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

Ph.D. Dissertation

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Department of Health Economics

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I. Theoretical background and aims of the dissertation

The development of medical technologies has contributed to the growth of health care expenditures as a global tendency (Banta and Luce, [1993]). 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 (Gulácsi [2007]). Accordingly, the criterion of cost-effectiveness has become crucial in reimbursement decisions in most of the countries of the European Union (Gulácsi, [2008]). For the evaluation of new drugs, these are compared to the available ones in terms of incremental costs and incremental health benefits (quality-adjusted life-years, QALYs) (Drummond, [2008]).

The dissertation elaborates three autonomous research questions in the field of health economics, with special focus on cost-effectiveness.

The first research (named **Part II** in the dissertation) is dealing with the German approach to cost-effectiveness analysis in health care that is interpreted in a distinct way compared to other European countries' practice (Pauly et al., [2012]; Jönsson, [2008]). The aim this research was to synthetize the German approach to cost-effectiveness analysis in health care and health technology assessment (HTA) based on the related literature with focusing on points which make the German approach specific. A brief comparison is also made with the HTA systems in Central Eastern European (CEE) countries, among them concentrating mainly on Hungary and some lessons to learn are highlighted and discussed.

The second research **(Part III)** presents a systematic review and analysis of the available evidences regarding the cost-effectiveness of biological drugs in a chronic rheumatic disease (V. Hevér, [2014], In: Péntek, [2014]). 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 (Laki et al. [2013]); (Kozma et al., [2009]). The introduction and continuous development of biologicals speeded up and extended health economic research worldwide; 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]). 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 (Gulácsi et al, [2014]). The aim of this study was to review systematically and analyse the available evidences both on clinical efficacy and cost-effectiveness of biological drugs for the treatment of the chronic debilitating disease of rheumatoid arthritis (RA). In addition, the challenges and opportunities of transferability of cost-utility (cost/QALY) results from other European countries to Hungary are assessed.

The third research **(Part IV)** elaborates an assessment of health related quality of life (HRQoL) and disease related costs in the field of oncology, namely the cancer of the urinary bladder (V. Hevér et al., [2014]). 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]). 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 (Ploeg, Aben and Kiemeney, [2009]). Cost-effectiveness analyses require input data on effectiveness in terms of health gain (considering also the quality of the life years gained, QALY) as well as on disease related costs on the social level (Kobelt, [2013]). For that purpose, appropriate HRQoL measures are required and validated language versions are needed for cross country comparisons. Moreover, in health economic evaluations the link between disease-specific HRQoL measures and health state utility tools is often used to calculate QALYs when preference based HRQoL data are not available (McTaggart et al., [2013]). 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 (Gulácsi et al., [2012]). According to the review of the international literature I have performed in the field of BC, not only in Hungary but in the CEE region in general, there is a scarcity of data reflecting local features from the recent decades and current practices on which health economic models could be built (Brodszky et al., [2010]). Thus, in the Hungarian context collection of local data via a cross-sectional survey is an opportunity to provide local inputs for cost-effectiveness analyses, consequently to support reimbursement-related decision-making.

The third objective of my thesis was, therefore, to perform an empirical study in order to develop and validate the Hungarian language version of a HRQoL questionnaire called Bladder Cancer Index (BCI); and assess the disease burden (HRQoL and cost of illness - CoI) of the Hungarian urinary BC 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-Bl), a generic health state measure (SF-36) and two preference-based utility instruments (EQ-5D and SF-6D) alongside the BCI. Thus the study allowed the analysis of cross-walks between disease-specific HRQoL and health state utility measures in order to assess whether QALYs can be estimated from disease-specific HRQoL results when utility scores are not available. The second main part of the empirical study deals with the estimation of disease burden in the financial sense including cost calculation in the Hungarian context.

Regarding the structure of the dissertation, its body comprises three autonomous publications in accordance with the three research questions introduced above. The first original 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.

II. Methodology

Each of the three Parts of the dissertation is associated with different methodology.

"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 (Health Policy, The European Journal of Health Economics and Value in Health).

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). Both the electronic search and the analysis of the results were performed in a validated, systematic and standardised way. Besides analysing the evidences, the quality assessment of the studies according to a standardized procedure, called Drummond-checklist was also provided (Drummond, [1996]).

In **Part IV**, first a systematic search of PubMed and review of the available literature was performed regarding HRQoL and CoI in BC. In the empirical study with the title of "Challenges in the assessment of disease burden: case study in a chronic disease" both qualitative and quantitative methods were applied which are specified below.

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; 7794-1I2012/EKU) and have therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Questionnaire survey and health related quality of life (HRQoL) 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 a BC-specific FACT-Bl 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.

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). Higher values indicate better HRQoL.

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.

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-Bl, 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-Bl, 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 bother 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-Bl 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 ≥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.

Cost of illness (CoI) in BC

Data regarding cost of illness were derived from two sources: (1) the cross-sectional survey detailed above (2) publicly available databases (National Health Insurance Fund)

(http://www.oep.hu). The following cost items were calculated: a) direct medical costs: one segment of medicines; b) direct non-medical costs: health care related transports, ambulance, informal care (help from others for self-care), social care and c) indirect costs: productivity loss related costs.

III. Main results

III.1. The German approach to cost-effectiveness analysis in health care

Two HTA agencies operate in Germany. Among them, German Agency of Health Technology Assessment (DAHTA) employs operational principles for establishing cost-effectiveness which are consistent with other HTA agencies in Europe whereas Institute for Quality and Efficiency in Health Care's (IQWiG) approach differs in several key points from the practice of other HTA organizations. So the practice of IQWiG is identified as the unique German approach in the literature. The most significant as well as debated points in the process of establishing cost-effectiveness are applying a disease/indication-specific threshold instead of an explicit one in terms of cost/QALY; and the efficiency frontier approach (Fricke and Dauben, [2009]; IQWiG, [2009]).

In contrast to other European HTA agencies applying cost-effectiveness 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 (Pauly et al., [2012]).

The efficiency frontier which is an extension of the standard approach of incremental cost-effectiveness ratios is organically connected with the previous debated issue (Markowitz, [1952]). 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 (IQWiG, [2009]).

Despite the German approach to cost-effectiveness analysis is heavily debated by several health economists, it represents such elements which might serve as examples 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 process is slightly transparent for the public as well as for stakeholders (Gulácsi et al., [2012]). On the whole, challenges for HTA in Hungary are partly similar to the ones in countries with a developed economy. However, there are very important differences as well, that is why transferability and adaptability issues have to be taken into consideration.

III.2. Transferability of health economic evaluations in the European Union: challenges for Hungary

The systematic literature review revealed 36 cost-utility analyses of biological therapies for RA. The majority of the studies (n=19) evaluated biological treatment for RA patients who have already failed at least one traditional disease modifying anti-rheumatic drug (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). Only one Hungarian study was available from the CEE region.

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 (funder perspective) but indirect costs (societal perspective) were ignored by many evaluations. Data from randomized controlled trials (RCT) were used the most frequently to assess effectiveness but in some cases 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.

Applying the Drummond-checklist on the 36 selected publications we found that reporting practices often failed to present key data appropriately (Drummond and Jefferson, [1996]). 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 this 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 incremental cost-effectiveness ratio (ICER) of infliximab+methotrexate therapy for RA patients who failed methotrexate monotherapy varied between 6 451 – 91 484 CAN$/QALY in a Canadian review (Van der Velde et al., [2011]). Not only the time horizon and discounting were deterministic but also different utility measures resulted quite diverse ICERs (37 209 – 80 620 CAN$/QALY) even if the same perspective was applied (Marra et al., [2007]). 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, that supports the generalizability of our observations in RA (V. Hevér, Brodszky and Gulácsi, [2014], In: Baji, [2013]; V. Hevér and Péntek, [2014], In: Baji, [2013]).

III.3. Challenges in the assessment of disease burden: case study in a chronic disease

The challenge for Hungary is how to produce local inputs for health economic evaluations quickly as well as in a valid way.

III.3.1. The empirical study – elaboration 1.

Altogether 151 patients with BC (males N=98, 65%). were involved in the cross-sectional survey with a mean age of 66.3 (SD 9.6) years and disease duration of 4.2 (SD 3.8) years.

Health related quality of life of the BC patients

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 average SF-36 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.

Relationship between FACT-Bl, SF-36, SF-6D and EQ-5D

Correlations between FACT-Bl, EQ-5D, EQ Visual Analogue Scale (EQ VAS), SF-36 and SF-6D were moderate or strong (r≥0.467). The association of the FACT-Bl and the two utility measures, namely the EQ-5D score and SF-6D, was strong.

Psychometric results of the Hungarian BCI

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. Accordingly, we can accept partially our predefined hypotheses about factor structure.

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), so our pre-specified hypothesis can be accepted partially. 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).

Correlations of the BCI subscales and the other disease-specific measure, the FACT-Bl 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-Bl (except one: bowel bother and EQ-5D score) which is in line with our predefined hypothesis.

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.

III.3.2. The empirical study – elaboration 2.

Each cost component is calculated according to the prices of 2012.

Direct medical costs

A segment (3 agents) of the applied medicines in BC was calculated in this category. The overall financial support by the National Health Insurance Fund for the 3 agents was 219.7 million HUF in 2012.

Direct non-medical costs

Average cost related to transport was 9 213.5 HUF/patient/year (S.D.=17 435 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 (S.D.=5 273.2 HUF/patient/year). Ambulance was used by solely 1 patient (0.0066%); the average cost was 2 646.4 HUF/patient/year (S.D.=24 173.4 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; S.D.=631 052.7 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; S.D.=10 436.8 HUF/patient/year).

Indirect costs

Productivity loss was associated with mean 267 007.3 HUF/patient/year (S.D.=893 110.8 HUF/patient/year).

IV. Implications for practice

Regarding the German approach to cost-effectiveness analysis (**Part II**) it would be beneficial to assess whether the German or rather the UK HTA approach is more transferable and applicable 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.

What are the opportunities for Hungary regarding economic evaluation? In rheumatoid arthritis 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 (**Part III.**) A great 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 Central and Eastern European 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.

The empirical study about the validation of the BCI questionnaire; HRQoL; and CoI of patients with BC (**Part IV**) represents an example of the implementation of this opportunity. Significant surplus values have been achieved by this research.

- The Hungarian version of the Bladder Cancer Index questionnaire developed by our study group proved to be a reliable and valid disease-specific instrument to assess HRQoL of

patients with BC. Validated language version of this measure enables the participation of Hungary in international multicentre trials and the comparison of the performance of the Hungarian BC onco-urology care with other countries' results.

- During the elaboration of the translation of the BCI questionnaire, 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 that analysed the link between disease-specific instruments (FACT-Bl, BCI) two preference-based utility measures (EQ-5D, SF-6D). Relations between BCI and EQ-5D and SF-6D, were weak, therefore, estimation of utility scores from the BCI in health economic evaluations is not supported by our results. However, modelling utility scores from the FACT-Bl seems to be a fruitful area for further research.

- Based on the HRQoL and cost data provided by our empirical study, a further research direction can be to assess and compare the cost/QALY of the diverse BC screening methods, a hot issue in the international literature, as well as BC treatments including both chemotherapeutical drugs and different surgical interventions. Taking the advantage of the QALY, comparison can be performed also with other medical fields with high health insurance expenditures (e.g. biological therapy in RA or other oncologic disorders) to support resource allocation decisions.

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VI. Own publications

VI.1. Publications in Hungarian

Journal articles:

Kovács, Á., Vártokné Hevér, N., Tóth, A., Pálffi, B. [2012]: A női vizeletinkontinencia epidemiológiája Magyarországon; kérdőíves vizsgálat 2011. *Magyar Urológia*, 24(4), 159-166 o.

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Conference abstract:

Majoros, A., Rencz, F., Vártokné, Hevér N., Tóth, A.: *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.

VI.2. Publications in English

Book chapters:

V. Hevér, N. [2013]: Biological treatment for the treatment of RA – systematic review of the health economic literature. In: Péntek, M.: *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.

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