cost-effectiveness of biological drugs for the treatment of rheumatoid arthritis*. ISBN: 978-963-503-575-5, pp.45-94.
- V. Hevér, N., Péntek, M., Balló, A., Gulácsi, L., Baji, P., Brodszky, V., Damásdi, M., Bognár, Z., Tóth Gy., Buzogány I., Szántó, Á. [2014]: Health related quality of life in patients with bladder cancer: A cross-sectional survey and validation study of the Hungarian version of the Bladder Cancer Index. Target Journal: *Pathology and Oncology Research* Submitted on 08.07.2014.
- V. Hevér N., Brodszky V., Gulácsi, L. [2013]: *Clinical manifestations, epidemiology and measures in adult Crohn's Disease*. In: Petra Baji: *Systematic review and analysis of evidences on clinical efficacy and cost-effectiveness of biological drugs for the treatment of adult Crohn's Disease*. ISBN: 978-963-503-558-8, pp.1-12.
- V. Hevér N., Péntek M. [2013]: *Biologics for adult Crohn' Disease – systematic review of the health economic literature*. In: Petra Baji: *Systematic review and*

analysis of evidences on clinical efficacy and cost-effectiveness of biological drugs for the treatment of adult Crohn's Disease. ISBN: 978-963-503-558-8, pp.60-83.

- Virkki, L., M. et al. [2008]: Cost-effectiveness of infliximab in the treatment of rheumatoid arthritis in clinical practice. *Clinical and Experimental Rheumatology*. 2008; 26(6): pp.1059-1066.
- Weinstein, M. C., Torrance, G., McGuire, A. [2009]: QALYs: The Basics. *Value in Health* 12(Suppl 1): pp.S5-9., doi: 10.1111/j.1524-4733.2009.00515.x.
- Welsing, P. M. et al. [2004]: Modeling the 5-year cost effectiveness of treatment strategies including tumor necrosis factor-blocking agents and leflunomide for treating rheumatoid arthritis in the Netherlands. *Arthritis and Rheumatology*. 51(6): pp.964-973., doi: 10.1002/art.20843
- Wong, J. B., Singh, G., Kavanaugh, A. [2002]: Estimating the cost-effectiveness of 54 weeks of infliximab for rheumatoid arthritis. *American Journal of Medicine*. 113(5): pp.400-408., doi: [http://dx.doi.org/10.1016/S0002-9343\(02\)01243-3](http://dx.doi.org/10.1016/S0002-9343(02)01243-3).
- Wong, K.A. et al. [2013]: Outpatient laser ablation of non-muscle-invasive bladder cancer: is it safe, tolerable and cost-effective? *British Journal of Urology International*, 112(5): pp.561-567., doi:10.1111/bju.12216.
- Yabroff, K. R., Borowski, L., Lipscomb, J. [2013]: Economic studies in colorectal cancer: challenges in measuring and comparing costs. *Journal of the National Cancer Institute Monographs*, 46: pp.62-78., doi: 10.1093/jncimonographs/lgt001.
- Yeung, C., Dinh, T., Lee, J. [2014]: The Health Economics of Bladder Cancer: An Updated Review of the Published Literature. *Pharmacoeconomics*. [Epub ahead of print], doi: 10.1007/s40273-014-0194-2.

VII. APPENDIX

VII.1. Methotrexate naive early RA patients – summary of cost-utility evidence identified

Data	Davies et al., USA (2009) ³⁰	Ven den Hout et al., The Netherlands (2009) ¹¹⁶	Kobelt et al., Sweden (2011) ⁵⁷	Schipper et al., The Netherlands (2011) ⁹⁸
Perspective	payer	societal	societal	health care; societal
Comparators	adalimumab+MTX, etanercept, infliximab+MTX, adalimumab+MTX/etanercept and palliative care (DMARD)	sequential monotherapy, step-up combination therapy, initial combination therapy with prednisone and initial combination therapy with infliximab (BeSt trial)	etanercept+MTX vs. MTX	MTX – MTX+LEF – MTX+anti-TNF; MTX+LEF – MTX+anti-TNF; immediate start with MTX+anti-TNF
Model structure	Individual patient simulation model based on the model by Bansback et al. ⁹ , five alternative sequences of therapies, lifetime horizon, 6 months cycles, responses according to ACR and associated HAQ score..	Individual sampling model	Markov model, 6 month cycles, lifetime horizon; adapted to early RA and transformation of the model to accommodate dose reductions and treatment switches.	Markov model, 3-month cycles, 5-year horizon, health states by disease activity

Data	Davies et al., USA (2009) ³⁰	Ven den Hout et al., The Netherlands (2009) ¹¹⁶	Kobelt et al., Sweden (2011) ⁵⁷	Schipper et al., The Netherlands (2011) ⁹⁸
Patient inputs	patient characteristics from the PREMIER trial	baseline characteristics: 508 patients with recent onset active RA from 20 Dutch medical centers were enrolled	Patients with the characteristics of the total population enrolled in COMET	registry
Sources of effectiveness evidence	Short-term trial data (PREMIER, ASPIRE and ERA) were used to determine the response rates and HAQ	Effectiveness from BeSt study	COMET trial. Discontinuation rates: South Swedish Biologics Registry (SSATG) to determine HAQ and DAS28	registry, efficacy data of anti-TNF were derived from patients with prior DMARD use

Data	Davies et al., USA (2009) ³⁰	Ven den Hout et al., The Netherlands (2009) ¹¹⁶	Kobelt et al., Sweden (2011) ⁵⁷	Schipper et al., The Netherlands (2011) ⁹⁸
Sources of cost data	<p>HAQ profiles were used to calculate direct and indirect costs.</p> <p>Monitoring and administration costs were calculated based on clinicians' assessments. To measure other direct medical costs (e.g ., physician visits, hospitalizations) a regression equation based in HAQ scores was used. Productivity costs were based on the proportion of annual average earnings lost associated with worsening HAQ scores</p>	<p>Costs reported by the patients were used. Besides, published costs or market costs were applied. In the primary analysis the friction cost method, in the secondary analysis the human capital method was used.</p>	<p>Population-based survey including direct costs and indirect costs (productivity losses in the Malmö area, combined with early retirement data for a more urban population in Stockholm area)</p>	<p>related to disease activity states (from a 48-week multicentre trial)</p>

Data	Davies et al., USA (2009) ³⁰	Ven den Hout et al., The Netherlands (2009) ¹¹⁶	Kobelt et al., Sweden (2011) ⁵⁷	Schipper et al., The Netherlands (2011) ⁹⁸
Utilities	<p>4 adalimumab trials were used to estimate utilities.</p> <p>HAQ scores were used to calculate utility values on a scale of 0 to 1 using a regression equation derived from HUI-3 utility scores. Patients' utility scores were modelled to decline by 0,28 for each one-unit increase in HAQ score</p>	<p>The British and Dutch EQ-5D utilities and the Short-Form 6D utility were calculated from EQ-5D and SF-36 questionnaires, respectively.</p> <p>Time-trade-Off method was used</p>	Utilities (EQ-5D) were taken from the same observational study in Malmö	related to disease activity states (EQ-5D data from a survey)
Discount rate	3.0%	3.0%	3.0%	4.0%

Data	Davies et al., USA (2009) ³⁰	Ven den Hout et al., The Netherlands (2009) ¹¹⁶	Kobelt et al., Sweden (2011) ⁵⁷	Schipper et al., The Netherlands (2011) ⁹⁸
Base case results	<p>adalimumab+MTX/etanercept of 19,663 US\$/QALY compared with adalimumab as sole TNF-antagonist and of 23,377 US\$/QALY for adalimumab+MTX compared with the etanercept sequence. The sequences of etanercept and infliximab+MTX were extendedly dominated.</p>	<p>Primary analysis: based on the British EQ-5D, QALY was 1,41 for strategy 4 (initial combination with infliximab) at a cost of €32,403. The ICER of strategy 4 compared with strategy 3 was €130,000.</p> <p>Secondary analysis: based on the Dutch EQ-5D, SF-6D and TTO cost-utility ratios of strategy 4 compared with strategy 3 were €140,000; €250,000 and €320,000 per QALY, respectively.</p> <p>With human capital method the cost-utility ratio of strategy 4 compared with strategy 3 was €22,000 per QALY</p>	<p>Incremental QALY was 1,25 and incremental cost was €15,546 for etanercept+MTX.</p> <p>This gives an ICER for this biologic strategy of €13,518.</p>	<p>anti-TNF strategy compared with the MTX strategy from the health-care perspective €138,056/QALY, €136,207/QALY from the societal perspective</p>

Data	Davies et al., USA (2009) ³⁰	Ven den Hout et al., The Netherlands (2009) ¹¹⁶	Kobelt et al., Sweden (2011) ⁵⁷	Schipper et al., The Netherlands (2011) ⁹⁸
Key sensitivity analysis	ICER was sensitive to many of the changes in parameters: DMARD withdrawal rate, HAQ progression on anti-TNF, HAQ progression response, age, direct costs, mortality and utility	-	Results were sensitive to the drop-out rate, the duration of treatment with reduced ETA-dose, time horizon and the perspective of the analysis	If estimate of 30% of the DMARD-naive patients achieving remission with anti-TNF was applied: healthcare perspective €116,598/QALY, societal perspective €114,982/QALY

VII.2. RA patients who failed at least one synthetic DMARD therapy - summary of cost-utility evidence identified

Data	Vera-Llonch et al., US (2008) ¹²¹	Virkki et al., Finland (2008) ¹²²	Kobelt et al., Sweden (2009) ⁵⁸	Sany et al., France (2009) ⁹⁵	Lekander et al., Sweden (2010) ⁶⁴	Schulze-Koops et al., Germany (2009) ¹⁰⁰	Soini et al., Finland (2012) ¹⁰⁶	Diamantopoulos et al., Italy (2012) ³²
Perspective	third party payer	healthcare payer	societal	health insurance coverage	societal	societal	healthcare payer	National Health Service

Data	Vera-Llonch et al., US (2008) ¹²¹	Virkki et al., Finland (2008) ¹²²	Kobelt et al., Sweden (2009) ⁵⁸	Sany et al., France (2009) ⁹⁵	Lekander et al., Sweden (2010) ⁶⁴	Schulze-Koops et al., Germany (2009) ¹⁰⁰	Soini et al., Finland (2012) ¹⁰⁶	Diamantopoulos et al., Italy (2012) ³²
Comparators	MTX versus MTX+abatacept (<60 kg:500 mg/vial; 60-100 kg: 750 mg/vial; >100 kg: 1 g)	infliximab vs. traditional DMARD	TNF blockers	before infliximab treatment compared to results after 1st and 2nd year of infliximab treatment	infliximab vs. no biological treatment (natural progression)	etanercept+M TX vs. MTX	adalimumab+ MTX, etanercept+M TX, or tocilizumab+ MTX were used as first biologics followed by rituximab+M TX and infliximab+M TX; supportive care (MTX)	tocilizumab Basecase: ETA – ADA – RTX -ABA – palliative vs. TOC – ADA – RTX – ABA – palliative care; Alternatives: ADA – ETA – RTX – ABA – palliative; INF – ETA – RTX ABA – palliative; adding TOC to standard-of-care: TOC

Data	Vera-Llonch et al., US (2008) ¹²¹	Virkki et al., Finland (2008) ¹²²	Kobelt et al., Sweden (2009) ⁵⁸	Sany et al., France (2009) ⁹⁵	Lekander et al., Sweden (2010) ⁶⁴	Schulze-Koops et al., Germany (2009) ¹⁰⁰	Soini et al., Finland (2012) ¹⁰⁶	Diamantopoulos et al., Italy (2012) ³²
Model structure	simulation model, horizon: 10 yrs and lifetime; 3-months cycles, simulation of 1000 patients	real life data, assumption for patients without infliximab therapy	discrete event simulation, 5-year and 10-year horizon	analysis of real world data	Markov model with five health state (HAQ) categories each with two DAS28 states	Monte-Carlo-Markov-Chain stimulation, 5 HAQ states.	individual sampling model, 6 months cycles, lifetime horizon	individual patient simulation model, 6-month cycles, lifetime horizon

Data	Vera-Llonch et al., US (2008) ¹²¹	Virkki et al., Finland (2008) ¹²²	Kobelt et al., Sweden (2009) ⁵⁸	Sany et al., France (2009) ⁹⁵	Lekander et al., Sweden (2010) ⁶⁴	Schulze-Koops et al., Germany (2009) ¹⁰⁰	Soini et al., Finland (2012) ¹⁰⁶	Diamantopoulos et al., Italy (2012) ³²
Patient inputs	women aged 55-64 years with moderate to severe RA, inadequate response to MTX	297 patients, mean age 51 yrs, 69% female, mean disease duration 12 years, HAQ 1,33	from a registry	mean age at entry 53.4 SD11.8 years, median DAS28 5.82 (5.15–6.56), NSAID treatment 90%, MTX 98.7%.	Individual sampling model using real-world patient -level data from the Stockholm TNF-alfa follow-up registry (STURE) n= 637, 1999 and 2008. 2 subgroups: were: patients with earlier- and late-stage RA	Individual sampling model using real-world patient -level data from the TEMPO study. 686 patients with active RA, mean disease duration >6 years.	moderate-sever RA, mean 52.5 years old, HAQ 1.51 at the baseline, weight 73 kg; 18% men	equivalent to baseline characteristics of tocilizumab trials' samples

Data	Vera-Llonch et al., US (2008) ¹²¹	Virkki et al., Finland (2008) ¹²²	Kobelt et al., Sweden (2009) ⁵⁸	Sany et al., France (2009) ⁹⁵	Lekander et al., Sweden (2010) ⁶⁴	Schulze-Koops et al., Germany (2009) ¹⁰⁰	Soini et al., Finland (2012) ¹⁰⁶	Diamantopoulos et al., Italy (2012) ³²
Sources of effectiveness evidence	AIM trial	follow-up results; patients without infliximab were assumed to progress a.a31 HAQ/year	registry	registry; dose escalation of infliximab was considered	STURE registry, the comparator arm (nonbiological treatment): ERAS study	TEMPO trial	mixed treatment comparison of bDMARD trials	tocilizumab: three phase III trials, mixed treatment comparison for the therapy sequences

Data	Vera-Llonch et al., US (2008) ¹²¹	Virkki et al., Finland (2008) ¹²²	Kobelt et al., Sweden (2009) ⁵⁸	Sany et al., France (2009) ⁹⁵	Lekander et al., Sweden (2010) ⁶⁴	Schulze-Koops et al., Germany (2009) ¹⁰⁰	Soini et al., Finland (2012) ¹⁰⁶	Diamantopoulos et al., Italy (2012) ³²
Sources of cost data	medical treatment costs	direct costs, official price lists; dose escalation of infliximab was considered	official price lists; cost of biological treatment was estimated based on three parameters: actual usage, dose of each of the agents, and adverse events; other costs were obtained from a survey and related to HAQ	official price lists, data obtained from patient self-questionnaire	The direct and indirect costs were based on an empirical study by Kobelt et al., where costs were stratified by functional status based on Swedish registry data. The cost for added life-years were also estimated derived from Ekman et al.	Costs: German database. Indirect costs were calculated using the human capital approach	(sensitivity analysis included productivity loss as well)	drugs: official prices, other direct costs: Italian survey

Data	Vera-Llonch et al., US (2008) ¹²¹	Virkki et al., Finland (2008) ¹²²	Kobelt et al., Sweden (2009) ⁵⁸	Sany et al., France (2009) ⁹⁵	Lekander et al., Sweden (2010) ⁶⁴	Schulze-Koops et al., Germany (2009) ¹⁰⁰	Soini et al., Finland (2012) ¹⁰⁶	Diamantopoulos et al., Italy (2012) ³²
Utilities	derived from HAQ (range: 0.86±0.16 – 0.03±0.33)	derived from HAQ (HAQ was measured in the follow up)	directly from a registry	derived from HAQ: EQ-5D=0.862–0.327*HAQ	Utilities were derived from an empirical study by Kobelt et al. and based on the current HAQ state and by disease activity	The instruments of HAQ and FFbH were used to generate utilities	derived from HAQ: EQ5D=0.82-0.11*HAQ-0.07*(HAQ*HAQ)	derived from HAQ: EQ-5D = 0.82 – 0.11 x HAQ - 0.07 x HAQ ²
Discount rate	3.0%	not applied	3.0%	not applied	3.0%	applied but not specified	3.0%	3.0%

Data	Vera-Llonch et al., US (2008) ¹²¹	Virkki et al., Finland (2008) ¹²²	Kobelt et al., Sweden (2009) ⁵⁸	Sany et al., France (2009) ⁹⁵	Lekander et al., Sweden (2010) ⁶⁴	Schulze-Koops et al., Germany (2009) ¹⁰⁰	Soini et al., Finland (2012) ¹⁰⁶	Diamantopoulos et al., Italy (2012) ³²
Base case results	10-year horizon: \$47 910 (\$44 641, \$52 136) / QALY; lifetime horizon: \$43 041 (\$39 070, \$46 725) / QALY	median ICER 51,884 Euro/QALY	5-year horizon: cost EUR 138,000 and 2.5 QALY gain. 10-year horizon: cost EUR 223,000 and 4.4 QALY gain.	QALY gain total sample: 0.15 Incremental net benefit (INB): The INB was, in the total sample significantly positive >249 663.	Infliximab: QALYs 1,019, costs €190,089. Non-biological: costs €166,824. ICER of infliximab vs. non-biological therapy: €22,830/QALY.	MTX: QALYs 1017,1, costs €162,520,668. Etanercept+M TX: QALYs 2119,6, costs €206,163,041. ICER etanercept+M TX vs. MTX: € 39,585.	Tocilizumab was more cost-effective than etanercept and adalimumab in comparison with MTX alone (and both etanercept and tocilizumab dominated adalimumab (tocilizumab+ MTX vs. MTX €17,057)	Tocilizumab dominates standard-of-care, also if ETA was replaced with adalimumab, but for INF replacement the ICER was €2,655. Adding TOC to standard-of-care: ICER 17,119/QALY .

Data	Vera-Llonch et al., US (2008) ¹²¹	Virkki et al., Finland (2008) ¹²²	Kobelt et al., Sweden (2009) ⁵⁸	Sany et al., France (2009) ⁹⁵	Lekander et al., Sweden (2010) ⁶⁴	Schulze-Koops et al., Germany (2009) ¹⁰⁰	Soini et al., Finland (2012) ¹⁰⁶	Diamantopoulos et al., Italy (2012) ³²
Key sensitivity analysis	10-year: \$40 190 to \$70 209 / QALY; \$37 551 to \$60 106 QALY	(n=79 (35%)of the patients with QALY gain had an ICER of ≤40,000 Euro/QALY)	initiating biological therapy at shorter disease duration is more beneficial (higher gain at a lower cost).	Subgroups with higher HAQ result more beneficial results.	ICER was sensitive to many of the changes in parameters, in particular age at start of treatment initiation and the rate of natural disease progression	Results were sensitive to cost of etanercept, cost of acquired disability, the probability of withdrawals, the discount rate of costs and discount rate of effects	The modelling assumptions only had a small impact on the relative results.	Tocilizumab dominant.

VII.3. RA patients who failed at least one biologic DMARD therapy - summary of cost-utility evidence identified

Data	Kielhorn et al., UK (2008) ⁵²	Vera-Llonch et al., US (2008) ¹²¹	Lindgren et al., Sweden (2009) ⁶⁶	Brodzky et al., Hungary (2010) ²³	Hallinen et al., Finland (2010) ⁴²	Merkesdal et al., Germany (2010) ⁷⁶	Malottki et al., UK (2011) ⁷⁰	Benucci et al., Italy (2011) ¹⁴
Perspective	National Health Service (NHS)	third party payer	societal	society (alternative analysis: health care payer)	societal perspective	health care payer	National Health Service (NHS)	not stated (drug costs considered)

Data	Kielhorn et al., UK (2008) ⁵²	Vera-Llonch et al., US (2008) ¹²¹	Lindgren et al., Sweden (2009) ⁶⁶	Brodszky et al., Hungary (2010) ²³	Hallinen et al., Finland (2010) ⁴²	Merkesdal et al., Germany (2010) ⁷⁶	Malottki et al., UK (2011) ⁷⁰	Benucci et al., Italy (2011) ¹⁴
Comparators	rituximab vs. therapy sequences: Scenario A: LEF, gold, CYC, palliative care; Scenario B: ADA+MTX, INF+MTX, LEF, gold, CYC, palliative care; compared to: RTX+MTX (every 9 months) included in the sequence	abatacept+MTX vs. MTX	rituximab (mean 2.4 years, 5.2 treatments) vs. second line TNF- α blocker treatment	rituximab (1 course; 3 yrs treatment) vs. palliative treatment	RTX+MTX; ABA+MTX; ETA+MTX; ADA+MTX; INF+MTX	rituximab vs. an alternative TNF- α inhibiting treatment as second-line biological treatment after etanercept therapy	Sequences starting with one of the following biologicals: adalimumab, etanercept, infliximab, rituximab, abatacept; and synthetic DMARDs	rituximab+MTX compared to baseline

Data	Kielhorn et al., UK (2008) ⁵²	Vera-Llonch et al., US (2008) ¹²¹	Lindgren et al., Sweden (2009) ⁶⁶	Brodszky et al., Hungary (2010) ²³	Hallinen et al., Finland (2010) ⁴²	Merkesdal et al., Germany (2010) ⁷⁶	Malottki et al., UK (2011) ⁷⁰	Benucci et al., Italy (2011) ¹⁴
Model structure	Markov model, lifetime horizon, 6-months cycles, 10 000 simulations	patient-level simulation model, 10 years and lifetime horizon	patient-level discrete event simulation model, lifetime horizon	Markov model, lifetime horizon	Markov model, lifetime horizon, response according to ACR20, ACR50 and ACR70 determined.	Markov model, lifetime microstimulation. Response according to ACR determined and associated HAQ score	individual sampling (Birmingham RA Model – BRAM)	NA (real life experiment), 1-year horizon

Data	Kielhorn et al., UK (2008) ⁵²	Vera-Llonch et al., US (2008) ¹²¹	Lindgren et al., Sweden (2009) ⁶⁶	Brodzky et al., Hungary (2010) ²³	Hallinen et al., Finland (2010) ⁴²	Merkesdal et al., Germany (2010) ⁷⁶	Malottki et al., UK (2011) ⁷⁰	Benucci et al., Italy (2011) ¹⁴
Patient inputs	81% female, baseline age 52.2 yrs, body weight 78 kg, HAQ 1.88; inadequate response to two nbDMARDs and one TNF α inhibitor	women, aged 55–64 years, (HAQ 1,8, EQ-5D 0,39) with moderately to severely active RA with at least 1 TNF- α blocker failure	base case: 52-year-old female patient with a HAQ of 1.9 at the start of the second biologic and a disease duration of 12 years	predominantly women (81%), mean age 52.5 years, moderate to severe RA, failure of nbDMARDs and at least 1 TNF α inhibitor (REFLEX trial)	Identical, hypothetical RA patients cohort with 3000 patients	Individual sampling model using baseline patient characteristics from the REFLEX trial. Patients having failed at least one prior DMARD therapy and one subsequent TNF-inhibiting therapy	from registry	moderate or severe RA (DAS28 5.84 \pm 0.8; DAS28-CRP 5.05 \pm 0.9; HAQ 2.04 \pm 0.44) with min. 1 TNF- α blocker failure

Data	Kielhorn et al., UK (2008) ⁵²	Vera-Llonch et al., US (2008) ¹²¹	Lindgren et al., Sweden (2009) ⁶⁶	Brodszky et al., Hungary (2010) ²³	Hallinen et al., Finland (2010) ⁴²	Merkesdal et al., Germany (2010) ⁷⁶	Malottki et al., UK (2011) ⁷⁰	Benucci et al., Italy (2011) ¹⁴
Sources of effectiveness evidence	REFLEX trial	ATTAIN trial	rituximab: REFLEX trial; second line TNF- α data from a registry	REFLEX trial	Effectiveness from published clinical trials	adjusted RCT data, expert opinion	randomized controlled trials	real life data (n=32)

Data	Kielhorn et al., UK (2008) ⁵²	Vera-Llonch et al., US (2008) ¹²¹	Lindgren et al., Sweden (2009) ⁶⁶	Brodzky et al., Hungary (2010) ²³	Hallinen et al., Finland (2010) ⁴²	Merkesdal et al., Germany (2010) ⁷⁶	Malottki et al., UK (2011) ⁷⁰	Benucci et al., Italy (2011) ¹⁴
Sources of cost data	drug, administration and monitoring costs, direct medical costs (official prices)	only direct medical costs were considered, varying by HAQ	drug costs: official price lists; data of a survey were used to calculate other costs as a function of HAQ and DAS28	official price lists (infliximab dose escalation was considered)	Resource use and costs were obtained from the Finnish treatment practice, one published study, the Finnish Unit Cost list and Finnish Medicine Tariffs	drug costs: German drug retail prices for pharmacists. The HAQ score groups and related inpatient costs: German registry. Indirect costs were estimated by impaired work capacity due to RA	only direct costs; official price lists	direct medical costs

Data	Kielhorn et al., UK (2008) ⁵²	Vera-Llonch et al., US (2008) ¹²¹	Lindgren et al., Sweden (2009) ⁶⁶	Brodszky et al., Hungary (2010) ²³	Hallinen et al., Finland (2010) ⁴²	Merkesdal et al., Germany (2010) ⁷⁶	Malottki et al., UK (2011) ⁷⁰	Benucci et al., Italy (2011) ¹⁴
Utilities	derived from HAQ: QoL =0.76–0.28xHAQ+0.05xfemale	EQ-5D derived from HAQ (national RA registry)	registry data were used to link utilities to HAQ and DAS28	EQ-5D derived from HAQ (linear regression)	QoL were estimated on the basis of the formula provided by Bansback et al. on the basis of HUI-3 and HAQ. ACR response	ACR response categories were converted into HAQ score improvement according to the data of the REFLEX trial	EQ-5D derived from HAQ	derived from HAQ
Discount rate	3.5%	3.0%	3.0%	5.0%	3%	3,5%	3.5%	not applied

Data	Kielhorn et al., UK (2008) ⁵²	Vera-Llonch et al., US (2008) ¹²¹	Lindgren et al., Sweden (2009) ⁶⁶	Brodzky et al., Hungary (2010) ²³	Hallinen et al., Finland (2010) ⁴²	Merkesdal et al., Germany (2010) ⁷⁶	Malottki et al., UK (2011) ⁷⁰	Benucci et al., Italy (2011) ¹⁴
Base case results	Scenario A, ICER: £14 690/QAL Y Scenario B, ICER: £11 601/QAL Y	ICER 10 years: \$50,576/QALY, lifetime \$45,979.	rituximab is dominant (incremental cost: - €2500, incremental QALY: 0.2)	1 course RTX, ICER: – €31,140/QAL Y, 3-year RTX: €26,223/QAL Y from societal perspective.	The ICERs of RTX compared to BSC was €30248/QAL Y; ADA vs. €50 941/QAL Y, ETA vs BSC €50 372/QAL Y, INF vs. BSC €36121/QAL Y, ABA vs. BSC €67 003/QAL Y.	ICER RTC vs stand seq. €24,517/QAL Y. When indirect costs were also included, the ICER was €15,565.	Compared to conventional DMARD alone RTX dominates TNF inhibitors (e.g. RTX-sDMARD: £21,100/QAL Y; ADA-RTX dominant, ETA-RTX dominant, INF-RTX dominant)	€23,696/QAL Y

Data	Kielhorn et al., UK (2008) ⁵²	Vera-Llonch et al., US (2008) ¹²¹	Lindgren et al., Sweden (2009) ⁶⁶	Brodzky et al., Hungary (2010) ²³	Hallinen et al., Finland (2010) ⁴²	Merkesdal et al., Germany (2010) ⁷⁶	Malottki et al., UK (2011) ⁷⁰	Benucci et al., Italy (2011) ¹⁴
Key sensitivity analysis	RTX dosing frequency: 12 months: 9759/QALY; 6 months: 23 774/QALY	ICER 10 years: \$46,675 - \$80,673/QALY; lifetime: 40,836 - 59,875/QALY.	Only if rituximab were administered every 4 months or less are costs for this strategy higher	ICERs - €31,140€/QALY and €21,980/QALY, respectively from the health care payer perspective (RTX vs. switch to a 2nd biological: RTX dominant)	Results were sensitive to the length of the treatment, negative QALYs, the discount rate and the impact of the Finnish system	Results were sensitive to the RTX dosing scheme, on changes to HAQ deterioration, discounting, rebound effect value, the model entry age or entry HAQ score, the risk multiplier and the effect of work capacity	the assumed time between RTX treatment had significant effect	subgroup analysis by the number of TNF- α blocker failures: ICER is more beneficial in patients with only 1 TNF- α blocker failure: €14,447/QALY

VII.4. DMARD naive RA patients – Quality assessment of the health economic evaluations by the Drummond checklist

✓ or X or NA (not applicable)

Checklist	Davies et al., US (2009) ³⁰	Kobelt et al., Sweden (2009) ⁵⁷	Van den Hout et al., The Netherlands (2009) ¹¹⁶	Schipper et al., The Netherlands (2011) ⁹⁸
<i>Research question</i>				
1. Costs and effects examined <input type="checkbox"/>	✓	✓	✓	✓
2. Alternatives compared ×	✓	✓	✓	✓
3. The viewpoint(s)/perspective of the analysis is clearly stated(e.g. NHS, society)	✓	✓	✓	✓

Checklist	Davies et al., US (2009) ³⁰	Kobelt et al., Sweden (2009) ⁵⁷	Van den Hout et al., The Netherlands (2009) ¹¹⁶	Schipper et al., The Netherlands (2011) ⁹⁸
<i>Selection of alternatives</i>				
4. All relevant alternatives are compared (including 'do nothing' if applicable)	✓	✓	✓	✓
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	✓	✓	✓
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	✓	✓	✓
<i>Form of evaluation</i>				

Checklist	Davies et al., US (2009) ³⁰	Kobelt et al., Sweden (2009) ⁵⁷	Van den Hout et al., The Netherlands (2009) ¹¹⁶	Schipper et al., The Netherlands (2011) ⁹⁸
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✓	✓	✓	✓
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	NA	NA	NA	NA
<i>Effectiveness data</i>				
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	✓	✓	✓

Checklist	Davies et al., US (2009) ³⁰	Kobelt et al., Sweden (2009) ⁵⁷	Van den Hout et al., The Netherlands (2009) ¹¹⁶	Schipper et al., The Netherlands (2011) ⁹⁸
10. Effectiveness data from RCT or review of RCTs	✓	✓	✓	X (cohort, registry)
11. Potential biases identified (especially if data not from RCTs)	X	X	✓	✓
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	✓	✓	✓	NA
Costs				
13. All of the important and relevant resource use included	✓	✓	X	✓

Checklist	Davies et al., US (2009) ³⁰	Kobelt et al., Sweden (2009) ⁵⁷	Van den Hout et al., The Netherlands (2009) ¹¹⁶	Schipper et al., The Netherlands (2011) ⁹⁸
14. All of the important and relevant resource use measured accurately (with methodology)	✓	✓	X	✓
15. Appropriate unit costs estimated (with methodology)	✓	X	✓	✓
16. Unit costs reported separately from resource use data	X	NA	X	✓
17. Productivity costs treated separately from other costs	✓	X	✓	✓
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion	X	✓	✓	✓

Checklist	Davies et al., US (2009) ³⁰	Kobelt et al., Sweden (2009) ⁵⁷	Van den Hout et al., The Netherlands (2009) ¹¹⁶	Schipper et al., The Netherlands (2011) ⁹⁸
<i>Benefit measurement and valuation</i>				
19. The primary outcome measure(s) for the economic evaluation	✓	✓	✓	✓
20. Methods to value health states and other benefits are stated	✓	✓	✓	✓
21. Details of the individuals from whom valuations were obtained are given	✓	✓	✓	✓
<i>Decision modelling</i>				

Checklist	Davies et al., US (2009) ³⁰	Kobelt et al., Sweden (2009) ⁵⁷	Van den Hout et al., The Netherlands (2009) ¹¹⁶	Schipper et al., The Netherlands (2011) ⁹⁸
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	✓	✓	✓
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	✓	X	✓
24. All model outputs described adequately	✓	✓	✓	✓
Discounting				
25. Discount rate used for both costs and benefits	✓	✓	✓	✓

Checklist	Davies et al., US (2009) ³⁰	Kobelt et al., Sweden (2009) ⁵⁷	Van den Hout et al., The Netherlands (2009) ¹¹⁶	Schipper et al., The Netherlands (2011) ⁹⁸
26. Do discount rates accord with NHS guidance?	X	X	X	✓(The Netherlands)
<i>Allowance for uncertainty</i>				
<i>Stochastic analysis of patient-level data</i>				
27. Details of statistical tests and CIs are given for stochastic data	✓	X	✓	✓
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs)	✓	✓	✓	✓

Checklist	Davies et al., US (2009) ³⁰	Kobelt et al., Sweden (2009) ⁵⁷	Van den Hout et al., The Netherlands (2009) ¹¹⁶	Schipper et al., The Netherlands (2011) ⁹⁸
29. Sensitivity analysis used to assess uncertainty in nonstochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	✓	✓	X	✓

VII.5. RA patients who failed at least one synthetic DMARD - Quality assessment of the health economic evaluations by the Drummond checklist

✓ or X or NA (not applicable)

Checklist	Vera-Llonch et al., US (2008) ¹²¹	Virkki et al., Finland (2008) ¹²²	Kobelt et al., Sweden (2009) ⁵⁸	Sany et al., France (2009) ⁹⁵	Lekander et al., Sweden (2010) ⁶⁴	Scultze-Koops et al., Germany (2009) ¹⁰⁰	Soini et al., Finland (2012) ¹⁰⁶	Diamantopoulos et al., Italy (2012) ³²
Research question								
1. Costs and effects examined <input type="checkbox"/>	✓	✓	✓	✓	✓	✓	✓	✓
2. Alternatives compared ×	✓	✓	✓	✓	✓	✓	✓	✓
3. The viewpoint(s)/perspective of the analysis is clearly stated(e.g. NHS, society)	✓	✓	✓	✓	✓	✓	✓	✓
Selection of alternatives								
4. All relevant alternatives are compared (including ‘do nothing’)	X (no other biologic	X (no other biological	✓	X (health status and costs	✓	✓	X (infliximab was	X (certolizumab

Checklist	Vera-Llonch et al., US (2008) ¹²¹	Virkki et al., Finland (2008) ¹²²	Kobelt et al., Sweden (2009) ⁵⁸	Sany et al., France (2009) ⁹⁵	Lekander et al., Sweden (2010) ⁶⁴	Scultze-Koops et al., Germany (2009) ¹⁰⁰	Soini et al., Finland (2012) ¹⁰⁶	Diamantopoulos et al., Italy (2012) ³²
if applicable)	therapies were considered)	drugs were considered)		before and after infliximab treatment ; no other alternatives)			considered only as second line biologic therapy)	pegol and golimumab not included)
5. The alternatives being compared are clearly described (who did what, to whom, where and	✓	✓	✓	✓	X	✓	✓	✓

Checklist	Vera-Llonch et al., US (2008) ¹²¹	Virkki et al., Finland (2008) ¹²²	Kobelt et al., Sweden (2009) ⁵⁸	Sany et al., France (2009) ⁹⁵	Lekander et al., Sweden (2010) ⁶⁴	Scultze-Koops et al., Germany (2009) ¹⁰⁰	Soini et al., Finland (2012) ¹⁰⁶	Diamantopoulos et al., Italy (2012) ³²
how often)								
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	X	✓	✓	✓	✓	✓	✓
<i>Form of evaluation</i>								
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✓	✓	✓	✓	✓	✓	✓	✓
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	NA	NA	NA	NA	NA	NA	NA	NA

Checklist	Vera-Llonch et al., US (2008) ¹²¹	Virkki et al., Finland (2008) ¹²²	Kobelt et al., Sweden (2009) ⁵⁸	Sany et al., France (2009) ⁹⁵	Lekander et al., Sweden (2010) ⁶⁴	Scultze-Koops et al., Germany (2009) ¹⁰⁰	Soini et al., Finland (2012) ¹⁰⁶	Diamantopoulos et al., Italy (2012) ³²
<i>Effectiveness data</i>								
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	✓	✓	✓	✓	✓	✓	✓
10. Effectiveness data from RCT or review of RCTs	✓	X	X (registry)	X (registry)	X	X	✓	✓
11. Potential biases identified (especially if data not from RCTs)	✓	X	X	X	X	X	✓	✓

Checklist	Vera-Llonch et al., US (2008) ¹²¹	Virkki et al., Finland (2008) ¹²²	Kobelt et al., Sweden (2009) ⁵⁸	Sany et al., France (2009) ⁹⁵	Lekander et al., Sweden (2010) ⁶⁴	Scultze-Koops et al., Germany (2009) ¹⁰⁰	Soini et al., Finland (2012) ¹⁰⁶	Diamantopoulos et al., Italy (2012) ³²
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	✓	X	X	X	X	X	✓	✓
Costs								
13. All of the important and relevant resource use included	X (only medical treatment costs)	X (only direct costs)	✓	✓	✓	✓	✓ (indirect costs in the sens. analysis)	X (only direct costs)

Checklist	Vera-Llonch et al., US (2008) ¹²¹	Virkki et al., Finland (2008) ¹²²	Kobelt et al., Sweden (2009) ⁵⁸	Sany et al., France (2009) ⁹⁵	Lekander et al., Sweden (2010) ⁶⁴	Scultze-Koops et al., Germany (2009) ¹⁰⁰	Soini et al., Finland (2012) ¹⁰⁶	Diamantopoulos et al., Italy (2012) ³²
14. All of the important and relevant resource use measured accurately (with methodology)	✓	✓	✓	✓	✓	X	✓	✓
15. Appropriate unit costs estimated (with methodology)	✓	✓	✓	✓	X	X	✓	✓
16. Unit costs reported separately from resource use data	✓	✓	✓	✓	NA	NA	✓	✓
17. Productivity costs treated separately from other costs	NA (no indirect costs)	NA (no indirect costs)	✓	✓	X	✓	✓	NA (no indirect costs)
18. The year and country to which	✓	✓	✓	✓	✓	✓	✓	✓

Checklist	Vera-Llonch et al., US (2008) ¹²¹	Virkki et al., Finland (2008) ¹²²	Kobelt et al., Sweden (2009) ⁵⁸	Sany et al., France (2009) ⁹⁵	Lekander et al., Sweden (2010) ⁶⁴	Scultze-Koops et al., Germany (2009) ¹⁰⁰	Soini et al., Finland (2012) ¹⁰⁶	Diamantopoulos et al., Italy (2012) ³²
unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion								
<i>Benefit measurement and valuation</i>								
19. The primary outcome measure(s) for the economic evaluation	✓	✓	✓	✓	✓	✓	✓	✓
20. Methods to value health states and other benefits are stated	✓	✓	✓	✓	✓	✓	✓	✓

Checklist	Vera-Llonch et al., US (2008) ¹²¹	Virkki et al., Finland (2008) ¹²²	Kobelt et al., Sweden (2009) ⁵⁸	Sany et al., France (2009) ⁹⁵	Lekander et al., Sweden (2010) ⁶⁴	Scultze-Koops et al., Germany (2009) ¹⁰⁰	Soini et al., Finland (2012) ¹⁰⁶	Diamantopoulos et al., Italy (2012) ³²
21. Details of the individuals from whom valuations were obtained are given	✓	✓	✓	✓	✓	✓	✓	✓
<i>Decision modelling</i>								
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	NA (follow up data)	✓	NA (registry data)	✓	✓	✓	✓
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	NA	✓	NA	X	✓	✓	✓

Checklist	Vera-Llonch et al., US (2008) ¹²¹	Virkki et al., Finland (2008) ¹²²	Kobelt et al., Sweden (2009) ⁵⁸	Sany et al., France (2009) ⁹⁵	Lekander et al., Sweden (2010) ⁶⁴	Scultze-Koops et al., Germany (2009) ¹⁰⁰	Soini et al., Finland (2012) ¹⁰⁶	Diamantopoulos et al., Italy (2012) ³²
24. All model outputs described adequately	✓	NA	✓	NA	✓	✓	✓	✓
<i>Discounting</i>								
25. Discount rate used for both costs and benefits	✓	X	✓	X	✓	✓	✓	✓
26. Do discount rates accord with NHS guidance?	✓ (US)	NA	✓	NA	X	X	✓ (Finland)	✓ (Italy)
<i>Allowance for uncertainty</i>								
<i>Stochastic analysis of patient-level data</i>								

Checklist	Vera-Llonch et al., US (2008) ¹²¹	Virkki et al., Finland (2008) ¹²²	Kobelt et al., Sweden (2009) ⁵⁸	Sany et al., France (2009) ⁹⁵	Lekander et al., Sweden (2010) ⁶⁴	Scultze-Koops et al., Germany (2009) ¹⁰⁰	Soini et al., Finland (2012) ¹⁰⁶	Diamantopoulos et al., Italy (2012) ³²
27. Details of statistical tests and CIs are given for stochastic data	✓	X	✓	X	X	X	✓	✓
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs)	✓	X	✓	X	X	✓	✓	✓
29. Sensitivity analysis used to assess uncertainty in nonstochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	✓	X	✓	X	✓	✓	✓	✓

VII.6. RA patients who failed at least one biologic DMARD - Quality assessment of the health economic evaluations by the Drummond checklist

✓ or X or NA (not applicable)

Checklist	Kielhorn et al., UK (2008) ⁵²	Vera-Llonch et al., US (2008) ¹²¹	Lindgren et al., Sweden (2009) ⁶⁶	Brodzky et al., Hungary (2010) ²³	Hallinen et al., Finland (2010) ⁴²	Merkesdal et al., Germany (2010) ⁷⁶	Malottki et al., UK (2011) ⁷⁰	Benucci et al., Italy (2011) ¹⁴
<i>Research question</i>								
1. Costs and effects examined <input type="checkbox"/>	✓	✓	✓	✓	✓	✓	✓	✓
2. Alternatives compared ×	✓	✓	✓	✓	✓	✓	✓	✓
3. The viewpoint(s)/perspective of the analysis is clearly stated(e.g. NHS, society)	✓	✓	✓	✓	✓	✓	✓	X
<i>Selection of alternatives</i>								

Checklist	Kielhorn et al., UK (2008) ⁵²	Vera-Llonch et al., US (2008) ¹²¹	Lindgren et al., Sweden (2009) ⁶⁶	Brodzky et al., Hungary (2010) ²³	Hallinen et al., Finland (2010) ⁴²	Merkesdal et al., Germany (2010) ⁷⁶	Malottki et al., UK (2011) ⁷⁰	Benucci et al., Italy (2011) ¹⁴
4. All relevant alternatives are compared (including 'do nothing' if applicable)	✓	X (switch between TNF inhibitors ignored)	✓	✓	✓	✓	✓	X (compared to baseline data)
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	✓	✓	✓	✓	✓	✓	✓
6. The rationale for choosing the alternative programmes or	✓	✓	✓	✓	✓	✓	✓	✓

Checklist	Kielhorn et al., UK (2008) ⁵²	Vera-Llonch et al., US (2008) ¹²¹	Lindgren et al., Sweden (2009) ⁶⁶	Brodzky et al., Hungary (2010) ²³	Hallinen et al., Finland (2010) ⁴²	Merkesdal et al., Germany (2010) ⁷⁶	Malottki et al., UK (2011) ⁷⁰	Benucci et al., Italy (2011) ¹⁴
interventions compared is stated								
<i>Form of evaluation</i>								
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✓	✓	✓	✓	✓	✓	✓	✓
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	NA	NA	NA	✓ (sensitivity analysis)	NA	NA	NA	NA
<i>Effectiveness data</i>								
9. The source(s) of effectiveness	✓	✓	✓	✓	✓	✓	✓	✓

Checklist	Kielhorn et al., UK (2008) ⁵²	Vera-Llonch et al., US (2008) ¹²¹	Lindgren et al., Sweden (2009) ⁶⁶	Brodzky et al., Hungary (2010) ²³	Hallinen et al., Finland (2010) ⁴²	Merkesdal et al., Germany (2010) ⁷⁶	Malottki et al., UK (2011) ⁷⁰	Benucci et al., Italy (2011) ¹⁴
estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)								
10. Effectiveness data from RCT or review of RCTs	✓	✓	✓	✓	✓	✓	✓	X (real life data)
11. Potential biases identified (especially if data not from RCTs)	✓	✓	✓	✓	X	X	✓	X
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of	✓	NA	NA	✓	✓	✓	✓	NA

Checklist	Kielhorn et al., UK (2008) ⁵²	Vera-Llonch et al., US (2008) ¹²¹	Lindgren et al., Sweden (2009) ⁶⁶	Brodzkiy et al., Hungary (2010) ²³	Hallinen et al., Finland (2010) ⁴²	Merkesdal et al., Germany (2010) ⁷⁶	Malottki et al., UK (2011) ⁷⁰	Benucci et al., Italy (2011) ¹⁴
effectiveness studies)								
Costs								
13. All of the important and relevant resource use included	X (only direct medical costs)	X (only direct medical costs)	✓	✓	✓	✓	X (only direct costs)	X (only direct medical costs)
14. All of the important and relevant resource use measured accurately (with methodology)	✓	✓	✓	✓	✓	✓	✓	✓
15. Appropriate unit costs estimated (with methodology)	✓	✓	✓	✓	✓	X	✓	✓

Checklist	Kielhorn et al., UK (2008) ⁵²	Vera-Llonch et al., US (2008) ¹²¹	Lindgren et al., Sweden (2009) ⁶⁶	Brodzky et al., Hungary (2010) ²³	Hallinen et al., Finland (2010) ⁴²	Merkesdal et al., Germany (2010) ⁷⁶	Malottki et al., UK (2011) ⁷⁰	Benucci et al., Italy (2011) ¹⁴
16. Unit costs reported separately from resource use data	✓	✓	✓	✓	✓	NA	✓	X
17. Productivity costs treated separately from other costs	NA (no indirect costs)	NA (no indirect costs)	✓	✓	X	✓	NA (only direct costs)	NA (no indirect costs)
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion	✓	✓	✓	✓	✓	✓	✓	X
<i>Benefit measurement and valuation</i>								

Checklist	Kielhorn et al., UK (2008) ⁵²	Vera-Llonch et al., US (2008) ¹²¹	Lindgren et al., Sweden (2009) ⁶⁶	Brodzky et al., Hungary (2010) ²³	Hallinen et al., Finland (2010) ⁴²	Merkesdal et al., Germany (2010) ⁷⁶	Malottki et al., UK (2011) ⁷⁰	Benucci et al., Italy (2011) ¹⁴
19. The primary outcome measure(s) for the economic evaluation	✓	✓	✓	✓	✓	✓	✓	✓
20. Methods to value health states and other benefits are stated	✓	✓		✓	✓	✓	✓	✓
21. Details of the individuals from whom valuations were obtained are given	✓	✓	✓	✓	✓	✓	✓	✓
<i>Decision modelling</i>								
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	✓	✓	✓	✓	✓	✓	NA

Checklist	Kielhorn et al., UK (2008) ⁵²	Vera-Llonch et al., US (2008) ¹²¹	Lindgren et al., Sweden (2009) ⁶⁶	Brodzky et al., Hungary (2010) ²³	Hallinen et al., Finland (2010) ⁴²	Merkesdal et al., Germany (2010) ⁷⁶	Malottki et al., UK (2011) ⁷⁰	Benucci et al., Italy (2011) ¹⁴
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	✓	✓	X (partly)	✓	✓	✓	NA
24. All model outputs described adequately	✓	✓	✓	✓	✓	✓	✓	NA
<i>Discounting</i>								
25. Discount rate used for both costs and benefits	✓	✓	✓	✓	✓	✓	✓	X
26. Do discount rates accord with NHS guidance?	✓	✓ (US)	✓ (Sweden)	✓(HUN)	X	X	✓	X

Checklist	Kielhorn et al., UK (2008) ⁵²	Vera-Llonch et al., US (2008) ¹²¹	Lindgren et al., Sweden (2009) ⁶⁶	Brodzkiy et al., Hungary (2010) ²³	Hallinen et al., Finland (2010) ⁴²	Merkesdal et al., Germany (2010) ⁷⁶	Malottki et al., UK (2011) ⁷⁰	Benucci et al., Italy (2011) ¹⁴
<i>Allowance for uncertainty</i>								
<i>Stochastic analysis of patient-level data</i>								
27. Details of statistical tests and CIs are given for stochastic data	X	✓	✓	X	X	✓	✓	X
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs)	X	✓	✓	X	✓	✓	✓	X
29. Sensitivity analysis used to assess uncertainty in nonstochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g.	✓	✓	✓	X (partly)	✓	✓	✓	X

Checklist	Kielhorn et al., UK (2008) ⁵²	Vera-Llonch et al., US (2008) ¹²¹	Lindgren et al., Sweden (2009) ⁶⁶	Brodzki et al., Hungary (2010) ²³	Hallinen et al., Finland (2010) ⁴²	Merkesdal et al., Germany (2010) ⁷⁶	Malottki et al., UK (2011) ⁷⁰	Benucci et al., Italy (2011) ¹⁴
methods to handle missing data)								

VII.7. Clinical manifestations, epidemiology and measures in adult Crohn's Disease. In: Petra Baji: Systematic review and analysis of evidences on clinical efficacy and cost-effectiveness of biological drugs for the treatment of adult Crohn's Disease. ISBN: 978-963-503-558-8, pp.1-12.

(Note: Cited references are available in the reference list of the book)

4. Clinical manifestations, epidemiology and measures in adult Crohn's Disease (V. Hevér N., Brodszky V, Gulácsi L)

4.1. Description of the health problem

Crohn's disease¹ (CD) is chronic inflammatory disease of the gastrointestinal tract of unknown origin. CD is related closely to another chronic inflammatory condition that involves only the colonic mucosa called ulcerative colitis (UC). CD and UC are frequently referred to as inflammatory bowel disease (IBD).

There are many theories on the cause of CD. There is a strong evidence that genetic disposition is a major key in acquiring CD.⁵⁶

CD is more common in developed countries suggesting the etiologic role of environmental factors such as diet, smoking, pollution, industrial chemicals, socioeconomic factors. Imbalance of intestinal bacterial flora, innate and acquired immunity have been suggested to play a key role in expression of CD.

CD can cause very variable symptoms and complaints: abdominal pain, diarrhea, and weight loss, less frequently poor appetite, fever, night sweats, rectal pain, and occasionally rectal bleeding. The inflammatory process can involve any part of the digestive tract, from the mouth to the anus, but mainly affects the distal ileum and the colon. Patients with CD can be

¹ It is named after the physician who described the disease in 1932. It also is called granulomatous enteritis or colitis, regional enteritis, ileitis, or terminal ileitis.

in relatively good condition with minimal signs of illness, but potentially life-threatening complications can develop.

Complications of CD may be related or unrelated to the inflammation within the intestine. Intestinal complications of CD include: obstruction, very rarely perforation of the bowel, abscesses; fistulae, and intestinal bleeding. About 20%–30% of patients present with perianal lesions and 15%–20% have or have had a fistula. During the disease course, the cumulative risk for perianal involvement is about 50%.¹⁶ Extra-intestinal complications involve the skin (erythema nodosumⁱ), joints (arthritis), spine, eyes (uveitis), liver (hepatitis, cirrhosis), and bile ducts (primary sclerosing cholangitis).

The disease usually fluctuates between periods of inactivity (remission) and activity (relapse). CD becomes symptomatic when the inflammation is florid, lesions are extensive or distal, associated with a systemic inflammatory reaction, or when they are complicated by strictures or abscesses and fistulas. Thus disease course is generally distinguished by a sequence of flare-up episodes and remissions of varying durations, whereas 10%–15% of patients undergo a chronic, continuous disease course.¹⁶

Due to the chronic character of the disease, CD patients are dealing with their disorder throughout most of their adult life and will need to balance the impact of their disease with their professional, social and personal lifestyles. Systematic review by Kohen et al. revealed that, compared with CD patients, the health related quality of life (HRQoL) was better in healthy controls and in UC patients (except pre-colectomy), but similar to or worse than that in many other medical conditions. The HRQoL was directly correlated with CD activity, and was worse in active disease than in remission. The HRQoL was improved only in the short term in surgically vs. medically treated CD patients.¹¹

The overall mortality of unselected CD patients is slightly but significantly higher than in the general population - primarily explained by deaths from gastrointestinal, respiratory, and genitourinary diseases.²⁴

Evidences illustrate that the economic burden of CD is also substantial. Yu et al. reviewed the literature for cost of illness studies from the US and Western Europe, inflated and converted

ⁱ painful red raised spots on the legs

the results to 2006 US dollar and Euro, respectively.⁸⁹ In the US estimated direct medical costs were \$18 022–18 932 per patient with CD per year, and €2898–6960 in Western European countries. Hospitalizations accounted for 53–66% of direct medical costs, with an average cost-per-hospitalization of \$37 459 in the US. Estimated indirect costs accounted for 28% of the total cost in the US and 64–69% in Europe. Hospitalization costs were the primary cost driver of total direct costs, accounting for 53–66% of direct medical costs. Hospitalization costs were \$37 495 per event in the United States and £7441 per event in the United Kingdom. Costs varied greatly across patients with different levels of disease severity. The costs of patients with severe disease (e.g., drug-responsive and drug-refractory) were 3- to 9-fold higher than the CD patient in remission in both the US and the United Kingdom. In the US, costs of patients in the top 25% of total costs averaged \$60 582 per year; the cost of patients who were in the top 2% of total costs incurred on average \$300 000 in direct medical costs. Indirect costs were a substantial portion of the total cost of CD, and accounted for 28% of the total cost in the US and 64% to 69% in Europe. There is a lack of cost of illness data from Eastern Central European countries.

4.2. Classification criteria

The Montreal classification criteria of CD considers the age at diagnosis, disease location and disease behaviour.⁷⁸

- Age at diagnosis: A1. below 16 y; A2 between 17 and 40 y; A3 above 40 y
- Disease location: L1 ileal, L2 colonic; L3 ileocolonic; L4 isolated upper disease – L4 is modifier that can be added to L1–L3 when concomitant upper gastrointestinal disease is present.
- Disease behaviour: B1 non-stricturing, non-penetrating; B2 stricturing; B3 penetrating; p perianal disease modifier - “p” is added to B1–B3 when concomitant perianal disease is present.

4.3. Epidemiology

Considerable differences can be observed in the incidence of IBDs across different geographic regions and over time. According to a comprehensive review of the literature⁵⁵ (1950-2010) the annual incidence rates vary by geographic region, with CD estimates ranging from 0.3 to 12.7 per 100,000 in Europe, 0.04 to 5.0 per 100,000 in Asia and the Middle East, and 0 to 20.2 per 100,000 in North America. For prevalence studies, the CD estimates ranged from 0.6 to 322 per 100,000 in Europe, 0.88 to 67.9 per 100,000 in Asia and the Middle East, and 16.7 to 318.5 per 100,000 in North America. Women and men are affected equally.⁵⁵

Studies that explored temporal trends showed that the incidence of IBD continues to increase in many regions of the world. Since 1980, 29% of UC studies have shown a statistically significant increasing incidence. (Table 1) The rising may be at least partly explained by the increased awareness of IBD by physicians and the public, as well as advancements in diagnostic methods.⁵⁵

Table 1 Incidence and prevalence of Crohn's disease in Eastern European countries.

Lead author	Year	Country	Region	Study period	CU (10 ⁵)	CD (10 ⁵)	Annual average change rate
INCIDENCE							
Bitter ⁶	1980	Czech	North Bohemia	1978	1.3	-	-
Lakatos ⁴⁴	2004	Hungary	Veszprém province	1977-2001	5.89 (2.15-9.63)	2.23 (0.5, 3.96)	11.1
Gheorge ³⁵	2004	Romania	National	2002-2003	0.97	0.42	-
PREVALENCE							
Lakatos ⁴⁴	2004	Hungary	Veszprém province	1991-2001	101	35	-
Gheorge ³⁵	2004	Romania	National	2002-2003	2.42	1.51	-

Source: Molodeczky et al., 2012.⁵⁵

The peak age for CD occurrence is 20–30 years. Pediatric IBD accounts for 7% to 20% of all IBD cases, based on varying results from population based studies.¹⁶ Recent data indicate higher rates of pediatric CD than UC; in France, pediatric CD incidence increased from 3.5/100,000 in 1990 to 5.2/100,000 in 2005, whereas pediatric UC remained at around 0.8/100,000. A similar trend has been reported in many areas of Europe and North America, except in Finland and northern California where the incidence of pediatric UC is higher than that of pediatric CD. These observations indicate that environmental factors affect incidence of IBD (mainly CD) in children, leading to many research investigations of pediatric cohorts.

4.4. Health status assessment in CD

In drug development trials for CD the proportion of patients achieving remission within the period of about four to eight weeks, based on the pharmacodynamic properties of the test drug, is an appropriate primary end-point to justify short-term treatment of active Crohn's disease.²⁵

An ideal measurement of the activity of CD does not exist. The Crohn's Disease Activity Index (CDAI) is the most commonly used score, so definition of remission of CD relies on CDAI value.

Secondary endpoints of trials include the proportion of responders time to remission, time to response; laboratory measures of inflammation; validated Quality of Life (QOL) measurement, e.g., inflammatory bowel disease questionnaire (IBDQ); assessment of endoscopic healing, e.g., Crohn's disease endoscopic index of severity (CDEIS); mean or relative change in CDAI score; steroid sparing effect such as: proportion in steroid-free remission; reduction in surgical procedures.

4.4.1. Clinical activity index - CDAI

The Crohn's disease activity index (CDAI) is a numerical calculation derived from the sum of products from a list of 8 items, and multiplied by weighting factors for each item to define the severity of "disease activity" in patients with CD.³³ (Table 2)

Table 2 CDAI items and weighting factors

Item (daily sum per week)	Weighting factor
Number of liquid or very soft stools	2
Abdominal pain score in one week (rating, 0-3)	5
General well-being (rating, 1-4)	7
Sum of physical findings per week	20
Arthritis/arthralgia	
Mucocutaneous lesions (e.g. erythema nodosum, aphthous ulcers)	
Iritis/uveitis	
Anal disease (fissure, fistula, etc)	
External fistula (enterocutaneous, vesicle, vaginal, etc)	
Fever over 37.8°C	
Antidiarrheal use (e.g. diphenoxylate)	30
Abdominal mass (no = 0, equivocal = 2, yes = 5)	10
47 minus hematocrit (males) or 42 minus hematocrit (females)	6
1-x (1-body weight divided by a standard weight)	1

Source: Freeman et al., 2008³³

CDAI scores of 150-219 define a mildly active disease, between 220-450 define a moderately active disease and scores > 450 define severely active disease. Remission is defined by reduction in CDAI score to less than 150, which is maintained for at least two weeks. A patient is called a responder, if remission has been achieved or a reduction of at least 100 in CDAI has been observed at the end of the treatment period.

4.4.2. Endoscopy - Crohn's disease endoscopic index of severity (CDEIS)

An endoscopic scoring system, namely the Crohn's disease endoscopic index of severity (CDEIS) has been developed and validated for monitoring activity in CD, and to assess severity of ileal and colonic disease.⁵⁴ However, it is time consuming and complicated, due to the analysis of multiple aspects of lesions. CDEIS is based upon the presence of four types of lesions: superficial ulcers, deep ulcers, ulcerated stenosis or non-ulcerated stenosis, all of which should be recorded in five different segments: terminal ileum, ascending colon, transverse colon, descending and sigmoid colon, and rectum.

The combination of values allows the calculation of a severity score, which ranges from between 0 and 30.

4.4.3. Imaging techniques - ultrasound, magnetic resonance, computer tomography

Ultrasound has been successfully used as the imaging method of choice in screening patients with clinically suspected CD; it may be the first diagnostic tool employed for young patients and can be used in the preliminary diagnostic work-up prior to further invasive tests. US is very useful for follow-up of known CD patients especially with abdominal mass. Nevertheless, the usefulness of ultrasound and Doppler imaging in assessing disease activity is still a matter of discussion.

Several studies attempted to correlate ultrasound and Doppler findings with clinical and biochemical activity, but the published results are controversial.

Computer tomography (CT and CT enterography (CTE) seem to be useful as markers in CD, but radiation exposure is a major disadvantage of these techniques. Magnetic resonance (MR) combined with the use of large volumes of oral contrast agents to provide bowel distension, allows the evaluation of bowel wall contrast enhancement, wall thickening and edema; findings useful for the assessment of CD activity.⁸⁷

4.4.4. Quality of life assessment - Inflammatory bowel disease questionnaire (IBDQ)

The Inflammatory Bowel Disease Questionnaire (IBDQ) is a widely used questionnaire for health-related quality of life (HRQoL) assessment in patients with inflammatory bowel

diseases (UC and CD). It was developed by Guyatt et al. as a physician-administered questionnaire regarding the patient's status during the last 2 weeks before administration. It consists of 32 questions divided into four dimensions: bowel symptoms (10 items), systemic symptoms (5 items), emotional function (12 items) and social function (5 items). Every question has graded responses from 1 (worst situation) to 7 (best situation), and thus the total score is ranging from 32 to 224 with higher scores representing better quality of life. The original IBDQ is proven to be a valid and reliable assessment tool that reflects important changes in the quality of life of patients with IBD. A self-administered version and a short form of the questionnaire have been validated and were also found valid and reliable.⁵⁸

4.5 Treatment goal in CD

The management plan for a patient with CD should take into account the activity, site and behaviour of disease, and should always be discussed with the patient.²⁰

Since there is no cure for CD, the goals of treatment are to 1) induce remissions, 2) maintain remissions, 3) minimize side effects of treatment, and 4) improve the quality of life, 5) escape surgical intervention. Treatment of CD and UC with medicines is similar but not the same.

4.6 Drug treatment of CD

Medications for treating CD include:

1. aminosalicylates
2. corticosteroids
3. antibiotics
4. immunomodulators:
 - azathioprine, methotrexate, cyclosporine
 - biological therapies - anti-tumor necrosis factor alpha (anti-TNF- α)
medications: adalimumab, infliximab

Biologic therapies (also called biologicals, biological agents) are genetically engineered medicines that have been made to treat human diseases.

Guidelines recommend that approaches be sequential - initially to induce clinical remission, and then to maintain remissions. Initial evidence of improvement should be seen within 2 to 4 weeks and maximal improvement should be seen in 12 to 16 weeks.

4.6.1 The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management

The second European evidence-based Consensus on the diagnosis and management of Crohn's disease formulated basic statements regarding the management of CD, including both drug and surgical treatment.²⁰ Some of the statements are listed next.

4.6.1.1. Mildly active localised ileocaecal Crohn's disease

Budesonide 9 mg daily is the preferred treatment. The benefit of mesalazine is limited. Antibiotics cannot be recommended. Very rarely no treatment is an option for some patients with mild symptoms.

4.6.1.2. Moderately active localised ileocaecal Crohn's disease

Moderately active, localised ileocaecal CD should preferably be treated with budesonide 9 mg/day, or with systemic corticosteroids. Antibiotics can be added if septic complications are suspected. Azathioprine/6-mercaptopurine or methotrexate in combination with steroids is also an appropriate option. Anti-TNF therapy should be considered as an alternative for

patients with objective evidence of active disease, who have previously been steroid-refractory, -dependent, or -intolerant. Risks should be carefully considered and discussed with patients.

4.6.1.3. Severely active localised ileocaecal CD

Severely active localised ileocaecal CD should initially be treated with systemic corticosteroids. For those who have relapsed, anti-TNF therapy with or without an immunomodulator is an appropriate option for patients with objective evidence of active disease. For some patients who have infrequently relapsing disease, restarting steroids with an immunomodulator may be appropriate. Surgery is a reasonable alternative for some patients and should also be considered and discussed.

4.6.1.4. Colonic disease

Active colonic CD may be treated with sulfasalazine if only mildly active, or with systemic corticosteroids. For those who have relapsed, anti-TNF therapy with or without an immunomodulator is an appropriate option for patients with objective evidence of moderate or severely active disease. For some patients who have infrequently relapsing disease, restarting steroids with an immunomodulator may be appropriate. Before initiating immunomodulator or anti-TNF therapy, surgical options should also be considered and discussed.

4.6.1.5. Extensive small bowel disease

Extensive small bowel Crohn's disease should be treated with systemic corticosteroids and thiopurines or methotrexate. For patients who have relapsed, anti-TNF therapy with or without azathioprine is an appropriate option if there is objective evidence of moderate or severely active disease. Adjunctive nutritional support is appropriate. Surgical options should

also be considered and discussed at an early stage. Patients who have clinical features that suggest a poor prognosis currently appear to be the most suitable patients for early introduction of thiopurines, methotrexate and or anti-TNF therapy.

4.6.1.6. Oesophageal and gastroduodenal disease

Oesophageal or gastroduodenal Crohn's disease may best be treated with a proton pump inhibitor, if necessary together with systemic corticosteroids and thiopurines or methotrexate. Anti-TNF therapy is an alternative for severe or refractory disease. Dilatation or surgery is appropriate for obstructive symptoms of disease.

4.6.1.7. Treatment according to the course or behaviour

A novel target for both clinical trials and the management of individuals with CD is the desire to change the pattern of future disease. The initial treatment of relapse should be based upon previously successful therapies. Any patient who has an early relapse (defined as an arbitrary period of <3 months) should be started on an immunomodulator to reduce the risk of a further relapse. Opinion remains divided whether to use the same treatment to induce remission and taper more slowly or use more potent induction therapy. It is important to confirm disease activity as a cause of recurrent symptoms, although unnecessary to re-evaluate the distribution of disease unless this will alter medical or surgical management. Patients who have a relapse of moderate or severe activity should be considered for anti-TNF therapy, since infliximab is more effective than azathioprine in early (duration <2 years), treatment-naïve patients with CD and there is a significant advantage in using the combination of infliximab and azathioprine. All anti-TNF agents are more effective when introduced at an early stage.

4.6.1.8. Steroid-refractory Crohn's disease

Patients with objective evidence of active disease refractory to corticosteroids should be treated with anti-TNF therapy, with or without thiopurines or methotrexate, although surgical options should also be considered and discussed at an early stage.

4.6.2. Biological drugs registered by the European Medicines Agency for the treatment of adult CD

Currently two tumor necrosis factor alpha (TNF- α) inhibitors, namely infliximab and adalimumab have registration by EMA for the treatment of adult CD.

Therapeutic indication of infliximab (Remicade) includes:

- treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.
- treatment of fistulising, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).

Adalimumab (Humira) is indicated for treatment of severe, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

VII.8. Biologicals for adult Crohn' Disease – systematic review of the health economic literature. In: Petra Baji: Systematic review and analysis of evidences on clinical efficacy and cost-effectiveness of biological drugs for the treatment of adult Crohn's Disease. ISBN: 978-963-503-558-8, pp....

(Note: Cited references are available in the reference list of the book)

6. Biologicals for adult Crohn' Disease – systematic review of the health economic literature (V. Hevér N, Péntek M)

Summary

Our systematic review revealed twelve cost-utility analysis of adalimumab and/or infliximab treatment for CD from the UK (n=5), US (n=4), Canada (n=2) and France (n=1). Studies were performed from the third party payer perspective and regardless of the chronic character of CD, most of the models included a short time horizon (1-year n=7, 5-year n=2).

Differences in comparators, methods, data, modelling approach prevent reliable interpretation of the results. Nevertheless, available cost-utility suggest that adalimumab treatment is likely to dominate infliximab. Sensitivity analyses revealed that with a sufficiently large price reduction infliximab treatment may have become cost-effective.

There were no cost-utility studies from Eastern Central European countries according to our international literature search.

6.1. Literature search

We performed a literature search for health economic evaluations of adalimumab and infliximab for the treatment of adult Crohn's Disease (CD). The search included the time period between 2007 – May 2012 and ran in the following databases: Ovid MEDLINE(R) 1946 to Present with Daily Update, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Web of Knowledge and Centre for Reviews and Dissemination (CRD). The search strategies applied are presented in Appendix 8.6.

Original articles of full economic evaluations presenting cost-utility data (cost/QALY) of adalimumab and/or infliximab for adult CD were retrieved by two independent reviewers.

Articles with full text in English or German were analysed. Data were extracted using a standard collection form and are presented in a table format but also short descriptive summary of each is provided. Quality of the economic evaluations was assessed using the checklist developed by Drummond et al.²³

Cost-utility analyses from before 2007 were captured by a systematic review.²² Dretzke et al. performed a systematic literature search for cost-effectiveness studies of biological drugs (adalimumab and infliximab) compared to no treatment, placebo, dietary intervention, drug treatment with aminosalicylates, methotrexate, corticosteroids (prednisolone, budesonide and hydrocortisone), azathioprine, metronidazole or surgical intervention for CD. The electronic literature search was closed in May / June 2007. No published economic studies were found for adalimumab but four health economic evaluations (presented in five publications) dealt with infliximab.^{2, 10, 42, 52, 53} Dretzke et al. performed a de novo cost-utility analysis of infliximab treatment versus standard care.²² All these analyses fulfilled the inclusion criteria of our current report.

6.2 Results

Our search resulted 180 hits, and 8 publications fulfilled our inclusion criteria.

The number of hits and included publications were as follows (publications overlapping between databases are listed only where first appeared):

- Ovid MEDLINE(R) 1946 to Present with Daily Update – 44 hits / 6 publications included

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations – 7 hits / 1 publication included
- Web of Knowledge – 93 hits / 0 publication included
- Centre for Reviews and Dissemination (CRD) - 36 / 1 publication included

The list of hits and reasons of exclusion are presented in Appendix 8.7.

An analysis from Canada was presented both as a health technology assessment report and an article thus the 8 publications reported 7 different health economic studies.

The systematic review by Dretzke et al. included 4 different analysis (presented in 5 publications) plus 1 de novo health economic analysis evaluating the cost-utility of infliximab in CD.²²

To sum up, altogether 12 cost-utility analysis presented in 13 publications were included in our report.

In the next sections first we give a summary of the five cost-utility studies (time period: - 2007) discussed by Dretzke et al.²² Then a short description of the seven health economic assessments from our additional search (2007-2012) is provided. Main data (characteristics and results) of the analysis are presented also in tables using a standardized extraction format. (Table 14, Table 15) Quality assessment of the economic evaluations according to the Drummond checklist²³ is presented separately. (Table 16)

6.2.1. Systematic review and economic evaluation by Dretzke et al. (2011)

6.2.1.1. Cost-utility assessments revealed by the literature search

In this systematic review²² incremental cost-utility ratio (ICUR)ⁱ was the outcome of the economic assessments. All the four studies conducted cost-utility analyses of infliximab. One study was performed in the US², one in France⁴², one in Canada⁵² and another in the UK¹⁰.

Studies from France and Canada considered non-fistulising CD, analysis from the US dealt with fistulising disease and the assessment from the UK considered both.

Non-fistulising disease (France, Canada, UK)^{10, 42, 52}

The comparator treatment strategies comprised surgery and medical treatment⁴², placebo¹⁰ or usual care⁵² in populations that were resistant/non-responsive to standard therapy. The time-horizon was 1 year⁵², life-time⁴² and it was not specified in one¹⁰. Both the French and Canadian models used a third-party payer perspective and, while not described, the UK HTA report likely used an NHS/PSS perspective in line with the NICE reference case.

The UK model compared single and ‘episodic’ treatment with placebo. Against placebo, episodic treatment (defined as a single 5 mg/kg dose plus up to three 5 mg/kg retreatments within a single year) was estimated to have an ICER of £62,016 per quality-adjusted life-year (QALY) when using effectiveness data from the 5 mg/kg dose group. Treatment with a single dose of infliximab (no episodic reinfusions) was found to be less cost-effective.¹⁰

The French model estimated the cost-effectiveness against usual care only. As neither total nor incremental QALY figures were given (and back-calculating is not reliable), incremental figures could not be calculated. Against usual care, ‘episodic’ treatment and maintenance treatments of infliximab were estimated to have ICERs of €63,700 and €784,057 per QALY (base year not given) respectively.⁴²

The converted results (to 2006 £) from the Canadian model suggested an ICER of £105,900 per QALY for single dose versus usual care, £280,600 per QALY for ‘episodic’ versus single-dose infliximab, and £407,000 per QALY for maintenance versus ‘episodic’ treatment with infliximab.⁵²

Probabilistic sensitivity analysis was conducted in only the Canadian model.⁵² This analysis suggested that usual care was favoured up to a threshold of approximately £105,000 per

ⁱ The incremental cost-utility ratio (ICUR) is often substituted in the literature by incremental cost-effectiveness ratio (ICER). In this chapter we use ICER as synonyme of ICUR.

QALY, with a single dose of infliximab favoured between this figure and approximately £251,000 per QALY in non-fistulising disease. While this study suggested that the rate of surgical admissions for drug-refractory treatment had little effect on cost-effectiveness, it was sensitive to the variations in the cost of infliximab. With a sufficiently large price reduction it suggested that infliximab treatment may have become cost-effective.

In the UK study, the one-way sensitivity analyses conducted on utility, duration of response and the rate of averted surgeries did not result in any ICER below £40,000/QALY.¹⁰

Fistulising disease (USA, UK)^{2, 10}

The comparator treatment strategies comprised placebo¹⁰ or the combination of 6-mercaptopurine/metronidazole (6MP/met) and/or infliximab in different regimens². Both studies used a 1-year time frame and third-party payer (NHS) perspective.

In fistulising disease, the UK model suggested a cost-effectiveness ratio of £102,000 (base year unclear) for initial infliximab treatment versus placebo.¹⁰

In the US model (converted to 2005 £), only cost-effectiveness ratios could be calculated as the outcomes figures were not given with sufficient precision. Against the comparator treatment of 6MP/met, the interventions had cost-effectiveness ratios of £274,100 per QALY (infliximab, with 6MP/met as second-line treatment), £278,000 per QALY (infliximab, with infliximab reinfusions as second line treatment) and £290,770 per QALY (6MP/met + episodic infliximab reinfusion).²

The UK model varied the rate of success in retreatment and reclosure of fistulas alongside the level of cost offset owing to averted surgeries. In no case did this produce a ratio below £80,000 per QALY.¹⁰ In the US model, all ICERs remained above £79,000/QALY (converted figures) regardless of the changes made in one-way sensitivity analyses other than in the price of infliximab. Only where the price of infliximab was reduced to £160 per dose (a reduction of 90% from the modelled price) did the ICER for ‘episodic’ reinfusion fall marginally below £30,000 per QALY (converted figures).²

6.2.1.2. Primary health economic evaluation by Dretzke et al.

The objective of this cost-effectiveness analysis was to estimate the incremental cost per QALY between (a) standard care, (b) induction therapy and (c) maintenance therapy for moderate and for severe CD. The time horizon for the Markov model developed from an NHS/PSS perspective was 1 year (with sensitivity analyses of 5, 10 and 20 years) and the cycle duration was 4 weeks, i.e. the model had 13 cycles and did not include mortality. Both the induction and maintenance model started with a cohort of patients suffering from a standard care refractory relapse. In the model at any time and on any given treatment, a patient was in remission, in relapse, undergoing surgery or in post-surgery remission. Utilities calculated as 1/13 of quality of life values from Gregor et al.

Effectiveness for infliximab and adalimumab treatment were derived from ACCENT I and CHARM, respectively. For infliximab treatment, induction (infliximab IND) involved a loading dose comprising treatment at 0, 2 and 6 weeks at 5 mg/kg (a loading dose) irrespective of response status at 4 weeks. Infliximab maintenance treatment (infliximab MNT) also involved the same treatment at 0, 2 and 6 weeks, but with additional doses at weeks 14 and 20 and every subsequent 8 weeks for those entering remission (except in the case of subsequent relapse). Adalimumab induction (adalimumab IND) involved a loading dose of 80 mg at week 0 and 40 mg at week 2, with no further treatment. Adalimumab maintenance (adalimumab MNT) involved the induction loading doses at weeks 0 and 2, with additional doses of 40 mg at weeks 4 and 6 regardless of response at week 4 (i.e. in either MNT remission or MNT relapse 2).

Total costs for each state were defined by drug costs (fixed) plus the costs for the corresponding standard care state (drawn from the relevant distribution). Non-hospitalisation medical costs were not included in the model except in the administration of infliximab.

For patients with severe disease, infliximab induction treatment was found to be cost-effective relative to maintenance treatment and standard care in over 99% of cases at all points up to £100,000/QALY. Likewise, adalimumab induction treatment was found to be cost-effective relative to maintenance treatment and standard care for thresholds up to £100,000/QALY (ICERs for severe CD: infliximab MNT £5.03M/QALY, adalimumab £4.98M/QALY, ICERs for moderate CD: infliximab MNT £13.9M/QALY, adalimumab MNT £13.9M/QALY).

6.2.2. Analysis of the articles revealed by the additional search

Kaplan et al., US (2007)⁴³

This study compared the cost-utility of two treatments of CD, the infliximab dose escalation strategy and adalimumab strategy, respectively. Although infliximab has proven to be an effective medication for patients with moderate to severe CD, loss of response to the 5 mg/kg dose is a common occurrence. After drug response is lost, the dose of infliximab is typically escalated to 10 mg/kg and/or the interval of administration is reduced. As for adalimumab, it offers an effective and safe option for infliximab failures.

Regarding the results, infliximab dose escalation strategy resulted in greater QALYs per patients than the adalimumab strategy (0.79 QALY per patient vs. 0.76 QALY per patient). The infliximab dose escalation strategy cost is \$28 367 per patient vs. \$18 074 per patient for a net difference of \$10 293. The resulting ICER of the infliximab dose escalation strategy vs. the switch to adalimumab therapy was \$332 032/QALY.

According to sensitivity analysis, the infliximab dose escalation strategy yielded more QALYs unless:

- the initial response rate for infliximab was below 31%
- the rate of remission for infliximab dose escalation at 1 year was <13%
- the mortality rate of infliximab was >4.8%
- the remission at 1 year for patients receiving non-anti TNF- α therapy exceeded 59%
- the proportion of patients receiving non-anti TNF- α therapy who required surgery was more than 57%

At these threshold values, the adalimumab strategy dominated the infliximab dose escalation strategy.

The ICER was below \$80 000/QALY when the mortality rate for adalimumab was above 28%. Otherwise, altering the estimate parameters for adalimumab, infliximab or non-anti TNF- α therapy response did not produce an ICER lower than \$80 000/QALY.

The most important factor that influenced the ICER was the drug cost for infliximab and adalimumab. When the average wholesale price of adalimumab was increased nearly three times its cost (\$1602 per 40 mg dose), the infliximab dose escalation strategy dominated both in cost and in effectiveness. In contrast, when the average wholesale price of infliximab for a 70 kg patient dosed at 10 mg/kg was reduced nearly by half (\$2498), the infliximab strategy was dominant. A decrease in cost by 33% (\$3055) yielded an ICER that was below \$80 000/QALY.

The decision analysis found that dose escalating infliximab prior to starting adalimumab yielded an excess of 0.03 QALY/patient. However, the cost to achieve this benefit was considerable.

Lindsay et al., UK (2008)⁴⁸

The purpose of this analysis was to assess the cost-effectiveness of infliximab scheduled maintenance treatment at the licensed dose of 5 mg/kg compared with standard care without infliximab, for the treatment of patients with active luminal CD or fistulising CD over a 5-year time frame.

As for the results, in active luminal CD, scheduled maintenance therapy with infliximab derived a mean additional 0.19 QALYs at an additional cost of £4873 compared with standard care without infliximab. Therefore, the ICER gained for infliximab against standard care, was £26 128. In fistulising CD, scheduled maintenance treatment with infliximab resulted in an additional 0.20 QALY at an additional cost of £5998 compared to standard care without infliximab. The estimated ICER gained was £29 752 in fistulising CD.

One-way sensitivity analysis was performed and results showed that patient weight and health state preferences had significant impact on ICERs. Because of the weight-based dosing of infliximab, patient weight had the greatest impact on the ICER with increasing of it to £38 848 in luminal CD and £44 206 in fistulising CD for an 80-kg patient. The change in health state preferences had the most significant impact on improving the ICERs with a 10%

increase in utilities resulting in an ICER of £23 752 in luminal CD and £27 047 in fistulising CD. The impact of the other parameters analyzed like patient age, time horizon, discount rate and administration cost of infliximab was less prominent. The one-way sensitivity analysis showed that results remained in the range of £23 752-£38 848 at 5 years for active luminal CD and £27 047-£44 206 at 5 years for fistulising CD.

The study showed that, infliximab was a highly effective and well-tolerated therapy for the management of moderate-to-severe and fistulising adult CD patients, and provided a significant clinical benefit over standard care. The economic analysis demonstrated that the incremental costs associated with achieving these clinical benefits are reasonable and that scheduled maintenance therapy with infliximab represented a cost-effective treatment option.

Bodger et al., UK (2009)⁸

The aim of the study was to assess the cost-effectiveness of infliximab and adalimumab for CD from the perspective of the UK NHS, incorporating recent trial and observational data. A Markov model was used to estimate the lifetime costs and effectiveness of infliximab and adalimumab in adult patients with moderate to severely active CD.

The model was developed to compare infliximab (5 mg/kg intravenous infusions at weeks 0, 2 and 6 for the induction of remission; then 8-weekly for maintenance of clinical remission) and adalimumab (80 mg subcutaneously at week 0, 40 mg at week 2 for the induction of remission; then 40 mg on alternate weeks for maintenance of remission), with standard care. These reflect the licensed regimens recommended for the management of adult CD in the UK. As for the results, the mean cost associated with standard care was £43 490. The model predicted patients experience 14.209 QALYs with standard care. With 1-year maintenance treatment for initial responders to infliximab, the cost increased to £50 330 with associated 14.568 QALYs. The resulting ICER vs. standard care is £19 050/QALY gained. The main cost increase of extending treatment to 2-years was £7900, for 0.333 additional QALYs. Compared with standard care, the ICER for 2 years of infliximab was £21 300/QALY gained. One year of therapy with adalimumab for initial responders to treatment costs £46 730, but resulted in 14.682 QALYs. Compared with standard care, this produced an ICER of £7190 per additional QALY gained. Two years' therapy with adalimumab cost additional £6360 and

produced 0,474 more QALYs. Compared with standard care, the ICER was £10 310. ICERs fell below the £30 000/QALY threshold for cost-effectiveness in the United Kingdom.

On the basis of the available evidence on the effectiveness of maintenance anti-TNF- α therapy the study showed that when compared with standard therapy both infliximab and adalimumab might represent a cost-effective use of healthcare resources when used for limited durations (e.g. up to 4 years) in initial responders. In contrast, lifelong therapy with either agent did not appear cost-effective.

Loftus et al., UK (2009)⁵⁰

This study evaluated the cost-effectiveness of adalimumab versus conventional, non-biologic pharmacotherapies in the maintenance of CD. The analysis was conducted from the perspective of the social decision maker considering the treatment options for a patient with moderate to severe or severe, active CD.

The authors modelled an intention-to-treat perspective, including initial responders and nonresponders because a decision maker did not know ex-ante whether a patient would respond to adalimumab or not.

The base case results indicated that hospitalization and nonhospitalization medical costs were substantially less for adalimumab therapy than for conventional, non-biologic therapies for patients with moderate-to-severe disease. The incremental cost of adalimumab therapy was £3046 greater than the cost of conventional, non-biologic therapy, including £3229 offset hospitalization costs and £798 offset nonhospitalization medical costs. Similarly, for patients with severe CD, the incremental cost of adalimumab therapy was £1890, including a hospitalization cost reduction of £5001 and nonhospitalization cost reduction of £1002. Average QALYs for adalimumab-treated severe CD-patients were 0.8516, compared with 0.7339 for conventional, non-biologic-treated patients, resulting in an incremental increase in QALYs of 0.1177 for patients with severe CD. The comparable incremental difference was 0.0903 for moderate-to-severe CD, also indicating additional QALYs with adalimumab therapy. The expected ICER was £33 731 for patients with moderate-to-severe CD and £16 064 for patients with severe CD.

The 1-year, base case cost-effectiveness model was extended to a lifetime model. Sensitivity analyses showed that in the lifetime model adalimumab patients were expected to continue on the drug for a median time of 7.6 years; the incremental increase in QALYs was 0.7801 for adalimumab-treated patients with severe CD and 0.5921 for moderate-to severe CD. The incremental costs were £5110 for patients with severe CD and £10 582 for moderate-to severe CD patients. The lifetime model estimated an ICER of £6550 per patient with severe CD and £17 873 per patient with moderate-to-severe CD. So the model results for patients with moderate-to-severe CD were more sensitive to the one-way sensitivity tests than the results for severe-only patients.

The results suggested that adalimumab maintenance therapy was somewhat cost-effective for patients with moderate-to-severe CD and very cost-effective for those with severe CD when compared with non-biologic pharmacotherapies.

Yu et al., US (2009)⁹⁰

The purpose of this study was to evaluate and compare the cost-effectiveness of adalimumab and infliximab maintenance therapies for patients with moderate-to-severe CD by employing results from the ACCENT I and CHARM studies. Specifically, the authors modelled a physician's decision to treat a patient with moderately to severely active CD who is a candidate for anti-TNF maintenance therapy in an intention-to-treat perspective, which included both initial responders and nonresponders.

The article is unique in that it represents a partial but preferable solution to the problem of incomplete data by using primary, patient observational-level data from one-trial and published, point estimated from another.

Regarding the results, patients receiving adalimumab maintenance therapy had expected QALYs of 0.865 compared with 0.851 for infliximab. This corresponded to an incremental increase of 0.014 in utility. Patients receiving infliximab 5 mg/kg maintenance therapy incurred \$4852 greater direct medical costs than patients receiving 40 mg adalimumab over a 56-week period, when the costs of hospitalization and other non-hospital medical resources were taken into consideration. The total incremental cost difference was -\$491 to \$6758 (cost saving).

The probabilistic sensitivity analyses showed that results were in the range of - \$17 500 000/QALY - \$54 298/QALY.

The results of the analysis suggest that adalimumab maintenance therapy in the treatment of CD was a cost-saving strategy versus infliximab maintenance therapy from a US private payer perspective. Given its greater clinical remission rate and substantially lower total costs, adalimumab appeared to dominate infliximab maintenance therapy in terms of both clinical and economic outcomes.

Ananthakrishnan et al., US (2011)¹

This study differs from the above outlined ones in term of the objective. The background of it is that nearly 70% of patients with CD undergo surgical resection, with one-quarter subsequently developing clinical recurrence within 12 months. Several options exist for the prevention of postoperative recurrence in CD, but the comparative cost-effectiveness of these competing strategies had not been previously analyzed.

The authors constructed a decision-tree model comparing various strategies to prevent postoperative recurrence in CD. There were five possible strategies: no treatment, antibiotics, azathioprine, upfront infliximab and tailored infliximab that consisted of no upfront therapy with initiation of infliximab. The base case 1-year clinical recurrence rate was 24% with reduction in recurrence by 41%, 77% and 99% for azathioprine, antibiotics and infliximab, respectively. The analysis was conducted from a third-party payer perspective and included all treatment and health state costs but not indirect costs. QALYs and direct costs were calculated over a 1-year time horizon.

Regarding the results, at the base-case analysis, the antibiotics (0.82 QALYs) and azathioprine (0.81 QALYs) arms were more effective and less expensive than the 'no treatment' strategy (0.80 QALYs). The most effective strategy was upfront infliximab (0.83 QALY); however, this was also the most expensive and resulted in a high ICER of \$777 732/QALY compared with 'no treatment'. The tailored infliximab arm was less effective than upfront use but had a more acceptable ICER. On increasing the recurrence rate to 78% (high-risk patients), upfront infliximab resulted in 0.07 QALYs (ICER of

\$130 580/QALY) gained compared with ‘no treatment’, where antibiotics, azathioprine and tailored infliximab arms dominated ‘no treatment’.

The study showed that use of antibiotics was the most cost-effective strategy to prevent postoperative recurrence. However, widespread use is precluded by high rates of intolerance and therapy cessation. Upfront infliximab use is the most efficacious strategy however routine use was not cost-effective across a wide range of recurrence rates. Tailoring infliximab use to patients with high risk of recurrent disease appeared to be a more cost-effective approach.

Assasi et al. (2009)³ and Blackhouse et al. (2012), Canada⁷

Assasi et al. launched an HTA in 2009 including a health economic assessment of biological therapies for CD.³ Results were also published in a peer-reviewed journal in 2012 by Blackhouse et al.⁷

The aim of the HTA was to evaluate the comparative clinical-effectiveness of anti-TNF- α drugs in patients with CD or UC with an inadequate response to conventional therapy and to determine the economic value of anti-TNF- α drugs compared with that of conventional therapy (5-aminosalicylic acid derivatives, immunosuppressant drugs, corticosteroids) and surgical interventions. We focus on CD results here.

Systematic literature search was undertaken for economic studies (search was updated and closed in September 2008). Regarding CD, seven health economic studies were revealed for this time period.^{2, 10, 21, 42, 43, 48, 52} These were coincident with results of the review by Dretzke et al. and our search for this time period confirming the validity of the search strategy applied.

They performed a de novo health economic assessment as well. A cost-utility analysis was conducted using a Markov model for CD patients refractory to conventional non-anti-TNF- α therapy with a CDAI of ≥ 200 . The time horizon in base case was 5 years. The cohort is assumed to be 37 years old and to weigh 73 kg. These assumptions were based on baseline data from the active treatment arms of anti-TNF- α induction trials. Three CD treatment strategies were compared in the model: usual care (corticosteroids, immunosuppressants), infliximab induction and maintenance, and adalimumab induction and maintenance. Infliximab induction therapy was assumed to include infusions of 5 mg/kg at weeks 0, 2, and 6. Infliximab maintenance therapy was assumed to include infusions of 5 mg/kg every eight

weeks. Adalimumab induction therapy was assumed to include a 160 mg subcutaneous injection at week 0 and an 80 mg subcutaneous injection at week 2. Maintenance therapy was assumed to include 40 mg subcutaneous injections every two weeks. The analysis was taken from the perspective of the publicly funded health care system.

The infliximab strategy had the highest expected costs, whereas the usual-care arm had the lowest expected costs. The costs for the usual care, adalimumab, and infliximab strategies were \$54,084, \$45,480, and \$17,107 respectively. Usual care had the lowest expected QALYs. Infliximab had the highest expected QALYs, though the QALYs for infliximab and adalimumab were nearly identical. Estimated QALYs for the usual care, adalimumab, and infliximab strategies were 2.721, 2.701, and 2.555 respectively. There was little difference in QALYs between adalimumab and infliximab. This may be surprising given that the use of infliximab led to higher initial remission and response rates. The use of adalimumab led to lower relapse rates. This means that patients retained longer benefit from the use of adalimumab compared with that of infliximab. The cost-utility of adalimumab compared with usual care is estimated to be \$193,305/QALY. The ICER of infliximab compared with adalimumab is estimated to be \$451,165/QALY. Based on these findings, usual care is the most cost-effective strategy, if a decision maker's willingness to pay for a QALY was less than \$193,305. Adalimumab is the most cost-effective strategy if willingness to pay for a QALY is between \$193,305 and \$451,164, whereas infliximab is cost-effective if willingness to pay for a QALY is \$451,165 or higher. The ICER of infliximab compared directly with usual care is \$222,955.

6.3. Discussion, conclusions

Cost-utility analysis of adalimumab and/or infliximab treatment for CD were performed in the UK (n=5), US (n=4), Canada (n=2) and France (n=1). There were no cost-utility studies from Eastern Central European countries according to our international literature search.

Six studies considered infliximab, five adalimumab and infliximab, and one adalimumab treatment. Studies were performed from the third party payer (publicly funded health care

system) perspective. The time horizon was 1-year (n=7), 5-year (n=2), lifetime (n=2) and was not specified in one. Data on effectiveness of adalimumab and infliximab were mostly derived from randomized controlled trials (ACCENT, CHARM). Various sources were incorporated to estimate utility values.

Comparators varied between studies. Infliximab was the first anti-TNF- α inhibitor registered for the treatment of CD thus it was compared to standard care (medical treatment) in the US (2001)², Canada (2002)⁵², France (2004)⁴² and UK (2008)⁴⁸. Another analysis from the UK (2003)¹⁰ compared infliximab to placebo treatment. One specific study in the US (2011)¹ analysed the cost-utility of five different treatments including two infliximab strategies for the prevention of recurrence after surgical resection: no treatment, antibiotics, azathioprine, upfront infliximab and tailored infliximab (that consisted of no upfront therapy with initiation of infliximab).

Adalimumab was compared to standard care in the UK (2009)⁵⁰. Both infliximab and adalimumab were compared to standard care in two other studies from the UK (2009, 2011)^{8, 22} and Canada (2012)⁷. Comparison of maintenance treatment with infliximab and adalimumab was analysed in the US (2009)⁹⁰ and dose escalation of infliximab versus switching to adalimumab was assessed also in the US (2007)⁴³.

Regarding the results, the comparison of cost-effectiveness results across studies is problematical. Differences in comparators, methods, data, modelling approach prevent reliable interpretation of the results of such comparisons thus it is not possible to draw definitive conclusions. Nevertheless, available cost-utility suggest that infliximab does not seem to be a cost-effective treatment when compared to standard care in CD whilst adalimumab has higher probability of being cost-effective. Adalimumab treatment is likely to dominate infliximab. However sensitivity analyses pointed out that results are highly sensitive to drug prices and patient weight. With a sufficiently large price reduction it suggested that infliximab treatment may have become cost-effective. Also, while the indirect productivity costs of non-treatment may be appreciable in CD, these costs were not included in the cost-effectiveness studies owing to a lack of evidence as to their magnitude.

Transferability of cost-utility results from the US and Canada, or even from the UK and France to Central and Eastern European jurisdictions is rather limited. These countries differ considerably in many aspects that might have significant impact on the results (e.g. GDP per capita, health and social care systems, demography, morbidity, health status of the given patient population, comparator medications, standard practice, prescription behaviours, reimbursement mechanisms and financing). On the other hand, considering the noticeable limitations in terms of health technology assessment capacity in the Central and Eastern European region it is essential to find out how these published results can be used. Managed transferability seems to be crucial for sustainable financing of biological medications for CD in Central and Eastern

Table 9 Summary of cost-utility evidence identified, search 2007-2012

Data	Kaplan et al., US (2007) ⁴³	Lindsay et al., UK (2008) ⁴⁸	Bodger et al., UK (2009) ⁸	Loftus et al., UK (2009) ⁵⁰
Perspective	not stated (direct costs were considered)	UK National Health Service	UK National Health Service	UK National Health Service
Comparators	infliximab (dose escalation) and adalimumab	infliximab scheduled maintenance therapy, standard care comprising immunomodulators and/or corticosteroids	infliximab, adalimumab, standard care	adalimumab maintenance therapy vs. nonbiologic pharmacotherapies

Data	Kaplan et al., US (2007) ⁴³	Lindsay et al., UK (2008) ⁴⁸	Bodger et al., UK (2009) ⁸	Loftus et al., UK (2009) ⁵⁰
Model structure	Decision analysis model. Response rate according to CDAI. 1-year time horizon	Markov model Response according to CDAI, 5-year time-horizon, the cycle lengths were selected to match the assessment visits in the ACCENT I and II trials	Markov model incorporating four health states: full response, partial response, nonresponse, surgery and death. Response according to CDAI. Lifetime horizon.	Regression model. Response according to CDAI, 1-year time-horizon

Data	Kaplan et al., US (2007) ⁴³	Lindsay et al., UK (2008) ⁴⁸	Bodger et al., UK (2009) ⁸	Loftus et al., UK (2009) ⁵⁰
Patient inputs	A hypothetical cohort of 35-year-old patients with moderate to severely active CD who achieved remission following induction by 5 mg/kg of infliximab at weeks 0, 2 and 6 but lost their response during maintenance therapy dosed every 8 weeks	Patient characteristics based on standard treatment protocols and ACCENT trial	Characteristics: 35-40 years of age, 40% men, at least 3 months since confirmed diagnosis of CD, CDAI score above 220.	Baseline patient characteristics from the CHARM study.
Sources of effectiveness evidence	Trials: GAIN, CHARM, ACCENT 1.	Luminal active CD: effectiveness from Targan et al. ACCENT I, Fistulising active CD: effectiveness from Present et al. ACCENT II	Effectiveness of adalimumab and infliximab from ACCENT I and CHARM trials.	Effectiveness of adalimumab arm based on the CHARM study.

Data	Kaplan et al., US (2007) ⁴³	Lindsay et al., UK (2008) ⁴⁸	Bodger et al., UK (2009) ⁸	Loftus et al., UK (2009) ⁵⁰
Sources of cost data	<p>The average wholesale prices for adalimumab and infliximab obtained from the 2006 Drug Topics Red Book.</p> <p>Additional costs of an infusion estimated from the American Medical Association Current Procedural Terminology code.</p> <p>Monthly costs for non-anti-TNF management derived from a Markov model</p>	<p>Drug costs based on NICE guidance.</p> <p>The cost of surgical interventions was estimated on the basis of data published in the NHS National Schedule of Reference Cost (NSRC).</p> <p>The cost of hospitalization and other assessments was adapted from the Jewell study.</p>	<p>Mean health state costs based on UK dataset. Unit costs of the biologic agents were taken from the British National Formulary.</p>	<p>Medical costs taken from Bassi et al.</p>

Data	Kaplan et al., US (2007) ⁴³	Lindsay et al., UK (2008) ⁴⁸	Bodger et al., UK (2009) ⁸	Loftus et al., UK (2009) ⁵⁰
Utilities	<p>Gregor et al. study was used to estimate utilities for CD states.</p> <p>A standard gamble approach was used to define utility scores and correlate them with the CDAI.</p>	<p>EQ-5D utility scores were used in the cost-effectiveness analysis. These based on published data from Casellas et al.</p>	<p>EQ-5D utility score was calculated from mid-point CDAI scores, based on the algorithm developed by Buxton et al.</p>	<p>Primary standard gamble-calculated data were used to derive health-utility estimates</p>
Discount rate	-	3.5%	3.5%	3.5%

Data	Kaplan et al., US (2007) ⁴³	Lindsay et al., UK (2008) ⁴⁸	Bodger et al., UK (2009) ⁸	Loftus et al., UK (2009) ⁵⁰
Base case results	<p>Infliximab dose escalation strategy: 0.79 QALYs at a cost of \$28 357 per patient; Adalimumab strategy: 0.76 QALYs at a cost of \$18 074 per patient.</p> <p>The ICER of the infliximab dose escalation strategy was \$332 032/QALY compared to the switch to adalimumab therapy.</p>	<p>Active luminal CD: scheduled maintenance therapy with infliximab derived 2.145 QALYs at a cost of £31 499.</p> <p>Fistulising CD: scheduled maintenance therapy with infliximab derived 2.449 QALYs at a cost of £37 488.</p> <p>The ICER was £26 128/QALY and £29 752/QALY for infliximab in luminal CD and in fistulising CD, respectively compared with standard care without infliximab.</p>	<p>Standard care: 14.209 QALY at a cost of £43 490.</p> <p>Infliximab - 1 year: 14.568 QALYs at a cost of £50 330. This produced an ICER of £19 050/QALY compared with standard care.</p> <p>Infliximab - 2 years: 14.901 QALYs at a cost of £58 230.</p> <p>This gave an ICER of £21 300/QALY compared with standard care.</p> <p>Adalimumab 1-year: 14.682 QALYs at a cost of £46 730. This produced an ICER of £7190/QALY compared with standard care.</p> <p>Adalimumab 2-years: 15.156 QALYs at a cost of 53 090.</p> <p>This gave an ICER of £10 310/QALY compared with standard care</p>	<p>Patients with severe CD:</p> <p>Adalimumab: 0.8516 incremental QALY at an incremental cost of £10 882.</p> <p>Non-biologic: 0.7339 incremental QALY at an incremental cost of £8992</p> <p>This produced an ICER of 16 064/QALY for adalimumab compared with non-biologic treatment.</p> <p>Patients with moderate-to-severe CD:</p> <p>Adalimumab: 0.8647 incremental QALY at an incremental cost of £9696.</p> <p>Non-biologic: 0.7743 incremental QALY at an incremental cost of £6649.</p> <p>This gave an ICER of 33 731/QALY for adalimumab compared with non-biologic treatment.</p>

Data	Kaplan et al., US (2007) ⁴³	Lindsay et al., UK (2008) ⁴⁸	Bodger et al., UK (2009) ⁸	Loftus et al., UK (2009) ⁵⁰
Key sensitivity analysis	Results were sensitive to the adalimumab mortality rate and the cost of infliximab and adalimumab.	Results were sensitive to many of the changes in parameters, in particular patient weight and health state preferences.	Results were sensitive to the duration of treatment and the analytic time horizon.	Results were sensitive to time horizon and costs.

Table 10 Summary of cost-utility evidence identified, search 2007-2012 (continuation)

Data	Yu et al., US (2009) ⁹⁰	Ananthakrishnan et al., US (2011) ¹	Blackhouse et al., Canada (2012) ⁷ and Assasi et al, Canada (2009) ³
Perspective	private payer	third-party payer	publically funded health care system
Comparators	adalimumab vs. infliximab	no treatment, azathioprine, antibiotics, upfront infliximab and tailored infliximab	infliximab, adalimumab, usual care
Model structure	Regression model Response according to CDAI. 1-year time-horizon	Decision tree model, 1-year time horizon	Markov model, time horizon 5 years, first cycle 12 weeks, subsequent cycles 8 weeks

Data	Yu et al., US (2009) ⁹⁰	Ananthakrishnan et al., US (2011) ¹	Blackhouse et al., Canada (2012) ⁷ and Assasi et al, Canada (2009) ³
Patient inputs	Patients with moderately to severely active CD who are candidates for anti-TNF- α maintenance therapy in an intention-to-treat perspective, included both initial responders and nonresponders.	A hypothetical cohort of 35-year-old patients who were in surgical remission after their first ileocolic resection.	adult CD patients refractory to conventional non-anti-TNF- α therapy with a CDAI ≥ 200 ; the model cohort is assumed to be 37 years of age and weighting 73 kg
Sources of effectiveness evidence	Effectiveness of adalimumab and infliximab from ACCENT I and CHARM trials.		Tagran et. al. trial 1997, ACCENT I (infliximab); Classic 1 trial, CHARM trial (adalimumab); placebo arms presented the 'usual care' strategy; GAIN trial (second line anti-TNF- α treatment)

Data	Yu et al., US (2009) ⁹⁰	Ananthakrishnan et al., US (2011) ¹	Blackhouse et al., Canada (2012) ⁷ and Assasi et al, Canada (2009) ³
Sources of cost data	Cost estimates based on Cohen et al., Feagan et al. and Hay and Hay.	<p>Drug costs obtained from the 2010 Drug Topics Red Book. Infusion costs derived from a previous decision model.</p> <p>The monthly costs of remission of active disease obtained from median costs from a recent analysis by Malone et al.</p> <p>The cost of surgery obtained from a previous Markov analysis.</p>	anti-TNF- α treatment, maintenance anti-TNF- α treatment, non anti-TNF- α outpatient medications, and surgery costs were considered; official price lists were used
Utilities	Standard gamble-calculated primary data were used to derive health-utility estimates	Health utility values for the health states obtained from the analysis by Lindsay et al.	average utilities: mild CD 0.82, moderate CD 0.73, severe CD 0.54, remission 0.82, drug responsive 0.73, drug refractory 0.54, surgical remission 0.82, surgery health state 0.54.
Discount rate	-	-	5.0%

Data	Yu et al., US (2009) ⁹⁰	Ananthakrishnan et al., US (2011) ¹	Blackhouse et al., Canada (2012) ⁷ and Assasi et al, Canada (2009) ³
Base case results	<p>Adalimumab: 0.865 QALYs at a cost of \$34 193</p> <p>Infliximab: 0.851 QALYs at a cost of \$39 045.</p>	<p>antibiotics: 0.8209 QALY at a cost of \$2,840.</p> <p>azathioprine: 0.814 QALY at a cost of \$3,218.</p> <p>Untreated: 0.805 QALY at a cost of \$3,924.</p> <p>Tailored infliximab: 0.8206 QALY at a cost of \$8,030.</p> <p>These strategies were eliminated.</p> <p>Upfront infliximab: 0.828 QALY at a cost of \$22 145.</p> <p>This gave an ICER of \$2,757,857/QALY for upfront infliximab compared with antibiotics.</p>	<p>usual care: \$17,017, 2.555 QALYs; adalimumab \$45,480, 2.701 QALYs; infliximab \$54,084, 2.721 QALYs. ICER: moving from usual care to adalimumab \$193,305/QALY, and from adalimumab to infliximab \$451,165/QALY.</p>

Data	Yu et al., US (2009) ⁹⁰	Ananthakrishnan et al., US (2011) ¹	Blackhouse et al., Canada (2012) ⁷ and Assasi et al, Canada (2009) ³
Key sensitivity analysis	Results were sensitive to hospitalization and other medical service unit costs, rates of hospitalization and excess uninfused infliximab and TNF- α antagonist.	Results were sensitive to rates of recurrent disease, effectiveness and costs of therapies; the treatment algorithm; utility of the health states and time horizon.	<p>Patient weight 40 kg, ICERs: adalimumab vs. usual care \$172,723/QALY, infliximab vs. adalimumab \$221,722/QALY.</p> <p>Patient weight 90 kg, ICERs: adalimumab vs. usual care \$213,866/QALY, infliximab vs. adalimumab \$681,022/QALY.</p> <p>Discount rate has little effect.</p> <p>If the cost of infliximab and adalimumab is assumed to be 50% lower than in the base case the cost per QALY of adalimumab compared to usual care becomes \$86,242 while the cost per QALY of infliximab compared to adalimumab becomes \$212,970.</p>

Table 11 Quality assessment of the health economic evaluations by the Drummond checklist, search 2007-2012

✓ or X or NA (not applicable)

Checklist	Kaplan et al., US (2007) ⁴³	Lindsay et al., UK (2008) ⁴⁸	Bodger et al., UK (2009) ⁸	Loftus et al., UK (2009) ⁵⁰	Yu et al., US (2009) ⁹⁰	Ananthakrishnan et al., US (2011) ¹	Blackhouse et al., Canada (2012) ⁷ (Assasi et al., 2009 ³);
<i>Research question</i>							
1. Costs and effects examined <input type="checkbox"/>	✓	✓	✓	✓	✓	✓	✓
2. Alternatives compared ×	✓	✓	✓	✓	✓	✓	✓
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	X	✓	✓	✓	X	✓	✓
<i>Selection of alternatives</i>							

Checklist	Kaplan et al., US (2007) ⁴³	Lindsay et al., UK (2008) ⁴⁸	Bodger et al., UK (2009) ⁸	Loftus et al., UK (2009) ⁵⁰	Yu et al., US (2009) ⁹⁰	Ananthakrishnan et al., US (2011) ¹	Blackhouse et al., Canada (2012) ⁷ (Assasi et al., 2009 ³);
4. All relevant alternatives are compared (including 'do nothing' if applicable)	✓	✓	✓	X (infliximab was not considered)	✓	✓	✓
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	✓	✓	✓	✓	✓	✓
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	✓	✓	X	X	✓	✓

Checklist	Kaplan et al., US (2007) ⁴³	Lindsay et al., UK (2008) ⁴⁸	Bodger et al., UK (2009) ⁸	Loftus et al., UK (2009) ⁵⁰	Yu et al., US (2009) ⁹⁰	Ananthakrishnan et al., US (2011) ¹	Blackhouse et al., Canada (2012) ⁷ (Assasi et al., 2009 ³);
<i>Form of evaluation</i>							
7. The choice of form of economic evaluation is justified in relation to the questions addressed	X	X	X	X	X	X	✓
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	NA (cost-utility analysis)	NA (cost-utility analysis)	NA (cost-utility analysis)	NA (cost-utility analysis)	NA (cost-utility analysis)	NA (cost-utility analysis)	NA (cost-utility analysis)
<i>Effectiveness data</i>							

Checklist	Kaplan et al., US (2007) ⁴³	Lindsay et al., UK (2008) ⁴⁸	Bodger et al., UK (2009) ⁸	Loftus et al., UK (2009) ⁵⁰	Yu et al., US (2009) ⁹⁰	Ananthakrishnan et al., US (2011) ¹	Blackhouse et al., Canada (2012) ⁷ (Assasi et al., 2009 ³);
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	✓	✓	✓	✓	✓	✓
10. Effectiveness data from RCT or review of RCTs	✓	✓	✓	✓	✓	X (partly)	✓
11. Potential biases identified (especially if data not from RCTs)	✓	✓	✓	✓	✓	X	✓

Checklist	Kaplan et al., US (2007) ⁴³	Lindsay et al., UK (2008) ⁴⁸	Bodger et al., UK (2009) ⁸	Loftus et al., UK (2009) ⁵⁰	Yu et al., US (2009) ⁹⁰	Ananthakrishnan et al., US (2011) ¹	Blackhouse et al., Canada (2012) ⁷ (Assasi et al., 2009 ³);
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	X	X	X	✓	X	X	✓
Costs							
13. All of the important and relevant resource use included	X (only direct costs)	X (only direct costs)	X (only direct costs)	✓	X (only direct costs)	X (only direct costs)	X (only direct costs)
14. All of the important and relevant resource use measured accurately (with methodology)	✓	X	✓	X	✓	X	✓

Checklist	Kaplan et al., US (2007) ⁴³	Lindsay et al., UK (2008) ⁴⁸	Bodger et al., UK (2009) ⁸	Loftus et al., UK (2009) ⁵⁰	Yu et al., US (2009) ⁹⁰	Ananthakrishnan et al., US (2011) ¹	Blackhouse et al., Canada (2012) ⁷ (Assasi et al., 2009 ³);
15. Appropriate unit costs estimated (with methodology)	X	✓	✓	X	✓	✓	✓
16. Unit costs reported separately from resource use data	NA	✓	X	NA	✓	X	✓
17. Productivity costs treated separately from other costs	NA	NA (only direct costs were considered)	NA (only direct costs were considered)	X	NA (only direct costs were considered)	NA (only direct costs were considered)	NA (only direct costs were considered)

Checklist	Kaplan et al., US (2007) ⁴³	Lindsay et al., UK (2008) ⁴⁸	Bodger et al., UK (2009) ⁸	Loftus et al., UK (2009) ⁵⁰	Yu et al., US (2009) ⁹⁰	Ananthakrishnan et al., US (2011) ¹	Blackhouse et al., Canada (2012) ⁷ (Assasi et al., 2009 ³);
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion	✓	✓	✓	✓	✓	✓	X (year was not provided)
<i>Benefit measurement and valuation</i>							
19. The primary outcome measure(s) for the economic evaluation	✓	✓	✓	✓	✓	✓	✓

Checklist	Kaplan et al., US (2007) ⁴³	Lindsay et al., UK (2008) ⁴⁸	Bodger et al., UK (2009) ⁸	Loftus et al., UK (2009) ⁵⁰	Yu et al., US (2009) ⁹⁰	Ananthakrishnan et al., US (2011) ¹	Blackhouse et al., Canada (2012) ⁷ (Assasi et al., 2009 ³);
20. Methods to value health states and other benefits are stated	✓	✓	✓	✓	✓	✓	✓
21. Details of the individuals from whom valuations were obtained are given	✓	✓	✓	✓	✓	✓	✓
<i>Decision modelling</i>							
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	✓	✓	✓	✓	✓	✓

Checklist	Kaplan et al., US (2007) ⁴³	Lindsay et al., UK (2008) ⁴⁸	Bodger et al., UK (2009) ⁸	Loftus et al., UK (2009) ⁵⁰	Yu et al., US (2009) ⁹⁰	Ananthakrishnan et al., US (2011) ¹	Blackhouse et al., Canada (2012) ⁷ (Assasi et al., 2009 ³);
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	✓	✓	✓	✓	✓	✓
24. All model outputs described adequately	✓	✓	✓	✓	✓	✓	✓
<i>Discounting</i>							
25. Discount rate used for both costs and benefits	X (1-year horizon, no discount)	✓	✓	✓	X (1-year horizon, no discount)	X (1-year horizon, no discount)	✓

Checklist	Kaplan et al., US (2007) ⁴³	Lindsay et al., UK (2008) ⁴⁸	Bodger et al., UK (2009) ⁸	Loftus et al., UK (2009) ⁵⁰	Yu et al., US (2009) ⁹⁰	Ananthakrishnan et al., US (2011) ¹	Blackhouse et al., Canada (2012) ⁷ (Assasi et al., 2009 ³);
26. Do discount rates accord with NHS guidance?	NA	✓	✓	✓	NA	NA	✓ (Canada)
<i>Allowance for uncertainty</i>							
<i>Stochastic analysis of patient-level data</i>							
27. Details of statistical tests and CIs are given for stochastic data	X	X	X	X	✓	✓	X
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs)	✓	✓	✓	✓	✓	✓	X

Checklist	Kaplan et al., US (2007) ⁴³	Lindsay et al., UK (2008) ⁴⁸	Bodger et al., UK (2009) ⁸	Loftus et al., UK (2009) ⁵⁰	Yu et al., US (2009) ⁹⁰	Ananthakrishnan et al., US (2011) ¹	Blackhouse et al., Canada (2012) ⁷ (Assasi et al., 2009 ³);
29. Sensitivity analysis used to assess uncertainty in nonstochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	✓	✓	✓	✓	✓	✓	✓

VII.9. The original (English) version of Bladder Cancer Index (BCI)

Bladder Cancer Index (BCI)

This questionnaire is designed to measure Quality of Life issues in patients with Bladder cancer and/or urinary diversions. In order to help us get the most accurate assessment, it is important that you answer all questions honestly and completely. As with all medical records, **information contained within this survey will remain strictly confidential.**

Name: _____

Hospital Number: _____

Date of Birth: _____

Today's Date Is: _____

Gender: Male Female

Urologist:

URINARY FUNCTION

This section is about your urinary habits. Please consider **ONLY THE PAST 4 WEEKS**.

1. Which of the following do you currently have?
 - Own (native) bladder 1
 - Ileal conduit/ ostomy..... 2
 - Neo-bladder..... 3
 - Continent urinary diversion/catheterizable pouch..... 4
(such as an Indiana, Koch, Miami, Maintz or UCLA pouch)
 - Other: Specify _____ 5

2. **Over the past 4 weeks**, how often did you typically feel the need to empty your bladder, neo-bladder, pouch or external appliance (bag) during the day?
 - More frequently than once an hour 1
 - Once an hour 2
 - Once every 2 hours 3 (Circle one number) 0/ Once every 3-5 hours 4
 - Only once or twice a day 5

3. **Over the past 4 weeks**, how often have you leaked urine while awake and doing your normal activities?
 - Every day 1
 - About once a week..... 2 (Circle one number)
 - Less than once a week..... 3
 - Not at all..... 4

4. **Over the past 4 weeks**, how often have you leaked urine while sleeping?
 - Every day 1
 - About once a week..... 2 (Circle one number)
 - Less than once a week..... 3
 - Not at all..... 4

5. **Over the past 4 weeks**, which of the following best describes your urinary leakage when you are awake?
 - No control whatsoever..... 1
 - Frequent dribbling..... 2 (Circle one number)
 - Occasional dribbling..... 3
 - Total control..... 4

6. **Over the past 4 weeks** , which of the following best describes your urinary leakage when you are sleeping?

- No control whatsoever..... 1
- Frequent dribbling..... 2 (Circle one number)
- Occasional dribbling..... 3
- Total control..... 4

27/

7. How big a problem, if any, has each of the following been for you **during the past 4 weeks?**
(Circle one number on each line)

	<u>No</u> <u>Problem</u>	<u>Very Small</u> <u>Problem</u>	<u>Small</u> <u>Problem</u>	<u>Moderate</u> <u>Problem</u>	<u>Big</u> <u>Problem</u>	
a. Urine leakage causing skin irritation.....	0	1	2	3	4	28/
b. Urine leakage causing body odor.....	0	1	2	3	4	29/
c. Blood in the urine	0	1	2	3	4	30/
d. Pain related to urination, stoma or catheterization.....	0	1	2	3	4	31/

8. How big of a bother, if any, has your bladder, stoma, neo-bladder or catheterizable pouch been for you **during the past 4 weeks?**

- No bother..... 1
- Very small bother..... 2
- Small bother..... 3 (Circle one number)
- Moderate bother..... 4
- Big bother..... 5

32/

9. **Over the past 4 weeks**, how much have difficulties with your bladder, stoma, neo-bladder or catheterizable pouch limited your activities? (Circle one number on each line)

	<u>Not</u> <u>at all</u>	<u>A little</u> <u>bit</u>	<u>Some</u> <u>what</u>	<u>Quite</u> <u>a bit</u>	<u>Very</u> <u>much</u>	
a. Social activities with friends.....	0	1	2	3	4	33/
b. Exercise	0	1	2	3	4	34/
c. Sleep	0	1	2	3	4	35/

BOWEL HABITS

The next section is about your bowel habits and abdominal pain.
Please consider **ONLY THE PAST 4 WEEKS**.

1. How often have you had rectal urgency (felt like I had to pass stool, but did not) **during the past 4 weeks?**

- More than once a day..... 1
- About once a day..... 2
- More than once a week..... 3 (Circle one number)
- About once a week..... 4
- Rarely or never..... 5

36/

2. How often have you had stools (bowel movements) that were loose or liquid (no form, watery, mushy) **during the past 4 weeks?**

- Never..... 1
- Rarely..... 2
- About half the time..... 3 (Circle one number)
- Usually..... 4
- Always..... 5

37/

3. How often have your bowel movements been painful **during the past 4 weeks?**

- Never..... 1
- Rarely..... 2
- About half the time..... 3 (Circle one number)
- Usually..... 4
- Always..... 5

38/

4. How many bowel movements have you had on a typical day **during the past 4 weeks?**

- One or less..... 1
- Two 2
- Three..... 3 (Circle one number)
- Four or more..... 4

39/

5. How big a problem, if any, has each of the following been for you during the past 4 weeks?
(Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Urgency to have a bowel movement	0	1	2	3	4	40/
b. Increased frequency of bowel movements.....	0	1	2	3	4	41/
c. Bloody stools	0	1	2	3	4	42/
d. Rectal/ Abdominal/ Pelvic pain.....	0	1	2	3	4	43/
e. Constipation	0	1	2	3	4	44/

6. Overall, how big a problem have your bowel habits been for you during the past 4 weeks?

Big problem.....	1	
Moderate problem	2	
Small problem.....	3	(Circle one number)
Very small problem.....	4	
No problem.....	5	45/

SEXUAL FUNCTION

The next section is about your sexual function and sexual satisfaction. Many of the questions are very personal, but they will help us understand the important issues that you face every day. Remember, THIS SURVEY INFORMATION IS COMPLETELY CONFIDENTIAL. Please answer honestly about **THE PAST 4 WEEKS ONLY**.

1. How would you rate each of the following during the past 4 weeks? (Circle one number on each line)

	<u>Very</u> <u>Poor</u>	<u>Poor</u>	<u>Fair</u>	<u>Good</u>	<u>Very</u> <u>Good</u>	
a. Your level of sexual desire?.....	1	2	3	4	5	46/
b. Your ability to reach orgasm (climax)?.....	1	2	3	4	5	47/
c. Your level of sensation in the genital area?	1	2	3	4	5	48/
d. Your ability to be sexually aroused?.....	1	2	3	4	5	49/
e. Your ability to have intercourse?.....	1	2	3	4	5	50/

2. Over the past 4 weeks, how often did you have any sexual activity?

Not at all.....	1					
Less than once a week.....		2				
About once a week.....			3		(Circle one number)	51/
More than once a week.....			4			

3. Over the past 4 weeks, how often have you had pain related to intercourse?

Never.....	1					
Seldom		2				
Not often.....			3		(Circle one number)	52/
Often.....			4			
Very often.....				5		

4. How big a problem, if any, has each of the following been for you during the past 4 weeks? (Circle one number on each line)

	<u>No</u> <u>Problem</u>	<u>Very Small</u> <u>Problem</u>	<u>Small</u> <u>Problem</u>	<u>Moderate</u> <u>Problem</u>	<u>Big</u> <u>Problem</u>	
a. Your level of sexual desire.....	0	1	2	3	4	53/
b. Your ability to have intercourse.....	0	1	2	3	4	54/
c. Your ability to reach orgasm.....	0	1	2	3	4	55/

5. Overall, how would you rate your ability to function sexually **during the past 4 weeks?**

- Very poor..... 1
- Poor..... 2
- Fair..... 3 (Circle one number)
- Good..... 4
- Very good..... 5

56/

6. Overall, how big a problem has your sexual function or lack of sexual function been for you **during the past 4 weeks?**

- No problem..... 1
- Very small problem..... 2
- Small problem..... 3 (Circle one number)
- Moderate problem..... 4
- Big problem..... 5

57/

THANK YOU VERY MUCH!!!

VII.10. The Hungarian version of the BCI

Húgyhólyagrák Index

Ez a kérdőív a húgyhólyagrakkal és/vagy vizelet-eltereléssel élő betegek életminőségének mérésére készült. Ahhoz, hogy a lehető legpontosabb felméréshez jussunk az Ön segítségével, fontos, hogy mindegyik kérdésre őszinte és teljes választ adjon. Ahogy minden egészségügyi adatfelvétel esetében, a **kérdőívben foglalt információk szigorúan bizalmasak maradnak.**

Név: _____

Kórház száma: _____

Születési dátum: _____

Mai dátum: _____

Neme: Férfi Nő

Urológus:

Szerzői joggal védett, 2003 The University of Michigan. Minden jog fenntartva.

VIZELÉSI FUNKCIÓKEz a rész az Ön vizelési szokásairól szól. Kérjük, **CSAK AZ ELMÚLT 4 HETET VEGYE FIGYELEMBE.**

1. Az alábbiak közül Ön melyikkel rendelkezik jelenleg?

- Saját (veleszületett) hólyag 1
 Bélkacs sztóma / hasfali vizeletsztóma 2
 Bélhólyag (bélből képzett újhólyag) 3
 Kontinens vizelet elterelés / katéterezhető sztóma 4
 (mint például Indiana, Koch, Miami, Maintz vagy UCLA tasak)
 Egyéb: részletezze 5

23/

2. **Az elmúlt 4 hét során** milyen gyakran érezte tipikusan annak szükségét, hogy ürítenie kell a húgyhólyagját, bélhólyagját, katéterezhető sztómáját vagy külsőleg felhelyezett zacskóját napközben? (Karikázzon be egy számot!)

- Óránként többször 1
 Óránként egyszer 2
 2 óránként egyszer 3
 3-5 óránként egyszer 4
 Naponta csak egyszer vagy kétszer 5

0/

3. **Az elmúlt 4 hét során**, milyen gyakran volt vizeletszivárgása, mialatt ébren volt, és végezte a szokásos tevékenységeit? (Karikázzon be egy számot!)

- Minden nap 1
 Körülbelül hetente egyszer 2
 Kevesebb mint hetente egyszer 3
 Egyáltalán nem 4

24/

4. **Az elmúlt 4 hét során** milyen gyakran volt vizeletszivárgása, mialatt aludt? (Karikázzon be egy számot!)

- Minden nap 1
 Körülbelül hetente egyszer 2
 Kevesebb mint hetente egyszer 3
 Egyáltalán nem 4

25/

5. **Az elmúlt 4 hétre vonatkozóan** az alábbiak közül melyik jellemzi legjobban az Ön ébrenlét alatti vizeletszivárgását? (Karikázzon be egy számot!)

- Egyáltalán semmilyen kontroll 1
 Gyakori csepegés 2
 Időnkénti csepegés 3
 Teljes kontroll 4

26/

6. Az elmúlt 4 hétre vonatkozóan az alábbiak közül melyik jellemzi legjobban az Ön alvás közbeni vizeletszivárgását? (Karikázzon be egy számot!)

Egyáltalán semmilyen kontroll	1
Gyakori csepegés	2
Időnkénti csepegés	3
Teljes kontroll	4

27/

7. Mekkora problémát jelentettek Önnek az alábbiak (ha egyáltalán bármit is), az elmúlt 4 hét során? (Karikázzon be mindegyik sorban egy számot!)

	<u>Semmilyen probléma</u>	<u>Nagyon kis probléma</u>	<u>Kis probléma</u>	<u>Mérsékelt probléma</u>	<u>Nagy probléma</u>	
a. Bőr-irritációt okozó vizeletszivárgás.....	0	1	2	3	4	28/
b. Testszagot okozó vizeletszivárgás.....	0	1	2	3	4	29/
c. Vér a vizeletben	0	1	2	3	4	30/
d. Vizeléssel, sztómával vagy katéterezéssel összefüggő fájdalom ...	0	1	2	3	4	31/

8. Mekkora kellemetlenséget jelentett Önnek (ha egyáltalán bármit is) a hólyagja, sztómája, bélhólyagja vagy katéterezhető sztómája az elmúlt 4 hét során? (Karikázzon be egy számot!)

Semmilyen kellemetlenség.....	1
Nagyon kis kellemetlenség.....	2
Kis kellemetlenség	3
Mérsékelt kellemetlenség.....	4
Nagy kellemetlenség.....	5

32/

9. Az elmúlt 4 hét során a hólyagja, sztómája, bélhólyagja vagy katéterezhető sztómája okozta nehézségek mennyire korlátozták a tevékenységeiben? (Karikázzon be mindegyik sorban egy számot!)

	<u>Egyáltalán nem</u>	<u>Egy kicsit</u>	<u>Némiképp</u>	<u>Meglehetősen</u>	<u>Nagyon</u>	
a. Barátokkal való társas tevékenység.....	0	1	2	3	4	33/
b. Testmozgás	0	1	2	3	4	34/
c. Alvás	0	1	2	3	4	35/

SZÉKELESI SZOKÁSOK

A következő rész az Ön székelési szokásairól és hasi fájdalomáról szól.
Kérjük, **CSAK AZ ELMÚLT 4 HETET vegye figyelembe!**

1. Milyen gyakran volt sűrű székelési ingere (úgy érezte, mintha székletet kellene ürítenie, de nem) az **elmúlt 4 hét során?** (Karikázzon be egy számot!)

- Több mint naponta egyszer 1
 Körülbelül naponta egyszer 2
 Több mint hetente egyszer 3
 Körülbelül hetente egyszer 4
 Ritkán vagy soha 5

36/

2. Milyen gyakran volt laza vagy folyékony (nem formázott, vizes, pépszerű) széklete (székletürítése) az **elmúlt 4 hét során?** (Karikázzon be egy számot!)

- Soha 1
 Ritkán 2
 Körülbelül az idő felében 3
 Általában 4
 Mindig 5

37/

3. Milyen gyakran volt fájdalmas a székletürítése az **elmúlt 4 hét során?** (Karikázzon be egy számot!)

- Soha 1
 Ritkán 2
 Körülbelül az idő felében 3
 Általában 4
 Mindig 5

38/

4. Hány székletürítése volt egy átlagos napon az **elmúlt 4 hét során?** (Karikázzon be egy számot!)

- Egy vagy kevesebb 1
 Kettő 2
 Három 3
 Négy vagy több 4

39/

5. Mekkora problémát jelentettek Önnek az alábbiak (ha egyáltalán bármit is), az elmúlt 4 hét során? Karikázzon be mindegyik sorban egy számot!

	<u>Semmilyen probléma</u>	<u>Nagyon kis probléma</u>	<u>Kis probléma</u>	<u>Mérsékelt probléma</u>	<u>Nagy probléma</u>	
a. Sürgető székletürítési inger.....	0	1	2	3	4	40/
b. Megnövekedett gyakoriságú székletürítés.....	0	1	2	3	4	41/
c. Véres széklet	0	1	2	3	4	42/
d. Végbél-, hasi-, medence-fájdalom	0	1	2	3	4	43/
e. Székrekedés	0	1	2	3	4	44/

6. Összességében mekkora problémát jelentettek Önnek a székelési szokásai az elmúlt 4 hét során? (Karikázzon be egy számot!)

Nagy probléma.....	1
Mérsékelt probléma.....	2
Kis probléma	3
Nagyon kis probléma	4
Semmilyen probléma	5

45/

SZEXUÁLIS FUNKCIÓK

A következő rész az Ön szexuális működéséről és szexuális elégedettségéről szól. A kérdések közül sok nagyon személyes jellegű, de ezek segítenek nekünk megérteni azokat a fontos kérdéseket, amelyekkel Ön naponta szembesül. Ne feledje, **A KÉRDŐÍVBEN SZEREPLŐ INFORMÁCIÓK TELJESEN EGÉSZÉBEN BIZALMASAK.** Kérjük válaszoljon őszintén, **CSAK AZ ELMÚLT NÉGY HÉTRE VONATKOZÓAN.**

1. Hogyan értékelné az alábbiakat az **elmúlt 4 hétre vonatkozóan**? (Karikázzon be mindegyik sorban egy számot!)

	Nagyon					
	rossz	Rossz	Közepes	Jó	Nagyon jó	
a. Szexuális vágyának szintje	0	1	2	3	4	46/
b. Orgazmus elérésére való képessége (szexuális tetőpont)	0	1	2	3	4	47/
c. Érzékelésének szintje a nemi szervek tájékán	0	1	2	3	4	48/
d. Szexuális izgalomra való képessége.	0	1	2	3	4	49/
e. Közösülésre való képessége	0	1	2	3	4	50/

2. Az **elmúlt 4 hét során** milyen gyakran volt bármilyen szexuális aktivitása? (Karikázzon be egy számot!)

Egyáltalán nem volt.....	1	
Kevesebb mint hetente egyszer	2	51/
Körülbelül hetente egyszer.....	3	
Több mint hetente egyszer.....	4	

3. Az **elmúlt 4 hét során** milyen gyakran volt közösüléssel összefüggő fájdalma? (Karikázzon be egy számot!)

Soha	1	
Ritkán.....	2	
Nem gyakran.....	3	52/
Gyakran	4	
Nagyon gyakran.....	5	

4. Mekkora problémát jelentettek Önnek az alábbiak (ha egyáltalán bármit is), **az elmúlt 4 hét során?** (Karikázzon be mindegyik sorban egy számot!)

	<u>Semmilyen probléma</u>	<u>Nagyon kis probléma</u>	<u>Kis probléma</u>	<u>Mérsékelt probléma</u>	<u>Nagy probléma</u>	
a. Szexuális vágyának szintje	0	1	2	3	4	53/
b. Közösülésre való képessége	0	1	2	3	4	54/
c. Orgazmus elérésére való képessége	0	1	2	3	4	55/

5. Összességében hogyan értékelné a szexuális működésre való képességét **az elmúlt 4 hét során?** (Karikázzon be egy számot!)

Nagyon rossz	1					
Rossz	2					
Közepes	3					56/
Jó	4					
Nagyon jó	5					

6. Összességében mekkora problémát jelentett Önnek a szexuális működése vagy annak hiánya **az elmúlt 4 hét során?** (Karikázzon be egy számot!)

Semmilyen probléma	1					
Nagyon kis probléma	2					
Kis probléma	3					57/
Mérsékelt probléma	4					
Nagy probléma	5					

NAGYON KÖSZÖNJÜK!