IS TRANSFERABILITY AN ISSUE?

USE OF HEALTH ECONOMIC STUDIES IN UKRAINE AND OTHER CENTRAL AND EASTERN EUROPEAN COUNTRIES

Is transferabiliteit een noodzakelijkheid?

Gebruik van gezondheidseconomische studies in Oekraïne en andere Centraal en Oost-Europese landen

THESIS

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
rector magnificus
Prof.dr. H.A.P. Pols
and in accordance with the decision of the Doctorate Board

The public defense shall be held on
Friday 18 September 2015 at 11.30 hrs

by

Olena Mandrik
Kyiv, Ukraine

Erasmus University Rotterdam

Doctoral Committee:

Promotors:

Prof.dr. J.L. Severens
Prof.dr. O. Zalis'ka

Other members:

Prof.dr. W.B.F. Brouwer
Prof.dr. C.A. Uyl - de Groot
Prof.dr. L. Gulasci

Copromotor: Dr. S. Knies

Contents

Chapter 1 Introduction 5

Part 1. Use of economic evaluations and need for transferability in Central and Eastern European and former Soviet countries 19

Chapter 2 Exploring expert opinions regarding use and transferability of economic evaluations in Central and Eastern Europe and former Soviet countries 21

Chapter 3. Transferability of economic evaluations to Central and Eastern European and former Soviet countries 43

Part 2. Practical applicability of transferability principles 71

Chapter 4. Cost for treatment of chronic lymphocytic leukemia in specialized institutions of Ukraine 73

Chapter 5. Economic value of in-vitro fertilization in Ukraine, Belarus, and Kazakhstan 87

Chapter 6. Cost comparison of treating chronic hepatitis c genotype one with pegylated interferons in Ukraine 107

Chapter 7. Impact of hypoglycemia on daily life of type 2 diabetes patients in Ukraine 121

Chapter 8. Cost-effectiveness of adding rituximab to fludarabine and cyclophosphamide for treatment of chronic lymphocytic leukemia in Ukraine 143

Chapter 9 General Discussion 163

Summaries 175
English
Dutch
Russian
Ukrainian

Acknowledgments 189

Curriculum vitae 191

Chapter 1

Introduction

Economic studies in health care decision making

Healthcare technology is defined as prevention and rehabilitation, vaccines, pharmaceuticals and devices, medical and surgical procedures and the systems within which health is protected and maintained. The medical, social, ethical and economic implications of development, diffusion and use of health technology are studied by health technology assessment (HTA) to provide for a transparent decision on creating health care policy [1]. HTA is a multidisciplinary process, the last part of which – i.e. economic evaluations – allows state authorities to decide on rationality of resource allocation.

Economic studies that unite research on costs (such as cost-of-illness analysis and budget impact studies) with comparative economic evaluations are widely used in healthcare decision making. The general purpose of an economic evaluation is to serve as input which will help decision makers choose from a wide range of treatment alternatives and use resources more efficiently. To provide a rationale for the decisions, thresholds are set defining the additional cost that governments are ready to pay for the additional therapeutic value.

Comparative economic evaluation is generally seen as a type of analysis which involves the identification, measurement and valuation of interventions, and then compares costs and consequences of two or more alternative interventions [3-5]. There are many methods of comparative economic evaluations, of which cost-minimization analysis, cost-effectiveness analysis, and cost-utility analysis are most commonly used. Cost-minimization analysis assumes close to equal effectiveness of alternatives and so compares only the related costs. In cost-effectiveness analysis, clinical parameters serve as a measure of effectiveness, while cost-utility analysis accounts for quality of life after an intervention, usually expressed in quality adjusted life years (QALYs) [2-5]. Because many countries currently include in their decisions the additional costs spent per QALY, cost-utility analysis has now become the most preferred method [3, 6]. Countries which have set thresholds defining the additional cost they are ready to pay for the additional therapeutic value use these in determining whether an intervention is cost-effective or not [3]; developing countries which have not yet done so may use the World Health Organization recommendations to consider a technology highly cost-effective, cost-effective or not cost-effective by comparing incremental cost per QALY to gross domestic product per capita [7,8]. Using economic evaluations in the healthcare decision making process is important for a number of reasons, including resource scarcity, a continual rise in healthcare expenditures due to the introduction of innovative treatments and the aging of populations. At the same time, application of economic evaluations in the healthcare decision making process varies from country to country. For example, in countries with centralized healthcare systems -- as is the case in many Western European countries -- the results of economic evaluations carry more weight than in countries with decentralized

systems (such as found in the US), where economic evaluations are used less formally or at a limited scope [9].

There are a number of international and country-specific guidelines defining how to conduct and report health economic studies and how to assess their components [10, 11]. At the same time the requirements for full economic evaluations, that is, evaluations including outcomes besides costs, are very diverse and may ask to include information on baseline risk, treatment effect, resource utilization, health state preferences, associated costs and studies transferability from other countries [12]. The topic of improving economic data transferability between jurisdictions is frequently addressed in economic policy research [9, 11, 12].

Transferability of economic evaluations

This dissertation uses the definition of transferability given by the International Society For Pharmacoeconomics and Outcomes Research (ISPOR) Task Force Report on Transferability [13]. That is to say, economic evaluations are considered to be generalizable if their results can be applied without additional adaptation to other countries, and they are considered to be transferable if adaptation (adjustments based on local parameters) is necessary in order for evidence to be transferred [13]. Specific elements of economic evaluations can be considered to have a high or a low transferability [12]. To the highly transferable elements belong parameters of economic evaluations from other countries that can be used in local studies [12]. Elements such as treatment effect and utility parameters are often seen as generalizable, even though several recent studies have concluded that adjustment to the local population may be needed in view of possible differences in general health between the populations in the countries involved [12, 14,15]. Low transferable elements are data that are accepted as valid only when collected in the local jurisdiction (for example unit prices, clinical practice, baseline risk) [11,12]. Besides those indicated above, other factors may impact the acceptability of data from other countries, such as level of expert knowledge in economic evaluations and general development of economic study methods in the country, as well as date of issue of guidelines [12].

To simplify transferability of economic evaluations between different countries, various approaches have been developed over time [11,14], including Heyland's generalizability criteria (1996) [16], Späth's transferability indicators (1999) [17], Welte's transferability decision chart (2004) [18], Boulenger's transferability information checklist (2005) [190], Urdahl's generalizability criteria (2006) [20], Turner's transferability checklist (2009) [21], and Antonanzas' transferability index (2009) [22]. While these approaches differ substantially in terms of complexity – primarily in the number of criteria included in the assessment, structure, cut-off points, and primary aim of application [11,14] – a

common element of most approaches is the use of critical and noncritical criteria for defining transferability of economic evaluations between jurisdictions.

The need for simple transferability of results of health economic studies is potentially more important in countries that have limited scientific and financial resources for conducting economic evaluations, as in many countries of the Central and Eastern European (CEE) region and the former Soviet Union.

Healthcare background for economic evaluations use in Central and Eastern European and Central Asian countries

Except for the Russian Federation, Turkey, Ukraine, Romania and Kazakhstan, most countries of the CEE region and the former Soviet Union have relatively small populations of fewer than 10 million people [23]. Excluding the Baltic countries (Estonia, Latvia and Lithuania) and Georgia, eleven of these countries (Russian Federation, Ukraine, Belarus, Moldova, Kazakhstan, Kyrgyz Republic, Tajikistan, Turkmenistan, Uzbekistan, Armenia and Azerbaijan) are currently organized under the heading of the Commonwealth of Independent States. Except for Estonia, Latvia, Lithuania, Russian Federation and Slovenia, all of which have gross domestic products (GDPs) per capita above 12 475 US$, and low-income Tajikistan [24], countries in this region belong to the middle-income countries (Appendix 1.1).

Despite the common historical background for many of the aforementioned countries, after gaining their independence, not only did their general political developments diverge, but also the reform of their inherited Semashko health care model went separate ways. While Bulgaria, Estonia, Latvia, Lithuania, Macedonia, Moldova, Romania, Serbia and Slovenia implemented a societal health insurance and reimbursement system [25-33], the other post-Soviet countries are applying different mixed models or are still in transition (Appendix 1.1). For example, a mixed financing scheme of general taxation and insurance contributions is applied in the Russian Federation [34], and in Kazakhstan a unified national healthcare system now substitutes for an unsuccessful earlier attempt at implementing societal health insurance [35]. As a result of these implemented changes, both expenditure on health per capita (highest in Estonia, Lithuania, Russian Federation, Slovenia) and expenditure on health as a percentage of GDP (highest in Georgia, Serbia, Slovenia) [23] vary and, as can be seen in Appendix 1.1, these variables are not directly related to each other. Except for a number of low-income countries (such as Armenia, Azerbaijan, Georgia, Moldova and Tajik Republic) state coverage for healthcare expenses in the region exceeds 50% [36].

Healthcare background in Ukraine

Despite current attempts to address population health needs, the crude adult death rates in Ukraine are higher than in the European Union [37]. Non-communicable diseases (cardio-vascular diseases and cancer) are responsible for nearly 70% of all deaths in Ukraine, followed by injuries and poisoning (14%), and communicable diseases (7%) [38,39]. The present donor funding is heavily focused on supporting human immunodeficiency virus (HIV) and hepatitis C virus (HCV) prevention, care, treatment and support programs, followed by maternal health and family planning [40-42].

Besides the current focus of healthcare policy on improving health indicators, reforming the healthcare system has been a continuous process since Ukraine achieved independence in 1991. This process does not come without challenges; among the current challenges are: inefficiency of health care financing, inequitable access to resources, high prevalence of out-of-pocket payments, and a free generic-oriented drug market without mandatory prescription. At the same time, free access to healthcare for all people in Ukraine is formally ensured by the Constitution [43].

The Ministry of Health is the central body that coordinates and controls a number of relevant health departments and policies in Ukraine [44]. In addition to general financing, the government addresses programs to urgent public health problems that are approved by resolution of the Cabinet of Ministers. The most urgent public health problems in Ukraine are: infectious diseases (vaccination of children), HIV/HCV, tuberculosis, cancer, diabetes and cardio-vascular diseases [45]. As a step toward a planned healthcare system, several reforms were proposed: giving greater autonomy to health facilities, switching from historical budgeting to budgets based on cost estimates, reimbursement implementation, and rationalization of hospital services to facilitate better resource allocation [46,47].

Currently there is no central HTA agency in Ukraine. Nonetheless, some HTA-related procedures are applied for the development of a State Drug formulary and the development of national treatment protocols. The State Formulary, maintained by the State expert center of the Ministry of Health, can be updated in two ways: 1) revision by experts of the Formulary committee; 2) by submissions from the drug manufacturers, who are required to provide an evidence dossier together with an official request [48]. The national treatment protocols are developed by the Department of Standardization for medical services of the State expert center of the Ministry of Health. Evidence for development of protocols is sought by the expert group of the department of Standardization and usually includes HTA guidance from other countries [49]. Both bodies may consider economic evidence, although officially or publicly available requirements for methodology and input parameters are lacking.

Still, non-governmental organizations and patient associations are calling for setting up a central HTA agency. Looking at the present state of affairs, however, it will not be easy to achieve good functioning of such an organizational structure. Critical factors are the unavailability of patients' registers (except in selected clinical areas, such as HIV or cancer), standardization and tariffing of medical services, insufficient number of experts in the field of HTA and economic evaluations, and a very limited state share in total healthcare expenditures, particularly in treatment spending.

The above issues highlight the difficulties in applying economic evaluations in the decision making processes in Ukraine and other CEE and former Soviet countries with a similar healthcare structure. It is argued, however, that opportunities to incorporate evidence from neighboring countries could significantly economize financial resources and optimize healthcare decision making in those countries.

Aim, objectives and outline of the thesis

The aim of this thesis, which is in two parts, is to explore transferability of health economic studies in CEE and former Soviet countries, using Ukraine as the primary example.

To reach this aim, the following objectives were addressed:

1. To assess the use of health economic studies and need for transferability in CEE and former Soviet countries (part 1);
2. To assess the practical applicability of transferability principles, transferability of health economic studies in general, and input parameters more specifically (part 2).

In part 1, chapter 2 analyses the current use and acceptability of economic evaluations in the CEE and former Soviet countries, factors that may have an impact on transferability of foreign economic studies to these countries, and the weighted importance of each factor. Chapter 3 presents characteristics of published economic evaluations from CEE and former Soviet countries that may require only simple adaptation to be used in countries with similar socio-economic and geographic characteristics, and specific transferability issues addressed in these studies.

In part 2, a number of case studies explore the transferability of input parameters and the impact of their variation on economic evaluations, and compare the results with those of studies carried out in other countries. As such, the impact of population differences is studied in chapters 5, 6 and 8, healthcare practice variations are investigated in chapters 4, 6, 7 and 8 and differences in unit costs are evaluated in chapters 4, 5, 6 and 8.

The transferability of cost of illness methods regarding the analysis of treatment cost for chronic lymphocytic leukemia in Ukraine is addressed in chapter 4. Next, the net present values for future populations conceived via in-vitro fertilization technologies in Belarus, Kazakhstan and Ukraine are analyzed in chapter 5. Chapter 6 provides an analysis of transferability of comparative cost studies and their elements to Ukraine, pertaining to the use of pegylated interferons as treatment of chronic hepatitis C. Chapter 7 analyzes the transferability of treatment outcomes in a qualitative study on the preferences and perceptions of type 2 diabetes patients in Ukraine who suffer from hypoglycemia. Chapter 8 reviews the transferability of comparative cost-effectiveness studies with regard to the use of rituximab for the treatment of chronic lymphocytic leukemia in both previously non-treated and relapsed/refractory patients in Ukraine.

In chapter 9 the main findings and conclusions of both part 1 and part 2 are presented together with their implications for the healthcare policy decision making process, organizational changes, and future research.

References

1. IHANTA. HTA Tools & Resources. Available from: http://www.inahta.org/hta-tools-resources/ [Assessed 29 December 2014].
2. Goodman CS. HTA 101: Introduction to Health Technology Assessment. 2004. Available from: https://www.nlm.nih.gov/nichsr/hta101/ta101_c1.html. [Assessed on 07 April 2014].
3. Drummond MFS, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the economic evaluation of health care programme. Third edition. Oxford: Oxford University Press; 2005.
4. World Health Organization. Workbook 8. Economic evaluation. 2000; p.38.
5. Drummond M. An Introduction to Health Economics. Brookwood, Surrey, UK: Brookwood Medical Publications; 1995.
6. Ramsey S, Willke R, Briggs A, Brown R, Buxton M, Chawla A, Cook J, Glick H, Liljas B, Petitti D, Reed S. Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report. Value Health. 2005; **8**(5): 521-33.
7. Edejer T. Tan-Torres, Baltussen R, Adam T, Hutubessy R, Acharya A, Evans DB, Murray CJL. Making choices in health: WHO guide to cost-effectiveness analysis. 2003. Available from: http://www.who.int/choice/publications/p_2003_generalised_cea.pdf. [Assessed on 17 November 2013].
8. World Health Organization. Cost effectiveness and strategic planning (WHO-CHOICE). 2014. Available from: http://www.who.int/choice/costs/CER_thresholds/en/. [Assessed on 07 April 2014].
9. Erntoft S. Pharmaceutical Priority Setting and the Use of Health Economic Evaluations: A Systematic Literature Review. Value in Health. 2011; 14: 587-599.
10. Drummond M, Brown R, Fendrick AM, Fullerton P, Neumann P, Taylor R, Barbie M. Use of Pharmacoeconomics Information—Report of the ISPOR Task Force on Use of Pharmacoeconomic/Health Economic Information in Health-Care Decision Making. Value in Health. 2003; **6**(4): 407-416.
11. Knies S. Transparency of transferability. Diagnosing international aspects of economic evaluations of health care technologies. Maastricht University: Maastricht. 2011; p.136.
12. Barbieri M, Drummond M, Rutten F, Cook J, Glick HA, Lis J, Reed SD, Sculpher M, Severens JL. What Do International Pharmacoeconomic Guidelines Say about Economic Data Transferability? Value in Health. 2010; 10: 1098-3015.
13. Drummond M, Barbieri M, Cook J, Glick HA, Lis J, Malik F, Reed SD, Rutten F, Sculpher M, Severens J. Transferability of Economic Evaluations Across Jurisdictions: ISPOR Good Research Practices Task Force Report. Value in Health. 2008; 8: 1098-3015.
14. Goeree R, He J, O'Reilly D, Tarride JE, Xie F, Lim M, Burke N. Transferability of health technology assessments and economic evaluations: a systematic review of approaches for assessment and application. Clinicoecon Outcomes Res. 2011; 3: 89-104.
15. Knies S, Evers S, Candel MJJM, Severens JL, Ament AJHA. Utilities of the EQ-5D: transferable or not? Pharmacoeconomics. 2009; 27(9): 767-779.
16. Heyland DK, Kernerman P, Gafni A, Cook DJ. Economic evaluations in the critical care literature: do they help us improve the efficiency of our unit? . Crit Care Med. 1996; 24: 1591–1598.
17. Späth HM, Carrere MO, Fervers B, Philip T. Analysis of the eligibility of published economic evaluations for transfer to a given health care system. Methodological approach and application to the French health care system. Health Policy. 1999; 49: 161–177.
18. Welte R, Feenstra T, Jager H, Leidl R. A decision chart for assessing and improving the transferability of economic evaluation results between countries. Pharmacoeconomics. 2004; 22(13): 857-76.
19. Boulenger S, Nixon J, Drummond M, Ulmann P, Rice S, de Pouvourville G. Can economic evaluations be made more transferable? Eur J Health Econ. 2005; 6(4): 334-46.
20. Urdahl H, Manca A, Sculpher MJ. Assessing generalisability in model-based economic evaluation studies: a structured review in osteoporosis. Pharmacoeconomics. 2006; 24(12): 1181-97.

21. Turner S, Chase DL, Milne R, Cook A, Hicks NJ, Rosten C, Payne L, Coles S, Bell E. The health technology assessment adaptation toolkit: description and use Int J Technol Assess Health Care. 2009; 25(Suppl 2): 37–41.

22. Antonanzas F, Rodriguez-Ibeas R, Juarez C, Hutter F, Lorente R, Pinillos M. Transferability indices for health economic evaluations: methods and applications. Health Econ. 2009; 18: 629–643.

23. Countries. World Health Organization. 2014. Available from: http://www.who.int/countries/en/. [Assessed on 12 April 2014].

24. Middle Income Countries Overview. The World Bank. 2011. Available from: http://www.worldbank.org/en/country/mic/overview. [Assessed on 17 May 2014].

25. Dimova A, Rohova M, Moutafova E, Atanasova E, Koeva S, Panteli D, van Ginneken E. Bulgaria: Health system review. Health Systems in Transition. 2012. p. 186.

26. Lai T, Habicht T, Kahur K, Reinap M, Kiivet R, van Ginneken E. Estonia: health system review. Health Systems in Transition. 2013. p. 196.

27. Health Care system in Latvia. Ministry of Health of the Republic of Latvia. 2012. Available from: http://www.vm.gov.lv/en/health_care/. [Assessed on 22 April 2014].

28. Murauskiene L, Janoniene R, Veniute M, van Ginneken E, Karanikolos M. Lithuania: health system review. Health Systems in Transition. 2013. p.150.

29. The former Yugoslav Republic of Macedonia. World Health Organization Country cooperation strategy at a glance. 2013. Available from: http://www.who.int/countryfocus/cooperation_strategy/ccsbrief_mkd_en.pdf. [Assessed on 22 April 2014].

30. Sautenkova N, Ferrario A, Bolokhovets G, Kanavos P. Availability and affordability of medicines and assessment of quality systems for prescription of medicines in the republic of Moldova. World Health Organization. 2012. p. 62.

31. Vlădescu C, Scîntee G, Olsavszky V, Allin S, Mladovsky P. Romania: Health system review. Health Systems in Transition. 2008. p.172.

32. Evaluation of the organization and provision of primary care in Serbia. A survey-based project in the regions of Vojvodina, Central Serbia and Belgrade. World Health Organization. 2010.

33. Albreht T, Turk E, Toth M, Ceglar J, Marn S, Pribaković Brinovec R, Schäfer M, Avdeeva O, van Ginneken E. Slovenia: Health system review. Health Systems in Transition. 2009. p. 168.

34. Popovich L, Potapchik E, Shishkin S, Richardson E, Vacroux A, Mathivet B. Russian Federation: Health system review. Health Systems in Transition 2011. p. 190.

35. Kastaga A, Kulzhanov M, Karanikolos M, Rechel B. Kazakhstan : Health system review. Health systems in transition. 2012. p. 154.

36. Health expenditure, public (% of total health expenditure). World Bank. 2014. Available from: http://data.worldbank.org/indicator/SH.XPD.PUBL. [Assessed on 12 April 2014].

37. Death rate, crude (per 1,000 people). The World Bank. 2011. Available from: http://data.worldbank.org/indicator/SP.DYN.CDRT.IN. [Assessed on 16 March 2014].

38. World Bank Group – Ukraine Partnership: Country Program Snapshot. p. 40.

39. [National health accounts in Ukraine in 2010]. Statistical report. State statistics service of Ukraine: Kyiv, 2012. Ukrainian.

40. [On execution of the programs of the Global Fund against AIDS, tuberculosis, and malaria in Ukraine]. The Order of the Parliament of Ukraine, 2013. Ukrainian

41. [The government will ensure full-size financing for programs on treatment of sick to AIDS and tuberculosis]. the Minsitry of Health. 2014. Available from: http://www.moz.gov.ua/ua/portal/pre_20140326_h.html. [Assessed on 04 June 2014]. Ukrainian.

42. [MOH will continue collaboration with USAID on protection against socially- dangerous diseases. the Minsitry of Health]. 2014. Available from: http://www.moz.gov.ua/ua/portal/pre_20140328_k.html. [Assessed on 04.06.2014]. Ukrainian

43. Lekhan V, Rudiy V, Richardson E. Ukraine. Health systems review, in Health systems in transition. 2010. p. 183.

44. [About the placement for the Ministry of Health of Ukraine], the Order of the President of Ukraine N 467/2011. Kyiv, 2011. Ukrainian

45. [Goal programs and actions]. Ministry of Health of Ukraine. 2014. Available from: http://www.moz.gov.ua/ua/portal/mtac_programs/. [Assessed on 04 June 2014]. Ukrainian.

46. [Ukraine Embarks on Major Health Reform]. 2011. Available from: http://www.healthsystems2020.org/content/news/detail/82467/. [Assessed on 16 March 2014]. Ukrainian

47. [MOH poposes simultaneous implementation of reimbursement and price control for insulin drugs]. Governmental Portal. 2014. Available from: http://www.kmu.gov.ua/control/uk/publish/article?art_id=247104689&cat_id=244277212. [Assessed on 04 June 2014]. Ukrainian.

48. [On approval of the Methodologic recommendations on monitoring and assessment of the functioning of the formulary system on the stage of its implementation]. the Order of the Ministry of Health of Ukraine, 2010. Ukrainian

49. [On creation and implementation of medical technological documents on standardization of medical help within the system of the Ministry of Health of Ukraine]. the Order of the of the Ministry of Health of Ukraine #751, 2011. Ukrainian.

50. GDP per capita (current US$). World Bank national accounts data, and OECD National Accounts data files. Available from: http://data.worldbank.org/indicator/NY.GDP.PCAP.CD. [Assessed on 13 April 2014].

51. Bramley T, Meyer K, Wery E. Why is Health Technology Assessment Important? 2013. Available from: http://www.ceb-institute.org/bbs/wp-content/uploads/2013/06/20130624_Sorenson-HTA-Importance-BBS-EFSPI-4June2013final.pdf. [Assessed on 12.04.2014].

52. Ibrahimov F, Ibrahimova A, Kehler J, Richardson E. Azerbaijan: Health system review. Health Systems in Transition. 2010. p. 117.

53. Richardson E, Malakhova I, Novik I, Famenka A. Belarus: health system review. Health Systems in Transition. 2013. p. 118.

54. Rukhadze T. An overview of the health care system in Georgia: expert recommendations in the context of predictive, preventive and personalised medicine. The EPMA Journal. 2013. 4.

55. Zoidze A, Rukhazde N, Chkhatarashvili K, Gotsadze G. Promoting universal financial protection: health insurance for the poor in Georgia – a case study. Health Research Policy and Systems. 2013; 11: 45.

56. Ibraimova A, Akkazieva B, Ibraimov A, Manzhieva E, Rechel B. Kyrgyzstan: Health system review. Health Systems in Transition. 2011. p. 152.

57. Khodjamurodov G, Rechel B. Tajikistan: Health system review. Health Systems in Transition. 2010. p. 154.

58. PMGroup. Country report Turkey. Pharmaceutical market Europe. 2011. Available from: http://www.imshealth.com/ims/Global/Content/Corporate/Press%20Room/IMS%20in%20the%20News/Documents/ICG_Turkey_Article.pdf. [Assessed on 22 April 2014].

59. Kutzin J, Cashin S, Jakab M. Implementing Health Financing Reform Lessons from countries in transition. 2010. World Health Organization on behalf of the European Observatory on Health Systems and Policies, p.425.

60. Self - assessment of public health services in the republic of Uzbekistan. Technical report. World Health Organization. 2011: Tashkent. Available from: http://www.euro.who.int/__data/assets/pdf_file/0003/148377/PHSS_report_MAH.pdf?ua=1. [Assessed on 22 April 2014].

Appendix 1.1 Summary on countries' characteristics

Country	Population size in mln. people [23]	Gross domestic product (GDP) per capita (2009-2013), US$ [50]	Life expectancy at birth (m/f) [23]	Health care system financing type	Total expenditure on health per capita, US$ [23]	Total expenditure on health as % of GDP [23]	State Health coverage (2009-2013), % [36]
Armenia	3	3 351	67/75	Mixed, taxation-base (state coverage for vulnerable population and social diseases) [51]	250	4.3%	41.8%
Azerbaijan	9.3	7 165	69/74	Inherited Soviet Semashko healthcare system (taxation-based) [52]	523	5.2%	22.8%
Belarus	9.4	6 685	66/77	Inherited Soviet Semashko healthcare system (taxation-based) [54]	794	5.3%	77.2%
Bulgaria	7.3	6 977	71/78	Compulsory and voluntary health insurance [25]	1 064	7.3%	56.3%
Estonia	1.3	16 844	71/81	Compulsory health insurance [26]	1 334	6.0%	79.9%
Georgia	4.4	3 507	70/78	Mixed: private insurance with state coverage for poor [54, 55]	564	9.9%	18%

Kazakhstan	16.3	12 121	62/72	Unified National healthcare system, transition from inherited Semashko model [35]	534	3.9%	57.8%
Kyrgyz Republic	5.5	1 155	66/73	Compulsory health insurance [56]	161	6.5%	60.1%
Latvia	2.1	13 947	69/79	Compulsory health insurance [27]	1 179	6,2%	56.7%
Lithuania	3	14 172	68/79	Compulsory health insurance [28]	1 337	6.6%	70.8%
Macedonia	2.1	4 565	73/78	Compulsory health insurance [29]	789	6.6%	64.1%
Moldova	3.5	2 038	66/ 75	Compulsory health insurance [30]	386	11.4%	45.5%
Russian Federation	143	1 4037	63/75	Mix of financing from compulsory sources (general taxation and payroll contributions for medical health insurance) and out-of-pocket payments [34]	1 316	6.2%	61.0%
Romania	21.8	8 437	70/78	Compulsory health insurance [31]	902	5.8%	77.7%
Serbia	9.6	5 190	72/77	Compulsory health insurance [32]	1 195	10.4%	61.2%

Slovenia	2.1	22 011	77/83	Compulsory health insurance [33]	2 519	9.1%	73.3%
Tajikistan	8	953	67/69	Inherited Soviet Semashko health system, very small transition (taxation-based) [57]	135	5.8%	29.6%
Turkey	73.9	10 666	73/78	Compulsory health insurance [58]	1 160	6.7%	73.9%
Turkmenistan	5.2	6 798	60/67	Inherited Soviet Semashko healthcare system, very small transition (taxation-based) [59]	251	2.7%	63.2%
Ukraine	45.5	3 867	65/76	Inherited Soviet Semashko healthcare system, transition period (taxation-based) [43]	528	7.2%	54.9%
Uzbekistan	28.5	1 717	67/72	Voluntary health insurance (health insurance funds and trust funds)[60]	190	5.4%	53.1%

Part 1

Use of economic evaluations and need for transferability in Central and Eastern European and former Soviet countries

Chapter 2

Exploring expert opinions regarding use and transferability of economic evaluations in Central and Eastern Europe and former Soviet countries

Mandrik O., Knies S., Kalo Z., Severens J.L.
Submitted

Abstract

We aimed to assess use of economic evaluations, geographic preferences, and major transferability factors in Central and Eastern European (CEE) and former Soviet countries. Eleven experts on technology reimbursement from eight countries were interviewed on their expertise and practice of using economic evaluations, transferability of economic evidence and importance of transferability factors (Welte's criteria).

In the countries studied, economic evidence is acceptable for decision making depending upon the perspective of the study, quality or methodology, costs source and assessment method, reliability of the study and population characteristics. Five experts from four countries confirmed direct use of foreign studies in local decision making. All except one respondent agreed that results of economic studies are not generalizable between CEE countries, but transferability is simpler than between different international regions. For transferring economic evidence, similar health care system and practices were named being most important, along with costs and countries' comparative economic development, perspective of the study, and disease epidemiology. Meanwhile, such factors as compliance, health status preferences, and case-mix are considered to be less important.

Despite experts acknowledging the limited relevance of foreign studies in local decision making, transferability principles are rarely applied in practice.

Introduction

Currently not only jurisdictions in Western European, Northern America, Australia and New Zealand, but regulatory establishments all around the world require submission of economic evidence of medical technologies for state purchase purposes or for price negotiations [1]. Because of the growing requirements of such submissions, the producer of a medical technology is expected to develop multiple country-specific dossiers in which the local context of economic studies is required. The methodology of economic evaluations is standardized by country guidelines or other relevant local normative documents [1-4], defining data requirements.

In the current article we used the definition of transferability by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force Report on Transferability [2] stating that economic studies can be considered as generalizable, if their results can be applied without additional adaptations to other jurisdictions. When adaptation to the local parameters is required, economic evaluations can be considered as transferable [2]. Elements of economic evaluations from other jurisdictions that can be used in local cost-effectiveness studies are considered highly transferable input parameters [1]. The analysis of twenty-seven guidelines [1] has shown that baseline risk, unit costs, and resources' use were considered to have a low generalizability and need adaptation to be transferable. Meanwhile, the ISPOR Task Force Report [2] suggests a necessity for justifying the need for local data or methods because this increases the burden on those undertaking studies in multiple jurisdictions, and simple model adaptation (price substitution) should be carried out when it is possible.

To systematically assess transferability of economic evaluations between different jurisdictions, a number of different approaches were developed over time [4,5]; first among the others were Heyland's generalizability criteria (1996) [6], Späth's transferability indicators (1999) [7], and Welte's transferability decision chart (2004) [8]. While the developed approaches differ substantially by complexity and structure, cut-off points, and primary aim of application (empirical or method-based economic evaluations) [4,5], the common element among a majority of the methods is using critical and noncritical criteria for defining transferability of economic evaluations between jurisdictions. Welte's decision model defines three general knock-out transferability criteria: the comparability of evaluated technologies and alternatives, acceptable quality of the study and, additionally, specific transferability criteria (see Appendix 2.1). This approach can be applied for both trial- and model-based economic evaluations and is one of the few that have been validated explicitly [9]. Furthermore, this instrument is easy usable in a qualitative manner without claiming to show a quantitative transferability results [10].

The need to have a simple adaptation of economic evaluations is potentially more important in the countries where the human resource and budget capacity for conducting economic studies is limited. Such countries may be low- and middle-income countries of Central and Eastern European (CEE) and former Soviet Union regions with no centralized HTA agency. In this case there is less interest by the producer of a medical technology to invest in the product's economic analysis because of random or short-term finance allocation. Nevertheless, it can be expected that similar to other countries [1], the decision makers in this region will prefer economic evaluations that are applicable to their own jurisdiction.

The objectives of this qualitative descriptive study were to explore the opinion of experts in technology reimbursement from CEE and former Soviet countries with no existing single HTA agency or with a recently created agency on 1) use and acceptance of economic evaluations; 2) geographic preferences for transferring HTA / health economic evidence; and 3) factors that have an impact on transferability of economic studies.

Methods

In order to reach the listed objectives, interviews with reimbursement experts from CEE and former Soviet countries where a formal HTA review is not implemented, were conducted. Potential respondents were selected by convenience method. Enrolment of the reimbursement experts was through personal connections or during specialized congresses (ISPOR or Society of Medical Decision Making - SMDM). The interviews were conducted either in person (nine interviews) or by Skype (two interviews). All involved respondents fulfilled the following criteria: residence in a country of interest; formal or advisory role in the national decision making process on health technology reimbursement; and agreement to hold an interview on the research topic in either the English, Russian, or Ukrainian language. In total, fourteen experts corresponding to the inclusion criteria were asked to participate in the study, from whom eleven experts from the following countries agreed to participate: Ukraine (3), Romania (2), Armenia (1), Estonia (1), Kazakhstan (1), the former Yugoslav Republic of Macedonia (1), Russian Federation (1), and Turkey (1). With experts' permission all interviews were recorded. Six from the interviewed respondents are employees of the Ministry of Health in the country of residence, while the remaining experts are members of advisory committees or execute governmental consulting services on pricing and/or reimbursement. The interviews were conducted on a personal basis on the conditions of identity confidentiality.

For the purposes of the study an interview guide (Appendix 2.2) with a semi-rigid structure (questions could be excluded or included depending on the responses of the interviewee) was used. The minimum interview time needed was 15 minutes, and the maximum was 46 minutes. Questions covered the following topics: respondents

experience in economic evaluations and transferability, their opinion on current practice of using economic evaluations in healthcare decision making and acceptance of economic studies, overall transferability of economic evaluations and their personal judgment on the importance of individual Welte's criteria. Besides this, experts were proposed to read a one-page extract from publications (Appendix 2.3), give a preference to one of the country-blinded economic evaluations in which the application of rituximab in treatment of chronic lymphocytic leukemia (CLL) was assessed and to provide their reasoning for case selection. After completion of the assessment the information on the origin of the studies (the USA and Ukraine) was disclosed, and the respondents were asked to reconsider their opinion on the study preferences for the decision-making process in their country.

All questions were addressed to the experts verbally. Description of the Welte's criteria [8] and methodological brief of two economic evaluations of the use of rituximab in treatment of CLL were presented in written form. The respondents interviewed by Skype were provided with the written materials before the interview and instructed not to open until instructions to do so were given. All interviews were transcribed by the interviewer. The interviews conducted in the Russian or Ukrainian language were double-back translated into English by two interpreters independently. The transcripts were analyzed by one researcher (OM) with an independent validity check of two interviews by SK, and one more by SK and JS (>20%). An inductive approach of the content analysis was used. This process included open coding, creating categories and their grouping under higher order headings and abstraction (or formulating a general description of the research topic) [11]. The headings of the categories corresponded to the objectives of the study identified above.

In the assessment of acceptance of economic evaluations by the decision makers, we decided to separate two groups of factors: "quality" and "reliability". By definition (Collins dictionary, http://www.collinsdictionary.com), quality is a "degree or standard of excellence", and so supposes acceptance of economic evaluation basing on objective judgment (such as, for example, correspondence of the study methodology to the accepted local standards). Meanwhile, reliability is "the ability (of a person or thing) to be trusted to work well or to behave in the way that you want them to", which includes a subjective judgment. Thus, under reliability we united factors that may have a subjective impact on the quality or its perception: references to the data sources, conflict of interests for authors of the study and the decision makers, perceived quality of the study by the authors' workplace or publication origin.

Results

Eleven experts in technology reimbursement in total (representing Ukraine, Romania, Armenia, Estonia, Kazakhstan, the former Yugoslav Republic of Macedonia, Russian Federation, and Turkey) were interviewed on their education, current use of economic evaluations in the decision making processes and transferability of economic studies. All reimbursement experts except one had at least some training in HTA and/or economic evaluations, and the majority of study programs in which experts took part were organized by international teams either abroad (short-course programs) or in the country of residence. It was also typical for one educational program to combine several methodology aspects: five out of eight HTA courses included economic evaluations, and four of them also presented material on transferability.

Use and acceptance of economic evaluations

The parameters focused on use and acceptance of economic evaluations in the study countries are summarized in Table 2.1. We distinguish four main issues regarding use and acceptance of economic evaluation: country of evidence and budget analysis, criteria taken into account when reviewing submitted economic evaluations, and barriers for economic evaluation use.

Table 2.1 Use and acceptance of economic evaluations: frequencies report (in total 11 respondents from 8 countries)

Use of economic evaluation studies and health technology assessment (HTA) reports	
HTA (or HTA elements) use in state healthcare decision making	All countries except Armenia
Account economic evidence from the other countries	Ukraine, Turkey, Estonia, and Kazakhstan (5 experts)
Use other countries reimbursement as example	Ukraine, Turkey
Report underestimation of economic evidence importance by healthcare decision makers	Ukraine and Romania (3 experts)
Report difference in personal preferences and current acceptance criteria	4 experts
Report preference for local data studies in decision making	3 experts for, 1 oppose
Significantly rely on budget impact	Romania, Estonia, Turkey
Recognize limited capacity for HTA review	2 experts

Criteria took into account when reviewing submitted economic evaluations, N of experts	
Quality/methodology applied	4
Reliability (data source, assumptions, experts involvement)	4
Study perspective	3
Local costs	3
Population characteristics	2
Reasoning for selection a country-blinded economic evaluation [a], N of experts	
Selected Case A (Case B)	5 (5)
Perspective (specified use of indirect costs)	8 (5)
Cost assessment method	4
Methodology	2
Would have a general preference to Ukraine	8
Acceptance of economic evaluations (summarized values), N of experts	
Perspective	9
Quality/methodology	8
Costs	5
Reliability (data source, assumptions, experts involvement)	5
Population characteristics	2

[a] Experts were proposed to give a preference to one of the Cases (Appendix 2.3) in which the application of rituximab in treatment of chronic lymphocytic leukemia was assessed and to provide a reasoning for case selection.

Experts from all the countries except Armenia declared use of economic evaluations in their decision making processes. The state bodies using HTA evidence may accept the economic evidence from other countries, as it was mentioned by the experts from Ukraine, Turkey, Estonia, and Kazakhstan. In Turkey not only evidence itself, but also the impact of the presented evidence on reimbursement decision in the country of the study origin may also have a potential impact on a governmental health supply or reimbursement decision: "*…we look on restrictions [for reimbursement – author]. If we see the economic evaluation was done in another country, we look how it is used in that country, how they use the results of economic evaluation there, and are there any restrictions on the drug usage…We look on reimbursement of the original molecule on the European market. After that we review for Turkey, because Turkey is a developing country…"*

Experts from Romania, Turkey, and Estonia mentioned that in the decision making process a preference to studies on local population is given by the members of relevant HTA committees, while another expert from Kazakhstan indicated that local origin and authorship of the study may have a negative context because of the lower perceived reliability of studies conducted in countries of the former Soviet Union and perceived high methodological quality of studies from specific western countries: "*…Because here also a lot depends on from which place this came from. For example, if you came and said that this was made by NICE, this would be accepted perfectly, if by Singapore - then not. The brand is important. Who did, which journal, - depends on this factor. In our country the foreign studies are loved. I mean they respect the level of studies that exists abroad. Sometimes it can be stereotype when we don't accept ours and look abroad, but this is a specificity of our mentality*"; "*if I account the country, despite some similarities between our countries, I would select case B [study done in US -authors]. Even if it is far away, even if it's American study, I don't rely on quality of the studies conducted in Ukraine… because in the post-Soviet space we have big problems with the high quality study design, that's a well-known problem. Maybe, this is not related to this particular study, but I don't know this"*.

Besides impact of the other factors, in Romania and Estonia, budget-impact has a recognized impact in the reimbursement decision, while in Turkey such analysis is decisive: "*It's mostly costs. We look on comparators, how much, the new drug pricing, and how many people are required to treat. So, mostly we review costs, budget impact. Everything else is mostly not important. … Its importance is 80-90%...*"

During the interview experts named conditions for acceptance of economic studies in the decision making process: reliability of the study (data source, assumptions) and its quality, use of the appropriate perspective and local costs, and relevant population characteristics. While using a practical case, eight of the experts accepted the evidence based on the perspective of the study, and five of them also specified problems especially in assessing indirect costs in their country. When both case argumentation and named

acceptance criteria were accounted in the assessment of important factors for accepting economic evaluations, the most frequently named were perspective, quality/methodology, costs assessment and study reliability.

Barriers for economic evaluation use

Despite the current level of economic studies use, some barriers in application of evidence in the decision making process may be observed. Experts from Ukraine and Romania noted that the decision makers either do not recognize or they underestimate the importance of economic evaluations in the health care resource allocation processes. Among the weaknesses in the currently applied HTA systems and use of economic evaluation the experts named the following: insufficient transparency of the governmental bodies, insufficient or low quality data for health economic studies and/or significant share of assumptions in the model inputs (especially if the societal perspective is required), insufficient resources to provide financing to all required innovative treatments even when economic evaluations show that the innovative treatment is cost-effective, insufficient labor capacity to conduct HTA studies and possible conflict of interest for the experts involved in HTA assessment and/or appraisal processes: *"...our governmental body is not enough transparent…"*; *"…sometimes they [experts – authors] are called to evaluate studies on medicines where they participated as clinical investigators. So, they participated in the study themselves and then they are called to evaluate clinical effectiveness of this drug…"*; "*when you look on economic evaluations people are making lots of assumptions … sometimes there are very robust findings even with some level of uncertainty you know that it will be even more robust when you transfer the results from one country to the other*"; "*Currently, it is not included [into state purchases – auth.] only because it is a very costly methodology for effective treatment of patients… there are no resources to cover all the sick with this treatment…"*.

The need for plans to establish more profound education for the experts involved in evidence evaluation was expressed by the respondents from Kazakhstan, Romania, and Turkey: "*Now economic evaluations in our country are far from being perfect. This is a trend of Commonwealth of Independent States countries in general because when someone speaks about pharmacoeconomics, for some reasons these are doctors or pharmacists…But this point always troubles me… in healthcare economics it is considered that anyone can do it. It is good if a person, in theory, has two educations. … I consider that economists should do economic evaluations, not the doctors…*"; "*most of the professors involved into HTA don't have a training necessary to do systematic review or critically appraise an article, they don't have a training in economic evaluation*"; *"…We are planning to educate, we are planning to use a Master degree course which will use modeling only for people who work for the government…"*.

Table 2.2 Transferability and generalizability of economic evaluations

Consideration regarding transferability and generalizability of economic evaluations, N of experts	
Results are not generalizable within one region	10 (1 -partly)
Results are easily transferable	7
Transferability is more difficult between the regions	10
Factors that should be first addressed when transferring economic evaluations [a], N of experts	
Healthcare system characteristics	8
Comparators (guidelines, practice)	7
Costs	5
Financial system characteristics	4
Perspective	3
Attitude (societal, physicians)	2
Incidence/prevalence	2
The most important Welte's criteria, N of experts	
Cost approach	7
Absolute and relative prices	5
Practice variation	5
Technology availability	4
Incidence and prevalence	4
The least important Welte's criteria [b], N of experts	
Compliance	5
Health status preferences	3
Case-mix	3

[a] Named by experts before being familiarized with Welte's criteria (Appendix 2.1)
[b] Five experts did not rank the least important transferability criteria.

Geographical preferences for transferability

Almost all experts consider the results of economic evaluations are not generalizable, neither between different regions nor within one geographic region, and they agree that transferability within one region is easier (Table 2.2).

Seven respondents consider that transferability within one geographic region (including CEE and former Soviet countries) should be easy to conduct even though local cost calculations are required and some other adaptations may be needed.

When the country origins of the presented case-studies were disclosed to the experts, the majority confirmed that knowing the country of origin of the study has an impact on their decision. They would give a general preference to use the case from Ukraine rather than the USA as it requires less adaptation, while several respondents indicated that closeness of methodological and input parameters to local requirements is more important than the study country itself: "*I would give more attention to the case made in this area, but not on 100%. The level of patient involvement, practice variation may be different, but may be closer in Ukraine and Romania than Western country"; "…We can't use cases without adaptation, our methods are so different… Because the USA is completely different, private insurance, and we are covered by the government, I would definitely prefer to have case from Ukraine, but with adaptation…"* Some other respondents also stated that as any case requires use of the local context and generalizability is not possible, the country of the study has no impact on their choice of the model for transferability: *"For economic evaluation we may use a framework, template, but not the study…each country has specific elements, especially from the side of healthcare characteristics. So, we can't just accept the ICER…"*

Factors that have an impact on transferability of economic studies

Before Welte's criteria were presented and described to the respondents, the most frequently named transferability factors were healthcare system characteristics and comparators (including actual clinical practice, patients pathways and guidelines), as well as correspondence of costs, financial characteristics of the country or healthcare (such as gross domestic product - GDP or spending of healthcare as a percentage of GDP), perspective, incidence/prevalence, and attitude among society or medical circles.

Most of the experts were not familiar with Welte's transferability criteria before the interview. From the presented Welte's criteria, the most important named were the following: cost approach, absolute and relative prices and practice variation, technology availability and incidence and prevalence, while the least important were compliance, health status preferences, and case-mix (Table 2.2).

The majority of experts noted that Welte's criteria fully describe all transferability issues; two experts also considered it important to have reliability of economic evaluations

and availability of priority assessment from the governmental perspective to be analyzed before transferring the economic studies across countries.

Discussion

Independently of the geographic location of the jurisdiction, we observed a consistency in the replies of the experts from the studied CEE and former Soviet countries regarding use and transferability of economic evaluations in healthcare decision making. The difference between known and applied transferability observed in this study and outlined below may be an issue of future policy application and development.

Use and acceptance of economic evaluations

While some countries, such as Kazakhstan, Turkey, Estonia and Romania have newly established HTA agencies, in the Russian Federation, the former Yugoslav Republic of Macedonia and Ukraine economic evaluations and/or HTA dossiers are taken into account to support the inclusion of medical products into the formularies, state purchase list, or therapeutic guidelines.

Having significantly less experience than Poland or Hungary, which implemented HTA almost a decade ago, the other CEE countries may require similar critical factors for HTA development, such as a mandatory role of HTA within an independent agency, explicit cost-effectiveness thresholds, and budget-impact importance [12], as the latter is a requirement for decisions in a number of CEE jurisdictions according to our study. While in many study countries economic evaluations are used more informally than on an obligatory or regular basis, this practice is not different from countries in Western Europe [3]. At the same time, Western European countries generally possess larger financial and labor resources [13] and may have less barriers for appropriate HTA system functioning. Identically to Poland and Hungary [12], some other CEE and former Soviet countries, while being on different stages of standardizing HTA approach, face human resource constraint, and may potentially face budget constraints as well if obligatory HTA is planned to be implemented. Lack of education was indicated as one of the major barriers for the use of economic evaluations in the study of Erntoft [3], something also observed within our study. In our study as well as in others, missing and insufficient data are considered to be a significant obstacle for using the preferred methodology of economic evaluations. At the same time, similar to other studies, we noticed a limited acceptability of sponsored studies [3].

Despite evidence from other countries being frequently taken into account in healthcare decision making of CEE and former Soviet countries, state committees generally prefer studies conducted in their local setting. The major factors that experts pay attention to in their decision to accept the evidence were methodology (study

perspective, population characteristics, costs assessment), study quality and a subjective perception of the study's reliability. Barriers to the use of economic evaluations in the USA, Canada and the UK identified by Erntoft [3] were similar to factors identified in our analysis.

Geographic preferences for transferring HTA evidence

In contradiction to current practice, there is a unified agreement between the respondents that economic evaluations cannot be generalized between countries. Independently of similarities between jurisdictions, differences in healthcare structures and costs differences will have an impact on the results of economic studies and so make it impossible to apply the evidence without adaptation. This conclusion corresponds to ISPOR Task Force Report [2] and a systematic review on generalizability of economic evaluations by Goeree et al. [14], indicating simple adaptation as a minimum need for transferring economic evaluations between countries. Meanwhile, our results suggest that transferability of studies should be simpler within one region, as the similar political and structural background of the countries may result in more similarities in methodology and input parameters of the models, and so will require less adaptation.

Factors that have an impact on transferability of economic studies

For transferring economic evidence, the healthcare system model and similarity of clinical practice (correct comparators) were named as the most important, together with costs and the countries' comparative economic development, perspective of the study and disease incidence/prevalence. Each of the indicated factors can be placed under the five broad characteristics defined by Goeree et al. [14] as important for geographical transferability, namely: patients, disease, provider, health care system, methodology.

The Welte's criteria [8] can be considered as an appropriate and complete instrument for transferability assessment, though such parameters as compliance, health status preferences and case-mix are considered to be less important for transferability of economic evaluations in CEE and former Soviet countries. While compliance is considered both less influential and difficult to assess, the reasons for leaving aside health status preferences are connected with the information gap on quality of life data in CEE and former Soviet countries and lack of its understanding and acceptance in some jurisdictions. Similar to Sculpher et al. [15] and Barbieri et al. [1], we observed greater attention paid by the technology reimbursement experts to ensure use of country-specific cost inputs in submitted economic evaluations, rather than clinical parameters or patient preference characteristics. Thus we conclude that outcome parameters are considered to be more generalizable between jurisdictions.

Despite each respondent naming at least one factor important for the transferability of economic evidence, it can be observed from the current study that

transferability principles are rarely used in the decision making process of the countries studied. Knowing the limitations of generalizability, experts may be skeptical about using foreign studies in a local decision making process while nonetheless applying this evidence.

As indicated by Drummond et al. [2], the approach for dealing with aspects of transferability is based on data availability and the attributes of various analytic methods. Limited data availability was an important factor for study perspective preferences (i.e., limited use of societal perspective) and so for study transferability, as it was observed in the current study.

When the model from the reference country is of appropriate quality and includes relevant study technology and comparators, and at the same time both jurisdictions have similar health care structures and disease incidence/prevalence, simple adaptation (or costs substitution) should be possible for countries of CEE and former Soviet Union region. The focus towards simple transferability is especially urged by the data insufficiency and lack of HTA education for technology reimbursement experts and decision makers, as indicated by study respondents.

Policy implication

Governmental bodies of countries wishing to enhance the use of HTA in health care decision making should, at a minimum, address the following barriers: non-transparency of the decision making process and lack of value of economic evaluations among the decision makers, limited capacity of HTA bodies and insufficient education of experts, insufficient or low quality input data and significant share of assumptions in economic models. Subjective individual experts' perception – that is primarily based on education – potentially may have significant impact on both acceptability and transferability judgments.

Although guidelines in many countries recommend using the societal perspective [16], this approach should be reconsidered in countries of CEE and former Soviet Union region which are in the process of implementing or have recently implemented single HTA agencies, because of data constraint issues.

The centralized or governmental HTA bodies of CEE and former Soviet countries should focus on a standardized approach for simple transferability of economic evaluations in order to avoid budget and labor constraints and provide rational decisions.

Limitations

A limitation of this study is its qualitative design. The sample of respondents included only a limited number of experts. Because experts were enrolled in the study by convenience, their background and expressed personal opinion may differ from other experts or decision makers of the countries studied. Moreover, observations obtained from the study countries may differ from other jurisdictions of the region.

Conclusions

Despite reimbursement experts acknowledging the limited relevance of international studies in local jurisdiction, transferability principles are rarely applied in practice. We suggest that an explicit transferability assessment may help to improve the use of economic evaluations within CEE and former Soviet countries which have a purpose of single HTA agency implementation.

References

1. Barbieri M, Drummond M, Rutten F, Cook J, Glick HA, Lis J, Reed SD, Sculpher M, Severens JL. What Do International Pharmacoeconomic Guidelines Say about Economic Data Transferability? Value in Health. 2010; 10: 1098-3015.
2. Drummond M, Barbieri M, Cook J, Glick HA, Lis J, Malik F, Reed SD, Rutten F, Sculpher M, Severens JL. Transferability of economic evaluations across jurisdictions: ISPOR Good Research Practices Task Force report. Value Health. 2009; 12: 409–418.
3. Erntoft S. Pharmaceutical Priority Setting and the Use of Health Economic Evaluations: A Systematic Literature Review Value in Health. 2011; 14: 587-599.
4. Knies S, Severens JL, Ament AJHA, Evers SMAA. Using cost-effectiveness results from abroad for local policy decisions. European Journal of Hospital Pharmacy. 2008; 14: 51-54.
5. Goeree R, He J, O'Reilly D, Tarride JE, Xie F, Lim M, Burke N. Transferability of health technology assessments and economic evaluations: a systematic review of approaches for assessment and application. Clinicoecon Outcomes Res. 2011; 3: 89-104.
6. Heyland DK, Kernerman P, Gafni A, Cook DJ. Economic evaluations in the critical care literature: do they help us improve the efficiency of our unit? . Crit Care Med. 1996; 24: 1591–1598.
7. Späth HM, Carrere MO, Fervers B, Philip T. Analysis of the eligibility of published economic evaluations for transfer to a given health care system. Methodological approach and application to the French health care system. Health Policy. 1999; 49: 161–177.
8. Welte R, Feenstra T, Jager H, Leidl R. A decision chart for assessing and improving the transferability of economic evaluation results between countries. Pharmacoeconomics. 2004; 22: 857-876.
9. Knies S, Ament AJ, Evers SM, Severens JL. The transferability of economic evaluations:testing the model of Welte. Value Health. 2009; 12: 730-738.
10. Essers BA, Seferina SC, Tjan-Heijnen VC, Severens JL, Novák A, Pompen M, Oron UH, Joore MA. Transferability of model-based economic evaluations: the case of trastuzumab for the adjuvant treatment of HER2-positive early breast cancer in the Netherlands. Value Health. 2010; 13: 375-380.
11. Elo S, Kynga SH. The qualitative content analysis process. Journal of Advanced Nursing. 2008; 62: 107–115.
12. Kolasa K, Kalo Z, Zah V, Dolezal T. Role of health technology assessment in the process of implementation of the EU Transparency Directive: relevant experience from Central Eastern European countries. Expert Rev. Pharmacoecon. Outcomes Res. 2012; 12: 283-287.
13. Gulacsi L, Orlewska E, Pe´ntek M. Health economics and health technology assessment in Central and Eastern Europe: a dose of reality. Eur J Health Econ. 2012; 13: 525–531.
14. Goeree R, Burke N, O'Reilly D, Manca A, Blackhouse G, Tarride JE. Transferability of economic evaluations: approaches and factors to consider when using results from one geographic area for another. Curr Med Res Opin. 2007; 23: 671-682.
15. Sculpher MJ, Pang FS, Manca A, Drummond MF, Golder S, Urdahl H, Davies LM, Eastwood A. Generalisability in economic evaluation studies in healthcare: a review and case studies. Health Technology Assessment. 2004; 8: 1-213.
16. Garrison Jr. LP, Mansley EC, Abbott III TA, Bresnahan BW, Hay JW, Smeeding J. Good Research Practices for Measuring Drug Costs in Cost-Effectiveness Analyses: A Societal Perspective: The ISPOR Drug Cost Task Force Report-Part II. Value Health. 2010; 13: 8-13.

Appendix 2.1 Specific knock-out Welte's criteria presented to the respondents

Methodological characteristics	Healthcare characteristics	Population characteristics
Perspective	Absolute and Relative prices	Disease incidence/prevalence
Discount rate	Practice variation	Case-mix (age, sex, race, etcetera)
Medical cost approach (tariffs, prices)	Technology availability	Life expectancy
Productivity cost approach (US panel approach, human capital approach, friction cost method)		Health-status preferences
		Acceptance, compliance, incentives to patients
		Productivity and work-loss time

Appendix 2.2 Interview guide

Dear…

This research aims to study current use of economic evaluations in the different countries of Eastern European and Asian region, as well as possible perspectives on their applications in the healthcare decision making process. The answers you provide will be analyzed together with the answers of other experts. The manuscript presenting the results of this survey will be published afterwards. Your identity will be kept anonymous, and no relation between you and any information provided by you will be presented. If any references from your interview will be included in the manuscript, you will be referred to simply: "Respondent X, Country"

If the information indicated below is not available, all of the experts are asked general questions prior to the interview:

Country_____

Place of work of the decision maker_____

Level of the decision maker: country level / regional level

Have an impact on the decisions in:

a) State purchases;
b) Reimbursement;
c) Protocols/Formulary/State purchase list;
d) National programs creation/execution.

1. A) Did you have any training on health technology assessment in the past? If yes, what kind and when?

B) Did you have any training on economic evaluations or pharmacoeconomics in the past? If yes, what kind and when?

C) (Asked if the previous answer is "yes"). Did you have any training on transferability of economic studies in the past? If yes, what kind and when?

2. Do you use economic evaluations in decision making process of drugs/devices reimbursement? Please explain or clarify your opinion.

3. How important to you is it to use economic evaluations in decision making? Please discuss.

4. How should an economic evaluation be performed (what criteria correspond) for you to accept the results of the study?

As you might know, conducting a full economic evaluation requires significant labor, time and financial resources. It is considered that in certain cases the results of the studies, conducted in one country can be used in the decision making process of another country (and so called "generalizable"). In the other cases, the results of an economic evaluation cannot be transferred directly to the other country, but with changes of some input parameters in the economic model it is possible to get results that fit to the decision making needs. In other cases, it is not possible either to use or to transfer results of the model, nor to apply the model itself. In these cases there is a need to develop a new model and, therefore, a new economic evaluation, specific to this country. The possibility to transfer results of economic evaluations from one country to another is called "transferability". The possible level of transferability may be defined by assessing different aspects of healthcare systems on various factors in each of the comparison countries.

5. Do you consider the results of economic evaluation generalizable within one region (for example, from a developing country of Central and Eastern Europe/Central Asia to your country)? Why or why not? (Please explain or clarify your opinion.)

6. Do you consider the results of economic evaluation generalizable between the regions (for example, from Western European countries, US to your country)? Why or why not? (Please explain or clarify your opinion.)

7. What in your opinion is important for transferability of economic studies from one country to another? Which factors influence the transferability of economic evaluations?

Experts are provided with two cases on use of rituximab in healthcare decision making process, conducted in two unidentified countries (marked as "CASE A" and "CASE B").

8. Please, read both of the provided cases of economic evaluations of rituximab use in treating chronic lymphocytic leukemia.

a) Can you use Case A in the decision making process in your country? Can you use Case B in the decision making process in your country? What are your thoughts about using the results of Case A or Case B in the decision making process in your country?

b) Which case is more applicable to your country? Why?

Experts are provided with the written description of Welte's criteria and, if needed, have the criteria explained to them.

9. Which three factors from Welte's criteria do you consider the most influential/important for transferability of the results to your country and which three factors do you consider the least influential/important? Why?

10. Please, look once more at the cases provided. How might your decision on transferability and applicability of these studies to the decision making process in your country change if you were to use Welte's criteria? Which of these criteria would you say is the most influential in your decision regarding these cases? Which criteria are the least influential?

11. Do you see any other factors that might make the results of these studies more applicable/ trustable in your country?

Now, let me tell you that in Case B, country Y actually was the USA, in Case A, country X actually was Ukraine, and country Z actually was the UK.

12. Please tell me now, would you be able to use Case A in the decision making in your country? Case B? Which case would you tell now is more applicable and reliable? Which case you can use more/better? Why?

Appendix 2.3 Description of the provided case studies

A recent phase III trial demonstrated improved progression free survival (PFS) and overall survival (OS) associated with adding rituximab to fludarabine and cyclophosphamide (R-FC) compared to FC in treatment of previously untreated chronic lymphocytic leukemia (CLL). A cost-effectiveness analysis of R-FC over FC was performed

Methodological parameters	Case A (rituximab in the country X)	Case B (rituximab in the country Y)
Perspective	1) Healthcare perspective	1) Third-party payer perspective; 2) Societal perspective
Horizon	Life-time	Life-time
Model description	Cost-effectiveness models calculate the incremental cost of a given technology per unit of benefit gained. Markov model with three-states (no disease progress, relapse, and death) was run using one month cycle time.	
Discount rate	3%	
Mortality data	Data from randomized controlled trial with vital mortality statistics for study country population	
Utilities included	Utility values for health states associated with CLL treatment based on the general population in the Z. A utility value of 0.78 for the progression-free or stable disease state and a value of 0.68 for the progressed disease state have been reported. The decrement in utilities for spouses /caregivers was not accounted in the model, neither for a period of caregiving nor in case of death of the patient.	Utility values for health states associated with CLL treatment based on the general population in the Z. A utility value of 0.78 for the progression-free or stable disease state and a value of 0.68 for the progressed disease state have been reported. It was assumed a 0.18 decrement to the spouse/partner for the patient having progression-free CLL and a 0.40 decrement if the patient progressed. Also included is a 0.60 decrement in the utility if the patient died, assuming a 1-year bereavement period.
Medical costs included	Drug and hospitalization costs for initial and salvage therapies.	Drug and administration costs for initial therapy, costs related to adverse events and salvage therapy costs.
Drug costs	A body surface area (BSA) of 1.72 m2 was assumed for drug dose calculation. Adjustment to the real-consumed dose was conducted	A body surface area (BSA) of 1.84 m2 was assumed for drug dose calculation. Adjustment to the real-consumed dose was conducted
Administration costs	The cost of administration was	The costs of drug administration are

	considered to be a part of the costs of hospitalization. From healthcare perspective these costs are not different for the treatment schemes as the duration of hospitalization during the six cycles of initial therapy is the same.	based on the number of hours spent administering the drug as well as the amount and number of drugs administered. These costs were based on the corresponding reimbursement rates.
Adverse event costs	No adverse events costs were included due to the difficulty of their assessment.	Neutropenia and leukocytopenia costs were calculated by DRG rates.
Indirect costs (caregiver resources)	No indirect costs were included as the healthcare perspective was used.	The cost for an informal caregiver was assessed from the literature ($275 per week for a patient with continuing cancer care and $385 per week for a patient with advanced, terminal cancer). Participation rate for persons aged 60 – 64 is approximately 55%, declining linearly to 15% by age 70. Expected costs of lost work productivity due to severe adverse events from the treatment were also included, taking into consideration the length of a full course of therapy and incidence of the adverse events.
Salvage therapy costs	The costs for salvage therapy were calculated from the results of the previously conducted retrospective analysis of hospital cards in the country X with the account of tariffs applied in the state purchases.	The costs for salvage therapy were calculated from the total price of the six most common regimens used in the treatment of patients with CLL in country Y after progression based on market tracking data. The insurance data on salvage therapies showed that approximately 22% of the patients who relapsed or were refractory were not treated with any therapy.

Chapter 3

Transferability of economic evaluations to Central and Eastern European and former Soviet countries

Mandrik O., Knies S., Kalo Z., Severens J. L.
Submitted

Abstract

The aim of this study is to analyze the quality and transferability issues reported in published peer-reviewed English-language economic evaluations based in healthcare settings of the Central and Eastern European (CEE) and former Soviet countries.

A systematic search of economic evaluations conducted for healthcare was performed for Armenia, Azerbaijan, Belarus, Bulgaria, Estonia, Georgia, Turkmenistan, Kazakhstan, Lithuania, the former Yugoslav Republic of Macedonia, Republic of Moldova, Romania, the Russian Federation, Serbia, Slovenia, and Ukraine. The included studies were assessed according to their characteristics, quality (using Drummond's checklist), use of local data, and the transferability of inputs and results, if addressed.

Most of the 34 economic evaluations identified were conducted from a healthcare or payor perspective (74%), with 47% of studies focusing on infectious diseases. The least frequently and transparently addressed parameters were the items' stated perspectives, relevant costs included, accurately measured costs in appropriate units, outcomes and costs credibly valued, and the uncertainties addressed. Local data were often used to assess unit costs, baseline risk and resource utilization, while jurisdiction-specific utilities were included in only one study. Only 32% of relevant studies discussed the limitations of using foreign data, and 36% of studies discussed the transferability of their own study results to other jurisdictions.

Transferability of the results is not sufficiently discussed in published economic evaluations. To simplify the transferability of studies to other jurisdictions, the following should be comprehensively addressed: uncertainty, the impact of influential parameters, and data transferability. Transparency reporting should be improved.

Introduction

The application of Health Technology Assessment (HTA), a policy analysis that examines short- and long-term consequences of the use of a health technology in decision making [1], has significantly sped up during the past years all around the world [2, 3]. At the same time, middle income countries, classified by the World Bank as countries with a gross national income per capita between $1,036 US and $12,475 US [4], face common problems in establishing HTA paradigms [2]. Most countries of the Central and Eastern European (CEE) and former Soviet Union regions are middle income countries, while many others from the same regions (for example, the Russian Federation), being nominally high-income markets, still possess 'middle-income characteristics'[2].

Among countries of the CEE region, Poland, the Czech Republic, Slovakia and Hungary have introduced HTA principles and so can be considered countries with an established HTA process [5, 6]. The other CEE and former Soviet countries, being in different stages of HTA implementation, frequently incorporate some HTA elements or emerge with an idea for HTA use in their healthcare decision making. Frequently, such countries have no well-defined structural plan for the implementation of HTA results in their healthcare decision-making process. Some of them express initiation for full or partial HTA implementation, while not being able to allocate significant financial or qualified scientific resources for substantiating policy decisions with evidence [6, 7]. In many countries (e.g., Hungary and Poland), HTA capacity building is a first mandatory step for HTA implementation, followed by the development and approval of methodological guidelines and, after having an appropriately organized scientific environment, approval of compulsory HTA in policy decisions [7,8]. In other countries (e.g., Slovakia) mandating HTA evidence prior to pricing and reimbursement decisions of pharmaceuticals is the first step of HTA implementation, which eventually creates the need for HTA training. However, insufficient or low-quality HTA capacity may lead to speculations and corruption rather than the benefits from early HTA implementations.

The other challenge for CEE and former Soviet countries with no central HTA agency is that when voluntary HTA dossier submissions exist, HTA may become a commercial promotional product rather than a decision-making tool. Although pharmaceutical companies, consulting firms, or private HTA agencies may become interested in this particular topic, the actual need for such an assessment is not always expressed by the government. For example, while health authorities may be equally interested in HTA for expensive medical services and procedures, most of the online Russian-language literature on HTA studies, which we acquired via an Internet search, is focused on pharmaceuticals.

Although HTA capacity is already considered to be very limited [2], the implementation of HTA research and the critical appraisal of completed studies in CEE and former Soviet countries with no single public HTA agency may involve a number of additional problems [6]. When the appropriate training in HTA methodologies and concepts (and more specifically economic evaluations, being the core concept within HTA) is provided to experts from national institutions with no formal education in HTA or related sciences, there is no guarantee that the training will be successful. Language barriers limit the impact of international training courses in English. Language limitations, together with quality considerations, are factors that influence the potential transferability and generalizability of local-language studies, which are frequently not referenced in the international databases.

The potential solution while operating in a narrow pool of high-quality economic studies can be generalizability or simplified transferability of economic evaluations across countries with defined similarities in healthcare systems and economic development [6]. The need for simple transferability of health economic studies is potentially more important in countries with limited scientific and financial resources for conducting economic evaluations, as it is in many countries of the CEE and former Soviet Union [2,5,7]. In this study we analyzed the scope of transferability issues that are addressed in published peer-reviewed English-language economic evaluations based in healthcare settings of the CEE and former Soviet countries with a recently formed or no centralized HTA agency. The research aim was operationalized by the following research questions:

1) What are the background characteristics of economic evaluations conducted in healthcare settings of CEE and former Soviet countries and published in English-language peer-review journals?
2) What is the quality of the retrieved studies based on Drummond's check-list for assessing economic evaluations?
3) To what extent is the transferability of economic evaluations addressed in the retrieved studies?
   a) In what respect were local and foreign inputs used in economic evaluations?
   b) Are the transferability of the inputs and the results of the study frequently discussed in these publications?

Methods

In September 2013, a systematic search for scientific literature on cost-effectiveness studies conducted in the selected CEE and former Soviet countries was performed (Armenia, Azerbaijan, Belarus, Bulgaria, Estonia, Georgia, Turkmenistan, Kazakhstan, Lithuania, Macedonia, Moldova, Romania, Russian Federation, Serbia,

Slovenia, and Ukraine). The methodology applied in this review was based on the recommendations of the CRD's guidance for undertaking reviews in healthcare by the University of York [9].

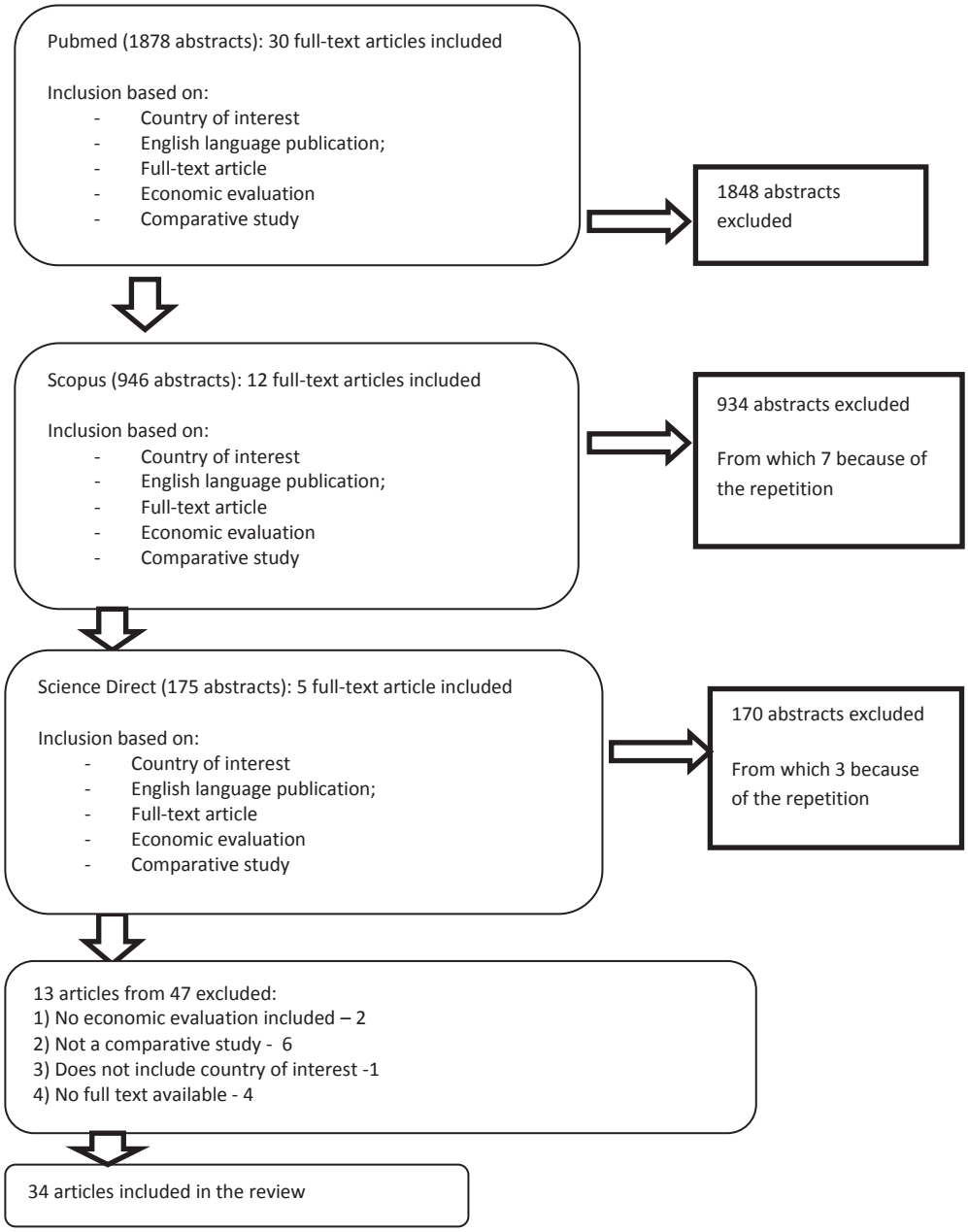

Figure 3.1 Flowchart outlining paper selection process for the systematic review

Data search

The search, selection, and analysis of the relevant articles were performed in a three-step procedure (Figure 3.1): initial assessment of the title, abstract, and keywords (Step 1); a full-text assessment of the selected references (Step 2); and analysis of the articles that fully corresponded to the inclusion criteria (Step 3). The search terms applied to full texts of publications in the PubMed database were as follows: "economic evaluation" + "country" (one from those indicated above); "cost" + "country". The extended search for key words within abstracts ("economic evaluation" + "country", "cost*" +"country") was conducted in the Science Direct and Scopus databases. The difference in search conditions among databases was highlighted by the unlimited number of word combinations appearing if the term "cost*" was searched in PubMed.
The following exclusion criteria were applied for Step 1: study older than 5 years (<2008) based on the publication-date of the ISPOR task force report on transferability in 2009 [10]; abstract not available, study written in a language other than English.

The inclusion criteria for Step 1 were the following: study includes at least one country of interest, study includes an economic evaluation, study published as a peer-reviewed article (abstract only, or congress report excluded) in the English language.

Full texts of the publications were analyzed on correspondence to the inclusion criteria during the second step: study includes comparative economic evaluation, conducted in healthcare setting of at least one country of interest, full text of the study available. Both trial-based and model-based economic evaluations were eligible for inclusion. All references included in the second step were summarized in the dataset with the following information: main author and year of publication, whether it is an economic evaluation or not, inclusion of a direct comparison of two or more technologies, countries included in the assessment, full text availability, decision on inclusion in the systematic review. Hard copies of potentially relevant full-text articles were received. Authors of the articles which corresponded to all inclusion criteria except full-text availability were contacted. If no full text of the article was received, the publication was withdrawn from the analysis, and the reason for this was recorded.

Data extraction and reporting

The following information was summarized from the included studies:

1) Technical characteristics of the publications: country and affiliation of the main and corresponding author (if differ), study sponsorship and type of sponsorship indicated.

2) Study characteristics: countries of analysis, clinical area, study technology and comparators, type of analysis and methods used, perspective, application of discounting, costs assessment (technology, medical, and productivity costs), outcome measure, type of sensitivity analysis applied.

3) Quality assessment using Drummond's check-list for assessing economic evaluations [11].

4) Use of local inputs for the main data categories according to Barbieri et al. [12]: baseline risk, treatment effect, health state preference values (utilities), resource utilization, unit costs (prices).

5) Addressed limitations regarding foreign data use and transferability of the received results to other jurisdictions.

The articles were assessed independently by two researchers (OM and either SK, ZK or JLS). The results of the two independent assessments during the third step were compared, and any disagreements were discussed. If no consensus was reached, a third researcher was involved in the final decision making.

Results

Out of the 47 full-text publications, 34 articles [13-46] were included in the systematic review. Fifteen of the studies (44%) had a main author (and corresponding authors, if different) not from a study country (Western European countries, the UK, or the USA). An academic establishment was the most common affiliation of the main author (25 or 74% of the studies). The study's sponsorship was indicated in 22 (65%) publications; of these, pharmaceutical companies sponsored 5 and conducted 2 more studies.

Background characteristics of economic evaluations

Some background characteristics of the studies are described in Table 3.1. In short, the majority of the retrieved studies were conducted in healthcare settings of Bulgaria, the Russian Federation, Slovenia, Lithuania, and Ukraine. The retrieved studies also included six cross-country studies, which additionally analyzed the application of a technology in Croatia, Tajikistan and Uzbekistan. Infectious diseases were the most frequently addressed topics in publications (16 or 47% of all studies), and the most frequently funded (87% of infectious disease studies were funded in comparison to 44% of all the other evaluations). Besides pharmaceutical companies, the other sponsors of studies on infectious diseases were international organizations, European and the USA grant committees, Ministries of Health or universities. In studies considering chronic disease topics, different cardiologic interventions and diabetes drugs were the most frequently addressed. Medicines were the most frequently researched interventions, among which vaccines had a significant share. Healthcare, governmental, or healthcare payor perspectives were predominant in the analyzed publications. Models were applied in two-third of the studies (Markov model was frequently used). Cost-utility analysis, with

quality-adjusted life years (QALY) at the effect side, was applied in more than half of the evaluations.

Table 3.1 Frequencies of the studies rankings by characteristics (34 articles in total)

Parameters	N (%)[1]
Perspective of the study is stated[2]	23 (68%)
Health care, state, or health care payer	25 (74%)
Societal	5 (15%)
Provider	3 (9%)
Employer	1 (3%)
Patient	1 (3%)
Discounting applied	21 (62%)
Both costs and outcomes are discounted at 3% (% from model studies)	10 (43%)
Both costs and outcomes are discounted at 5% (% from model studies)	4 (17%)
Unequal discounting for costs and effects (% from model studies)	4 (17%)
Productivity costs included	5 (15%)
Outcomes used	
Quality adjusted life years [3]	18 (53%)
Life-years gained	13 (38%)
N of cases/deaths averted	6 (18%)
Disability adjusted life years	5 (15%)
Sensitivity assessed[4]	27 (79%)
Probabilistic sensitivity analysis reported (% from model studies)	11 (47%)
Only univariate analysis	11 (32%)
Only univariate with multivariate analyses	4 (12%)
Bootstrap	1 (3%)

[1] Rounding is applied; [2] Number of studies used several perspectives; [3] One study assessed quality of life using WHOQOL-BREF instrument; [4] Two studies indicated that sensitivity analysis was applied, but did not report the results

Quality of economic evaluations

The summary of the assessment of the articles is presented in Table 3.2.

Table 3.2 Frequencies of the studies' rankings by Drummond's check-list for assessing economic evaluations, use of local data and transferability addressed (34 articles in total)

Parameters	Yes	Partially	No	Unclear
Comprehensive description of alternatives given	27 (79%)	0	6 (18%)	1 (3%)
Effectiveness is established	22 (65%)	3 (9%)	2 (6%)	7 (20%)
All relevant costs included	18 (53%)	0	6 (18%)	10 (29%)
All relevant outcomes included	29 (85%)	2 (6%)	3 (9%)	0
Costs measured accurately in appropriate units	17 (50%)	0	1 (3%)	16 (47%)
Outcomes measured accurately in appropriate units	26 (76%)	5 (15%)	1 (3%)	2 (6%)
Outcomes and costs valued credibly	13 (38%)	5 (15%)	3 (9%)	13 (38%)
Incremental analysis performed	27 (79%)	1 (3%)	4 (12%)	1 (3%)
Uncertainty addressed	12 (35%)	11 (32%)	9 (26%)	2 (6%)
Results include issues of purchasers concern	18 (53%)	7 (21%)	5 (15%)	4 (12%)
Conclusions justified by the evidence presented	25 (74%)	4 (12%)	5 (15%)	0
Results can be applied to the local population	31 (91%)	1 (3%)	1 (3)%	1 (3%)
Unit costs retrieved from local data	28 (82%)	4 (12%)	1 (3%)	1 (3%)
Resource utilization retrieved from local data	23 (68%)	2 (6%)	1 (3%)	8 (24%)
Utility parameters retrieved from local data	1 (3%)	0	0	0
Baseline risk received from local data	23 (68%)	2 (6%)	0	0
Treatment effect received from local data	15 (44%)	2 (6%)	16 (47%)	1 (3%)
Transferability of study to other jurisdiction was discussed	4 (12%)	8 (24%)	22 (65%)	-
Limitations of the results regarding foreign data used [2]	4 (16%)	4 (16%)[a]	17 (68%)	9 (26%)

[1] Rounding is applied; [2] from applicable

Using Drummond's check-list for assessing economic evaluations (including considerations of internal and external validity of the study, such as methodology applied and healthcare setting) we observed that the following criteria were ranked as “no” and “unclear” in more than 30% of studies: perspective stated, all relevant costs included, costs measured accurately in appropriate units, outcomes and costs valued credibly, and uncertainty addressed. Appraisal criteria such as comprehensive description of alternatives given, all relevant outcomes included, outcomes measured accurately in appropriate units, outcomes and costs adjusted for different times, incremental analysis performed, and conclusions justified by the evidence presented, were ranked as “yes” more than other Drummond criteria. Insufficient information on costs components and assessment methods frequently made it impossible to evaluate the quality of these data.

Address of transferability in economic evaluations

In 10 out of the 23 studies the use of a country-adapted model was clearly stated. The frequencies on other transferability issues ranking are presented in Table 3.2. Unit costs were most frequently based on local data; there was only one study which did not apply local unit costs. The baseline risk and resource utilization were also frequently assessed using local inputs, while the utility parameters were clearly identified as local in only one study.

Limitations of the results regarding the use of foreign data were discussed at least partially in 8 studies, and 12 studies at least partially discussed the transferability of study results to other jurisdictions. Several studies briefly discussed the generalizability of the results or individual parameters (such as baseline risk, prevalence), while the studies of Berkhof et al. [15] and Winetsky et al. [46] generalized the received results to the other countries of the region (or conducted a simple transferability assessment).

Discussion

The results of this systematic review of economic evaluations conducted in CEE and former Soviet countries allowed us to conclude a low transparency of data reporting in the analyzed publications as well as insufficient consideration of inputs and results transferability in these studies.

Background characteristics of economic evaluations

We did not observe any proportional difference in the number of available English-language peer-review publications referenced in the international databases based on the country’s size or level of HTA development. While the topic of the study may be sponsorship-driven, the number of publications submitted to international journals may depend on publication activity of the local research teams. This conclusion is

supported by the observation that in the countries with a relatively high number of publications (such as Bulgaria and Lithuania) the articles are frequently published by the same research teams. Additionally, we observed a trend for sponsored studies and for studies conducted under international co-authorship (either the first author or the corresponding author is not affiliated with the study country) to be of higher quality as assessed by Drummond's criteria. While it could be noticed that studies on some technologies were of better quality (e.g., vaccines), we believe that the main factor influencing study quality is the authors' affiliation and source of sponsorship. A similar observation of higher quality of economic studies conducted by international rather than local teams was made in a systematic review of economic studies in Vietnam [47].

While it appears that medical interventions other than pharmaceuticals as well as studies on chronic conditions may be of higher interest for the decision makers, the analyzed publications tend to present more analysis related to drug treatment, especially vaccination, and focus more on infectious diseases than on chronic diseases.

Despite the fact that most guidelines on economic evaluations recommend using the societal perspective [48], its application in CEE and former Soviet countries is limited. Only a few studies used a limited or not purely societal perspective as defined by the ISPOR task force report [49]. Data availability and decision makers' acceptance are the key factors in defining the perspective of the study [10] which, in the studied countries, majorly concern healthcare or third-party payors.

Quality of economic evaluations

Insufficient quality of economic evaluations is the first knock-out criterion in assessment of studies' transferability [50] and lack of transparency in the reporting of health economic studies is the major concern of decision makers around the world [3, 51]. At the same time we observed a significant indistinctness in reporting the methodology of economic evaluations conducted in healthcare settings of CEE and former Soviet countries. This reporting approach may improve by using standardized instruments, such as the CHEERS statement [52].

Absence of a clearly stated perspective of the study causes difficulties in the assessment of both the credibility of the study and its application in the decision making context. The description of the economic model used and its authorship was frequently lacking. Together with missing reporting on internal and external (between-model) validation [53], this may create difficulties for the transferability of study results.

While costs measurement fully depends on the perspective of the analysis, both type of input data should be transparent, appropriately documented and available for readers [49].

However, incompleteness of data, the sample size required to estimate population-representative costs and effects, data heterogeneity and generalizability of

trials' results are required [53], but rarely reported, in the trial-based economic evaluations conducted in healthcare settings of CEE and former Soviet countries. At the same time in countries with high data uncertainty, comprehensive probabilistic sensitivity assessment in modeled studies may improve the perceived quality (or reliability) of a study and thus the use of economic evaluations in the decision-making process [3].

Consideration of transferability of economic evaluations

While economic evaluations conducted in CEE and former Soviet countries typically apply local costs, baseline risk and resource utilization measurement, the effectiveness and utilities are frequently extrapolated from other countries or international studies. This observation corresponds to the conclusions of other authors defining baseline risk, unit costs, and resource use as parameters of low transferability [12, 54] and is supported by the results of expert interviews conducted on the use and transferability of economic evaluations to CEE and former Soviet countries (chapter 2).

Many guidelines recommend using utility values from the jurisdiction of interest [10]. The evidence suggests that utilities may vary between countries [55]. Meanwhile, taking into account the data constraints, the decision makers from CEE and former Soviet countries may review generalizability of outcomes while addressing its uncertainty using statistical approaches.

Moreover, we observed that the limitations of foreign data use, as well as the possibility of transferring the study to the other jurisdictions, are rarely described in the analyzed publications. Clear presentation of these parameters together with defining major impact factors on the results of economic evaluations and addressing data uncertainty will improve the transferability of studies.

Limitations

This study is limited to the study selection criteria: 1) English-language publications only; 2) studies published from 2008 onward; 3) articles with full-text availability. Search limitations could result in non-inclusion of some of the relevant studies. Drummond's criteria were used to assess the quality of economic evaluation. This instrument is a general questionnaire and does not provide a total scoring of the quality of the assessed papers, leaving the conclusion on each article to the subjective judgment of the people assessing it. Because of the limited number of selected articles, the study does not have the statistical power to provide an assessment of relationships between different characteristics.

Conclusion

Because of the limited HTA capacity, geographic transferability is an important alternative to following an evidence-based decision-making process in many of the CEE and former Soviet countries [56]. Meanwhile, countries of the CEE and former Soviet region require an adapted approach to addressing the use and transferability of economic evaluations in healthcare decision making. Because of the information (data and knowledge) constraints, this approach may not always correspond to the international guidelines on economic evaluations or practices used in HTA-experienced countries. As such, healthcare (or third-party payor) perspectives may be preferable to a societal one, and the generalizability of utilities may be considered to be appropriate, while local data should be used for baseline risk, unit costs, and resources consumption.

To simplify the transferability of published studies to the other jurisdictions, uncertainty, the impact of influential parameters, and data transferability should be comprehensively addressed when reporting studies. Additionally, the transparency of study reporting, especially study perspective, model details, and costing methodology, should be improved significantly.

References

1. Bingefors K, Pashos PC, Smith MD, Berger ML. Health Care Cost, Quality, and Outcomes: ISPOR Book of Terms. Lawrenceville, NJ: International Society for Pharmacoeconomics & Outcomes Research; 2003.
2. Danko D. Health technology assessment in middle-income countries: recommendations for a balanced assessment system. J. Mark. Access & Health Policy. 2014; 2:1-10.
3. Drummond M, Brown R, Fendrick AM, Fullerton P, Neumann P, Taylor R, Barbieri M. Use of Pharmacoeconomics Information—Report of the ISPOR Task Force on Use of Pharmacoeconomic/Health Economic Information in Health-Care Decision Making. Value Health. 2003; 6:407-416.
4. The World Bank. Middle Income Countries Overview. 2011. Available from: http://www.worldbank.org/en/country/mic/overview. [Assessed on 17 May 2014].
5. Kolasa K, Kalo Z, Zah V, Dolezal T. Role of health technology assessment in the process of implementation of the EU Transparency Directive: relevant experience from Central Eastern European countries. Expert Rev. Pharmacoecon. Outcomes Res. 2012;12:283-287.
6. Gulacsi L, Orlewska E, Pe´ntek M. Health economics and health technology assessment in Central and Eastern Europe: a dose of reality. Eur. J. Health Econ. 2012;13:525–531.
7. Kaló Z, Bodrogi J, Boncz I, Józsa C, Jona G, Kövi R, Pásztélyi Z, Sinkovits B. Capacity Building for HTA Implementation in Middle-Income Countries: The Case of Hungary. Value Health Reg. Issues.2013;2:264 – 266.
8. EUnetHTA Work Package 8. EUnetHTA Handbook on Health Technology Assessment Capacity Building. Catalan Agency for Health Technology Assessment and Research. Catalan Health Service. Department of Health Autonomous Government of Catalonia Barcelona, Spain;2008.
9. CDR. Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking systematic reviews in health care. University of York, York; 2009.
10. Drummond M, Barbieri M, Cook J, Glick HA, Lis J, Malik F, Reed SD, Rutten F, Sculpher M, Severens J. Transferability of economic evaluations across jurisdictions: ISPOR Good Research Practices Task Force report. Value Health. 2009;12:409–418.
11. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the economic evaluation of health care programme. Third edition. Oxford: Oxford University Press; 2005.
12. Barbieri M, Drummond M, Rutten F, Cook J, Glick HA, Lis J, Reed SD, Sculpher M, Severens JL. What Do International Pharmacoeconomic Guidelines Say about Economic Data Transferability? Value Health. 2010;10:1098-3015.
13. At'kov OY, Azarov AV, Zhukov DA, Nicoloyannis N, Durand L. Influenza vaccination in healthy working adults in Russia. Observational study of effectiveness and return on investment for the employer. Appl. Helth Econ. Health Policy. 2011;9:89-99.
14. Alistar SS, Owens DK, Brandeau ML. Effectiveness and Cost Effectiveness of Expanding Harm Reduction and Antiretroviral Therapy in a Mixed HIV Epidemic: A Modeling Analysis for Ukraine. PLoS Med. 2011;8.
15. Berkhof J, Bogaards JA, Demirel E, Diazb M, Sharmac M, Kim JJ. Cost-Effectiveness of Cervical Cancer Prevention in Central and Eastern Europe and Central Asia. Vaccine. 2013; 31S: 71–79.
16. Cecchini M, Sassi F, Lauer JA, Lee YY, Guajardo-Barron V, Chisholm D. Chronic Diseases: Chronic Diseases and Development. Tackling of unhealthy diets, physical inactivity, and obesity: health effects and cost-effectiveness. Lancet. 2010;376:1775–84.
17. Cornier N, Petrova E, Cavailler P, Dentcheva R, Terris-Prestholt F, Janin A, Ninet B, Anguenot JL, Vassilakos P, Gerbase A, Mayaud P. Optimising the management of vaginal discharge syndrome in Bulgaria: cost effectiveness of four clinical algorithms with risk assessment. Sex. Transm. Infect. 2010;86:303-309.

18. De Smedt D, Kotseva K, De Bacquer D, Wood D, De Backer G, Dallongeville J, Seppo L, Pajak A, Reiner Z, Vanuzzo D, Georgiev B, Gotcheva N, Annemans L. Cost-effectiveness of optimizing prevention in patients with coronary heart disease: the EUROASPIRE III health economics project. Eur. Heart J. 2012;33:2865–2872.

19. Floyd K, Hutubessy R, Kliiman K, Centis R, Khurievae N, Jakobowiak W, Danilovits M, Peremitin G, Keshavjee S, Migliori GB. Cost and cost-effectiveness of multidrugresistant tuberculosis treatment in Estonia and Russia. Eur Respir J. 2012;40: 133-142.

20. Griffiths UK, Clark A, Shimanovich V, Glinskaya I, Tursunova D, Kim L, Mosina L, Hajjeh R, Edmond K. Comparative Economic Evaluation of Haemophilus influenzae Type b Vaccination in Belarus and Uzbekistan. PLoS ONE. 2011;6. doi: 10.1371/journal.pone.0021472.

21. Ivanova A, Petrova G, Wrona W, Valov V, Stoimenova A, Czech M. Modelling the long-term effect of diabetes therapy. an example with liraglutide. Comptes rendus de l'Acad´emie bulgare des Sci. 2011;64.

22. Janković SM, Kostic M, Radosavljević M, Tešić D, Stefanović-Stoimenov N, Stevanović I, Raković S, Aleksić J, Folić M, Aleksić A, Mihajlović I, Biorac N, Borlja J, Vučković R. Cost-effectiveness of four immunomodulatory therapies for relapsingremitting multiple sclerosis: a Markov model based on data a Balkan country in socioeconomic transition. Vojnosanit Pregl. 2009;66:556-562.

23. Jit M, Yuzbashyan R, Sahakyanc G, Avagyand T, Mosinae L. The cost-effectiveness of rotavirus vaccination in Armenia. Vaccine. 2011;29:9104– 9111.

24. Kamusheva MS, Gerasimov N, Petrova GI. Intestinal Gel Levodopa + Carbidopa in Parkinson's Patients with Frequent and Prolonged Akinesia – An Economic Evaluation. Int. J. Pharm. Sci. Rev. Res. 2013; 22:244-246.

25. Lakic D, Bogavac-Stanojević N, Jelic´-Ivanovic´Z, Kotur-Stevuljevic´ J, Spasic´ S, Kos M. A Multimarker Approach for the Prediction of Coronary Artery Disease: Cost-Effectiveness Analysis. Value Health. 2010;13:770-777.

26. Lakić D, Petrova G, Bogavac-Stanojević N, Jelić-Ivanović Z, Kos M. The cost-effectiveness of hypertension pharmacotherapy in serbia: a markov model. Biotechnol. & Biotechnol. Eq. 2012;26:3066-3072.

27. Mihajlović J, Pechlivanoglou P, Sabo A, Tomić Z, Postma MJ. Cost-Effectiveness of Everolimus for Second-Line Treatment of Metastatic Renal Cell Carcinoma in Serbia. Clin. Ther. 2013;35:1909-1922.

28. Navers˘nik K, Mrhar A. Cost-Effectiveness of a Novel e-Health Depression Service. Telemed. J. E. Health. 2013;19:110-116.

29. Nizalova O, Vyshnya M. Evaluation of the impact of the mother and infant health project in Ukraine. Health Econ. 2010;19:107–125.

30. Obradovic M, Mrhar A, Kos M. Cost-effectiveness analysis of HPV vaccination alongside cervical cancer screening programme in Slovenia. Eur. J. Public Health. 2010;20:415–421.

31. Perikhanyan A. Effectiveness and cost-effectiveness of coronary artery bypass surgery versus drug eluting stents in Armenia: a feasibility study. Georgian Med. News. 2011;6:44-50.

32. Petrova G, Ivanova A, Czech M, Valov V, Wrona W, Niewada M, Savova A. Liraglutide vs. exenatide in combination with metformin and/or sulfonylurea therapy in type 2 diabetes mellitus therapy in bulgaria. a modelling study. Comptes rendus de l'Acad´emie bulgare des Sci. 2011;64:1507-1514.

33. Sava FA, Yates B, Lupu V, Szentagotai A, David D. Cost-effectiveness and cost-utility of cognitive therapy, rational emotive behavioral therapy, and fluoxetine (Prozac) in treating depression: a randomized clinical trial. J. Clin. Psychol. 2009;65:36-52.

34. Sirli R, Sporea I, Martie A, Popescu A, Dănilă M. Contrast enhanced ultrasound in focal liver lesions--a cost efficiency study. Med Ultrason. 2010. 12, 280-5.

35. Smit R. Explanation of "cost-effectiveness of tick-borne encephalitis vaccination in Slovenian adults". Vaccine. 2014; 32:1227-8.

36. Bogavac-Stanojević N, Dopsaj V, Jelić-Ivanović Z, Lakić D, Vasić D, Petrova G. Economic evaluation of different screening alternatives for patients with clinically suspected acute deep vein thrombosis. Biochem. Med. (Zagreb). 2013;23:96-106.

37. Jasmina T, Genchev G, Savova A, Dantchev N, Petrova G. Cost-effectiveness and activities of daily living in patients with complex regional pain syndrome type I. Int. J. Pharm. Sci. Rev. Res. 2012;17:16-21.

38. Tole SP, Sanders GD, Bayoumi AM, Galvin CM, Vinichenko TN, Brandeau ML, Owens DK. Cost-effectiveness of voluntary HIV screening in Russia. Int J STD AIDS. 2009;20:46-51.

39. Uusküla A, Müürsepp A, Kawai K, Raag M, Jürisson M, Pillsbury M. The epidemiological and economic impact of a quadrivalent human papillomavirus (HPV) vaccine in Estonia. BMC Infect Dis.2013;13.

40. Valov V, Palmer J, Czech M, Savova A, Petrova G. Cost-effectiveness of biphasic insulin aspart 30 vs. human premix insulin in type 2 diabetes from the payer's perspective in Bulgaria. Biotechnol. & Biotechnol. 2012;26:2937-2944.

41. Vanagas G, Padaiga Z. Healthcare spending in the case of a HPV16/18 population-wide vaccination programme. Scand. J. Public Health. 2012;40:406-11.

42. Vanagas G, Padaiga Z, Kurtinaitis J, Logminiene Z. Cost-effectiveness of 12- and 15-year-old girls' human papillomavirus 16/18 population-based vaccination programmes in Lithuania. Scand. J. Public Health. 2010;38:639-47.

43. Vanagas G, Padaiga Z, Mickevičienė A. Cost-effectiveness and cost-utility of the treatment of chronic hepatitis B with peginterferon alfa-2a, interferon alfa, and lamivudine in Lithuania. Medicina (Kaunas). 2010;46:835-42.

44. Vanagas G, Padaiga Z, Bagdonas E. Cost-utility analysis of methadone maintenance treatment in Lithuania. Medicina (Kaunas). 2010;46:286-92.

45. Vassall A, Chechulin Y, Raykhert I, Osalenko N, Svetlichnaya S, Kovalyova A, van der Werf MJ, Turchenko LV, Hasker E, Miskinis K, Veen J, Zaleskis R. Reforming tuberculosis control in Ukraine: results of pilot projects and implications for the national scale-up of DOTS. Health Policy Plan. 2009;24:55-62.

46. Winetsky DE, Negoescu D, DeMarchis EH, Almukhamedova O, Dooronbekova A, Pulatov D, Vezhnina N, Owens DK, Goldhaber-Fiebert JD. Screening and rapid molecular diagnosis of tuberculosis in prisons in Russia and Eastern Europe: a cost-effectiveness analysis. PLoS Med. 2012;9.

47. Tran BX, Nong VM, Maher RM, Nguyen PK, Luu HN A Systematic Review of Scope and Quality of Health Economic Evaluation Studies in Vietnam. PLoS ONE. 2014; 9(8): e103825. doi:10.1371/journal.pone.0103825.

48. Knies S, Severens JL, Ament AJHA, Evers SMAA. The transferability of valuing lost productivity across jurisdictions. Differences between national pharmacoeconomic guidelines. Value Health. 2010;13:519-527.

49. Hay JW, Smeeding J, Carroll NV, Drummond M, Garrison LP, Mansley EC, Mullins CD, Mycka JM, Seal B, Shi L. Good Research Practices for Measuring Drug Costs in Cost Effectiveness Analyses: Issues and Recommendations: The ISPOR Drug Cost Task Force Report—Part I Value Health. 2010;13:3-7.

50. Welte R, Feenstra T, Jager H, Leidl R. A decision chart for assessing and improving the transferability of economic evaluation results between countries. Pharmacoeconomics.2004;22:857–876.

51. Erntoft S. Pharmaceutical Priority Setting and the Use of Health Economic Evaluations: A Systematic Literature Review Value Health. 2011;14:587-599.

52. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, Augustovski F, Briggs AH, Mauskopf J, Loder E. CHEERS Task Force. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. BMJ. 2013;346.

53. McGhan WF, Al M, Doshi JA, Kamae I, Marx SE, Rindress D. The ISPOR Good Practices for Quality Improvement of Cost-Effectiveness Research Task Force Report. Value Health. 2009;12:1086-99.

54. Goeree R, Burke N, O'Reilly D, Manca A, Blackhouse G, Tarride JE. Transferability of economic evaluations: approaches and factors to consider when using results from one geographic area for another. Curr. Med. Res. Opin. 2007;23:671-682.

55. Knies S, Evers SM, Candel MJJM, Severens JL, Ament AJHA. Utilities of the EQ-5D: transferable or not? Pharmacoeconomics. 2009;27:767-779.

56. Goeree R, He J, O'Reilly D, Tarride JE, Xie F, Lim M, Burke N. Transferability of health technology assessments and economic evaluations: a systematic review of approaches for assessment and application. Clinicoecon Outcomes Res. 2011;3:89-104.

Appendix 3.1 Ranking of the studies using Drummond's check-list for assessing economic evaluations a

Author, year	Per-spect-ive[1]	Rese-arch question[1]	Descript-ion of alter-natives	Estab-lished effect-iveness	Rele-vant costs	Rele-vant out-comes	Costs in appro-priate units	Out-comes in appro-priate units	Outcome s & costs credi-bility	Dis-count-ing	Incre-mental ana-lysis	Un-certain-ty ad-dressed	Results of pur-chasers concern	Con-clusion justi-fied
Alistar, 2011	No	Yes	Yes	U[1]	U[2]	Yes	U[3]	Yes	U[4]	Yes	Yes	Yes	Yes	Yes
At'kov, 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	U[5]	NA	NA[6]	Yes	Yes	Yes
Berkhof, 2013	No	P	Yes	P[7]	Yes	Yes	No[8]	Yes	P[9]	Yes	Yes	Yes	Yes	Yes
Bogavac-Stanojević, 2013	Yes	Yes	Yes	U[10]	No[11]	Yes	U[12]	Yes	U[12]	NA	Yes	P[13]	P[14]	Yes
Cecchini, 2010	No	P	Yes	Yes	U[15]	Yes	U[12]	Yes	U[12]	Yes	Yes[16]	Yes	Yes	Yes
Cornier, 2010	Yes	Yes	Yes	U[17]	Yes	Yes	Yes	Yes	Yes	NA	No	No[18]	Yes	Yes
DeSmedt, 2012	No	Yes[19]	No	Yes	No[20]	Yes	U[12]	Yes	U[12]	No	Yes	U[21]	U[22]	Yes
Floyd, 2012	Yes	P	Yes	No[23]	Yes	Yes	Yes	Yes	No[24]	No	Yes	Yes	P	No[25]
Griffiths, 2011	Yes	Yes	Yes	Yes	No[26]	Yes	Yes	Yes	U[27]	Yes	Yes	P[18]	P	Yes
Ivanova, 2011	Yes	Yes	No	Yes	No[28]	Yes	U[12]	U[12]	U[12]	Yes	Yes	U	No	Yes

Janković, 2009	Yes	Yes	No[29]	Yes	No[30]	Yes	Yes	Yes	Yes	Yes	P	Yes	P[31]	Yes
Jasmina T., 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	No[32]	U [33]	No[34]
Jit, 2011	Yes	P	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	P	Yes	Yes
Kamusheva, 2013	Yes	P	No	No[35]	No[36]	No[37]	U	No[38]	P [39]	No	Yes	No	No[40]	No[41]
Lakic, 2010	Yes	Yes	Yes	Yes	Yes	No[42]	Yes	Yes	Yes	NA	Yes	P[13]	P[43]	Yes
Lakic, 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	P[13]	Yes	Yes
Mihajlović, 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	P[44]	Yes	Yes	Yes	Yes	Yes
Naversnik, 2013	Yes	Yes	U	U[45]	Yes	P[46]	U[12]	P	U	NA	Yes	Yes	U[47]	Yes
Nizalova, 2010	No	No	Yes	Yes	U[12]	No[48]	U[12]	P	Yes	NA	No	No	No[49]	P
Obradovic, 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Perikhanyan, 2011	Yes	P	Yes	Yes	U[12]	Yes	U[12]	Yes	U [12]	No	Yes	Yes	U[50]	No[51]
Petrova, 2011	Yes	Yes	No[52]	Yes	Yes	Yes	U[12]	Yes	U [12]	Yes	Yes	P[13]	No	P [53]
Sava, 2009	No	Yes	Yes	Yes	U[12]	Yes	U[12]	P [16]	No[54]	No	No	No	No [55]	No[56]
Sirli, 2010	No	No	Yes	P[57]	U [58]	P[59]	Yes	P[60]	No[61]	NA	Yes	No	Yes	P[62]
Smit, 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Tole, 2009	No	Yes	Yes	U[63]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	P[13]	Yes	Yes
Uukula, 2013	No	Yes[64]	Yes	U[65]	U[66]	Yes	Yes	Yes	Yes	Yes	Yes	P[13]	Yes	Yes
Valov, 2012	Yes	Yes	Yes	Yes	Yes	Yes	U[12]	Yes	Yes	Yes	Yes	P[67]	Yes	Yes
Vanagas, 2010	No	Yes	Yes	Yes	U [66]	Yes	U[12]	Yes	P[3]	Yes	Yes	P [13]	Yes	Yes
Vanagas, 2010	No	Yes	No[68]	P [69]	Yes	Yes	U[12]	P	U. for costs[12]	NA	No	No	P[69]	P [69]
Vanagas, 2010	Yes	Yes	Yes	Yes	U[12]	Yes	U[12]	Yes	U [70]	Yes	Yes	P[13]	Yes	Yes
Vanagas, 2012	Yes	Yes	Yes	Yes	U[12]	Yes	U[12]	Yes	U[12]	Yes	U[12]	No	P[71]	Yes
Vassal, 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	P[16]	Yes	No	Yes	Yes
Winetsky, 2012	Yes	Yes[64]	Yes	U[12]	Yes	Yes	Yes	U[72]	P[73]	P[16]	Yes	Yes	Yes	Yes

[a] Four assessment types were used: Unclear – U; Partially – P; Yes; No.

[1]Certain parameters reference to the specific small districts and so can differ; [2] Direct costs only, perspective is not clear; [3] No detailed costs description; [4]No relevant description; [5] More information required; [6] Cost saving; [7] "No" for screening; [8] Assessment and source of costs and volume data; [9] "No" for costs; [10] No information on statistical significance between the groups; [11] Costs in case of false-positive result are ignored; [12] Insufficient information; [13] Not explicit; [14] No other studies comparison; [15] No clear perspective; [16]"Yes" for costs; [17] Small sample, no randomization; [18] Limited; [19] Also Partially; [20] No clear cost description and perspective stated; [21] Value is not clear; [22] Not clear who is a decision maker; [23] Observation is made on the small groups; [24] Costs are not up-to-date, methods for disability adjusted life years (DALY) is not clear; [25] In regard to costs components and extrapolation; [26] No indirect costs; [27] Indian data are used for meningitis rate in Uzbekistan; [28] Health care facility visit costs with no other costs description; [29] Comparators are not described; [30] Out of pocket costs, informal and formal care are missing; [31] No comparison between alternatives; [32] Not reported; [33] Not clear what is a meaning of received incremental cost-effectiveness ratio (ICER) for decision makers; [34] Inappropriate comparison with a threshold; [35] Unified Parkinson's Disease Rating Scale measure at two time points, no time horizon, only 12 patients on different retrospective controls; [36] Only drugs cost included; [37] Only Unified Parkinson's Disease Rating Scale, side-effects, long-term effect are missing; [38] Difference in effect measurement between treatment and control; [39] No for outcomes; [40] Alternatives and costs omitted; [41] Inappropriate comparison with threshold; [42] Life expectancy and quality adjusted life years (QALY) are missing; [43] Long-term effect is missing; [44] Administration and hospitalization costs are missing, one-expert assessment is done for some items; [45] Small sample from a local trial; [46] Utility values are based on

mapping from clinical status; [47] Difference of perspectives in aim and discussion; [48] Missing life years gained, value of life is taken from economically different country; [49] Incremental cost-effectiveness ratio (ICER) is missing, no generalizability is discussed; [50] Unclear how much study is of interest using patients' perspective; [51] Possible selection bias for outcomes, perspective in discussion doesn't correspond to the study; [52] One comparator, no arguments for selection; [53] Body mass index impact in the discussion; [54] Costs are protocol driven, no source data and clarity on utilities calculation; [55] No generalizability, protocol driven costs, generic price omitted, uncertainty ignored; [56] Protocol driven costs, no generalizability; [57] Sensitivity and specificity are not addressed; [58] No perspective indicated, cost of side effect omitted; [59] No perspective stated, false results ignored, only surrogate outcome; [60] Sensitivity and specificity are ignored; [61] Unclear for costs; [62] No correction for false positive and false negative cases; [63] Uncertain screening effectiveness data; [64] But also partially; [65] Reference to unpublished clinical data; [66] No clarity on the perspective; [67] Limited to population uncertainty; [68] Incomplete description; [69] For a short run; [70] Insufficient information for costs, outcomes are taken from Asian studies; [71] No comparison with other studies, except their own study; [72] Insufficient information on quality adjusted life years (QALY) calculation; [73] Many costs are based on Tajikistan data and assessed by interviews.

Appendix 3.2 Rankings of the studies by transferability parameters

Author, year	Results can be applied to the local population	The unit costs retrieved from local data	The resource utilization retrieved from local data	The utility parameters retrieved from local data	The baseline risk received from local data	The treatment effect received from local data	Transferability issues were discussed (for other jurisdiction)	Limitations of the results regarding foreign data be used
Alistar, 2011	Yes	Yes (reference to reports on Ukraine)	Unclear (insufficient information)	No (not indicated, assessed by reference)	Yes	No (behavioral risk)	Partially (Generalizability discussed)	No
At'kov, 2011	Yes	Yes	Yes	NA[1]	Yes	Yes	Partially (limited)	NA[1]
Berkhof, 2013	No (cost assessment may not be accepted)	Partially (more no than yes)	No (unified hypothetical approach)	No (not indicated, most probably by reference)	Yes	Partially (only for alternative - no action scenario)	No (but data were generalized between the countries)	Partially (limited)
Bogavac-Stanojević, 2013	Yes	Yes	Yes	NA[1]	Yes	Yes	No	NA[1]

Cecchini, 2010	Yes	Unclear (reference to multi-country analysis)	Unclear (certain parameters, as television watch are reported as local)	NA[1]	Yes	Unclear (insufficient information)	Partially (risks generalizability)	Partially (limited)
Cornier, 2010	Yes	Yes	Yes	NA[1]	Yes	Yes	Partially (the prevalence and internal generalizability)	NA[1]
DeSmedt, 2012	Yes	Yes	Unclear (insufficient information)	No	Yes	Yes	No	No
Floyd, 2012	Yes (but only for 1 region in Russia)	Partially (2d line drugs by the WHO)	Yes	NA	Yes	Yes	Partially (Generalizability discussed)	No
Griffiths, 2011	Yes	Partially (not treatment costs of meningitis sequelae)	Yes	NA	Partially (used when reliable local data are available)	No	No	No
Ivanova, 2011	Yes	Yes	Partially	No	No	No	No	Partially (limited)

Janković, 2009	Yes	Yes	Yes	No	No	No	Yes	No
Jasmina T, 2013	Yes	Yes	Yes	NA[1]	Yes	Yes	No	NA[1]
Jit, 2011	Yes	Yes	Yes	NA	No	No	No	Yes
Kamusheva, 2013	Yes	Yes	Unclear	NA[1]	Yes	Yes	No	NA[1]
Lakic, 2010	Yes	Yes	Yes	NA[1]	No	Yes	No	No
Lakic, 2012	Yes	Yes	Yes (assumption for some)	No	Yes	Partially (drug efficacy from literature)	No	No
Mihajlović, 2013	Yes	Yes	Yes	No	No	No	No	Yes
Naversnik, 2013	Yes	No (literature for service utilization costs from UK, stated in discussion)	Unclear	No	Yes	Yes	No	Yes
Nizalova, 2010	Yes	Yes	Yes	NA[1]	Yes	Yes	No	NA[1]

Obradovic, 2010	Yes	Yes	Yes	No	Yes	No	Partially (comparison of cost per service in Slovenia and European Union)	No
Perikhanyan, 2011	Yes	Yes	Yes	NA[1]	Yes	Yes	Partially (mentioning possibility to be used in other countries)	NA[1]
Petrova, 2011	Unclear	Yes	Unclear	No	No	No	No	No
Sava, 2009	Yes	Yes	Yes	No	Yes	Yes	No	NA[1]
Sirli, 2010	Yes	Yes	Yes	NA[1]	NA[1]	Yes	No	No
Smit, 2012	Yes	Yes	Yes	No	Yes	No	No	No
Tole, 2009	Yes	Yes	Yes	No	Yes	No	Yes	No
Uukula, 2013	Yes	Yes	Yes	No	Partially (cancer mortality -US)	No	No	No

Valov, 2012	Yes	Yes	Yes	No	Yes	No (RCT[2] IMPROVE is cross-country study, not including Bulgaria)	No	No
Vanagas, 2010	Yes	Yes	Yes	No	Yes	No	No	No (vaccination effect only)
Vanagas, 2010	Yes	Yes	Yes	Yes	NA[1]	Yes	No	NA [1]
Vanagas, 2010	Yes	Yes	Unclear	NA	No	No	No	Yes
Vanagas, 2012	Yes	Yes	Unclear	NA	Yes	No (effectiveness of vaccine is international RCT[2])	Yes	Partially (internal jurisdiction)
Vassal, 2009	Yes	Yes	Yes	No	Yes	Yes (program effect)	Partially (transferability within the country (the other regions))	No

Winetsky, 2012	Partially (yes for Tajikistan, cant tell - Russia, and Latvia)	Partially (Yes for Tajikistan, Partially for Russia and Latvia.)	Partially (yes for Tajikistan)	No	Yes	No	Yes	No

[1]NA – not applicable; [2]RCT –randomized controlled trial.

Part 2

Practical applicability of transferability principles

Chapter 4

Cost for treatment of chronic lymphocytic leukemia in specialized institutions of Ukraine

Mandrik O., Corro Ramos I., Zaliska O., Gaisenko A., Severens J.L. Value in Health Regional Issues. 2013; 2(2): 205-209.

Abstract

The aim of this study is to identify the cost of treatment for chronic lymphocytic leukemia (CLL) in specialized hospitals in Ukraine from a health care perspective and to understand if patient characteristics are related to these costs.

Cost analysis from a health care perspective was performed using retrospective data between 2006 and 2010 from patient-file databases of two specialized hospitals in Ukraine. Costs related only to CLL diagnosis (drug treatment and in-hospital expenses) were calculated. Uncertainty was assessed using bootstrapping and multivariate sensitivity analyses. Linear regression analysis was used to analyze if patients' characteristics have an impact on healthcare costs. Additionally one-way ANOVA (Welch test) and paired-sample t-test were conducted to compare mean costs of treatment between the two hospitals and difference in mean expenses for drugs and in-hospital stay.

The number of patients in the data was 145. The average annual cost for a patient's drug treatment is 2,047 EUR. The cost of hospitalization was significantly lower (t=5.026; Sig 2-tailed =0.000) and equal to 541 EUR per person, resulting in total expenditures of 2,589 EUR. Mean total costs in the bootstrap analysis were equal to 2,584 EUR (median 2,576 EUR, 97.5 percentile 3,223 EUR; 2.5th percentile 1,987 EUR). The regression analysis did not reveal a relation between sex of the patient, number of years a patient lives with the disease, and age at the time of hospitalization and healthcare costs, while hospital choice was an influential parameter (Beta=-0.260; Sig=.002). Significant difference in mean costs of two analyzed hospitals was also confirmed by one-way ANOVA (Welch statistics 19.222, p=0.000).

Drug treatment comprises the largest portion of total costs but differences between hospitals exist. Because many patients in Ukraine pay out of pocket for in-hospital drugs, these costs are a high economic burden for CLL patients.

Introduction

Globally, there are approximately 7.4 million cancer deaths per year, which is approximately 13% of deaths from all causes. Since the population of many countries around the world is aging, it can be expected that cancer incidence will increase [1]. Chronic hematologic malignancies are comparatively rare oncologic diseases. In Ukraine in 2010 the officially-registered total morbidity rate for patients with diagnosed leukemia was 7.8 per 100,000 people, of which 39.3% did not live a year after diagnosis [2]. Chronic lymphocytic leukemia (CLL) is the most frequent form of leukemia in Western countries, and it accounts for approximately 30–40% of all leukemias [3,4]. It is characterized by the clonal proliferation and accumulation of neoplastic B lymphocytes in the blood, bone marrow, lymph nodes, and spleen. Although the median age of patients at diagnosis is higher than retirement age and so has no significant impact on state productivity loss [5], the economic impact of CLL is significant due to long duration and high expenses related to treatment, combined with low cure rates. Nevertheless, early diagnosis and effective treatment of hematologic malignancies shifts the indicators of a patient's life expectancy to positive values [6]. For example, in the USA for the time period 1999-2005, 5-year survival for leukemia was 82% (79% for CLL), although in 1975-1977 this indicator was close to Ukrainian data – 35% [7,8].

In-hospital medical care to patients with CLL is generally provided in 35 hematologic departments, based in district hospitals (16), state city hospitals (12), oncologic dispensaries (4), and specialized Institutes of the National Academy of Medical Science of Ukraine (3) [2,9]. To the latter one belong two hematologic institutes and the National Cancer Institute, which is a leading state institution additionally responsible for methodological and scientific development in this clinical area. The treatment schemes for the patients with CLL are based on a clinical protocol that proposes a number of treatment options for CLL patients and was first developed and approved under an order of the Ministry of Health (MOH) of Ukraine in 2010 [10]. State pharmaceutical provision for adult oncologic patients is granted through a national treatment program "Oncology" for the years 2011-2016, although governmental financing is insufficient and drug treatment is usually paid out of pocket by patients [11].

Although CLL has a significant impact on patients' quality of life [12,13], studies exploring the economic costs and burden of hematologic malignancies are relatively sparse in English-language publications worldwide [14,15]. Possible reasons for such a lack of information appear to include the low incidence rate and aged study population (over 60 years old), which make broad, well-designed economic analyses a challenge for most researchers [5,16]. The limited cost reviews identified cost drivers for CLL as chemotherapy costs, intravenous immunoglobulin costs, transplantation costs and costs

associated with the differential staining cytotoxicity assay with the main cost drivers related to the treatment chosen [16].

The healthcare system itself, including organization of medical help to oncologic patients, is going through a stage of transformation, which includes implementation of a universal reimbursement system to begin 2016, and standardization of medical help with enhanced control on follow up of clinical protocols and more strict division between primary, secondary and tertiary levels of medical help. Taking into account that the major recipients of the central state budget are specialized institutions (tertiary level of help), the primary aim of this research was to identify the cost of treatment for CLL in specialized hospitals in Ukraine from a health care perspective and to understand if patient characteristics are related to these costs.

Methods

The study was conducted from a healthcare perspective and accounted direct medical costs with the aim of seeing which costs are going to be paid by the Ministry of Health after the health care system transformation.

Analysis included data from databases of two specialized hospitals that are the recipients of State financing through the national treatment program “Oncology”, - National Cancer Institute and State Institute of Hematology. These hospital databases were made in the programs Access and Word for the purpose of data storage and included all of the information available in hard copies of hospital cards; the data were typed into the hospital databases retrospectively by qualified personal (hospital assistants). Afterward, data from the two hospital databases were transferred into Excel and SPSS databases created for the purpose of data analysis.

The study population included all newly-diagnosed and relapsed patients (145 in total) who were hospitalized during the period from 2006-2010 with the diagnosis CLL and whose data were recorded in the electronic database. The information derived from the hospital cards (excluding patients’ identification information) contained the following data: sex of the patient, age during diagnosis and treatment, number of years a patient lives with the disease, year of treatment, therapies prescribed and duration of treatment, the number of hospitalizations per year and their duration. Stage of the patient's disease and health state on ECOG criteria were excluded from the factor list, as data on these parameters were frequently missing.

Costs related only to CLL diagnosis for the last observational year were calculated. These costs included drug expenses and in-hospital costs. The cost of diagnostics, medical procedures, hotel services, and medical personnel are included into the integral in-hospital cost, based on data of the economic department of the National Cancer Institute. These costs reflect the approximation of costs for oncologic patients in a

specialized hospital and are equal to 16.3EUR per patient-day (2010) [17]. Out-of-hospital healthcare costs were not calculated because according to the clinical protocol [10] treatment of CLL patients should be conducted only in hospital. The average length of hospital stay and drug costs were assessed by retrospective analysis of patient file data.

To assess drug usage, daily defined doses and total amount received during the year were recorded. To calculate drug costs we used a step-wise approach to determine an average price, depending on the availability of information: tariff in governmental purchases (2010); price, registered in the MOH; and distributors' price.

Multivariate sensitivity analysis was conducted. Price deviations for sensitivity test of all drugs were calculated using the minimum and maximum prices from the available sources (hospital purchases, state registered prices, and distributors' prices). There are no defined general tariffs for hospital stay in Ukraine, which are relatively low in comparison to medical costs in the European countries and may vary from 3.4 to 19.2 EUR (2010) [17-19].

All statistical analyses were performed in IBM SPSS Statistics 20 (SPSS Inc., Chicago, Illinois) and bootstrapping (1000 replications) was performed in Microsoft Excel 2010. To analyze if choice of the hospital, age and sex of a patient, have an impact on total health care costs, logarithmic data transformation was performed on the non-normally distributed costs and a linear regression analysis was applied. Because of frequently missing data for the parameter "stage of the disease", as a proxy for disease progression we included "number of years patient is living with the disease" in the linear regression analysis. Based on Cook's distance (0.028571), which measures the effect of deleting a given observation and so allows to define data points with large residuals, we excluded six outliers to improve the residuals plot and model validity. Simultaneously one-way ANOVA (Welch test) was conducted to compare mean costs of treatment in the two hospitals involved (asymptotically F distributed).

Paired-sample t-test was used to compare difference in mean expenses for drugs and in-hospital stay.

Results

Overall, data of 113 patients from the first hospital (State hematology institute) and of 32 patients from the second hospital (National Cancer Institute) were analyzed. Patients were aged 40 to 85 (mean age 62.9, mean age during diagnosis 60.3, s.d. 9.8). From the sample, 27.6% (40 patients) were newly diagnosed Due to the limited sample size, the distribution of patients by sex was not equal in different age groups with total proportion of males equal to 60.7% (88 men).

Values of the cost items (drugs) and cost deviations for sensitivity test are presented in Table 4.1.

Table 4.1 Price values of the drugs for the cost and sensitivity analyses

Drugs*	Base-case price(EUR per mg)	Range used in sensitivity analysis, (EUR per mg)	Source**
Alemtuzumab (inj)	0.4500	-	Tariff in governmental purchases 2010
Bleomycin (inj)	1.5100	1.5100-1.6300	Distributors' price
Chlorambucil	0.0080	0.0080-0.2290	Tariff in governmental purchases 2010
Cyclophosphamide (Adriablastine)	1.0600	0.6700-1.4500	Price, registered in the MOH
Cyclophosphamide (other generics)	0.0077	0.0010-0.0120	Tariff in governmental purchases 2010
Dexamethasone (inj)	0.0200	0.0040-0.0840	Price, registered in the MOH
Dexamethasone (po)	0.0002	-	Price, registered in the MOH
Doxorubicin (inj)	0.1300	0.1300-0.4400	Tariff in governmental purchases 2010
Etoposide phosphate (po)	0.1000	0.0980-0.1000	Price, registered in the MOH
Fludarabine (Fludara inj.)	3.7400	3.2200-3.7400	Tariff in governmental purchases 2010
Fludarabine (Netran inj.)	0.7700	-	Tariff in governmental purchases 2010
Fludarabine (Netran po.)	0.1500	-	Tariff in governmental purchases 2010
Fludarabine (other generics)	2.7800	0.7600-3.3700	Price, registered in the MOH
Methylprednisolone (inj)	0.1100	0.0140-0.1100	Price, registered in the MOH
Methylprednisolone (po)	0.0260	0.0220-0.0300	Price, registered in the MOH
Mitoxantrone (inj)	0.3800	0.3800-3.8300	Tariff in governmental purchases 2010
Prednisolone (inj)	0.0160	0.0130-0.0170	Price, registered in the MOH
Prednisolone (po)	0.0072	0.0072-0.0077	Price, registered in the MOH
Rituximab (inj)	2.0300	1.3500-2.9600	Tariff in governmental purchases 2010
Vincristine (inj)	3.6700	2.8600-4.0600	Tariff in governmental purchases 2010
Vinblastine (inj)	0.6300	0.4000-0.6300	Price, registered in the MOH

* Trade name is indicated if the product was prescribed specifically by it

** To value the use of the drugs from a healthcare perspective, we used a step-wise approach to determine an average price, depending on the availability of information: tariff in governmental purchases (2010); price registered in the Ministry of Health; distributors' price.

As can be seen in Table 4.1, the highest cost per mg was for fludarabine, vincristine and rituximab. Rituximab and fludarabine (if Fludara was prescribed) had the highest price per average daily dose, equal to 312.03 EUR for fludarabine and 237.93 EUR for rituximab. As drug expenditures depend not only on cost per item, but also on total volume used, we present cost-items utilization and characteristics of population using it in Table 4.2.

The data are presented for items that were used by more than 3% of patients. Cyclophosphamid, fludarabine and vincristine were prescribed to the largest percent of patients. Characteristics of the study population using specific cost items showed significant difference in the percent of males prescribed cyclophosphamide, mitoxantrone and chlorambucil in comparison to the other drugs. No significant difference in the patients' age was observed, although on average the age of patients receiving alemtuzumab was lower and those receiving chlorambucil was higher. From Table 4.2 also it may be observed that injectable form of fludarabine is prescribed significantly more than the oral form.

The average annual costs for a patient's drug treatment are 2,047 EUR. The average cost of in hospital stay is equal to 542 EUR per person, resulting in total expenditures of 2,589 EUR. The research showed that expenses for drugs significantly exceeded hospitalization costs (t=5.026; Sig 2-tailed = 0.000).

Mean total costs in the bootstrap analysis were equal to 2,584 EUR (median 2,576, 97.5th percentile 3,223 EUR; 2.5 percentile – 1,987 EUR). Sex of the patient, number of years a patient lives with the disease, and age at the time of hospitalization, did not have a significant impact on the health care costs per patient. Hospital choice (Beta=-0.260; Sig=.002) was a strong determinant of health care costs. One-way ANOVA also showed a significant difference in mean costs of two hospitals involved (Welch statistics 19.222, p=0.000).

The results of the multivariate sensitivity analysis showed that in the best-case (lowest cost) scenario the average annual spending on drug treatment of a CLL patient is 1,659 EUR, and in the worst case scenario is 2,332 EUR. The deviation of drug costs does not exceed 12% on the negative side and 19% on the positive side. Annual cost of hospitalization ranges from 251 to 597 EUR per person and depends on the type of hospital at which a patient is treated.

Table 4.2 Drug utilization related to patients' population characteristics

Drugs*	Patients using the drug, %	Average age of patients using this item (s.d.), years	Males among ones who are using this drug, N (%)	Prescriptions during the first year of treatment, N (%)	Mean volume per patient (in mg)
Alemtuzumab (inj)	10.3	57.90 (9.25)	9 (60.00)	0 (0.00)	87.14
Chlorambucil (po.)	7.6	74.45 (4.61)	5 (45.50)	6 (54.5)	4.76
Cyclophosphamide (inj. Adriablastine)	4.8	64.29 (5.85)	6 (85.70)	4 (57.10)	7.24
Cyclophosphamide (all brand names)	66.2	62.95 (9.13)	59 (61.50)	29 (30.20)	2900.34
Dexamethasone (inj)	10.0	60.07 (8.71)	19 (65.50)	7 (24.10)	22.70
Dexamethasone (po)	5.4	59.20 (6.50)	3 (60.00)	1 (20.00)	4.41
Fludarabine (Fludara inj.)	44.4	60.56 (8.82)	36 (57.10)	13 (20.60)	377.87
Fludarabine (po.)	3.4	59.80 (8.35)	3 (60.00)	0 (0.00)	30.48
Fludarabine inj (all brand names)	47.6	60.65 (8.82)	40 (58.00)	13 (18.80)	411.79
Methylprednisolone (po.)	4.8	56.29 (10.42)	4 (57.1)	1 (14.3)	22.59
Mitoxantrone (inj)	5.5	58.12 (6.31)	7 (87.50)	0 (0.00)	4.35
Prednisolone (inj)	5.5	60.63 (10.64)	5 (62.50)	2 (25.00)	224.63
Prednisolone (po)	26.2	66.63 (8.07)	26 (68.40)	14 (36.80)	179.37
Rituximab (inj)	12.4	59.28 (6.72)	13 (72.20)	5 (27.80)	258.62
Vincristine (inj)	31.0	64.51 (9.57)	34 (75.60)	17 (37.80)	1.66

s.d.: standard deviation; inj. : injection ; p.o. : per os (oral) ;
* Trade name is indicated if a product was prescribed not by generic, but by a trade name with a high frequency (for cyclophosphamide and fludarabine).

Discussion

A literature review was conducted in the database PubMed to explore whether our results were consistent with results from studies in other countries and to understand if factors that impact cost of other cancer conditions are similar to those affecting CLL. The search was limited to a ten year period of English-language articles studying multiple-cancer conditions. The literature review showed that the major factors influencing cost of cancer conditions are related to patients' characteristics, such as stage at diagnosis and stage at treatment, degree of co-morbidity, age and gender of a patient and tumor site. Lal et al., Longo et al. (2006, 2007), and Yabroff et al. recorded increased costs due to higher stage of the disease during treatment [20-23]. Akushevich et al. in a retrospective analysis on oncologic patients in the USA, determined that the highest costs exist in the period of treatment immediately after diagnosis [24]. Yabroff et al. also recorded that both first and last stage of the disease at the time of treatment are associated with higher costs [23]. The results of the studies by Lal et al. and Kurse et al. [20,25] demonstrate a connection between the degree of comorbidity and treatment costs. The impact of patient's age on cost of cancer was significant in a number of studies, but differed in scale and type of impact [20-22; 24,25]. Some research described an impact of tumor site on total costs of the diseases [21,22,24]. Yabroff et al. showed that cost for treatment of localized diseases is lower, which is supported by the study of Lai et al. who note the highest costs of hematological malignancies among other types of cancer [23].

Only two of the economic analyses describing an impact of factors on cost of treatment specifically for CLL were found. They showed a positive correlation between age and cost of drug treatment [26,6]. Danese et al. also concluded that male gender is associated with higher cost for CLL drugs treatment [26].

Similar to the study by Stephens (2005) [16], cost of therapy was found to be the main driver for CLL treatment costs, significantly exceeding hospitalization costs. Despite previous research suggesting the major factors influencing cost of cancer conditions are stage at diagnosis and stage at treatment, degree of co-morbidity, age and gender, tumor site and type of the therapy received, our study on the Ukrainian sample from two specialized institutions showed only hospital choice had a significant impact on cost of drug treatment. A possible explanation may be risk-patient selection or difference in treatment practice within the hospitals. A high use of injectable forms of drugs as fludarabine and dexamethasone was also observed in the study. As no health technology assessment agency currently exists, there are no recommendations comparing injectable and oral forms developed in Ukraine. Nevertheless, NICE [27] recommends giving preference to oral form of fludarabine because of its higher efficiency. Rationality of injectable form of fludarabine use in CLL treatment practice may be a potential topic for further research in Ukraine.

Ukraine is a country with a post-Semashko model of the healthcare system. Currently there is no state reimbursement system implemented in Ukraine. However, limited reimbursement for in-hospital treatment is provided under governmental programs for such diseases as AIDS, tuberculosis, diabetes, cardiovascular diseases and cancer. These in hospital state purchases cover from 7 to 40% of oncologic patients' needs depending on the region and hospital type [28,29]. Major expenses on drugs are covered by patients' out of pocket payments. Thus, high cost of treatment of chronic conditions, such as CLL, may be a significant economic burden, especially for patients with low income.

The average annual cost of drug treatment for CLL patient is 2,047 EUR, with the majority of costs paid out-of-pocket. From the first of December, 2011, the minimum annual subsistence level in Ukraine is equal to 1,155 EUR for people of working age and 920 EUR for the retired population. This number is lower than annual costs of drug treatment for patients with CLL in Ukraine, according to current clinical practice in specialized hospitals. This may mean possible significant economic impact of the disease on vulnerable populations (e.g. elderly poor), taking into the account only limited governmental subsidy. With high costs for treatment of hematologic malignancies [15,26], and insufficient reimbursement level for drug treatment in Ukraine [9], treatment of CLL in specialized hospitals may be financially difficult for economically-unprotected patients because of high therapy costs.

Implications

Our analysis indicates that there is likely to be a significant difference in treatment practice of CLL within different hospitals of Ukraine resulting in a significant deviation in drug expenditures. Therefore, it is not clear if treatment standards are followed within the hospitals and if the schemes used are evidence-based and rational. These issues should be explored further in future studies.

Limitations

Retrospective analysis allowed us to make an estimation of treatment costs for CLL in specialized medical institutions of Ukraine and to explore its correlation with patient characteristics. However, our research suffered from several limitations.

The conducted research does not allow us to assess economic burden of CLL in Ukraine. It is expected that costs of treatment in the current study may be higher than in the regional oncology dispensaries because of larger state subsidiaries and patients' expenditures on drugs.

Moreover, data on stage of the patient's disease and health state on ECOG criteria were missing and thus excluded from the factor list; however, these parameters may have a potential impact on CLL costs.

We conducted a linear regression analysis on logarithmic transformed costs data while excluding six outliers basing on Cook's distance. Leaving outside these six observations might increase significance of the statistical analysis and strength of the relation between the independent variable (hospital choice) and dependent variable (healthcare costs).

Conclusions

Drug treatment comprises the largest portion of total costs, which presumably may be a high economic burden for a CLL patient who is the major payer of treatment expenses in Ukraine. Costs of drug treatment significantly depended on type of the hospital selected.

References

1. Dranitsaris G, Truter I, Lubbe MS, Amir E, Evans W. Advances in Cancer Therapeutics and Patient Access to New Drugs. PharmacoEconomics. 2011; 29(3): 213-224.
2. National Cancer Institute. National Cancer Register. 2011; 12, Available from: http://users.iptelecom.net.ua/~ucr/eng/index_e.htm [Accessed 3 December, 2011].
3. Cheson BD, Bennett JM, Grever M, Kay N, Keating MJ, O'Brien S, Rai KR. National Cancer Institute sponsored working group guidelines for chronic lymphocytic leukemia; revised guidelines for diagnosis and treatment. Blood 1996; 87:4990–7.
4. Kalil N, Cheson BD. Management of chronic lymphocyteic leukaemia. Drugs Aging 2000;16:9–27.
5. Redaelli A, Botteman MF, Stephens JM, Stephens JM, Brandt S, Pashos CL. Economic burden of acute myeloid leukemia: a literature review. Cancer Treat Rev. 2004;30(3):237-47.
6. Rozman C, Montserrat E. Chronic Lymphocytic Leukemia. N. Engl. J. Med. 1995; 333:1052-1057.
7. American Cancer Society. Cancer facts and figures. 2010. Available from: http://www.cancer.org/acs/groups/content/@nho/documents/document/acspc-024113.pdf [Accessed 7 February, 2012].
8. National Cancer Institute. Surveillance, Epidemiology, and End Results Program, 1975-2005, Division of Cancer Control and Population Sciences. 2008. Available from:http://seer.cancer.gov/csr/1975_2005/ [Accessed 7 February, 2012].
9. [Achievements and challenges of the domestic haematology]. Ukraiinskiy medyuchnuy chasopyus.2011. Available from: http://www.umj.com.ua/wp-content/uploads/2011/06/Hematolodji.pdf [Accessed 09 March, 2013]. Russian.
10. [About approval of the clinical protocols on medical help provision for patients on specialty “Hematology”]. the Order of the Ministry of Health of Ukraine #647 from 30.07.2010. Ukrainian.
11. [About approval of the concept of pharmaceutical sector development in health care branch in Ukraine for the years 2011-2020]. The Order of the Ministry of Health of Ukraine #769 from 13.09.2010. Ukrainian.
12. Levin TT, Li Y, Riskind J, Rai K. Depression, anxiety and quality of life in a chronic lymphocytic leukemia cohort. Gen Hosp. Psychiatry. 2007;29(3):251-6.
13. Shanafelt TD, Bowen D, Venkat C, Slager SL, Zent CS, Kay NE, Reinalda M, Sloan JA, Call TG. Quality of life in chronic lymphocytic leukemia: an international survey of 1482 patients. Br. J. Haematol. 2007;139(2):255-64.
14. Goor KM, Schaafsma MR, Huijgens PC, van Agthoven M. Economic assessment on the management of chronic lymphocytic leukaemia. Expert Opin. Pharmacother. 2005;6(7):1179-89.
15. Kasteng F, Sobocki P, Svedman C, Lundkvist J. Economic evaluations of leukemia: a review of the literature. Int. J. Technol Assess Health Care. 2007;23(1):43-53.
16. Stephens JM, Gramegna P, Laskin B, Botteman MF, Pashos CL. Chronic lymphocytic leukemia: economic burden and quality of life: literature review. Am J Ther. 2005;12(5):460-6.
17. Mandrik O, Zalis’ka O. [Assessment of pharmacoeconomic aspects of chronic lymphocytic leukemia treatment in Ukraine]. Upravlinnya, economica, ta zabezpechenya yakosti v farmacii.2012; 3(23): 62-67. Ukrainian.
18. Golyachenko O, Shulgay AG, Golyachenko A, Panchishyun NY, Smirnova VL, Golyachenko GB, Romanyuk LM, Lisovska NO, Fedchishyun NE. [Cost of medical help]. Novosti medicinyu I farmacii.2012; 5(403). Available from: http://www.mif-ua.com/archive/article_print/27173. [Accessed 09 March, 2013]. Ukrainian.

19. [Reforming of the secondary medical help in Ukraine: basic problematic and solution options] Combined report on the project EuropeAid/123236/C/SER/UA. EPOS Health Consultants/NI-CO/ECORY. Available from: Shttp://www.eu-shc.com.ua/UserFiles/File/SR_V04_ua.pdf. [Accessed 09 March, 2013].

20. Lal A, Bhurgri Y, Rizvi N, Virwani M, Memon RU, Saeed W, Sardar MR, Kumar P, Shaikh AJ, Adil S, Masood N, Khurshed M. Factors influencing in-hospital length of stay and mortality in cancer patients suffering from febrile neutropenia. Asian Pac. J. Cancer Prev.2008; 9(2):303-8.

21. Longo CJ, Deber R, Fitch M, Williams AP, D'Souza D. An examination of cancer patients' monthly 'out-of-pocket' costs in Ontario, Canada. Eur. J. Cancer Care (Engl).2007; 16(6):500-7.

22. Longo CJ, Fitch M, Deber RB, Williams AP. Financial and family burden associated with cancer treatment in Ontario, Canada. Support Care Cancer.2006;14(11):1077-85.

23. Yabroff KR, Lamont EB, Mariotto A, Warren JL, Topor M, Meekins A, Brown ML. Cost of care for elderly cancer patients in the United States. J. Natl Cancer Inst. 2007; 99(1):14-23.

24. Akushevich I, Kravchenko J, Akushevich L, Ukraintseva S, Arbeev K, Yashin AI. Medical cost trajectories and onsets of cancer and noncancer diseases in US elderly population. Comput Math Methods Med. 2011. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21687557

25. Kuse R, Colberg H, Marbé W, Kodalle O, Kalmár P, Lohfert C. Which factors render cost-covering lump-sum charging difficult for the treatment of patients with acute leukemias? Onkologie. 2001; 24(3): 292-4.

26. Danese M., Gleeson M, Reyes C. Cost of chronic lymphocytic leukemia (CLL) in Medicare patients. J Clin Oncol 26. 2008 (May 20 suppl; abstr 17531).

27. Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia. NICE technology appraisal guidance TA29. National Institute for Health and clinical services. 2001. Available from: http://publications.nice.org.uk/guidance-on-the-use-of-fludarabine-for-b-cell-chronic-lymphocytic-leukaemia-ta29/guidance. [Accessed 09 March, 2013].

28. [On efficiency of costs use by the Ministry of Health]. State finance inspection of Ukraine. Available from: http://www.dkrs.gov.ua/kru/uk/publish/article/75100;jsessionid=5305963B5762BAF2C3E27BEAC3E2A6F6. [Accessed 09 March, 2013]. Ukrainian.

29. Adamchuk I. [The program exists, where is effectiveness?]. State finance inspection of Ukraine. Available from: http://www.dkrs.gov.ua/kru/uk/publish/printable_article/51727;jsessionid=BB368B7E53A135A1BF1A7994BC73505E. [Accessed 09 March, 2013]. Ukrainian.

Chapter 5

Economic value of in-vitro fertilization in Ukraine, Belarus, and Kazakhstan

Mandrik O., Knies S., Severens J.L. ClinicoEconomics and Outcomes Research. 2015;7: 347—356.

Abstract

An economic value calculation was performed to estimate the lifetime net present value of in-vitro fertilization (IVF) in Ukraine, Belarus, and Kazakhstan.

Net lifetime tax revenues were used to represent governmental benefits accruing from a hypothetical cohort of an IVF-population born in 2009 using the methodology of generational accounting. Governmental expenses related to this population included social benefits, education and healthcare, unemployment support and pensions. Where available, country-specific data referencing official sources were applied.

The average healthcare cost needed to achieve one additional birth from the governmental perspective varied from $2,599 in Ukraine to $5,509 in Belarus. The net present value from the population born using IVF was positive in all countries: for Ukraine ($9,839), Belarus ($21,702), and Kazakhstan ($2,295). The break-even costs of drugs and supplies per IVF procedure is expected to be $3,870, $8,530 and $1,780, respectively. Probabilistic sensitivity analyses based on 5000 simulations show that the average net present value per person remains positive: $1,894 (s.d. $7,619), $27,925 (s.d. $12,407) and $17,229 (s.d. $24,637) in Ukraine, Belarus, and Kazakhstan, respectively.

Financing IVF may represent a good investment in terms of governmental financial returns even in lower-income countries with state-financed healthcare systems such as Ukraine, Belarus and Kazakhstan.

Introduction

Infertility is a common problem in many countries. In Central and Eastern European and Central Asian regions, countries report high rates of abortions, while at the same time displaying higher levels of secondary infertility (females with previous life births). Additionally, the prevalence of primary infertility (females with no previous life births) is significantly higher in Ukraine than in other countries of the region, reaching a level equal to or above 3% of the female population [1].

Despite an increasing medical demand for infertility treatments, public funding challenges for in vitro fertilization (IVF) exist in a number of jurisdictions. While some countries (such as France, Spain and Israel) provide full coverage of IVF treatments as a matter of policy, others either partially cover expenses (e.g. Portugal, Sweden, Turkey), or fail to cover it at all (e.g. India, China) [2]. Meanwhile, when coverage for IVF is absent or incomplete -- as exists throughout the United States – it may lead to cases where IVF treatments are unaffordable to couples who need it most.

Moreover, and of particular interest from a governmental perspective, a number of economic studies have concluded that there are long-term financial benefits to be gained from creating new citizens who will eventually become future taxpayers. The cost-efficiency of state investments in IVF is assessed by calculation of net income, usually expressed through taxes and other state revenues received from the working population. Economic evaluations revealed that there were net tax benefits of IVF financing in both high-income countries (e.g. USA, UK, Denmark, Sweden) [3-7] and medium-income countries like Brazil [8]. Net income gained from the IVF populations in all countries studied was positive, however the largest gain was found for the UK (£109 939), while the smallest gain was found for Brazil (US$ 61 428).

While encouraging, these results may not be easily used in the decision making process in other countries [9], such as those of the Central and Eastern European (CEE) region. Besides putative differences in healthcare systems and population characteristics, the country's wealth must be taken into account when considering the efficiency of medical technologies. For example, in lower-income countries, costly medical technologies potentially may be less cost efficient than they would be in higher-income countries. Countries of the CEE region have, on average, a much lower Gross Domestic Product (GDP) than their Western European or North American counterparts; thus, the generalizability may be questionable for economic studies on IVF subsidies from high-income countries (like the USA and the UK) to lower-income jurisdictions.

Finally, the economic impact for the population (expressed as the difference between state spending and economic benefits), may not be directly proportional to the GDP, depending more on internal policy of the country, such as tax level, social

contributions, net revenues from public enterprises, and so on. Thus, financing of IVF also may be cost-efficient for governments of countries with relatively low GDP per capita level. For example, while having universal healthcare coverage and free access to medical procedures for their respective populations, governments in former Soviet Union countries (such as Ukraine, Belarus, Kazakhstan) do not consider IVF a priority and, thus, provide only limited, insufficient funds for its coverage. However, economic analysis may be a justification for reexamining their policies where IVF coverage is concerned.

With the above discussion as a rationale, the present study was conducted to: (1) assess the economic cost and benefits of financing IVF technologies (one cycle per woman) in Ukraine, Belarus and Kazakhstan from the governmental perspective; (2) explore relations between GDP per capita and level of financial impact on the population; and (3) address transferability of the received results to other countries of CEE region.

Methods

Model Design

Similar to previous studies, an economic model using the methodology of generational accounting was developed to estimate for Ukraine, Belarus and Kazakhstan whether publicly funded IVF treatments result in a financial benefit, by calculating the net revenue gained from a child conceived via IVF in each country [3-8]. Generational accounting evaluates whether there will be sufficient tax revenue in the future to pay for current investments into IVF programs by calculating the net present value (NPV) of lifetime net taxes (gross taxes minus financial expenditures of the government on population). Because taxation remains the main source of revenue for most states [5], using this applied approach provides an appropriate assessment of rationality for IVF investments by the governments.

In the model we defined five stages during which populations have different expenses and revenues: i) prenatal; ii) early childhood (from birth until school); iii) late childhood (period when individual receives education including high school); iv) employment; and v) retirement. The prenatal stage includes costs of IVF procedures. During the childhood stage the cohort is a receiver of financial flows from the state that consists of social support, sick leave payments, medical help and education financing. During the employment period, the population provides revenue to the state in the form of tax payments, but also receives unemployment support and medical help. After retirement, the employment rate decreases, likewise tax contribution, but pension and healthcare are provided until the end of life. For each age category, state spending and income from population are calculated.

Similar to Connolly et al. [4-6] and Kröger et al. [8], the following formula was applied for assessing the NPV of lifetime net taxes:

$$NPV = \sum_{t=0}^{T} \left(\frac{Rt - Et}{(1+r)^t} \right) - K0$$

Where:
Rt = sum of the governmental revenues from individuals age t
Et = sum of the governmental expenditures from individuals age t
r = discount rate
T = life expectancy
K_0 = direct IVF costs.

As NPV is used to estimate how much future returns from the investment are worth today, NPV > 0 represents profitable investment, NPV = 0 represents investment that is neither profitable nor unprofitable, and NPV < 0 represents unprofitable investment [7].

IVF costs and outcome

Base-case scenario

Applying IVF success rates, the costs per IVF-born cohort and cost per live birth is calculated. Because Belarus specific data for this parameter were not available, it was assumed in the base case that the success of IVF was equal in all three countries to 31.9% on average (success rate of IVF for 35-37-year old women based on the data of SART summary report on 154,412 cycles conducted during the year 2011) [10]. The percentage of boys born as a result of intervention was assumed to be equal to the naturally-born cohort and was assessed from data on sex ratios (51.70%, 51.5%, and 48.5% boys born in Ukraine, Belarus, and Kazakhstan, respectively) [11-13].

Country-specific state-registered prices were used to assess costs of drugs and medical supplies, while the need in quantities of the defined medical products per one IVF cycle was assessed from the National State reproductive program in Ukraine (and considered to be similar for Belarus and Kazakhstan) [14-16].

Despite all three countries providing universal free healthcare, country-specific pregnancy-related costs are unknown and, for this reason, medical care expenditures were accounted using costs per outpatient (during IVF procedures and pregnancy) and inpatient (delivery) visits by WHO-CHOICE estimates [17]. The average number of visits

during one IVF cycle was calculated assuming the following referrals: first appointment (1 visit), preparation (1), initiation (1), visits during treatment with fertility medications (5 visits), egg harvesting (1), embryo transfer (1), consultation (1). Nine monthly visits to gynecologists and three hospitalization days were accounted for during pregnancy and delivery.

Although IVF procedures frequently result in multiple births, only one-child pregnancy was assumed in the base-case scenario. Moreover, while during early perinatal stage IVF children may require more medical assistance, in the life-duration model used here children conceived with IVF were considered to be comparable to those conceived naturally.

Country-specific scenario

IVF-success data and rates of multiple deliveries due to IVF were used to understand if these country-specific parameters have a significant impact on the results. The following assumptions were used in this scenario:

1. The birth rate from IVF procedure was calculated from data on IVF success rate and multiple pregnancies from the study conducted by Kupka et al. [18];
2. Because of the low incidence of triple births (1% for both Ukraine and Kazakhstan) [18] this parameter was accounted together with dual births
3. Because no Belarus-specific data were available, the rate of births due to IVF was calculated as an average in Russia, Belarus, Kazakhstan [18];
4. Negative health impact and higher costs associated with multiple pregnancies included the following:

- Higher probability to die during neonatal period (6.4 times) [19];
- Higher medical costs during the first year of life (the calculated cost ratio between single and dual births - 3.29) [19];
- Doubled payments for "maternity support" because of multiple births.

State expenses on population

In all three analyzed countries child benefits are provided to the families of newborns. The first-child allowance was accounted in all of the cases, as it was considered that IVF is applied by childless families. It was also considered that one parent is not employed, thus receives monthly financial support for three years in Belarus ($82.10/month) and Ukraine ($16.26/month) and for one year in Kazakhstan ($214.2/month) as ensured by state policies in these countries (Estimation was made by the data of Labor informational resource, http://mojazarplata.by; http://mojazarplata.kz; mojazarplata.com.ua; accessed 16/08/2013). Basing estimates on data from accounting departments in three companies (two in Ukraine and one in Kazakhstan, 485 employees total), it was considered that mothers spend 15 sick leave days paid by the government annually (per child from 3 to 6 years) and 10 days per child aged 7 to 12 years.

In the model, people receive healthcare services throughout their lives and educational services from 0 to 19 years. Average expenses of governmental support for unemployed were calculated using official unemployment rates among population of working age, coverage with financial support for unemployed, duration of unemployment and the amount of financial support.

From retirement until death the population receives a pension from the government. Because data on disability prevalence was unavailable, no additional costs besides those associated with regular healthcare were accounted.

State income

Government revenue accrues from income tax on population of working age or from the aged population who continue to work and pay taxes. As no age-stratified income is available for the study countries, average salary and tax rates were applied for the entire lifetime of the cohort.

Though governments receive additional revenue from other sources (e.g., land taxes, business and enterprise payments, social contributions), income taxes are argued to be the largest part of state revenues; therefore, the impact of population increase on state income was assessed as direct taxes from salaries on official employment. No country-specific data was available bearing on a relationship between age and income, thus average salaries, taxes and employment rates were applied to calculate the income from the working-age population. Moreover, a percentage of the retired population who are officially employed was used to calculate additional income from this group.

Other input parameters of the model

Life expectancy at birth for children born in 2009 was applied [20]. All costs provided in the national currencies were transferred into US$ according to the National Banks exchange rates on November 22, 2014. Rate per 1$ was equal to 15.096 UAH (Ukraine), 10780.00 BYR (Belarus) and 180.87 KZT (Kazakhstan). State expenses before birth of the IVF cohort were adjusted to current prices (2014) using the inflation index for consumer prices [21]. Governmental payments and incomes were assumed to grow annually with the rate of annual GDP growth [22] while being discounted at 3% in the deterministic model. The complete list of model input parameters together with full reference list are provided in Appendix 5.1.

Validity of the model

The parameters possible for state regulation were varied in one-way sensitivity analysis with break-even costs calculation. Subcategory analysis for women of different age categories presenting variations in IVF success rates was conducted to analyze an impact of IVF success rate on the results of economic analysis and, moreover, to assess

the possible implication of limiting financing for different groups. As drug costs are frequently negotiable, the impact of changes in IFV expenses on NPV was assessed. Additionally, one-way sensitivity analyses with 0% to 10% discounting were conducted.

Probabilistic sensitivity analysis (PSA) on the most influential parameters with 5000 simulations was conducted to ensure the validity of the calculation. Because the aim of PSA was to assess the uncertainty related to long duration of the model (cohort lifetime), the prenatal parameters which potentially can be controlled by the government (i.e., age of mother and IVF costs) were excluded from this assessment. Moreover, the IVF success rate was varied in the PSA to address the uncertainty of the procedure success. Costs included in the early-childhood period were not varied in PSA because of the low impact on a lifetime model and no data on deviation parameters. A number of prognostic factors (such as a possible tax decrease in Ukraine, prolongation of the retirement age to the average in OECD region for all three countries) were assessed from publicly available information sources describing current political trends that may affect model results. Because healthcare expenditures already are relatively low in the study countries, it was assumed they may only increase from current values or remain the same. If multiple data sources were available, the source providing the largest data deviation was used. The complete range of parameters and the distributions used in the PSA are presented in the Appendix 5.1.

Table 5.1 Neonatal costs of IVF[a] population in Ukraine, Belarus, and Kazakhstan

Parameter		Ukraine	Belarus	Kazakhstan
Drugs and supplies costs	Option 1 IVF drugs costs per cycle (47% cycles), $	741	1,795	927
	Option 2 IVF drugs costs per cycle (43% cycles), $	538	1,129	1,243
	Option 3 IVF drugs costs per cycle (10% of cycles), $	782	1,902	905
	Medical supplies costs per cycle, $	75	88	79
	Average drugs and supplies costs, per 1 cycle, $	732	1,607	1,049
Health Care expenditures per 1 IVF cycle, $		48	58	147
Health care pregnancy and delivery expenditures, per 1 birth, $		153	287	409
Average costs needed to receive 1 IVF birth, $		2,599	5,509	4,157

[a]IVF – in-vitro fertilization

Results

The observed cost variation for different schemes of IVF cycles applied resulted in a difference in average cost per cycle, with the lowest one observed in Ukraine ($732 per cycle) and the highest one in Belarus ($1,607 per cycle).

Using a similar IVF success rate, the average cost of one IVF birth from the governmental perspective varied from $2,599 in Ukraine to $5,509 in Belarus (see Table 5.1).

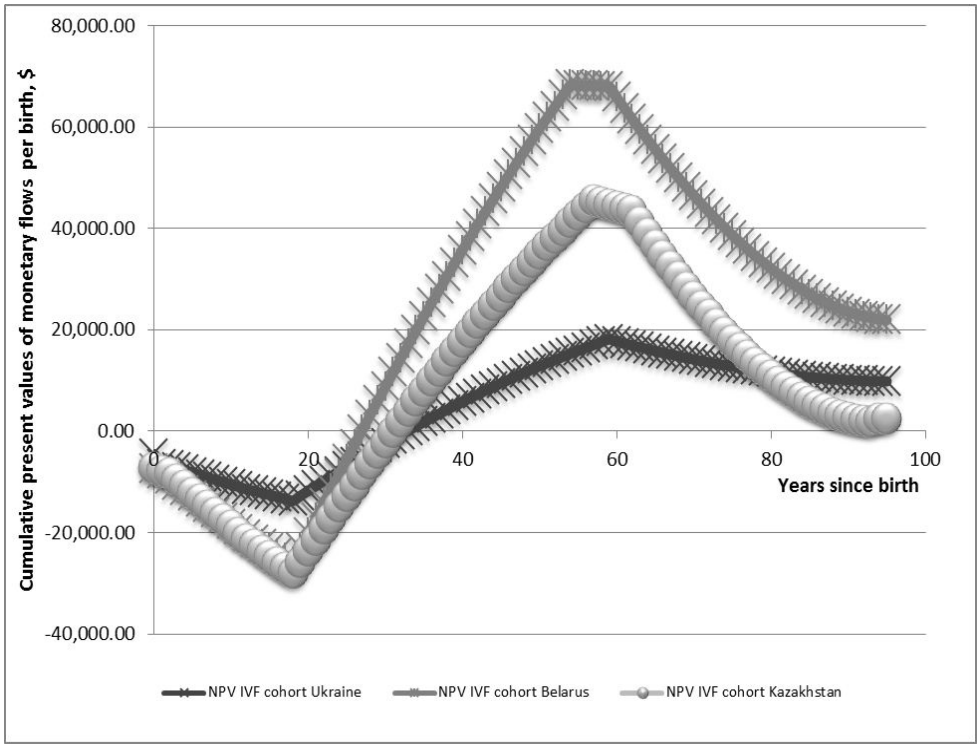

Figure 5.1 Projected net present value for IVF-conceived child in Ukraine, Belarus and Kazakhstan

Projected lifetime net revenues from the IVF cohort are illustrated in Figure 5.1, where changes in NPV depending on the age of IVF cohort are observed. While in the early stages of an individual's life net monetary flows are negative for the government -- education, health and social support are provided to the family by state without financial returns -- during the working years, the individual's financial balance tips positive for the government, as state revenue is collected as tax payments and lower social expenses are

paid. Advancing in age, individuals begin to provide less revenue to the state while simultaneously receiving increased social spending, primarily because of pension payments.

Because the net revenue positions for an IVF- and a naturally-conceived child follow similar trajectories, where the only difference between the two is the additional cost of IVF investment required for conception, the graph presents the NPV for an IVF-conceived individual only. In light of the observed difference in expenses on population in the three study countries, IVF may be considered an attractive economic option in Ukraine, Belarus and Kazakhstan with discounted NPVs of $9,839, $21,702 and $2,295, respectively (see Table 5.2).

Table 5.2 Cost and income of IVF[a]-conceived population in Ukraine, Belarus, and Kazakhstan

Scenario	Lifetime NPV[b*] ($)		
	Ukraine	**Belarus**	**Kazakhstan**
Expenses			
Social (maternity) support and sick leaves, $	2,976	5,734	5,700
Education, $	4,045	6,021	7,050
Health Care costs, $	7,617	35,463	42,024
Unemployment, $	31	2.17	52,342
Pension, $	8,881	55,852	45,125
Total state expenses on IVF population, $	26,150	106,580	104,108
Revenue			
Revenue from population, $	37,687	128,282	106,403
Net income			
Net present value of IVF, $	9,839	21,702	2,295
Net present value of IVF in country-specific scenarios, $	8,879	21,139	2,040

[a]IVF – in-vitro fertilization; [b]NPV – net present value; * - average per one birth.

When country-specific IVF birth rates were applied in the model considering both IVF success rate and multiple pregnancies (Table 5.2), the results did not change

significantly. A possible explanation of the small impact of higher-cost IVF children stems from the positive economic impact of the individual in general. As such, higher frequency of multiple births in IVF population compensates for the additional expenses related to IVF newborns and the higher mortality during neonatal stage.

The PSA based on 5,000 simulations shows that the average NPV per person remains positive: $1,894 (s.d. $7,619), $27,925 (s.d. $12,407) and $17,229 (s.d. $24,637) in Ukraine, Belarus and Kazakhstan, respectively. At the same time, the ranges and standard deviations for Ukraine and Kazakhstan indicate that under some circumstances (meaning of inputs) financing of IVF can become negative for these countries.

Table 5.3 One-way sensitivity analysis (mothers' age, IVF[a] drugs costs, and discounting rate)

Scenario	Lifetime NPV[b]($)		
	Ukraine	Belarus	Kazakhstan
Mothers' age			
NPV of IVF conceived child, mother age < 35 years (40.1% of success rate)	10,339	22,770	3,061
NPV of IVF conceived child, mother age 38-40 years (21.6% of success rate)	8,673	19,212	507
NPV of IVF conceived child, mother age 41-42 years (12.2% of success rate)	5,890	13,270	Negative
NPV of IVF conceived child, mother age >42 years (4.2% of success rate)	Negative	Negative	Negative
IVF drugs' cost			
Cost of IVF drugs, 50% increase	8,691	19,183	650
Cost of IVF drugs, 100% increase	7,544	16,663	Negative
Break even cost of IVF drugs and supplies per one cycle, $	3,870	8,530	1,780
Cost of pregnancy and delivery, 50% increase	9,782	21,583	2,150
Discounting rate			
Discounting rate, 0%	10,986	Negative	Negative
Discounting rate, 5%	1,544	13,907	1,826
Discounting rate, 10%	Negative	Negative	Negative

[a]IVF – in-vitro fertilization; [b]NPV – net present value

The results of one-way sensitivity analysis (Table 5.3) shows a positive NPV until the mother's age is above 42 years in Ukraine and Belarus, while in Kazakhstan the break-even age of the mother (age at which financing IVF remains economically beneficial for

the government) is 38-40 years. The costs of IVF drugs and supplies impact significantly the results of the economic analysis. A negative NPV was obtained using a discount rate of 10% in all three countries, as well as with a discount rate of 0% in Belarus and Kazakhstan.

In the PSA with a fixed 0% discount rate a negative NPV was obtained for Ukraine and Kazakhstan ($19,962, s.d. $ 33,263 and $44,084, s.d. $89,815, respectively) and positive for Belarus ($24,328,s.d. $ 63,580). The instability of these results is indicated by the value of the standard deviation, which exceeds the average value.

Discussion

The results presented in this article show how public financing of IVF in three former Soviet Union countries (Belarus, Kazakhstan and Ukraine) will generate a positive return to the state in future tax contributions. Understanding the financial benefits from medical technologies not related to life-saving technologies is especially important in jurisdictions where financial resources are limited, such as in low- and middle-income countries like Ukraine, Belarus and Kazakhstan. Economic evidence in terms of cost minimization or budget impact techniques may be applied to rationalize financing a limited number of IVF cycles, or to define an intent-to-treat patient population. While in Belarus nearly 600 children were born via state-financed IVF treatments [23], Ukraine [16] and Kazakhstan together report just about 600 IVF cycles to be state financed (personal communication), although in Kazakhstan this number is expected to rise in 2015. The present research shows that financing IVF may have a positive NPV, not only in high-income but also in lower-income countries. Based on the average cost per child conceived with IVF in a state clinic and using current levels of financial flows between populations and governments of Ukraine, Belarus and Kazakhstan, the discounted returns to state all were positive over the projected lifetime of an individual, with higher uncertainty of results for Ukraine and Kazakhstan. A higher NPV from financing IVF in Ukraine, Belarus and Kazakhstan can be achieved by limiting coverage of the procedure to women of younger age and by negotiating lower prices with IVF drug suppliers.

In Western European countries and Brazil the discounted NPV of IVF ranged from $61,428 (Brazil) to $177,002 (UK; exchange rate 1 pound = US $ 1.61 on 09.09.2014), while in the countries of the CEE region studied here the financial returns to the state were significantly lower, though still positive [3-8]. However, an interesting observation from this study is that the NPV derived from an IVF population may not always be proportional to the income level of the country, expressed in GDP per capita. For example, the lowest financial return in the present study was observed in the country with the highest GDP per capita, Kazakhstan. It should be noted that GDP per capita is not always the best approach for evaluating the income of a country's population, as wealth can be distributed unequally, an especially common case in countries with a developing economy.

Meanwhile, it also may be assumed that state income from population may not be related linearly to the country's wealth in general in cross-country comparisons, because of differences in taxation policies and government spending.

Another interesting conclusion resulted from the probabilistic model applied, in which we tried to account for possible changes of the input parameters that may be expected during the long run of the model (lifetime of the IVF cohort). While applying the individual prognostic factors for each country, it appeared that the NPV in the probabilistic model may differ from the deterministic model, a finding explained by differences in economic forecast for a long time horizon. Moreover, opposite the deterministic model, the NPV of the IVF population may be higher in Kazakhstan than in Ukraine, if changes in the taxation policy (which are currently under political discussion) will be applied in the future. Because of the long horizon of generational accounting models we suggest that it is obligatory to apply PSA in order to define stability of the received results under conditions of possible political and economic change.

The sensitivity analysis with the 0% discount rate has shown inaccuracy of using this value in a life-duration model based on generational accounting. The assumption in the model that annual expenses increase proportionally to GDP makes the expenses on the retired population inaccurately higher than on the working population in countries with larger values for pensions and GDP growth.

The generational accounting framework from the governmental perspective used in this model assesses costs and benefits attributed to conceiving an IVF child as an investment required to achieve a live birth with consequent long-term economic returns. This economic model was used to assess cost efficiency of state investments in countries with nationally-funded health services (Ukraine, Belarus, and Kazakhstan) where both investments (financing IVF procedures) and returns (tax received) will present a financial flow between two stakeholders, population and state. This model may be potentially applied to other countries with similar political, economic and healthcare structures, where major state revenues are expected to come from tax payments (such as Russia, Georgia, or Azerbaijan). While results of the current study showed positive economic balance with stability of the received results by PSA in Ukraine, Belarus and Kazakhstan, the transferability of the model to other countries of the region may be assessed in the future.

In most western European countries a complete IVF treatment consists of a maximum of three IVF cycles, where treatment choices for each cycle can differ. In a cost-effectiveness analysis reflecting the "real-world" situation conducted in the Netherlands, it was found that combining several transfer policies was not cost-effective, and so the single-choice treatment option should be preferred: elective single embryo transfer, standard treatment policy or double embryo transfer [24].

A cost-effectiveness analysis of replacing one, two or three embryos per cycle of IVF in specific populations of women (< 38 years, ≥ 38 years; 1 cycle, 2 cycles and ≥ 3 cycles) has shown that the most cost-effective and least cost-effective scenarios occurred, respectively, with younger and older women who received three or more cycles, in the move from one embryo transfer to two embryo transfers [25]. Meanwhile, in the current study we assessed only two scenarios: a) expenses and incomes related to one birth only with the IVF success rate aiming at the minimum budget impact for the intervention financing; b) expenses and incomes related to IVF birth according to the current countries data on multiple births and cycle success rate. Accounting cost-efficiency of different IVF procedures in future studies may show increases in state benefits from IVF financing.

Limitations

While taxation-based income may represent a reasonably accurate means of estimating future economic benefits for the state, it should be noted that population also contributes to other financial governmental flows, such as trade and enterprise development, which was not accounted for in the current model. The model also did not account for possible emigration of people to other countries. This may particularly affect the results of economic studies in Belarus, where the unemployment rate is assessed by the number of people receiving unemployment support from the government.

The model accounts for linear increases in spending and earning, based on average values from a retrospective historical assessment of the countries' input parameters. As a consequence, the impact of unpredictable economic crises or growth also was not accounted for in the evaluation. Another model limitation is that the calculation applied average earnings in the population, ignoring the possibility of wealthier generations in the future.

While the return of state investments was assessed from the narrow governmental perspective using only future net tax contributions, we may consider that with the broader assessment of net marginal contributions from individuals the net state benefit from IVF-conceived children will present an even more attractive economic option.

Conclusion

The results of this study may have implications for IVF reimbursement policy not only in Ukraine, Belarus and Kazakhstan, but in other settings with comparable populations and financial flows between population and governments – particularly those which may be considering universal coverage for fertility treatments. While income from a population may not be directly proportional to GDP per capita, it appears that financing IVF technologies collectively may represent a promising potential for state financial returns.

References

1. Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. PLoS Med. 2012; 9(12): e1001356.
2. Ory SJ, Devroey P. IFFS Surveillance 2013. The International Federation of Fertility Societies. Available from: http://c.ymcdn.com/sites/www.iffs-reproduction.org/resource/resmgr/iffs_surveillance_09-19-13.pdf. [Assessed on 15 November 2013].
3. Collins J. Cost-effectiveness of in vitro fertilization. Semin Reprod Med. 2001; 19(3):279-289.
4. Connolly M, Hoorens S, Ledger W. Money in--babies out: assessing the long-term economic impact of IVF-conceived children. J Med Ethics. 2008;34(9):653-654.
5. Connolly M, Gallo F, Hoorens S, Ledger W. Assessing long-run economic benefits attributed to an IVF-conceived singleton based on projected lifetime net tax contributions in the UK. Hum Reprod. 2009;24(3):626-632.
6. Connolly MP, Pollard MS, Hoorens S et. al. Long-term economic benefits attributed to IVF-conceived children: a lifetime tax calculation. Am J Manag Care. 2008;14(9):598-604.
7. Svensson A, Connolly M, Gallo F, Hägglund L. Long-term fiscal implications of subsidizing in-vitro fertilization in Sweden: a lifetime tax perspective. Scand J Public Health. 2008;36(8):841-9.
8. Kröger GB, Ejzenberg D. The fiscal outcome of artificial conception in Brazil-creating citizens in developing countries. Hum Reprod. 2012;27(1):142-5.
9. Welte R, Feenstra T, Jager H, Leidl R. A decision chart for assessing and improving the transferability of economic evaluation results between countries. Pharmacoeconomics. 2004;22(13):857-76.
10. Clinic Summary Report. All SART Member Clinics. Available from: https://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?ClinicPKID=0. [Assessed on 05 May 2013].
11. The World Factbook. Belarus. Available from: https://www.cia.gov/library/publications/the-world-factbook/geos/bo.html. [Assessed on 31 October 2013].
12. The World Factbook. Kazakhstan. Available from: https://www.cia.gov/library/publications/the-world-factbook/geos/kz.html. [Assessed on 31 October 2013].
13. The World Factbook. Ukraine. Available from: https://www.cia.gov/library/publications/the-world-factbook/geos/up.html. [Assessed on 31 October 2013].
14. [Price lists for drugs and biologic additives]. Center of the medical and pharmaceutical information of Kazakhstan. Available from: http://mpi.kz/index.php/. [Assessed on 05 May 2013]. Russian.
15. Center of Expertise and trials in health care. Ministry of Healthcare of the Belarus Republic. Available from: http://www.rceth.by/. [Assessed on 05 May 2013]. Russian.
16. [National State Reproductive program. Economic Justification of the program]. Ministry of Health of Ukraine. 2014. Ukrainian.
17. The World Health Organization. Choosing Interventions that are Cost Effective (WHO-CHOICE). Country-specific unit costs. Updated in 2011. Available from: http://www.who.int/choice/country/country_specific/en/. [Assessed on 16 November 2013].
18. Kupka MS, Ferraretti AP, de Mouzon J, et al. The European IVF-monitoring (EIM) Consortium, for the European Society of Human Reproduction and Embryology (ESHRE). Assisted reproductive technology in Europe, 2010: results generated from European registers by ESHRE. *Human Reproduction*. 2014; 29(10): 2099–2113.
19. Chambers GM, Hoang VP, Lee E, et al. Hospital costs of multiple-birth and singleton-birth children during the first 5 years of life and the role of assisted reproductive technology. *JAMA Pediatr*. 2014; 168(11):1045-1053.
20. Life expectancy at Birth. World Health Statistics. The Global Health Observatory. Available from: http://apps.who.int/gho/data/?vid=61740#. [Assessed on 01 February 2012].

21. Inflation, consumer price (%). The World Bank. Available from: http://data.worldbank.org/indicator/FP.CPI.TOTL.ZG. [Assessed on 23 November 2014].

22. GDP growth (annual %) The World Bank national accounts data and OECD National Accounts data files. Available from: http://data.worldbank.org/indicator/NY.GDP.MKTP.KD.ZG/countries/1W-KZ-UA-BY?display=graph. [Assessed on 31 October 2013].

23. [On approval of the National program of demographic safety of the Republic of Belarus for 2011-2015]. Order of the President of the Republic of Belarus from 11 August 2011 #357. Belarus.

24. Fiddelers AA, Dirksen CD, Dumoulin JC, van Montfoort AP, Land JA, Janssen JM, Evers JL, Severens JL. Cost-effectiveness of seven IVF strategies: results of a Markov decision-analytic model. Human Reproduction. 2009; 24(7): 1648–1655.

25. Jones CA. Doctoral Dissertation, Oxford University. “Economic Evaluation of Alternative Embryo Transfer Policies in In Vitro Fertilisation”, 2006.

Appendix 5.1 Input parameters in deterministic and probabilistic models

Parameter	Country	Deterministic value	Minimum meaning	Maximum meaning	Reference
GDP, $	Ukraine	3,615	2,985.5	7,600	[1-3]
	Belarus	6,480	5,820	16,000	[1,3,4]
	Kazakhstan	11,356	11,356	13,900	[1,3]
GDP growth, %	Ukraine	4.03	0.20	5.20	[5,6]
	Belarus	7.74	4.30	7.74	[5,6]
	Kazakhstan	7.46	1.2	8.9	[5]
Total tax rates as % from the salaries	Ukraine	55.36	33.60	55.36	[7]
	Belarus	47.54	42.79	52.29	[8]
	Kazakhstan	31.00	31.00	37.20	[9]
Average monthly salary for males, $	Ukraine	379.37[a]	289.75	637.91	[2]
	Belarus	483.94[a]	421.49	620.14	[10,11]
	Kazakhstan	779.00[b]	598.85	1,564.53	[12-14]
Average monthly salary for females, $	Ukraine	301.73[a]	230.45	507.35	[2]
	Belarus	384.90[a]	335.22	439.22	[10-12]
	Kazakhstan	410.85[b]	315.77	824.98	[13-15]
Average monthly pension, $	Ukraine	129.24	104.84	145.72	[2,16,17]
	Belarus	219.94	99.32	228.44	[11,12]
	Kazakhstan	240.24	192.19	269.07	[18]
Average monthly unemployment support, $	Ukraine	82.02[c]	68.06	103.22	[2,16,17]
	Belarus	17.00[c]	13.33	20.00	[19]
	Kazakhstan	119.72[d]	95.78	143.66	[20]

Unemployed from working population, %	Ukraine	7.00	6.40	8.80	[2,21]
	Belarus	1.00	0.50	1.60	[19,22]
	Kazakhstan	5.20	5.20	6.60	[14,23,24]
Retired population working, %	Ukraine	15.00	13.50	18.00	[2]
	Belarus	22.00	19.80	26.40	[12]
	Kazakhstan	16.00	14.40	19.20	[14]
Retire age males, years	Ukraine	60[e]	60	65	[16, 25]
	Belarus	6[e]	60	65	[16, 25]
	Kazakhstan	63[e]	63	65	[25,26]
Retire age females, years	Ukraine	60[e]	60	65	[16, 25]
	Belarus	55[e]	55	65	[16, 25]
	Kazakhstan	58[e]	58	65	[25,26]
State expenditures on education, $	Ukraine	247.94	191.60	253.05	[2,27]
	Belarus	291.60	336.96	453.60	[22,28]
	Kazakhstan	352.65	340.68	681.36	[24,28]
State expenditures on health care, $	Ukraine	231.49	231.49	253.05	[29]
	Belarus	362.88	362.88	453.80	[29]
	Kazakhstan	488.31	488.31	794.92	[29]
Fertility success rate, %		31.9	31.20	32.5	[30]
Discounting, %		3.00	-	-	[31]

[a] Assumption: 22.8% difference in male/female salaries according to State statistics report (Ukraine) [2]; [b] Assumption: 61.9% difference in male/female salaries according to State statistics report (Kazakhstan)[14]; [c] Average monthly support received for 12 months; [d] Average monthly support received for maximum 4 months (under the law “On obligatory social insurance” of the republic of Kazakhstan) ; [e] Assumed that retirement age will not be lowered from existing.

Reference list to Appendix 5.1

[1]The World Bank. GDP per capita (current US$) The World Bank national accounts data, and OECD National Accounts data files. Available from: http://data.worldbank.org/indicator/NY.GDP.PCAP.CD. [Assessed on 31 October 2013].

[2]State Committee of Statistics of Ukraine. [Social protection of the population of Ukraine. The compendium of statistics]. Kyiv, 2011. P119. Ukrainian.

[3]The World Factbook. GDP per capita (PPP). Available from: https://www.cia.gov/library/publications/the-world-factbook/rankorder/2004rank.html. [Assessed on 31 October 2013].

[4]National statistical committee of the Republic of Belarus. [Gross Domestic Product]. Available from: http://belstat.gov.by/homep/ru/indicators/gross.php. [Assessed on 31 October 2013]. Russian.

[5]The World Bank. GDP growth (annual %) The World Bank national accounts data, and OECD National Accounts data files. Available from: http://data.worldbank.org/indicator/NY.GDP.MKTP.KD.ZG/countries/1W-KZ-UA-BY?display=graph. [Assessed on 31 October 2013].

[6]The World Factbook. GDP growth rate. Available from https://www.cia.gov/library/publications/the-world-factbook/rankorder/2003rank.html. [Assessed on 31 October 2013].

[7]Ukrainian Business Consulting Group. [Taxes in Ukraine 2013. The general review of the taxation system]. Analytical report. Available from: http://www.ubc.ua/articl_tax1.html. [Assessed on 15 November 2013]. Russian.

[8][Retentions from the salaries of the employees: reflection in the accounting and documentation processes] Commentaries on the legislation of the Republic of Belarus. Available from: http://accountantrb.blogspot.com/2012/09/blog-post_3307.html. [Assessed on 15 November 2013]. Russian.

[9]Karazhat Consulting. [Taxes and Tax documentation]. Available from: http://www.karazhat.kz/taxes. [Assessed on 15 November 2013]. Russian.

[10]National statistical Committee of the Republic of Belarus. [Annual data. Salaries]. Available from: http://belstat.gov.by/homep/ru/indicators/wages.php. [Assessed on 15 November 2013]. Russian.

[11]National statistical Committee of the Republic of Belarus. [Income and expenses of population]. Available from: http://belstat.gov.by/homep/ru/indicators/doclad/2012_7/15.pdf. [Assessed on 15 November 2013]. Russian.

[12]Ministry of labor and social protection of population of the Republic of Belarus. [Occupation of population]. Available from: http://www.mintrud.gov.by/ru/populbusy. [Assessed on 12 January 2013]. Russian.

[13]Agency of the Republic of Kazakhstan on statistics. [Salaries of the employers]. Available from: http://www.stat.kz/news/Pages/n2_17_03_11.aspx. [Assessed on 17 October 2011]. Russian

[14]Agency of the Republic of Kazakhstan on statistics. Analytical Report. Available from: http://www.stat.kz/publishing/DocLib1.doc. [Assessed on 08 December 2013]. Russian

[15]Agency of the Republic of Kazakhstan on statistics. [Monitoring of the village development.] Available from: http://www.stat.kz/Pages/default.aspx. [Assessed on 15 November 2013]. Russian.

[16]Social Security Administration. Office of Retirement and disability policy. Social Security Programs Throughout the World: Europe. Available from: http://www.ssa.gov/policy/docs/progdesc/ssptw/2012-2013/europe/ssptw12europe.pdf. [Assessed on 17 November 2013].

[17]European center for social welfare policy and research. Affiliated to the United Nations. Strategy Paper for pension policy in Ukraine. March, 2012. P. 46.

[18] Legal web portal of Kazakhstan [The sizes of pensions in Kazakhstan]. Available from: http://www.zakon.kz/4465367-razmery-pensijj-v-kazakhstane.html. [Assessed on 15 November 2013]. Russian.

[19] National statistical Committee of the Republic of Belarus. [Occupation of population and unemployment]. Available from: http://belstat.gov.by/homep/ru/indicators/doclad/2012_12/14.pdf. [Assessed on 15 November 2013]. Russian.

[20] The Ministry of Labor and social protection of population of the Republic of Kazakhstan. [Unemployment payments]. Availble from: http://www.enbek.gov.kz/node/251200. [Assessed on 15 November 2013]. Russian.

[21]The World Bank. Unemployment, total (% of total labor force). Available from: http://data.worldbank.org/indicator/SL.UEM.TOTL.ZS. [Assessed on 31 October 2013].

[22]The World Factbook. Belarus. Available from: https://www.cia.gov/library/publications/the-world-factbook/geos/bo.html. [Assessed on 31 October 2013].

[23]The World Factbook. Kazakhstan. Available from: https://www.cia.gov/library/publications/the-world-factbook/geos/kz.html. [Assessed on 31 October 2013].

[24]The World Bank. World Bank group – Kazakhstan. Partnership program snapshot. April, 2013. Available from: http://www.worldbank.org/content/dam/Worldbank/document/Kazakhstan-Snapshot.pdf. [Assessed on 01 February 2014].

[25]Organization of European cooperation and development. Statistics on average effective age and official age of retirement in OECD countries. Available from: http://www.oecd.org/els/emp/ageingandemploymentpolicies-statisticsonaverageeffectiveageofretirement.htm. [Assessed on 16 November 2013].

[26]Social Security Administration. Office of Retirement and disability policy. Social Security Programs Throughout the World: Asia and the Pacific. Available from: http://www.ssa.gov/policy/docs/progdesc/ssptw/2012-2013/asia/ssptw12asia.pdf. [Assessed on 17 November 2013].

[27]The World Factbook. Ukraine. Available from: https://www.cia.gov/library/publications/the-world-factbook/geos/up.html. [Assessed on 31 October 2013].

[28]The World Bank. Public spending on education, total (% of GDP). Available from: http://data.worldbank.org/indicator/SE.XPD.TOTL.GD.ZS. [Assessed on 06 November 2013].

[29]The World Bank. Health Expenditure, total (% of GDP). Available from: http://data.worldbank.org/indicator/SH.XPD.TOTL.ZS. [Assessed on 06 November 2013].

[30]Clinic Summary Report. All SART Member Clinics. Available from: https://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?ClinicPKID=0. [Assessed on 05 November 2013].

[31]Edejer T. Tan-Torres, Baltussen R., Adam T., Hutubessy R., Acharya A., Evans D.B., Murray C.J.L. Making choices in health: WHO guide to cost-effectiveness analysis. World Health Organization 2003. P.313. Available from: http://www.who.int/choice/publications/p_2003_generalised_cea.pdf. [Assessed on 17 November 2013].

Chapter 6

Cost comparison of treating chronic hepatitis C genotype one with pegylated interferons in Ukraine

Mandrik O., Knies S., Golubovska O., Duda O., Dudar L., Fedorchenko S., Zaliska O., Severens J. L. Open Med. 2015; 10: 25-33.

Abstract

Based on the pivotal trial showing no clinically relevant differences between pegylated interferon α-2b (Peg-α-2b) and α-2a (Peg-α-2a) combined with ribavirin for treatment of chronic hepatitis C virus (HCV) genotype 1 infection in Ukraine, a cost-minimization was performed using a 1 year time horizon and both a healthcare and patients' perspective. A decision tree reflects treatment pathways. Drug costs were based on drug labeling and adjusted to the average body mass in Ukraine. Subgroup analysis was applied to deal with heterogeneity of patient's weight causing dose changes. A break - even price of Peg-α-2a and Peg-α-2b (based on the average dose) was calculated. Univariate sensitivity analyses and probabilistic sensitivity analysis were carried out to reflect decision uncertainty. For an average body weight, total medical costs per patient differ from $9220 for Peg-α-2b to $9513 for Peg-α-2a from a healthcare perspective, and from $15,212 to $15,696 from a patients' perspective. Sensitivity analyses show these results are robust. With average body weight, the break-even price of Peg-α-2b may be 7.3% higher than Peg-α-2a to have similar total costs.

Introduction

Chronic hepatitis C virus (HCV) infection is a disease with a global prevalence rate of about 180 million individuals, and every year three to four million people are newly infected [1-3]. The impact of HCV on human health is evident, as 80% of acute hepatitis C cases transform into a chronic form and 10-20% of these cases progress to hepatocellular carcinoma [3].

Currently, reliable official statistics in Ukraine are limited and mainly consist of data on acute HCV infection with jaundice and do not take into the account patients without jaundice and other clinically apparent manifestations who comprise nearly 85% of all morbid events [4, 5]. Ukraine is considered a country with a moderate prevalence of hepatitis C estimated at 1.5 to 3.5% of the population or 700,000 to 1.61 million of people [6]. Additionally, HCV infection rates among high risk groups in Ukraine, primary drugs users, homosexual males, and female sex workers, reach 40 to 60%, essentially exceeding the average global rate [7].

In Ukraine as in most countries, if treatment is indicated, the standard of HCV treatment is a combination therapy using either pegylated interferon α-2b (Peg -α-2b) or α-2a (Peg -α-2a) with ribavirin. Response to therapy is measured in terms of sustained virological response (SVR), which is defined as undetectable HCV RNA concentrations 6 months after completion of therapy. Successful treatment of HCV depends on the virus genotype. The most common and least responsive to therapy are patients who have HCV genotype 1 (estimated 43.7% of all HCV cases or 302,000 to 704,000 people in Ukraine) [6, 8, 9].

The proportion of subjects who achieve early virological response (defined as a 2 log or greater decrease in HCV RNA levels at week 12) and also have an SVR is called a positive predictive value. A difference in the predictability of viral clearance between Peg -α-2b + ribavirin and Peg -α-2a + ribavirin may cause a cost difference in treatment because a lower positive predictive value may result in a longer duration of therapy without achieving success.

Despite a great deal of research on this topic, transferring results from previous studies conducted in US or Western European countries may not be possible due to different socio-economic systems, healthcare settings, cost parameters and their relation to different perspectives, as is the case for Ukraine.

A large multicentre randomized double-blind direct comparative study (ClinicalTrials.gov number, NCT00081770) on treating patients who were infected with HCV genotype 1 with Peg -α-2b or Peg -α-2a was conducted in US on 3070 patients, applying treatment patterns similar to real-life clinical practice [10]. Treatment-naïve patients with genotype 1 without contraindications were given pegylated interferon in

combination with high-dose ribavirin (on average 1000 mg per week) for 48 weeks [10-14]. During the treatment, patients'HCV-RNA was measured after 4, 12, 24, and 48 weeks, the results of which indicated intermediate treatment success. The rates of SVR and tolerability did not differ significantly between the two available pegylated interferons + ribavirin regimens, with SVR rate of 39.8% (95% confidence interval [CI], 36.8 to 42.8) for standard-dose Peg -α-2b, and 40.9% (95% CI, 37.9 to 43.9%) for Peg -α-2a. Although no statistically significant difference in efficacy between Peg-α-2a and Peg -α-2b was reported [10], drugs differed in the predictability of viral clearance (positive predictive value on week 12 was equal to 82% and 76% for Peg -α-2b + ribavirin and Peg -α-2a + ribavirin, respectively) and relapse rates that may result in differences in treatment cost.

No extensive cost analysis were conducted in the above mentioned study because an earlier US cost-effectiveness analysis for a hypothetical cohort of 100 HCV patients with mixed genotypes based on the level of positive predictive value [13] showed no clinically relevant difference in treatment outcome and lower cost of treatment with Peg -α-2b + ribavirin compared to Peg -α-2a + ribavirin. As stated above, differences in healthcare systems and perspectives of analysis may arouse a potential difficulty for transferring these US-based results (adjusting the costs and/or the cost-effectiveness estimate) to other countries [15]. Moreover, in routine clinical practice in Ukraine, an HCV genotype test is performed before treatment initiation. As treatment standards and drug instructions recommend different schemes for genotype 1 versus other HCV genotypes [16, 17], we considered that cost analysis should be also conducted separately for different HCV genotypes with clinical data based on a direct comparative trial.

No studies to our knowledge have been published on the assessment of pegylated interferon efficiency in countries belonging to the Commonwealth of Independent States (CIS) region. Therefore, we aimed to study the costs of using Peg -α-2b in comparison to Peg -α-2a both combined with ribavirin for patients with HCV genotype 1 infection in the Ukrainian healthcare setting.

Materials and methods

For analysing the costs of using Peg -α-2b in comparison to Peg -α-2a both combined with ribavirin for patients with HCV genotype 1 infection in the Ukrainian healthcare setting, we used a decision analytic approach. Because no information on life-long treatment effects is available in the literature, a one year time horizon reflecting length of treatment for genotype 1 patients was defined. This relatively short time horizon makes a decision tree analysis the appropriate method to obtain accurate cost estimations.

The structure of the decision tree was based on US-study protocols' recommendations [11, 16,17]. The treatment response in the model was based on the US-based comparative trial which assessed response at 6 months after the last dose of

pegylated interferon. We assumed that no additional medical services were received after treatment was discontinued or completed. Our cost analysis was conducted from both the healthcare and patients' perspectives (parties which are frequent payers for treatment of HCV in the Ukrainian health care setting) with only direct medical expenses included in the calculation. Cost per SVR achieved was calculated since a non-significant difference in effect may have a meaningful difference in costs. Break-even price of Peg-α-2a and Peg-α-2b (the point at which cost-effectiveness results were equal) was evaluated as well.

Clinical input data

Similar to the trial [10] in the model, virological test procedures for HCV-RNA were defined after the 4th, 12th, 24th, and 48th week of therapy initiation. After each virological test, some patients discontinued treatment with Peg -α-2b + ribavirin or Peg -α-2a + ribavirin due to treatment failure or adverse effects (Figure 6.1).

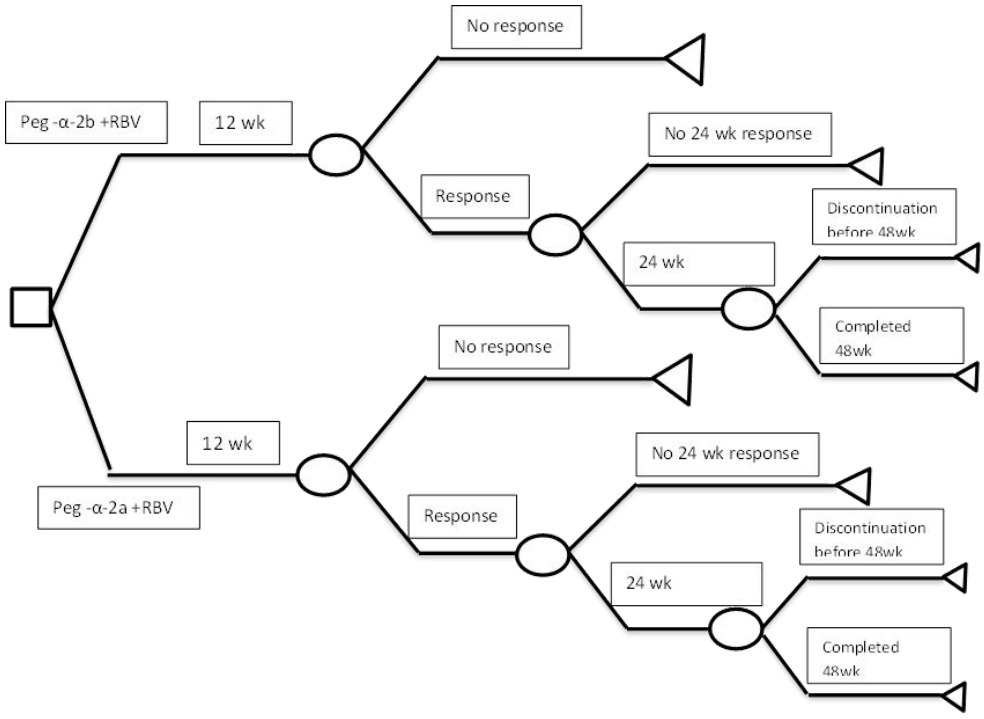

Figure 6.1 Decision tree comparing two strategies for genotype 1 HCV treatment

These discontinuation numbers were retrieved from the clinical trial report (ClinicalTrials.gov number, NCT00081770; the report was provided by MSD Outcome Research), excluding those patients whose follow up data were missing. This resulted in a difference in the number of patients continuing treatment after each virological test (treatment week 12 and 24). According to the trial report, a number of patients discontinued treatment between visits on 24th and 48th weeks (2.85% for Peg -α-2b and 5.7% for Peg -α-2a). In the model, these patients were assumed to be in treatment for 36 weeks on average. Drug dose selection was based on drug labeling; a dosage of the Peg -α-2b preparation was adjusted according to the patient's weight, in contrast to a fixed dose of 180 mcg for Peg -α-2a. The analysis was conducted using the adequate dose according to drug labelling (100 mcg dose for Peg -α-2b and 180 mcg for Peg -α-2a) and to average body weight in Ukraine (74 kg).

Cost input data

Cost analysis from the health care perspective included costs of drug treatment and costs of medical personnel. While costs of the pegylated interferons were determined from state registered prices, expenses of medical personnel services were calculated according to medical services norms in Ukraine (time per patient consultation equalled 12 minutes and the number of working hours per week was 33 hours for a physician and 38.5 hours for a nurse) [18].

Table 6.1 Cost of drug treatment: HCV genotype 1

Regime	Drug costs (Healthcare perspective), $[1]	Drug costs (Patient's perspective), $[2]
Peg-α-2a (180 mcg)	264.02	316.82
Peg-α-2b (120mg)	277.20	332.64
Peg-α-2b (50mg)	265.00	318.00
Peg-α-2b (80mg)	268.20	321.84
Peg-α-2b (100mg)	275.90	331.08
Peg-α-2b (150mg)	283.05	339.66

[1] Prices as given on the website of the Ministry of Health of Ukraine (http://www.moz.gov.ua/ua/portal/register_prices_drugs/) on 01.01.14.

[2] Drugs prices with the distributors and trade margins established by the Order of Cabinet of Ministers of Ukraine #880 from 24.09.2012.

Patients' perspective costs were defined by out of pocket payments for drugs and laboratory tests (antibodies to HCV, quantitative prolactin). Patient payments for drugs were assessed from the state registered prices with the distributors and trade margins established by the Order of the Cabinet of Ministers of Ukraine from 24.09.2012 (Tables 6.1, 6.2). A test for antibodies to HCV (usually conducted once on treatment initiation) costs $13.77 (exchange rate 1 USD = 7.99 UAH on 01.01.2014 by the National Bank of Ukraine) [19].

The costs related to ribavirin (weight dependent) were not considered in the model in both perspectives because due to company policies of the manufacturers of both drugs, ribavirin is provided free of charge by the companies when purchasing pegylated interferons. Because the reported adverse event profiles for both of the drugs were similar [10], the costs associated with adverse events were not included.

Table 6.2 Decision-tree model input parameters

Parameter, measure	Value in deterministic model	Source	Value in PSA	Source
The proportion of patients who completed 48 week Peg 2b, %	47.89%	[16]	43.89-51.89%	ClinicalTrials.gov number, NCT00081770
The proportion of patients who completed 48 week Peg 2a, %	55.26%	[16]	51.51-59.41%	ClinicalTrials.gov number, NCT00081770
SVR Peg-2a, %	40.90%	[16]	37.90-43.90%	McHutchison et al., 2009 [10]
SVR, Peg-2b,%	39.80%	[16]	36.80-42.80%	McHutchison et al. ,2009 [10]
Average monthly salary of a medical worker, $[1]	$296.00	[20]	$236.80-355.20	20% variation from the data in deterministic model
Cost of the laboratory test on quantitative prolactin, $[1]	$84.05	[19]	$47.56-$120.53	Dolkar's initiative for Viral Hepatitis patients care, 2009 [20]

[1] Exchange rate UAH/USD is 7.99 on 01.01.2014 by National Bank of Ukraine

Sensitivity analysis

To reflect the uncertainty inherent in the research, univariate sensitivity analyses were performed using alternative assumptions regarding providers' costs and diagnostics' costs. To reflect decision uncertainty, probabilistic sensitivity analysis (PSA) (1000 draws using Monte Carlo simulation) were carried out. In the PSA, cost of drugs and medical personal were varied in range ±20%, and costs of the laboratory analysis on quantitative prolactin were derived from the minimum to maximum price lists of the laboratories providing their services in Ukraine (Table 6.2) [19].

For valuing parameters in the model from the original trial data, patients with missing outcomes were excluded. For instance, the confidence interval (CI) with 95% CI for the parameter "number of patients who completed 48 week treatment" was not available, while the 95% CI for negative and positive 48 weeks responders was almost similar between both drugs compared. We assumed that the 95% CI for 48 weeks completers had a similar range to positive 48-weeks responders for both strategies (±4% Peg-α-2b and ±3.75% for Peg-α-2a). The number of 48-week completers caused changes in cohort drug costs, laboratory cost, and medical personal costs.

We used subgroup analysis to deal with heterogeneity of patient's weight causing changes in doses of Peg-α-2b according to drug labelling; less than 40 kg: 50 mcg of Peg-α-2b; 40-64 kg: 80 mcg of Peg-α-2b; 65-75 kg: 100 mcg of Peg-α-2b; 75-85 kg: 120 mcg of Peg-α-2b; more than 86 kg: 150 mcg of Peg-α-2b.

Results

The results of the cost analysis are presented in the Table 6.3. Total medical costs per one patient (accounting the average body mass in Ukraine) varied from $9220 for Peg-α-2b to $9513 for Peg-α-2a from a healthcare perspective, and from $15,212 for Peg-α-2b to $15,696 for Peg-α-2a from a patient's perspective. The total cost for an estimated population of patients with HCV genotype 1 in Ukraine varied from a minimum of $2.780 billion (for Peg-α-2b) to $2.868 billion (for Peg-α-2a) and to a maximum of $6.487 billion (for Peg-α-2b) to $6.693 billion (for Peg-α-2a) from a healthcare perspective. Using break-even point analysis, it was defined that a price of Peg-α-2b should be 7.3% higher than Peg-α-2a to have equal/similar total costs. The cost per successfully treated patient, defined as having an SVR, was lower for Peg-α-2b in comparison to Peg-α-2a from patients' perspective and almost similar between treatments from a healthcare perspective.

Table 6.3 Economic outcomes per patient infected with HCV genotype 1

Regimen, weekly	Healthcare perspective		Patient's perspective	
	Total costs, $	Cost/SVR, $	Total costs, $	Cost/SVR, $
Peg-α-2a (not weight dependent,180 mcg)	9513	23,202	13,969	28,539
Peg-α-2b (expected dose consumption in Ukraine, average 100mcg)	9220	23,165	15,212	28,352
Peg-α-2b (mode trial dose,120mcg)	9264	23,276	15,283	28,482

Table 6.4 Sensitivity of cost differences to uncertainty in input values (per patient)

Parameter estimates	Cost difference (Healthcare perspective), $	Cost difference (Patient's perspective), $
Base-case result	293	360
Patients' weight		
<40kg	657	797
>86 kg	54	74
Cost of medical assistance		
Maximum value	293	-
Minimum value	293	-
Cost of HCV laboratory test		
Maximum value	-	304
Minimum value	-	312

The results of univariate sensitivity analyses in genotype 1 patients are shown in Table 6.4. The costs of medical assistance and laboratory tests did not have a significant impact on total cost difference. For the subgroup analyses, the cost difference between Peg -α-2b and Peg -α-2a varied from 6.90% (weight less than 40 kg) to 0.56% (weight more than 86 kg) from a healthcare perspective, and from 6.81% (weight less than 40 kg) to 0.63% (weight more than 86 kg) from a patient's perspective. The costs per patient and costs per SVR in accordance to the mode trial dose of Peg-α-2b [16] were slightly higher than using body mass-based calculation for Ukraine, though a general cost difference in favour of Peg-α-2b was observed.

PSA results showed an average cost difference of 2.19 and 2.25% from the healthcare and patients perspectives respectively (median 3.84%, std. error = 1.37% from the healthcare; median 3.80%, std. error = 1.34% from the patients' perspective) in favour of Peg -α-2b + ribavirin. Mean SVR rates as a result of the PSA (40.08% for Peg -α-2b + ribavirin and 41.03% for Peg -α-2a + ribavirin) were similar to the deterministic data confirming the validity of the calculations.

Discussion

The results from this cost comparison suggest that therapy with Peg -α-2b + ribavirin may be less costly than Peg -α-2a + ribavirin for patients with genotype 1 HCV infection in cases in which no statistically significant difference in the rates of SVR achieved is assumed [10]. As the positive predictive value is higher for Peg -α-2b among patients with genotype 1 with no effect on clinical outcome (SVR), it leads to a lower number of patients receiving treatment when successful outcome is not possible, and so to lower cost per successful treatment because the probability of successful treatment is equal between the strategies. The results of the sensitivity analyses showed that input parameters such as cost of medical assistance and laboratory tests do not affect the results of the base case analysis substantially. Because Peg -α-2b allows weight-based dosing, the subgroup analyses showed the economic advantage may be higher for patients with lower weight and lower for patients with higher weight than average. Adjustment to the patient's body weight can lead to additional cost reductions from both patients' and healthcare perspectives.

Due to possible price changes for pharmaceutical products on the Ukrainian market as a result of negotiation policy of distributors and producers participating in state tender purchases (no reimbursement currently exists in Ukraine), we consider that the break-even price instead of the actual price should be considered to determine cost efficiency of the product in Ukraine. Price variation because of negotiations is a frequent action on the Ukrainian state pharmaceutical market, and a similar strategy was announced by the Ministry of Health of Ukraine in relation to access to hepatitis

treatment. The higher positive predictive value of Peg -α-2b may lead to cost savings as long as the price of Peg -α-2b is not more than 7.3% higher than Peg -α-2a.

Treatment with pegylated interferon + ribavirin for chronic hepatitis patients is considered to be a standard therapy in many countries. In Ukraine, application of this scheme competes with interferon + ribavirin treatment (from 40 to 60% of the prescriptions by experts' estimates [personal communication]). As final clinical outcomes of HCV treatment such as virus eradication and prevention of death and progression to cirrhosis and hepatocellular carcinoma occur over a long period of time and are difficult to measure, SVR can serve as a surrogate indicator whether the treatment goal has been achieved [22]. Several studies indicate the association of SVR with improvements in liver histology, probability of developing liver decompensation, quality of life, and survival [23-28]. While the majority of the population of Ukraine cannot afford expensive drug products [29], patient access to treatment with pegylated interferon plus ribavirin is crucial in the Ukrainian health care setting.

The methods used here, a decision analysis using data from one pivotal trial, allowed us to derive essential clinical parameters for valuing the model parameters (such as number of patients continuing the therapy after each measurement of virological control). Another direct comparative trial focused on measuring SVR as an outcome of treatment of naïve patients with genotype 1 HCV (instead of mixed genotypes). These data were not included in our model as no significant clinical difference in the limited treatment groups (37 patients in each one) was reported [18]. Since these results are similar, we do not expect differences in the results of economic evaluation if these additional data were to be incorporated to value parameters in the model.

While the largest comparative trial was used for clinical input data, it should be noted that the previous systematic review [31] provided assessment of efficacy with pegylated interferon treatment for patients with a mixed genotype, while no genotype-specific comparison was conducted. Meanwhile, for treatment naïve HCV patients with genotype 1, there were only four studies were SVR was used as efficacy measure. Two of these trials, conducted by Sinha et al and Yenice et al., included a limited number of patients, enrolling 42 and 80, respectively [30,32]. Two studies by Rumi et al. and Ascione et al., both conducted in Italy (178 patients and 181 patients with genotype 1 HCV, respectively), reported the same probability ($p=0.04$) for Peg -α-2a + ribavirin to be clinically superior to Peg -α-2b + ribavirin [33,34]. The current cost-minimization analysis was based on the clinical data from the largest trial available which showed no statistically significant difference between treatment arms. The weighted pooled data from the three trials has shown almost similar SVR rates for genotype 1 patients (41.5% for Peg -α-2a + ribavirin and 40.2 % for Peg -α-2b + ribavirin) to the data used in the current study [10,33,34]. While this adjustment has no impact on the results of the current cost-minimization study, the cost for one SVR reached remained equal for both drugs.

Several economic studies on treatment of naïve patients with chronic HCV infection have been published in different countries [12-14, 30,31]. The most recent study on pegylated interferons was conducted for the US [13], applying similar methodology as our study, defining the cost-efficacy of Peg -α-2b + ribavirin scheme for patients with HCV (genotypes 1,2,3). Though the aim of the study was similar, the perspective of the US-study was one of a managed care organization. Thus, using the transferability criteria for cost-effectiveness estimates as stated by the ISPOR taskforce on transferability [15], it may not be applicable for Ukraine, where major treatment costs for HCV treatment are partially covered by patients' payments and partially by government through state purchases. Despite the difference in perspectives, Malone et al. reached the similar conclusion, stating that treating with Peg -α-2b + ribavirin provides cost savings in comparison to Peg -α-2a + ribavirin because fewer patients are treated beyond 12 weeks when achieving SVR is unlikely [13]. The indicated study suggested that although both Peg -α-2a and Peg -α-2b have demonstrated similar SVR overall, for genotype 1, there is a significant difference in early virological response rates. Thus, using Peg -α-2a + ribavirin for genotype 1 patients may cause more treatments' consumption for the patients' cohort without additional health benefit over those treated with Peg -α-2b.

A number of other economic studies compared treatment with interferons and pegylated interferons for genotype 1 HCV treatment-naïve patients [12,14,31], confirming cost-effectiveness of the latter one. A study in Spain, conducted by Buti et al. [12], also defined treatment with Peg -α-2b + ribavirin as the optimal strategy which includes adjustment to the patient's body weight for 48 weeks and good therapeutic compliance. Siebert et al. concluded that Peg -α-2b + ribavirin could reduce the incidence of liver complications, prolong life, improve quality of life, and be cost effective for the initial treatment of HCV in patients in Germany [30]. Sullivan et al. evaluated cost-effectiveness of Peg -α-2a + ribavirin versus traditional interferon, coming to the similar conclusion on efficiency pegylated interferons in patients in the US. In our analysis comparing two pegylated interferons, we observed similar results with the study of Malone et al. [11], though due to differences in sources of clinical outcomes (SVR rates), cost components, and prices, the total costs were different. Thus, the results from our study may help to assess costs for HCV genotype 1 treatment in Ukraine and may be more easily transferable to other CIS countries.

This analysis suggests that use of Peg -α-2b + ribavirin may be preferred to Peg -α-2a + ribavirin in treatment of genotype 1 HCV infected patients due to lower costs associated with treatment, given the earlier finding of comparable clinical efficacy. Use of Peg -α-2b + ribavirin in comparison to Peg-α-2a + ribavirin could lead to a cost reduction of $88 to $206 per patient if the treatment for all the cohort of genotype 1 HCV patients is provided. Price of Peg -α-2a would have to be lower to achieve similar efficiency to Peg -α-2b.

References

1. Davis KL, Mitra D, Medjedovic J, Beam C, Rustgi V. Direct economic burden of chronic hepatitis C virus in a United States managed care population. J Clin Gastroenterol. 2011; 45: 17-24.
2. Ray Kim W. Current focus: Global epidemiology and burden of hepatitis C. Microbes and Infection. 2002; 4: 1219-25.
3. Lavanchy D. Evolving epidemiology of hepatitis C virus Clinical Microbiology and Infection. 2011; 17: 107-15
4. [On some issues of infectious diseases registration, accounting and reporting]. Decree of the Cabinet of Ministers of Ukraine of 21.02.2001, No. 157. Ukrainian.
5. [To stop hepatitis in Ukraine is a mutual obligation of state and society]. News release by the Ministry of health of Ukraine. 2010-05-19. 1(1): 1 screen. Available from: http://www.moz.gov.ua/ua/portal/pre_20100519_3.html. [Assessed on 17 December 2012]. Russian.
6. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology. 2013; 57: 1333-42.
7. [Every fifth Ukrainian of 1000 persons is infected with Hepatitis C. Governmental Portal]. 2010-12-29. 1(1): 1 screen. Available from: http://www.kmu.gov.ua/control/uk/publish/article?art_id=243957905&cat_id=35884. [Assessed on 24 July 2012]. Ukrainian.
8. Yurchenko T, Stepchenkova T, Karnets I, Ashworth K, Cheusova T. [The results of a study on the prevalence of HIV, HCV and HBV genotypes in some regions of Ukraine]. Retrovirology. 2012; 9: 55. Russian.
9. Davis GL, Wong JB, McHutchison JG, Manns MP, Harvey J, Albrecht J. Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C. Hepatology. 2003; 38: 645-52.
10. McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, Nyberg LM, Lee WM, Ghalib RH, Schiff ER, Galati JS, Bacon BR, Davis MN, Mukhopadhyay P, Koury K, Noviello S, Pedicone LD, Brass CA, Albrecht JK, Sulkowski MS. IDEAL Study Team. Peginterferon Alfa-2b or Alfa-2a with Ribavirin for Treatment of Hepatitis C Infection. N Engl J Med. 2009; 361: 580-93.
11. National Institutes of Health Consensus Development Conference Statement: Management of Hepatitis C. Gastroenterology. 2002; 123: 2082-99.
12. Buti M, Casado MA, Fosbrook L. Esteban R. Financial Impact of Two Different Ways of Evaluating Early Virological Response to Peginterferon-α-2b Plus Ribavirin Therapy in Treatment-Naïve Patients with Chronic Hepatitis C Virus Genotype 1. Pharmacoeconomics. 2005; 23: 1043-55.
13. Malone DC, Tran TT, Poordad FF. Cost-Efficacy Analysis of Peginterferon alfa-2b plus Ribavirin Compared With Peginterferon alfa-2a plus Ribavirin for the Treatment of Chronic Hepatitis C. J Manag Care Pharm. 2005; 11: 687-94.
14. Sullivan SD, Jensen DM, Bernstein DE, Hassanein TI, Foster GR, Lee SS, Cheinquer H, Craxi A, Cooksley G, Klaskala W, Pettit K, Patel KK, Green J. Cost-effectiveness of combination peginterferon alpha-2a and ribavirin compared with interferon alpha-2b and ribavirin in patients with chronic hepatitis C. Am J Gastroenterol. 2004; 99: 1490-6.
15. Drummond M, Barbieri M, Cook J, Glick HA, Lis J, Malik F, Reed SD, Rutten F, Sculpher M, Severens J. Transferability of economic evaluations across jurisdictions: ISPOR Good Research Practices Task Force report. Value Health. 2009; 12: 409-18.
16. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, Management, and Treatment of Hepatitis C: An Update. Hepatology. 2009; 49: 1335-1374.
17. Management of Hepatitis C Virus Infection. European Association of Hepatic Studies. 2011. Available from: http://www.easl.eu/_clinical-practice-guideline/issue-5-released-march-2011-updated-june-2011-management-of-hepatitis-c-virus-infection. [Assessed on 24 July 2012].

18. [On approval of the standard of working time for employees of health care institutions and establishments]. The Order of the Ministry of Health of Ukraine No. 319. Available from: http://moz.gov.ua/ua/portal/dn_20060525_319.html. [Assessed on 24 July 2012]. Ukrainian.

19. [Dolkar's initiative for Viral Hepatitis patients care. Hepatitis C in Ukraine: unrecognized epidemy]. 2009. Available from: http://hepatit.org.ua/wp-content/uploads/2010/02/HCV_UA_report-2009.pdf. [Assessed on 05 October 2011]. Ukrainian.

20. [Average monthly salary by occupation type for the period starting from the year 2013]. National statistics service of Ukraine. Available from: http://www.ukrstat.gov.ua/operativ/operativ2013/gdn/Zarp_ek_p/zpp2013_u.htm. [Assessed on 19 January 2014]. Ukrainian.

21. Yenice N, Mehtap O, Gümrah M, Arican N. The efficacy of pegylated interferon alpha 2a or 2b plus ribavirin in chronic hepatitis C patients. Turk J Gastroenterol. 2006; 17: 94-8.

22. Talwani R, Gilliam BL, Rizza SA, Nehra V, Temesgen Z. Current status of treatment for chronic hepatitis C virus infection. Drugs Today (Barc). 2012; 48: 219-31.

23. Berenguer J, Alvarez-Pellicer J, Martín PM, López-Aldeguer J, Von-Wichmann MA, Quereda C, Mallolas J, Sanz J, Tural C, Bellón JM, González-García J. GESIDA3603/5607 Study Group, Sustained virological response to interferon plus ribavirin reduces liver-related complications and mortality in patients coinfected with human immunodeficiency virus and hepatitis C virus. Hepatology. 2009; 50: 407-13.

24. Camma C, Di Bona D, Schepis F, Heathcote EJ, Zeuzem S, Pockros PJ, Marcellin P, Balart L, Alberti A, Crax A. Effect of peginterferon alfa-2a on liver histology in chronic hepatitis C: A meta-analysis of individual patient data. Hepatology. 2004; 39: 333-42.

25. Bruno S, Stroffolini T, Colombo M, Bollani S, Benvegnù L, Mazzella G, Ascione A, Santantonio T, Piccinino F, Andreone P, Mangia A, Gaeta GB, Persico M, Fagiuoli S, Almasio PL. Italian Association of the Study of the Liver Disease (AISF), Sustained virological response to interferon-alpha is associated with improved outcome in HCV related cirrhosis: a retrospective study. Hepatology. 2007; 45: 579-87.

26. Veldt BJ, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP, Zeuzem S, Manns MP, Hansen BE, Schalm SW, Janssen HL. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis, Ann Intern Med. 2007; 147: 677-84.

27. George SL, Bacon BR, Brunt EM, Mihindukulasuriya KL, Hoffmann J, Di Bisceglie AM. Clinical, virologic, histologic, and biochemical outcomes after successful HCV therapy: A 5-year follow-up of 150 patients. Hepatology. 2009; 49: 729-38.

28. Fernández-Rodríguez CM, Alonso S, Martinez SM, Forns X, Sanchez-Tapias JM, Rincón D, Rodriguez-Caravaca G, Bárcena R, Serra MA, Romero-Gómez M, Fernandez I, Garcia-Samaniego J, Fuente J, Solá R, Moreno-Otero R, Planas R. Group for the Assessment of Prevention of Cirrhosis Complications and Virological Response (APREVIR), Peginterferon plus ribavirin and sustained virological response in HCV-related cirrhosis: Outcomes and factors predicting response. Am J Gastroenterol. 2010; 105: 2164-72.

29. Nemchenko AS, Kosyachenko KL, Nemchenko OA. Drugs pricing. Apostrof, Kharkiv, 2012. 304.

30. Siebert U, Sroczynski G, Rossol S, Wasem J, Ravens-Sieberer U, Kurth BM, Manns MP, McHutchison JG, Wong JB. German Hepatitis C Model (GEHMO) Group, International Hepatitis Interventional Therapy (IHIT) Group, Cost effectiveness of peginterferon α-2b plus ribavirin versus interferon α-2b plus ribavirin for initial treatment of chronic hepatitis C. Gut. 2003; 52: 425-32.

31. Sullivan SD, Jensen DM, Bernstein DE. Cost-effectiveness of combination peginterferon alpha-2a and ribavirin compared with interferon alpha-2b and ribavirin in patients with chronic hepatitis C. Am J Gastroenterol. 2004; 99: 1490-6.

32. Awad T, Thorlund K, Hauser G, Stimac D, Mabrouk M, Gluud C. Peginterferon alpha-2a is associated with higher sustained virological response than peginterferon alfa-2b in chronic hepatitis C: systematic review of randomized trials. Hepatology. 2010; 51: 1176-84.

Chapter 7

Impact of hypoglycemia on daily life of type 2 diabetes patients in Ukraine

The Chapter is based on:
Mandrik O., Severens J.L., Doroshenko O., Pan'kiv V., Kravchun N., Vlasenko M., Hulchiy M., Baljuk M., Komisarenko Y., Martsynik E., Sokolova L., Zalis'ka O., Mankovsky B. J. Multidiscip Healthc. 2013; 6: 249–257.

Abstract

This study evaluates the impact of hypoglycemia on lives of Ukrainian patients with type 2 diabetes mellitus. The secondary objective was to explore patient-physician relationships and attitudes of patients toward various informational resources on diabetes management. Three focus groups with 26 patients were conducted. Qualitative information was evaluated using content analysis. The results show that patients with type 2 diabetes mellitus in Ukraine are adapting to potential attacks of hypoglycemia, however, they still experience periodic manifestations of hypoglycemia that significantly affect patients' psychological well-being. This result is similar to observations made in other countries. Ukrainian patients elder than 40 years old receive information on disease management majorly from endocrinologists, and rarely use Internet resources on diabetes management. Information provision was especially important on early stage of the disease when patients lack information on hypoglycemia manifestations and could fail to identify it and manage it properly.

Introduction

Hypoglycemia is a common complication of treating diabetes mellitus [1] and is characterized with (but not limited to) the following symptoms: sweating, palpitations, shaking, hunger, confusion and drowsiness [2]. Research on the daily lives of patients with hypoglycemia conclude that the frequency of hypoglycemic episodes is correlated with lower general health, greater fear and anxiety, lower health-related quality of life (HRQoL), higher risk of long-term complications and mortality, reduced work productivity, and problems performing certain daily activities [1,3-10]. Some of the major issues explored in past research include the frequency of hypoglycemic symptoms and their characteristics [11], patients' understanding of hypoglycemic symptoms and their severity [9,12,13], limitation on daily life because of hypoglycemia, and psychological impact of hypoglycemia [9,10,14].

Past research points to several other factors that can have an impact on how patients manage hypoglycemia caused by type 2 diabetes mellitus. For example, patient's education has a direct impact on awareness and, therefore, on the severity of hypoglycemia [11]. Various informational resources can be used for patients' awareness programs. In a number of countries, information on diabetes (including hypoglycemia) management is usually provided by the primary care practitioner [8,15-17]. In such cases patient-doctor relationships become very important for effective disease management. An apparent lack of concern by healthcare providers can have a negative impact on emotional state of patients [14,18].

This previous research has been conducted largely in developed countries. Unfortunately there is little to no research on this topic conducted in Ukraine or any other developing country in the Eastern Europe. It is also recognized that a number of factors, such as receiving insulin therapy, obesity, diabetes complications, age, sex, employment status, educational level, level of physical activity, and ethnicity, among others, might have an impact on perceived HRQoL of type 2 diabetic patients. These various factors vary from region to region and might be influenced by country-specific socioeconomic and lifestyle factors. Thus, the results from past research might not be generalizable between geographic regions.

There are no studies available for Ukraine or other developing country of the Eastern Europe that give insight on potential impact of hypoglycemia on daily life of patients with type 2 diabetes. At the same time focus groups were often used in studies with focus on impact of hypoglycemia on patient's lives [10,12,14]. For these reasons, this study was undertaken to evaluate the perceived burden of hypoglycemia on patients' daily life in one of the developing countries, Ukraine. The primary objective of this qualitative study was to evaluate, through focus groups with type 2 diabetes mellitus patients with at least one reported case of hypoglycemia during the last year of treatment,

the symptoms that are experienced, how they are managed, how hypoglycemia episodes can limit patients' daily life, and what is the psychological impact of hypoglycemia from the perspective of Ukrainian patients. A secondary objective was to explore patient-physician relationships and attitudes of patients toward various informational resources on diabetes management in Ukraine.

Methods

Focus groups of patients with hypoglycemia

We selected the focus groups method to evaluate impact of hypoglycemia on patient's lives, to assess hypoglycemia awareness and most frequently used sources of information for the management of diabetes mellitus 2nd type [10,12,14]. General principles of the focus group method [19-21] and past focus group studies conducted on patients with type 2 diabetes mellitus [10,12,14] were referenced for discussion guide design and data analysis.

A purposive sampling strategy was applied to recruit an age-homogeneous group with participants older than 40 years, and having at least one reported case of hypoglycemia during the last year of medical observation. A total of three focus groups (women N =14, men N = 5 and 7) with patients from one of the largest urban cities of Ukraine and its surrounding were conducted. The gender division aimed to stimulate more open discussion among the participants and to eliminate a gender bias [12]. The focus group with men was conducted 2 times because of lower recruitment rate versus women. All focus groups were organized at independent clinical location with aim not to influence disclosure of information by the participants.

All participants confirmed knowledge of Russian language as fluent. If eligible, potential participants were contacted by their physician to explain the purpose of the research with an invitation, and receive a verbal agreement to participate. Institutional Review Board approval was received prior to the initiation of the study.

The majority of the participants were not acquainted with each other. Thus, an informal introduction session was organized for participants prior to the focus groups to help to open up. Before starting the focus groups, all participants were again introduced to the study structure and purposes, requested to read and sign an informed consent form, and complete a brief questionnaire on their socio-demographic and disease characteristics. The discussion during the focus groups was led by an experienced moderator with a background in life and social sciences. All sessions were audiotaped with permission of the participants, and after completion transcribed verbatim.

A guide was constructed to discuss the following: symptoms patients experienced during hypoglycemia events and their frequency/severity (for this they were also provided

a visual measurement aid), the actions they undertook when experiencing such symptoms, the impact of hypoglycemia on their work, daily activities, physical activities, family and social life, fear of hypoglycemia, and depression and/or other psychological effects/symptoms they experienced. Additionally, patients were asked about their experience in communication with physicians, and source of information on disease management they use. Patients were encouraged to add anything they considered important after each of the topic and at the end of the focus groups.

After the focus group discussion was completed, patients were asked to complete one generic (Questionnaire on State of Health EQ-5d-3L) and one disease specific (Russian-version of "Questionnaire on Low Blood Sugar Level in Adults" developed by the University of the Virginia in 1998) instrument assessing HRQoL that were used in the previous studies [7,9]. The main objective of using these instruments was to evaluate their acceptability and validity among Russian-speaking patient populations in Ukraine, to capture any missing data for patients who might have been less eager to participate in conversations, and to compare the results received orally and in written form.

Data analysis

Descriptive statistics was used to characterize the sample group in terms of clinical and socio-demographic characteristics. Qualitative information from the focus group discussions was evaluated. A content analysis was used for aspects identified by more than three patients in each gender group. The transcripts were analyzed by two researchers independently. Categories for data analysis were selected in accordance with the written focus group protocol as follows:

1) Symptoms and management of hypoglycemia;
2) Hypoglycemia as a limitation;
3) Psychological impact of hypoglycemia.

We grouped similar events and incidents into sub-categories, selected in accordance with the participants' replies under similar categories, for easier results presentation [10,14].

Results

Eighteen men and fifteen women with the defined profile were contacted, from which twelve men and fourteen women agreed to participate in the focus groups. Table 7.1 shows the demographic and clinical characteristics of the sample as reported by the patients in the written form. The difference between men and women in education and family status is proportional to general population [22]. From socio-economic parameters

we can also note a high unemployment rate among type 2 diabetic patients. The sub-categories retrieved from the groups' discussion are presented in the Table 7.2.

Table 7.1 Demographic and clinical characteristics

Characteristic	Men N = 12	Woman N = 14	Total N = 26
Mean age (SD)	47.33 (6.77)	57.71 (5.54)	52.92 (8.00)
Less than 2 years history of diabetes mellitus type 2, N (%)	2 (17)	1 (8)	3 (12)
More than 5 years history of diabetes mellitus type 2, N (%)	6 (50)	8 (58)	14 (54)
City residents, N (%)	12 (100)	13 (93)	25 (96)
Residing with a family, N (%)	8 (67)	13 (93)	21 (81)
With higher education degree or above, N (%)	5 (42)	6 (43)	11 (42)
Employed, N (%)	5 (42)	7 (50)	12 (46)
Not working because of diabetes mellitus type 2, N (%)	7 (58)	2 (14)	9 (35)
Household income of study participant below 375 USD/month [a]	10 (83)	12 (86)	22 (85)
Self indicated as of low-income level, N (%)	9 (75)	9 (64)	18 (69)
Using oral blood-sugar lowering medications, N (%)	6 (50)	13 (93)	19 (73)
Constant insulin users, N (%)	6 (50)	2 (14)	8 (31)

[a] Exchange rate applied at 1USD /8 UAH.

Category 1 Symptoms and management of hypoglycemia

In general, patients participating in the focus groups demonstrated a high level of awareness of their hypoglycemia symptoms, which included: shakiness, hunger, sweating (both men and women), and additionally sleepiness, dizziness, moodiness/irritation, weakness, problems thinking, and loss of vision among women. For example, one 54-year old woman participant described hypoglycemia as the following: ". . . when you get or are

hungry, an internal tremor begins. And then it intensifies and all your body begins . . . Both your arms, and feet, and weakness, and dizziness . . . ." In the written visual form men also indicated weakness and nervous excitation as a frequent symptom.

All participants generally agreed that the most common action taken when hypoglycemia symptoms occur is the consumption of candies, fruits and sweet liquids. Participants also were aware of the consequences of failing to take measures at the onset of hypoglycemia symptoms, most frequently indicating such consequences as loss of consciousness and coma.

A number of participants (5 men and 7 women) indicated that for a long time they did not know they were experiencing hypoglycemia manifestations: "I just did not pay attention in the beginning. . . " (men, 46 years); ". . . I simply did not know what was happening to me" (woman, 49 years). Most patients indicated that they independently established the connection between their feeling of sickness and low blood sugar level after having blood sugar measured at the moment of hypoglycemic condition. Others indicated that their hypoglycemic condition was detected during their hospitalization with a serious clinical condition. Four of six men, who took insulin, indicated that they started to experience hypoglycemia symptoms after initiating insulin therapy. Both men and women indicated that they lacked information on hypoglycemia manifestations at the early stage of developing diabetes mellitus and, therefore, failed to identify it and manage it properly.

Table 7.2 Categories and sub-categories characterizing daily life for type 2 diabetes mellitus patients experiencing hypoglycemia

Categories as defined in the protocol	Sub-categories as defined based on the input of participants
Symptoms and management of hypoglycemia	Symptoms of hypoglycemia and their frequency
	Actions in case of event
	First time hypoglycemia was diagnosed
Hypoglycemia as a limitation	Hypoglycemia and adaptation
	Hypoglycemia and social life limitation
Psychological impact of hypoglycemia	Depression and fear of hypoglycemia
	Actions caused by hypoglycemia fear

Category 2 Hypoglycemia as a limitation

The majority of focus group participants (9 men and 5 women) remarked about adapting their rhythm, daily routine and way of life to cope with periodically occurring hypoglycemia attacks (Table 7.3).

Table 7.3 Social, physical, and psychological impact of hypoglycemia (data based on focus group session only)

Events reported during focus groups	Men (N = 12)	Women (N = 14)
Sub- category: Hypoglycemia and social life limitation		
Decrease in work productivity	0	3
Decrease in physical activities	4	5
Decrease in mobility (going out, or number of long trips)	3	5
Adaptation of social daily life (like 'eating schedules')	6	5
Absence of impact on driving	5	N/A
Sub-category: Hypoglycemia and adaptation		
Some daily routine adaptation	12	13
Awareness about the problem and readiness to help among relatives and close friends	7	9
Working schedule adaptation	6	5
Sub-category: Depression and fear of hypoglycemia		
Periodic fear or psychological discomfort	12	13
Fear to collapse/enter coma	10	10
Depressive states	0	7
Fear-related change in insulin time injection	6	0
Fear-related excessive food consumption	0	3
Attempts to prevent hypoglycemia when feel possible onset	5	6

Adaptation included a decrease in the number of trips, stress prevention, regular food consumption, and urgent preventive actions as soon as she/he began to experience the symptoms of hypoglycemia. All of the participants still experience hypoglycemic events periodically because of physical exercise (6 women), medications (4 men), stress (4 men and 5 women), and disruptions in the regime (7 men and 8 women). Two men and four women noted that hypoglycemic events happen to them more frequently during a certain time of the day (usually morning) or during a certain season.

Participants indicated that hypoglycemia has no significant effect on their family life. However, men reported that they try to avoid irritation and family stresses, or prefer to stay alone. Some women indicated a feeling of discomfort in relations with their relatives.

Regarding work productivity, three of the women participants indicated a substantial decrease in productivity because of frequent hypoglycemic events: "It is not just a decrease, I can't do anything" (woman, 49 years). Additionally, women tried to refrain from informing colleagues about the state of their health, being afraid of criticism and possible influence on labor relations. In large groups and social settings, the participants also mainly stay silent about their diabetes because they do not want to burden others with their health problems, or they are ashamed.

Men tried to adapt their working day to the state of their health and 7 of them disclosed that they had to leave their jobs because of diabetes mellitus. Employed participants indicated that they needed to change their working day schedules to prevent hypoglycemia attacks.

Regarding physical exercise, participants revealed that they used to limit physical exertion (4 men and 5 women). Driving a car was not associated with any specific problem (none of the women drives a car). Almost no difficulties in performing usual daily activities was noticed by participants, but shopping for a long period of time can be a problem for some of them.

Answers provided by participants in the printed EQ-5D-3L Form (Table 7.4) stated that they have some difficulties with mobility (walking), feel moderate pain/discomfort, and experience anxiety/depression.

Table 7.4 Answers Provided by Participants in Printed EQ-5D-3L Form (Russian Version)

Indicators of quality of life [a]		Sex		
		Men	Women	Total
		N (%)	N (%)	N (%)
1. **Mobility**	I have no problems in walking about	4 (33)	2 (14)	6 (23)
	I have some problems in walking about	8 (67)	12 (86)	20 (77)
2. Self care	I have no problems with care	12 (100)	9 (64)	21 (81)
	I have some problems washing or dressing myself	0 (0)	5 (36)	5 (19)
3. Usual activities	I have no problems with performing my usual activities	6 (50)	4 (29)	10 (38)
	I have some problems with performing my usual activities	6 (50)	10 (71)	16 (62)
4. Pain / Discomfort	I have no pain or discomfort	2 (17)	2 (14)	4 (15)
	I have a moderate pain or discomfort	10 (83)	12 (86)	22 (85)
5. Anxiety / Depression	I am moderately anxious or depressed	12 (100)	14 (100)	26 (100)

[a] None of focus group participants indicated the most severe state (third level) in all five categories

Category 3 Psychological impact of hypoglycemia

The fear and psychological discomfort was observed as an important aggravating factor of hypoglycemia among patients with type 2 diabetes mellitus (Table 7.3). During the discussion, everyone except one woman mentioned periodic fear or psychological discomfort because of hypoglycemia. Twenty participants confirmed that they had a fear of collapsing (because of diverse reasons). Men mainly associated the condition of psychological discomfort with anxiety and the inability to foresee hypoglycemic events, and fear of a hypoglycemia events happening at an inopportune moment or in public. Woman mainly connected the condition of psychological discomfort with unpredictability of hypoglycemia manifestations, feeling of fear, anxiety, depression, mood swings, irritation and permanent alertness to prevent the occurrence of hypoglycemia symptoms. At the same time, unlike men, women were the most afraid of losing consciousness when alone, without anyone nearby who would be able to rescue them: "Psychologically you are

afraid each time that something can happen to you. You are going and waiting for something to happen. I am always afraid . . . " (woman, 52). Fear of a hypoglycemic event also has a significant impact on participants' behavior: it causes them to shift the time of insulin intake (men), eat an additional meal (women), and limit long trips (both genders) as presented in the Table 7.3.

Twenty two of 26 participants (10 men and 12 women) indicated feeling a moderate pain/discomfort on the EQ-5D-3L. All 26 participants indicated that they feel anxiety and/or depression. According to the HFS Form, for men the most frequent manifestations of anxiety (experienced by nearly half of men) were difficulties maintaining control when it is necessary to bear responsibility for other people, and difficulties performing important tasks because of low blood sugar. For women, the most frequent anxiety manifestations, expressed in the HFS, were the concern that in case of attack there will be no meal, fruits or juice within their reach.

Hypoglycemia reporting, awareness and sources of information

Focus group participants revealed that they receive information about diabetes from different sources, but mainly from their endocrinologist. Only 7 persons of 26 indicated that they additionally searched for information regarding diabetes in the published lay or scientific literature, and only 4 participants (all men) indicated that they use Internet sources to research information regarding diabetes. During the discussion, 6 people also shared a positive impact of patients' diabetic educational programs or communication with other patients on information provision. Opinions about whether or not discuss the problem of hypoglycemia with their physician differed among study participants. Participants (8 men and 4 women) said that they do not completely trust their physician, and that it is sometimes easier for them to experiment to select the most effective methods for hypoglycemia prevention. An interesting difference between the gender groups was observed: while the majority of women indicated that their doctor is asking about hypoglycemia events during each visit, most of the men participants stated that either the physician did not have time for such questions, or the patient himself is not interested in information provided by the endocrinologist. Several of the men participants described the situation of communication with the doctor as follows: "Theoretically he ("physician" - authors) knows everything, but practically he was not in such a situation", "How can you trust the physician, if the physician does not trust you. . . ", "They ("physicians" - authors) do not particularly raise this problem, maybe, because they are not interested in it" (men, 49, 52, 53 years).

Discussion

This study aimed to evaluate the symptoms that are experienced and the management of hypoglycemia, how hypoglycemia episodes might limit patients' daily life, and what is the perceived psychological impact of hypoglycemia among Ukrainian patients. In general, our findings were similar to those reported in other countries.

Relating to symptoms experienced by the patients, autonomic symptoms (shakiness, hunger, sweating) were named more frequently by focus groups participants of both genders. Neuroglycopenic symptoms (weakness, dizziness, and irritability) were also frequently reported by women, though we acknowledge that these symptoms can be related to the other health problems. We observed a difference in symptoms reporting between men and women, with a higher number of symptoms reported among women during the discussion, which is similar to the findings by Marrett et al. [7].

Similar to the findings of other studies [14,23], it appears that Ukrainian patients with a long history of the disease (as perceived by patients) are adapting to hypoglycemia. Most of the patients were well informed about the disease symptoms, severity, and the actions required to treat/manage it. Focus group participants not only were able to adjust their nutrition schedule and level of physical activities to manage the disease, but they also adapted their daily activities, working schedules, and private relations to help prevent hypoglycemia and make it more manageable. In the majority of cases, not only family, but also close friends and colleagues of a patient with diabetes mellitus are well informed about his/her state and able to provide help in case of emergency, a result observed in previous research [10]. However, as observed in the study by Wu et al. [14], some participants in this study also preferred to conceal having diabetes at work or in large social settings. Others reported trying to hide not the diabetic state itself but rather the negative health symptoms caused by hypoglycemia, fearing that their health limitation might negatively affect their employment. Like the study by Dickinson and O'Reilly et al. [23], we conclude that family, friends and the work environment can have a significant positive impact on managing type 2 diabetes mellitus complications and on patients' well-being.

We found that "adaptation" to diabetes and associated hypoglycemic states do not always mean absence of negative changes in daily routine: the number of men indicated leaving their job because of diabetes complications, and working women reported a significant decrease in their work productivity because of frequent symptoms such as dizziness and weakness. Because of the need to be constantly alert to the symptoms of hypoglycemia, participants indicated that hypoglycemia events cause disruptions in their daily routines.

The possibility of hypoglycemia events can lead to fear of hypoglycemia and hypoglycemia-related depressions, which are significant factors negatively influencing

patients' well-being. Most of the participants indicated verbally that they experienced periodic anxiety and depression because of the possibility of hypoglycemic events, and all patients confirmed this in written form. While some participants (mostly men) are afraid that such events can happen to them in public, others (mostly women) are afraid of hypoglycemic events happening when they are alone and no one is available to provide assistance. The fear of hypoglycemia influences many patients' lives by limiting their social activities, or causing changes in their diabetes management routines (e.g., timing of their food intake or insulin injection). Similar findings were observed by other researchers [24]. These results are in line with the findings from large-scale studies on the impact of hypoglycemia on quality of life. Based on a survey of 1984 participants, Marrett et al. [7] concluded that patients who experience severe or frequent hypoglycemic episodes report lower general health and greater fear of hypoglycemia compared with patients without a history of hypoglycemia. Hypoglycemia symptom severity was also positively associated with fear of hypoglycemia and lower HRQoL in another study conducted in the Asia-Pacific region by Sheu et al. [9]. A number of studies in Western countries (UK, France, Sweden, Germany) have explored the relationship of hypoglycemia with decreased HRQoL and fear of hypoglycemia in patients with type 2 diabetes mellitus, and have reported similar results [1,3-6,25,26]. Taking into account results from the previous and our study, we can expect that in patients with type 2 diabetes in Ukraine, there should be a similar impact of hypoglycemia on HRQoL, despite any socio-economic differences between the countries (allowing for some disparities such as gender gaps in automobile usage and other such habits).

Regarding information provision on disease management, we found that endocrinologists are the most common source of information for type 2 diabetes patients in Ukraine. Primary care practitioners are not typically consulted by patients, and Internet resources are also rarely used. These results differ from practice in European countries or the USA, where general practitioners or nurses play important roles in informational support [8,15-17], and the level of Internet users among patients with type 2 diabetes reaches approximately 50% [27].

Despite the fact that in Ukraine, patients are consulted by specialists (endocrinologists) and not by primary care physician, as in some other countries [8, 15-17], our results showed that some patients do not rely on their physician and are hesitant to talk to physicians about hypoglycemia, which is a common tendency of diabetic patients also reported in other studies [14,28]. This might result in the underreporting of hypoglycemia by type 2 diabetes mellitus patients in Ukraine. Underreporting of hypoglycemia was also shown in the study on 392 participants treated with combinations of oral anti-hyperglycemic agents [1].

Basing on retrospective experience of focus-groups participants, we also suppose that newly-diagnosed patients with type 2 diabetes mellitus can experience difficulties in

managing their condition. Being not aware of hypoglycemic symptoms, newly diagnosed patients might not associate their poor health state with complications of diabetes mellitus, but rather with some other reasons, such as menopause (among women), cardiovascular diseases, and so forth. This leads to impaired awareness that can significantly decrease proper hypoglycemia management and perceived quality of life [11,29]. We suggest that hypoglycemia awareness programs are important on early stage of type 2 diabetes mellitus.

The shared experience by the focus group participants suggests that Ukrainian patients experience negative feelings about their state and dissatisfaction in their communications with their physician, and this is similar to the findings from other studies [7-10,30]. We consider that provision of disease management by primary care practitioner (family doctor or qualified nurse) can improve level of informational support for Ukrainian patients because of increase in duration and frequency of consultations.

Limitations and design considerations

The participants were invited to take part in the focus groups by their physician. Despite that study was conducted by independent researchers at independent clinical location, the selection of participants might potentially bias intention of patients to participate in the research.

All except one of the participants were residents of the large urban city of Ukraine. It is possible that the difference between city and village populations (income and education level) can affect reported outcomes. We suspect that village residents with type 2 diabetes mellitus who experience hypoglycemia symptoms might be less knowledgeable about the symptoms and their management, and they might be less likely to report them to their treating physician. In addition, the level of awareness of the focus group participants might be higher than that of an ordinary patient with similar symptoms because of inclusion criteria.

The unemployment rate among focus group participants is significantly higher than the average unemployment rate (14%), especially among men. Taking into account lower participation rate among men, we conclude that employment state has an impact on tendency among men to participate in the study. The majority of participants also indicated their family income level to be lower than average in Ukraine. Although it was not our research question, it might be possible that patients with type 2 diabetes in Ukraine experience higher economic vulnerability, an issue which can be explored in future work on diabetes mellitus.

We chose to give participants the HRQoL instruments only after the focus group discussion to prevent patients from talking about events they could potentially have rather than their true personal experiences. We did observe certain difference in the responses provided during the discussion and in writing: EQ-5D-3L instrument allowed conclusion on worse health state in comparison to HFS form; the participants had a trend

to report more symptoms and higher disease severity (especially for men) when they answered the written form. It is possible that men were less inclined than women to share information openly in a group setting out of fear that it would make them appear weak and/or it would lower their esteem in other participants' eyes, a frequent finding in focus group research [19]. We believe that providing questionnaires in our study has added valuable insight on patients' experience of hypoglycemia. Future research might be designed to include a time break between these two parts if the study is repeated to reduce the impact of the group discussion on privately obtained information.

Participation in the focus group

We also observed more difficulties in arranging the men focus groups, in terms of involving patients in the study and finding appropriate times and dates for them to gather together for discussion. Although no reasons were provided, a previous hypoglycemia focus group study contained significantly more woman participants than men (14 versus 4, respectively), perhaps for similar reasons [10].

It is worth noting that a history of at least one episode of hypoglycemia about which a participant had informed his/her physician was a criterion for participation in our focus groups. This means that the level of awareness of our focus group participants might be higher than that of an ordinary diabetes patient with similar symptoms.

Conclusion

The qualitative assessment of hypoglycemia's impact on the lives of patients with type 2 diabetes mellitus using a focus group methodology demonstrated general similarity between Ukrainian patients and patients in the other countries. We found serious negative effects of hypoglycemia on psychological and emotional states of participants, as well as limitation of patients' lives because of both hypoglycemia symptoms themselves and the fear of experiencing them. In contrast to the findings from the other countries, Ukrainian patients rely on endocrinologist, as a major informational source, and almost do not use electronic informational resources on diabetes management. Though many of the participants were not satisfied with their patient-doctors communication, we conclude that information provision is especially important on early development of the disease when patients lack information on hypoglycemia manifestations and can fail to identify it and manage it properly.

References

1. Stargardt T, Gonder-Frederick L, Krobot KJ, Alexander CM. Fear of hypoglycaemia: defining a minimum clinically important difference in patients with type 2 diabetes. Health and Quality of Life Outcomes. 2009; 7:91.
2. McAulay V, Deary IJ, Ferguson SC, Frier BM. Acute Hypoglycemia in Humans Causes Attentional Dysfunction while Nonverbal Intelligence is Preserved. Diabetes Care. 2001; 24(10): 1745-1750.
3. Currie CJ, Morgan CL, Poole CD, Sharplin P, Lammert M, McEwan P. Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes. Curr Med Res Opin. 2006; 22(8): 1523-34.
4. Davis TM, Brown SG, Jacobs IG, Bulsara M, Bruce DG, Davis WA. Determinants of Severe Hypoglycemia Complicating Type 2 Diabetes: The Fremantle Diabetes Study. The Journal of Clinical Endocrinology & Metabolism. 2010; 95(5): 2240-2247.
5. Fidler C, Elmelund CT, Gillard S. Hypoglycemia: an overview of fear of hypoglycemia, quality-of-life, and impact on costs. J Med Econ. 2011; 14(5): 646-55.
6. Lundkvist J, Berne C, Bolinder B, Jönsson L. The economic and quality of life impact of hypoglycemia. Eur J Health Econ. 2005; 6(3): 197-202.
7. Marrett E, Radican L, Davies MJ, Zhang Q. Assessment of severity and frequency of selfreported hypoglycemia on quality of life in patients with type 2 diabetes treated with oral antihyperglycemic agents: A survey study. BMC Research Notes. 2011; 4:251.
8. Pera PI. Living with diabetes: quality of care and quality of life. Patient Preference and Adherence. 2011; 5(1): 65-72.
9. Sheu WH, Ji LN, Nitiyanant W, Baik SH, Yin D, Mavros P, Chan SP. Hypoglycemia is associated with increased worry and lower quality of life among patients with type 2 diabetes treated with oral antihyperglycemic agents in the Asia-Pacific region. Diabetes Res Clin Pract. 2012; 96(2): 141-148.
10. Sutton L, Chapman-Novakofski K. Hypoglycemia education needs. Qual Health Res. 2011; 21(9): 1220-1228.
11. Henderson JN, Allen KV, Deary IJ, Frier BM. Hypoglycaemia in insulin-treated Type 2 diabetes: frequency, symptoms and impaired awareness. Diabet. Med. 2003; 20: 1016–1021.
12. Coyne KS, Margolis MK, Kennedy-Martin T, Baker TM, Klein R, Paul MD, Revicki DA. The impact of diabetic retinopathy: perspectives from patient focus groups. Family Practice. 2004; 21: 447–453.
13. Guisasola AF, Povedano TS, Krishnarajah G, Lyu R, Mavros P, Yin D. Hypoglycaemic symptoms, treatment satisfaction, adherence and their associations with glycaemic goal in patients with type 2 diabetes mellitus: findings from the Real-Life Effectiveness and Care Patterns of Diabetes Management (RECAP-DM) Study. Diabetes Obes Metab. 2008; 10 Suppl 1: 25-32.
14. Wu FL, Juang JH, Yeh MC. The dilemma of diabetic patients living with hypoglycaemia. Journal of Clinical Nursing. 2011; 20: 2277–2285.
15. Abdulhadi N, Al Shafaee M, Freudenthal S, Ostenson CG, Wahlström R. Patient-provider interaction from the perspectives of type 2 diabetes patients in Muscat, Oman: a qualitative study. BMC Health Serv Res. 2007; 9(7): 162.
16. Brez S, Rowan M, Malcolm J, Izzi S, Maranger J, Liddy C, Keely E, Ooi TC. Transition from specialist to primary diabetes care: a qualitative study of perspectives of primary care physicians. BMC Fam Pract. 2009; 6(10):39.
17. Meyfroidt S, Aeyels D, Van Audenhove C, Verlinde C, Peers J, Panella M, Vanhaecht K. How do patients with uncontrolled diabetes in the Brussels-Capital Region seek and use information sources for their diet? Prim Health Care Res Dev. 2012; 30: 1-11.

18. Quah JH, Luo N, Ng WY, How CH, Tay EG. Health-related quality of life is associated with diabetic complications, but not with short-term diabetic control in primary care. Ann Acad Med Singapore. 2011; 40(6): 276-86.

19. Fern EF. Advanced Focus Group Research, Sage Publications, Thousand Oaks, CA; 2001.

20. Liamputtong P. Focus Group Methodology: Principle and Practice, SAGE Publications Ltd; 2011.

21. Litosseliti L. Using Focus Groups in Research. Continuum Research Methods Series, Continuum International Publishing Group; 2003.

22. Social and Demographical characteristics of Households in Ukraine in 2012 (based on households survey). State Service of Statistics of Ukraine. Statistical Report. Available from: http://www.ukrstat.gov.ua/druk/katalog/kat_u/2012/06_2012/zb_sd_2012.zip. [Assessed on 02 February 2013]. Ukrainian.

23. Dickinson JK, O'Reilly MM. The lived experience of adolescent females with type 1 diabetes. The Diabetes Educator. 2004; 30(1): 99-107.

24. Sutin DG. Diabetes mellitus in older adults: time for an overtreatment quality indicator. Journal of the American Geriatrics Society. 2010; 58(11): 2244–2245.

25. Redekop WK, Koopmanschap MA, Stolk RP, Rutten GE, Wolffenbuttel BH, Niessen LW. Health-related quality of life and treatment satisfaction in Dutch patients with type 2 diabetes. Diabetes Care. 2002; 25(3): 458-63.

26. Vexiau P, Mavros P, Krishnarajah G, Lyu R, Yin D. Hypoglycaemia in patients with type 2 diabetes treated with a combination of metformin and sulphonylurea therapy in France. Diabetes Obes Metab. 2008; 10 Suppl 1:S16-24.

27. Cho AH, Arar NH, Edelman DE, Hartwell PH, Oddone EZ, Yancy WS. Jr. Do diabetic veterans use the Internet? Self-reported usage, skills, and interest in using My HealtheVet Web portal. Telemed J E Health. 2010; 16(5): 595-602.

28. Gonder-Frederick LA, Cox DJ, Ritterband LM. Diabetes and behavioral medicine: the second decade. J Consult Clin Psychol. 2002; 70(3): 611-625.

29. Bailey CJ. Hypoglycaemia: a limiting factor. British Journal of Diabetes & Vascular Disease. 2010; 10(1): 2-4.

30. Hepburn DA, Deary IJ, Freir BM. Classification of symptoms of hypoglycaemia in insulin-treated patients using factor analysis: relationship to hypoglycaemia unawareness. Diabetic Med. 1992; 9: 70-75.

Appendix 7.1 Guide for the Patient Focus Group on Hypoglycemia

I. Introduction (15 min)

- Welcome words and introduction of the moderator and participants.
- Explanation of the general purpose of the focus group, and the way the participants were selected.
- Discussion of the objectives and the procedure for the focus group.
- Explanation of the presence of the recorder, and the purpose of tape recording / presence of observers.
- Development of the common basic rules and principles of the discussion, such as the value of each opinion, the rules "to speak one at a time," and “be prepared that the moderator may interrupt the discussion to ensure that all issues can be addressed”.
- Explanation of the schedule of the meeting, breaks and location of toilets.
- Discussion on the issue of confidentiality, signing the consent.
- Inform the group that the information being discussed will be analyzed in general, and that the names of participants will not be used in the analysis of the discussion.
- Introduction to the participants (briefly) the study protocol.
- Filling in the questionnaire of individual data.
-

II. Discussion (50-90 min)

1. What comes to your mind first when you think about the hypoglycemia? How would you describe your state/feelings during the hypoglycemia?
2. After providing the answers, focus-group participants receive a brief description of hypoglycemia symptoms (Picture) and mark all of the symptoms that they experienced.
2.1. When did you experience these symptoms the first time?
2.2. How frequently do you experience the symptoms described?

2.3. How frequently these symptoms are so strong, that …

Your working productivity decrease?
You can't perform your work?
You can't perform your house-hold duties?
3. Which actions do you take when you experience the symptoms indicated above?
3.1. Do you intake drugs to cope with hypoglycemia? If "yes", than which ones and how frequently?
3.2. Do you increase foods consumption? If "yes", than which ones and in what amount?
3.3. Do you increase water consumption? If "yes" than to what amount?
3.4. Do you take any other actions? If "yes", than which ones?
3.5. Do you report to your doctor the cases of hypoglycemia? If "yes", than how frequently (which exactly symptoms and in which cases you report)?
4. Do you experience psychological discomfort due to hypoglycemia events?
Are you afraid to get a hypoglycemia event?
Do you feel ashamed if you get hypoglycemia event?
How chance to have hypoglycemia influence your mental well-being?
Describe discomfort you experience when you get hypoglycemia?
Describe not satisfaction with yourself and/or depression you connects with possibility to get hypoglycemia event?
5. Are you aware of ‘no action’ consequences? Which of the possible consequences you can recall?
In case focus-group participants are not able to reply, they are provided with a brief description of possible consequences

6. Are your relatives/colleagues aware of signs of hypoglycemia, do they know how to act in this case?
7. How frequent are hypoglycemia cases (within a year/month) in your life? How many from these cases you would characterize as mild/moderate/strong?
8. How do you learn about your disease, specifics of the life with diabetes, about treatment? Which sources do you trust the most?

Possible answers:

From individuals	From media
endocrinologist	Internet (websites, search engines)
nurse	Information from organizations (e.g., Diabetic Union of Ukraine)
nutritionist	specialized magazines
pharmacist	TV (for example, programs on health)
stomatologist	Newspapers
ophthalmologist	Booklets, brochures, etc., from clinics and health care workers
Other health care workers	Information from pharmaceutical companies, pharmacies, drug supplier
I myself have a medical degree and worked in the field of medicine	Printed reports of clinical trials, laboratory research
The family, including family members with diabetes	
Friends, neighbors, colleagues, acquaintances, other patients	
Classes and workshops, support groups	
Participation in the clinical trials	

9. How did attacks of hypoglycemia affect your daily activity?
For example:
- working
- driving
- fitness activities
- bicycle
- housework
- shopping

10. How did episodes of hypoglycemia affect your family and social life?
- Discomfort / irritation for close people
- Relationships with family and friends
- Relationships with colleagues

III. Questionnaire on quality of life (20 min)

IV. Concluding remarks (10 min)

Wrap up

Are there any other issues that we have not discussed? What else you need to know about hypoglycemia?

Appendix 7.2 Individual data of the focus group participant

We ask you to fill in the short demographic profile to enable profound analysis of the results of the focus group discussion
Age (years) _____

How many years have passed since you were diagnosed with diabetes? *(circle one option)*

- <2 years
- ≥2 years but <5 years
- ≥5 years but <10 years
- ≥10 years

Which antidiabetic medication do you intake? *(circle one option)*

- Insulin, that is……
- Sugar reducing medicines, that are……
- Combined therapy from both drugs indicated above, that are……
- Do not take therapy at all

Where do you get information about the course and treatment of diabetes? *(multiple answers possible, mark all applicable)*

- From the endocrinologist
- From the other physician
- From the nurse
- Searched in the specialized literature
- Searched online sources
- From unknown people
- From relatives and acquaintances

Your gender

- Male
- Female

Place of residence *(circle one option)*

- Kyiv
- Other city
- Village

Family state *(circle one option)*

- Live within a family
- Live separately

Level of education *(circle one option)*

- Uncompleted secondary school
- Secondary school
- Professional training
- High School

Are you employed? *(circle one option)*

- I am working

- I do not work due to diabetes complications
- I do not work due to other reasons

How do you access your social level? *(circle one option)*

- Low-income
- Middle income
- High-income

Estimated level of household income (per month) *(circle one option)*

- < 1.000 UAH
- 1.000 – 3.000 UAH
- 3.000 – 6.000 UAH
- 6.000 – 10.000 UAH
- ≥10.000 UAH

Do you use Internet? *(circle one option)*

- Yes
- No
- Thank you!

Chapter 8

Cost-effectiveness of adding rituximab to fludarabine and cyclophosphamide for treatment of chronic lymphocytic leukemia in Ukraine

Mandrik O., Corro Ramos I., Knies S., Al M., Severens J.L.
Cancer Management and Research; accepted for publication

Abstract

The aim of this study was to assess the cost-effectiveness, from a healthcare perspective, of adding rituximab to fludarabine and cyclophosphamide scheme (FCR versus FC) for treatment-naive and refractory/relapsed Ukrainian patients with chronic lymphocytic leukemia (CLL).

A decision-analytic Markov cohort model with three health states and one-month cycle time was developed and run within a life time horizon. Data from two multinational, prospective, open-label phase 3 studies were used to assess patients' survival. While utilities were generalized from the UK data, local resource utilization and disease-associated treatment, hospitalization, and side effect costs were applied. The alternative scenario was performed to assess the impact of lower life expectancy of the general population in Ukraine on the incremental cost-effectiveness ratio (ICER) for treatment-naive patients. One-way, two-way, and probabilistic sensitivity analyses were conducted to assess the robustness of the results.

The ICER (in US dollars) of treating CLL patients with FCR versus FC is $8,704 per quality-adjusted life year (QALY) gained for treatment-naive patients and $11,056 for refractory/relapsed patients. When survival data were modified to the lower life expectancy of the general population in Ukraine, the ICER for treatment-naive patients was higher than $13,000. This value is higher than three times the current gross domestic product per capita in Ukraine. Sensitivity analyses have shown a high impact of rituximab costs and a moderate impact of differences in utilities on the ICER. Furthermore, probabilistic sensitivity analyses have shown that for refractory/relapsed patients the probability of FCR being cost-effective is higher than for treatment-naive patients and is close to one if the threshold is higher than $15,000.

State coverage of rituximab treatment may be considered a cost-effective treatment for the Ukrainian population under conditions of economic stability, cost-effectiveness threshold growth, or rituximab price negotiations.

Introduction

Chronic lymphocytic leukemia (CLL) is a progressive oncological disease characterized by the clonal proliferation and accumulation of neoplastic B lymphocytes in the blood, bone marrow, lymph nodes and spleen. According to the Ukrainian National Cancer Register the total morbidity rate for patients with diagnosed leukemia was 7.8 per 100,000 people [1]. No national Ukrainian statistical data on CLL prevalence are available; however, if we assume the same distribution as in the US exists for the four major types of leukemia, up to 3.7 per 100,000 people are estimated to be CLL related [2]. The clinical course of this disease can be highly diverse and dependent on many factors, such as stage of the disease by K. Rai (from 0 to IV) and J. Binet (from A to C), chromosomal abnormalities, or mutations of the immunoglobulin heavy variable chain gene [3-5].

With the exception of blood band marrow transplantation – which has significant limitations by age and comorbidities – CLL remains an incurable condition. According to the national treatment protocol in Ukraine there are a number of treatment options for CLL patients [5]. Besides the "watch and wait" strategy for patients with the asymptomatic state of CLL, monotherapies are currently available: cytotoxic drugs including alkylating agents (chlorambucil, cyclophosphamide and bendamustine), antimetabolites or purine analogues (fludarabine or cladripine), mitoxantrone (an anthracycline) and prednisolone (a corticosteroid), as well as a number of therapeutic chemotherapy combination schemes [3,5]. One of the most frequently prescribed schemes for CLL patients treated in specialized hospitals of Ukraine is a combination of fludarabine with cyclophosphamide (FC) [6].

Rituximab, a monoclonal antibody that targets the CD20 cell surface antigen, is recommended for use in combination with chemotherapy for both treatment- naive patients, refractory patients (those experienced treatment failure or disease progress within 6 month of the last treatment) or relapsed (those experienced a response to therapy, but progressed after 6 or more months). Despite being one of the most expensive drugs used in CLL treatment in Ukraine, rituximab was included in the state tender purchases the previous years [6,7]. As an additive to FC, rituximab has been shown to be a promising medical product according to clinical trial data on both previously treated and untreated CLL patients [4,8].

The cost-effectiveness of FCR (combination of rituximab with FC) versus FC scheme in treatment of naive or refractory/relapsed patients was previously confirmed in Spain, the US and the UK [9-11]. In Spain the incremental cost-effectiveness ratio (ICER) was €19,343 per quality adjusted life-year (QALY) gained for the first-line treatment and €24,781 for the second-line treatment over a 10-year horizon [9]. In the US study the ICER was $23,530 per QALY considering a third-party payer and $31,513 per QALY considering a societal perspective over the life-time horizon [10]. In the UK rituximab also was

considered to be a cost-effective option with an ICER of £13,189 per QALY for FCR versus FC in the treatment of naive patient population; however its combination with other chemotherapy agents was not recommended by the National Institute for Health and Care Excellence (NICE) [11].

To the best of our knowledge no economic evaluation on rituximab use was performed in Ukraine, nor any other country of the Central and Eastern European (CEE) or former Soviet region. Because of differences in treatment practice, perspectives, unit costs (including hospitalization) and demographic characteristics (both patients and general population), generalizability to Ukraine of the economic evaluations mentioned above is not possible. While no cost-effectiveness threshold has been established in Ukraine, the WHO considers technologies with a threshold of less than one GDP per capita to be very cost-effective, and those with a threshold of less than three GDP per capita to be cost-effective [12]. In 2013 the GDP per capita in Ukraine was equal to US$ 3,900, according to data of the World Bank [13].

In sum, the aim of this study was to assess, from a healthcare perspective using a life time horizon, the cost-effectiveness of FCR compared to FC for treatment-naive and refractory/relapsed Ukrainian CLL patients.

Methods

Framework / Structure of the model

Two decision-analytic Markov cohort models with the same structure were developed in Microsoft® Excel 2007 to assess the incremental costs and benefits associated with adding rituximab to the chemotherapy scheme FC. These models were run on two populations using data from two randomized controlled trials, one with treatment naive and one with refractory/relapsed patients. Three health states were defined in the models with a cycle time of one month: 1) stable or progression-free state; 2) disease-progressed state; and 3) death. Assessment of the incremental costs and benefits from a healthcare perspective was conducted using a life-time horizon. Quality adjusted life years (QALYs) comprised the main outcome in both models with uniform 3% discounting for both costs and effects [14].

Target population

We considered the modeled cohort of treatment-naive patients to be identical to the trial population from a published prospective, open-label, phase 3 study on 817 randomly assigned (1:1) patients carried out in 190 centers in 11 countries. Enrolled in this study were treatment-naive patients diagnosed with immunophenotypically confirmed CLL in Binet stage C (31% in FC and 31% in FCR) or those with confirmed active disease in

Binet stages A (5% in FC and 4% in FCR) or B (63% in FC and 64% in FCR). Mean age of patients was 61 years and74% were males. Eastern Cooperative Oncology Group (ECOG) performance status of 0 was reported in 58% of FC and 56% of FCR groups [4] (Eastern Cooperative Oncology Group (ECOG) performance status is the criteria used to assess how the disease affects daily living abilities of patients, where "0" is a fully active person and "5" is dead; see the web-site of ECOG for details: http://www.ecog.org/).

The modeled cohort of refractory/relapsed patients was considered to be identical to the trial population from an international, multicenter, open-label, phase 3 study on 552 randomly assigned (1:1) patients carried out in 88 centers in 17 countries. Patients who had received one prior line of therapy, such as single-agent chlorambucil (or combined with prednisone/prednisolone), single-agent fludarabine (or another nucleoside analog), or an alkylatorcontaining combination regimen, but not an alkylator/nucleoside analog combination were enrolled in that study. The distribution of CLL patients by confirmed Binet stages in this trial was the following: stage C (31% in FC and 31% in FCR), stage A (11% in FC and 9% in FCR), and stage B (58% in FC and 60% in FCR).Mean age of patients was 62 years in FC and 63 in FCR groups, 66% (FC) and 68% (FCR) were males. An ECOG performance status of 0 was reported in 59% of FC and 61% of FCR groups [8].

Treatment and treatment effect

According to trial data and national clinical guidelines [4,8], CLL patients on FCR scheme should receive the following doses of drugs during each cycle: fludarabine (25mg/m^2/d), cyclophosphamide (250mg/m^2/d) for 3 days, rituximab (375 mg/m2 on day one of the first cycle and 500 mg/m^2 on day one of subsequent cycles). In the model, dose-per-patient was calculated using an average body surface among the Ukrainian population (1.86 m^2). We considered that the Markov cohort population did not receive full courses of therapy similar to the trials population [4,8], so the final average doses of each drug were adjusted to the average consumed doses (by treatment adherence in trials) .

Survival data

Overall survival (OS) and progression-free survival (PFS) were retrieved from the trials' publications presenting Kaplan-Meier plots [4,8]. The reported observation period equal to 61 months for treatment-naive patients and to 57 months for previously-treated patient (52 months for PFS during FC treatment) was chosen [4,8]. There was no information available on characteristics of Ukrainian CLL patients by Binet stages and ECOG performance status. At the same time, by gender and age distribution Ukrainian CLL patients were similar to trial populations selected as clinical data sources [4,6,8]. Two parametric extrapolation methods were applied. A Weibull model was selected to incorporate monotonic hazards, while a log-logistic model was selected as an alternative

to incorporate non-monotonic hazards. The model that provides the closest parametric estimation was selected for cohort survival assessment.

Costs

In line with recommendations of the ISPOR taskforce report on transferability [15], unit costs and resource utilization were retrieved from local sources. From the health care perspective, the following costs were included in the model: initial therapy costs, hospitalization costs, adverse events costs and salvage costs (Table 8.1). Unit drug costs were included in the deterministic model by the most frequently prescribed trade names [6]. Unit drug prices were retrieved from the website of Ukraine's Ministry of Health (accessed on 06.06.2014 from http://www.moz.gov.ua/ua/portal/register_prices_drugs/). Costs of grades 3 and 4 adverse events reported with a frequency greater than or equal to 5% were accounted for in the model calculations. Opinion of experts from specialized institutions of Ukraine and hospital records were used to define the most frequently prescribed treatment schemes for these conditions.

A previously-published costing study in Ukraine was used to assess costs of salvage treatment [6]. Because of data obsolescence, these costs were considered to grow by the consumer price index for pharmaceuticals and health care for the last four years (5.7%). Additionally, the model took into consideration the monthly growth in costs for salvage treatment proportional to an average monthly consumer price index for pharmaceuticals and health care (0.11875%) [16]. Data of specialized hospitals in Ukraine were used to determine an average duration of hospitalization due to a relapse, as well as daily costs of hospital stay excluding pharmaceutical treatment [6]. Similar to pharmaceutical treatments, hospital stay unit costs were considered to grow proportionally to an average consumer price index for pharmaceuticals and health care. The exchange rate of the National Bank of Ukraine on 04.06.2014 (11,833UAH per US$) was used in all calculations.

Utilities

No country-specific utility data was available for CLL patients, nor for the general Ukrainian population, therefore, utilities of health states associated with CLL treatment (values of 0.78 for the progression-free or stable disease state and 0.68 for the progressed disease) were assumed generalizable from the UK [17].

Sensitivity analyses and data transferability

We used sensitivity analyses to address uncertainty in the defined input parameters specific for Ukraine and those generalized from other populations. Using univariate analyses we assessed the impact of variations in rituximab costs, hospitalization costs, salvage treatment costs, costs of side effects, average monthly index of consumption prices and discount rates. Multivariate analysis was applied because the UK

data on utilities for different cancer states were generalized to the Ukrainian population for whom local data was absent.

The two trials used a multinational sample as a source of survival data for Markov cohort CLL patients [4,8]. Although the patient's country of enrolment in the trials was not reported, we assume that most were enrolled in countries with developed economies, where life-duration of the general population differs from those in Ukraine. Therefore we report an alternative scenario with Ukraine-specific mortality rate for non-CLL related causes to assess the impact of this parameter on the ICER. For this the gender- and age-specific difference in death probability among general population in the US and Ukraine was calculated. For this the difference in death probabilities between US and Ukrainian males and females of different age was firstly calculated using states statistic data [18,19]. Afterwards, the death probability among the population identical to the cohort by sex and age characteristics was retrieved. As the next step the OS and PFS from the trial were added to the positive or negative coefficient of mortality difference depending on the age of the patient during therapy initiation. The survival analysis with Weibull extrapolation was performed on the received adjusted data to ensure higher reliability of the received results.

Additional scenario analyses were conducted to assess the impact of survival analysis on cost-effectiveness results. We varied duration of patients' observation period in the trials and assessed impact of these changes on the results of survival analysis and economic evaluations. Probabilistic sensitivity analyses with 5000 runs were conducted to define overall uncertainty of the model. Both deterministic and probabilistic model parameters are presented in Table 8.1.

Table 8.1 Resource use, costs, and utilities and patients' characteristic input data used in both deterministic and probabilistic models

Parameter	Deterministic value	Data source	Range used in sensitivity analyses	Comments
Resource use				
Annual number of hospitalization days (for salvage patient), days	34	Analysis of the hospital records [6]	27.2-40.8	20% variation from the average, flat distribution

Refractory/relapsed patients				
Total dose of fludarabine received during 6 cycles of the therapy, mg	202.69	Trial dose adjusted to percentage of patients received therapy on each cycle and body surface among Ukrainian population	186-279	Average trial dose received by Ukrainian patient during 4 to 6 cycles of the therapy, flat distribution
Total dose of cyclophosphamide received during 6 cycles of the therapy, mg	2,131.56		1,860-2,790	
Total dose of rituximab received during 6 cycles of the therapy, mg	4,854.60		3,720-5,580	
Treatment naive patient				
Total dose of fludarabine received during 6 cycles of the therapy (Patients on FC[a] treatment), mg	223.2	Trial dose adjusted to average number of cycles received by the patients in the trial and body surface among Ukrainian population	186-279	Average trial dose received by Ukrainian patient during 4 to 6 cycles of the therapy, flat distribution
Total dose of cyclophosphamide received during 6 cycles of the therapy (Patients on FC[a] treatment), mg	2,232		1,860-2,790	
Total dose of fludarabine received during 6 cycles of the therapy (Patients on FCR[b] treatment), mg	241.8		186-279	
Total dose of cyclophosphamide received during 6 cycles of the therapy Patients on FCR[b] treatment), mg	2,418		1,860-2,790	
Total dose of rituximab received during 6 cycles of the therapy (Patients on FCR[b] treatment), mg	4,231.5		3,487.5-5,347.5	

Unit costs				
Fludarabine costs, US$ per mg	3.31	Costs of drugs the most frequently prescribed via state budget [6]	1.89-3.31	Range of costs available on the state market, flat distribution
Cyclophosphamide costs, US$ per mg	0.0022		0.0022-0.036	
Rituximab costs, US$ per mg	2.24		1.76-2.24	
Hospitalization costs per day, US$	16	Cost of hospitalization stay in specialized hospital of Ukraine 2010 [6,16]	13-19	20% costs variation, flat distribution
Salvage therapy costs, US$ per month	177.06[c]	Cost of relapse treatment in specialized hospital of Ukraine 2010 [6,16]	141.64-212.47	20% costs variation, flat distribution
Average monthly index of consumption prices	0.1188%	Calculated as average from the last 4 years	-	-
Average body surface	1.86	Average body surface in Ukraine	-	-
Side effects costs				
Average cost per on treatment naïve patient (FC[a]), US$	74	Average costs by the most frequently prescribed trade names (hospital cards analysis [6] and expert's opinion)	64-248	Minimum and maximum costs by prices for each generic name, registered on the web-site of the Ministry of Health, flat distribution
Average cost per on treatment naïve patient (FCR[b]), US$	106		96-335	
Average cost per on refractory/relapsed patient (FC[a]), US$	67		58-194	
Average cost per on refractory/relapsed patient (FCR[b]), US$	68		60-182	

Utilities					
Progression-free survival		0.78	[17]	0.75-0.82	CI, normal distribution [17]
Overall survival		0.68	[17]	0.64-0.72	CI, normal distribution [17]
Survival analysis: refractory/relapsed patients					
Progression-free survival FC[a] scheme	Lambda	0.01958		±0.001381	
	Gamma	1.15346		±0.020872	
	Correlation coefficient	-0.99051400			
Overall survival FC[a] scheme	Lambda	0.00436		±0.000742	
	Gamma	1.24444		±0.046098	
	Correlation coefficient	-0.99598300			
Progression-free survival FCR[b] scheme	Lambda	0.02847	Weibull estimation	±0.00237	Weibull analysis, normal distribution
	Gamma	0.95491		±0.024185	
	Correlation coefficient	-0.99062300			
Overall survival FCR[b] scheme	Lambda	0.00594		±0.00039	
	Gamma	1.09334		±0.017784	
	Correlation coefficient	-0.99524000			

Survival analysis: treatment naive patients					
Progression-free survival FC[a] scheme	Lambda	0.013576		±0.000681	
	Gamma	0.000681		±0.013858	
	Correlation coefficient	-0.99259			
Overall survival FC[a] scheme	Lambda	0.000994		±0.042679	
	Gamma	1.511907		±0.042679	
	Correlation coefficient	-0.99722	Weibull estimation		Weibull analysis, normal distribution (Beta for Lambda overall survival on FCR scheme)
Progression-free survival FCR[b] scheme	Lambda	0.005851		±0.000451	
	Gamma	1.219618		±0.020593	
	Correlation coefficient	-0.99513			
Overall survival FCR[b] scheme	Lambda	0.000213		±0.00014	
	Gamma	1.809901		±0.168617	
	Correlation coefficient	-0.99808000			

[c]- Monthly salvage costs were calculated from a previous study on cost-of treatment of CLL in Ukraine by recalculating the annual costs to monthly costs. The received costs were assumed to grow from the time of the assessment on consumer price index for pharmaceuticals and health care for the last four years. Each time the conversion of the costs was conducted from local currency (UAH).

Results

Treatment with rituximab resulted in both a longer expected survival and a gain in QALYs compared to the standard therapy (Table 8.2). The gain in expected number of life years was 1.60 for both treatment-naive and refractory/relapsed patients treated with the FCR vs FC scheme in the base-case scenario. Associated costs were higher with FCR rather than FC treatment in the base case and all alternative scenarios (Table 8.2).

The difference in QALYs gained and costs was smaller in the scenarios where survival analysis was conducted on the trial data with the longer follow-up (and the opposite). When survival data on treatment-naive patients were extrapolated to 65 months, the incremental value of QALYs became negative. There was a smaller observed difference in both QALYs and costs for the FC and FCR treatment-naive population, when adjustment to the expected higher mortality among the general population of Ukraine was conducted.

Table 8.2 Cost-effectiveness analysis of adding rituximab to fludarabine plus cyclophosphamide scheme in treatment-naive and refractory/relapsed patients

Conditions	Cost difference	QALY[a] difference	ICER[d] (US$/QALY[a])
Treatment naive patients			
Base-case scenario FCR[b] vs. FC[c]	US $10,827	1.24	US $8,704
Scenario 1: Ukraine-specific mortality among general population	US $8,022	0.62	US $12,897
Scenario 2: 56 months survival data	US $16,881	2.61	US $6,475
Scenario 3: 60 months survival data	US $15,204	2.22	US $6,851
Scenario 4: 62 months survival data	US $7,677	0.62	US $12,343
Scenario 5: 65 months extrapolated survival data	US $4,786	-0.83	dominated
Treatment experienced patient			
Base-case scenario FCR[b] vs. FC[c]	US $13,081	1.18	US$11,065
Scenario 1: 52 months survival data, ICER[d] (US$ per QALY[a])	US $ 14,660	1,53	US $9,557

[a]QALY - quality adjusted life years; [b]FCR – rituximab plus fludarabine and cyclophosphamide scheme; [c]FC - fludarabine and cyclophosphamide scheme; [d]ICER- incremental cost effectiveness ratio.

Table 8.3 Univariate and multivariate sensitivity analysis: impact of costs variations on cost-effectiveness results

Parameters of variation and values		ICER[a], treatment naive patients		ICER[a], treatment experienced patients	
		US$/QALY[b]	% of change from base ICER	US$/QALY[b]	% of change from base ICER
Average monthly index of consumption prices	0%	$8,501	2%	$10,677	4%
	0.2375% (doubled [d])	$8,907	-2%	$11,453	-4%
Discounting, annual	0%	$6,904	21%	$8,754	21%
	5%	$10,194	-17%	$13,010	-18%
	10%	$15,041	-73%	$19,494	-76%
Multivariate (discounting and average monthly index of consumption prices)	0%	$6,645	24%	$8,297	25%
	Doubled [d]	$11,184	-28%	$14,440	-31%
Rituximab costs	50% [d]	$4,538	48%	$6,471	42%
	25% [d]	$2,455	72%	$4,173	62%
	120% [d]	$10,371	-19%	$12,903	-17%
Hospitalization costs	50% [d]	$8,673	0%	$10,895	2%
	25% [d]	$8,657	1%	$10,810	2%
	120% [d]	$8,717	0%	$11,133	-1%
Salvage therapy costs	50% [d]	$8,563	2%	$10,298	7%
	25% [d]	$8,492	2%	$9,914	10%
	120% [d]	$8,761	-1%	$11,372	-3%

Side effects costs (FCR[c])	50% [d]	$8,662	0%	$11,036	0%
	25% [d]	$8,640	1%	$11,022	0%
	120% [d]	$8,722	0%	$11,076	0%
Utilities	0.78 - PS[e] 0.88 PFS[f]	$7,710	11%	$9,744	12%
	0.58 - PS[e] 0.68 -PFS[f]	$9,993	-15%	$12,800	-16%
	0.58 - PS[e] 0.88 -PFS[f]	$7,786	11%	$10,838	2%

[a]ICER- incremental cost effectiveness ratio; [b] QALY - quality adjusted life years; [c]FCR – rituximab plus fludarabine and cyclophosphamide scheme; [d] –from deterministic value; [e]PS – progression state; [f]PFS – progression free state.

For every expected QALY gained, US$8,704 will be needed in the base-case scenario for state coverage of treatment-naive patients, which can be considered a cost-effective option. The ICER of treating refractory/relapsed patients with the FCR scheme is close to the cost-effectiveness threshold within the base-case scenario (ICER US$11,056; threshold of three GDP per capita is US $11,700). The incremental cost-effectiveness ratio of FCR use for treatment-naive patients will be close to $13,000 if a higher mortality among the general population in Ukraine is considered in the survival analysis. This ICER for treatment-naive patients is above the theoretical cost-effectiveness threshold in Ukraine.

As can be seen from Table 8.3, an increase in the average consumer price index and discount rate caused a higher ICER for both treatment-naive and refractory/relapsed patient populations. Similarly, multivariate analyses with zero values for both discounting and average monthly index of consumer prices resulted in ICERs of US$6,645 and US$8,297, respectively. Rituximab cost was the only cost parameter having a significant impact on the ICER in both populations. Changes in utilities had a moderate impact on cost-effectiveness results.

The results of PSA showed a high probability for FCR treatment to be cost-effective for both treatment-naive patients (cost difference US$13,118, s.d. US$8,079; QALYs difference 2.21, s.d. 1.78; ICER US$5,938) and refractory/relapsed patients (cost difference US$14,290, s.d. US$2,455; QALYs difference 1.68, s.d. 0.45; ICER US$8,485) with the threshold of US$11,000 (Figure 8.1). As the threshold value increases, the probability of FCR being cost-effective is higher for refractory/relapsed patients. In particular, when the threshold is higher than US$15,000, the probability of FCR being cost-effective

converges to one for refractory/relapsed patients and to 0.80 for treatment-naive patients (Figure 8.2).

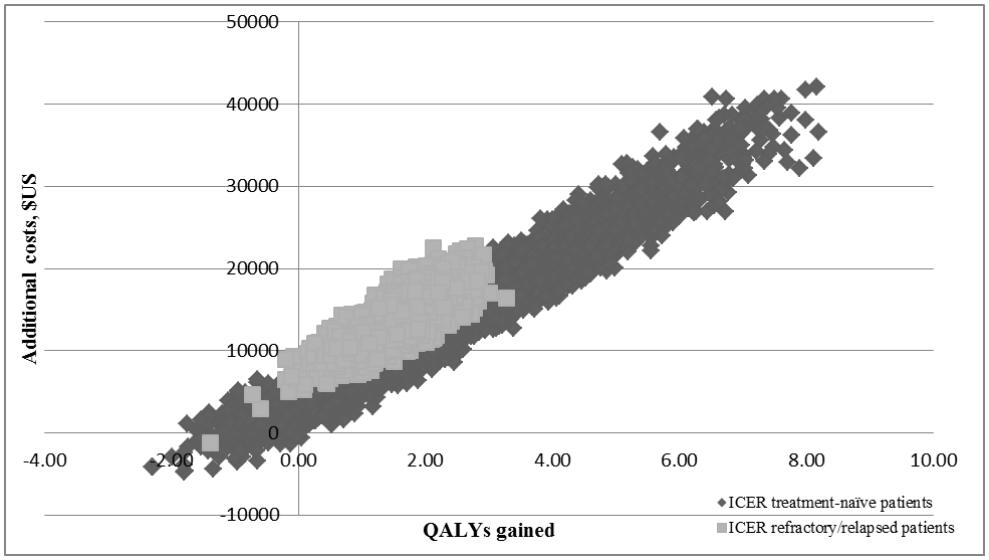

Figure 8.1 Cost-effectiveness plane: adding rituximab to treatment of naive and refractory/relapsed patients

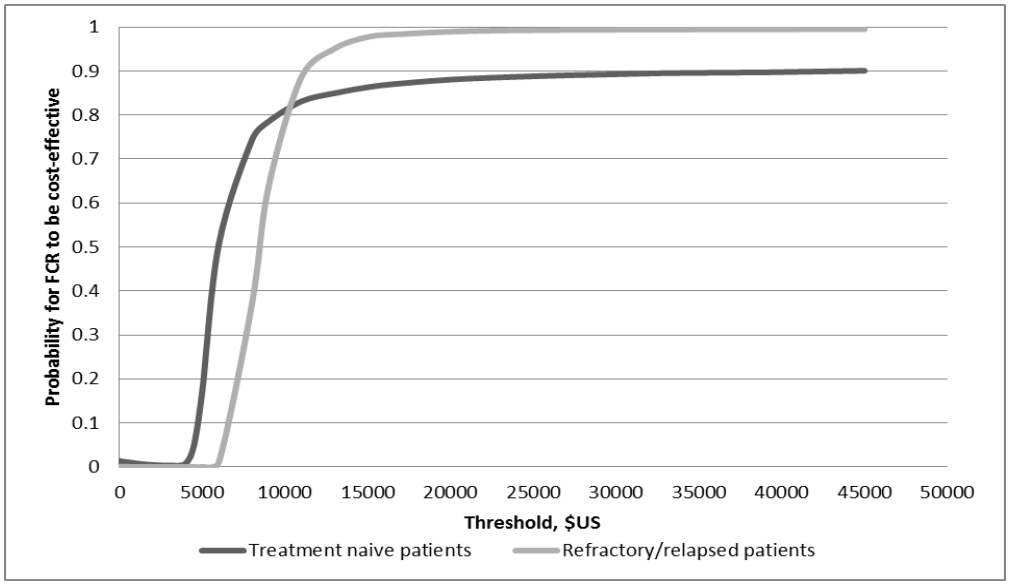

Figure 8.2 Cost-effectiveness acceptability curves

Discussion

Neither for treatment-naive nor for refractory patients does adding rituximab to the FC scheme make it a cost effective option when using a threshold of US$3,900 [13]. However, use of the FCR scheme can still be considered a cost-effective option when using the theoretical threshold of three times the GDP per capita in Ukraine. As such, we conclude that providing this drug should not be considered the highest priority, but should depend on budget availability. This conclusion is supported by the decision uncertainty demonstrated by the sensitivity analyses; thus, the state coverage of this drug for both treatment-naive and refractory/relapsed population remains a possibility to be argued.

The Ukrainian Ministry of Health purchases rituximab annually for CLL patients' needs without recommendations on its actual use. Nearly US$1.4 mln of state budget was spent on rituximab purchase in 2013 [7]. However, based on current evidence there is a higher rationality for it to be provided for the treatment naive patient population, rather than for refractory/relapsed patients. At the same time, if the theoretical threshold will become higher as a result of an improving Ukrainian economy, then coverage of refractory/relapsed patients is likely to become more cost-effective option than that for the treatment-naive population, an outcome primarily related to the higher stability of the results. On the other hand, in an unstable economic environment, adding rituximab to FC treatment of refractory/relapsed patients may not be a cost-effective option from a health care perspective, taking into account that any increase in the discount rate, treatment costs, or inflation rate (index of consumer prices) leads to an ICER estimate close or above the value of the theoretical threshold. Because rituximab cost was the most influential parameter, price negotiation may be applied to ensure that state spending on this treatment is rational.

Because multinational clinical data were used for both models, we were concerned with how much the trial population would be representative for Ukraine. While published data were used to populate the models, the cohort population in both models was not different by gender and age characteristics from both trial population and profiles of CLL patient in Ukraine in terms of mean age of naive patients (60.3), age of refractory/relapsed patient (62.8) and the fact that 67% of patients were male [6]. Moreover, we considered that because of differences in age at diagnosis between different countries, if trial data were primarily retrieved from economically-developed countries, the mortality from other causes in CLL trial population may be different from those in Ukraine. We conclude that if such a case exists, then it is doubtful that the use of rituximab in CLL population in Ukraine will be cost-effective.

As stated in the introduction, until now the cost-effectiveness of rituximab was assessed only in health care settings of economically more developed countries, such as the US [10], the UK [11], and Spain [9]. While all studies used three-stage models, the

perspectives, model durations and data extraction approaches differed. Methodological differences and non-generalizability of data limited transferring results of these studies to Ukraine. The third-party perspective is not applicable for Ukraine and, because of the significant number of assumptions [10], the societal perspective also is not considered. Additionally, the use of parametric extrapolation methods for survival analysis instead of raw trial data was considered important because of the high impact of survival parameters on the ICER. While no relation between the country's income expressed by GDP per capita and the cost-effectiveness of FCR in comparison to FC scheme has been shown in prior research [9,10,11], in our study we see a significant difference in the values of the ratios observed. We also note an important similarity between our study and one conducted in the Spanish health care setting [9]; namely, treating treatment-naive patients with FCR scheme appeared to be more cost-effective than for refractory/relapsed patients.

Limitations

As a limitation we should point out that data pertaining to the trial population and the mortality rate from non-CLL causes among trial populations were not available, thus may not correspond to the Ukrainian population. Moreover, Ukrainian costs data are limited and based on one study assessment.

Conclusions

State coverage of rituximab treatment may not be considered a cost-effective treatment option for the Ukrainian population compared to current care; however, it may become cost-effective under conditions of economic stability, cost-effectiveness threshold growth or rituximab price negotiations. Taking into account the WHO recommendations on cost-effectiveness thresholds and current GDP per capita in Ukraine, state coverage of FCR scheme for treatment-naive patients is more economically argued than that for refractory/relapsed patients.

References

1. Fedorenko ZP, Goulak LO, Gorokh YL. Cancer in Ukraine, 2011 - 2012. [Incidence, mortality, activities of oncological service]. Kyiv: National Cancer Institute of Ukraine; 2013. Ukrainian.
2. Facts spring 2014. Leukemia and lymphoma society. 2014; 26. Available from: http://www.lls.org/content/nationalcontent/resourcecenter/freeeducationmaterials/generalcancer/pdf/facts.pdf. [Assessed 20 October 2014].
3. Dretzke J, Barton P, Kaambwa B, Connock M, Uthman O, Bayliss S, Meads C. Rituximab for the treatment of relapsed/refractory chronic lymphocytic leukaemia. *Health Technol Assess.* 2010; 14(Suppl. 2): 19-26.
4. Hallek M, Fischer K, Fingerle-Rowson G, Fink AM, Busch R, Mayer J, Hensel M, Hopfinger G, Hess G, von Grünhagen U, Bergmann M, Catalano J, Zinzani PL,Caligaris-Cappio F, Seymour JF, Berrebi A, Jäger U, Cazin B, Trneny M, Westermann A, Wendtner CM, Eichhorst BF, Staib P, Bühler A, Winkler D, Zenz T,Böttcher S, Ritgen M, Mendila M, Kneba M, Döhner H, Stilgenbauer S; International Group of Investigators; German Chronic Lymphocytic Leukaemia Study Group. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*. 2010; 376(9747): 1164-1174.
5. Order of the Ministry of Health of Ukraine #647 from 30.07.2010. [About approval of the clinical protocols on medical help provision for patients on specialty "Hematology"]. Ministry of Health. Available from http://moz.gov.ua/ua/portal/dn_20100730_647.html. [Assessed on 17 September 2014]. Ukrainian.
6. Mandrik O, Carro Ramos I, Zalis'ka O, Gaysenko A., Severens J.L.. Cost of drugs treatment for chronic lymphocytic leukemia in Ukraine. Value in Health Regional Issues. 2013; 3: 205-209.
7. Order of the Ministry of Health of Ukarine #358 from 7 of May 2013. [About distribution of drugs for treatment of oncohematologic patients, that were purchased within the centralised order by the costs of State Budget of Ukraine in 2013]. Ministry of Health. Available from http://www.moz.gov.ua/docfiles/dod358_2013.pdf. [Assessed on 17 September 2014]. Ukrainian.
8. Robak T, Dmoszynska A, Solal-Céligny P, Warzocha K, Loscertales J, Catalano J, Afanasiev BV, Larratt L, Geisler CH, Montillo M, Zyuzgin I, Ganly PS,Dartigeas C, Rosta A, Maurer J, Mendila M, Saville MW, Valente N, Wenger MK, Moiseev SI. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. J Clin Oncol. 2010; 28(10): 1756-1765.
9. Casado LF, García Marco JA, Gilsanz F, González M, Ríos E, de la Serna J, Urbano A, Vicente V, Rubio-Terrés C, Castro AJ. [Economic evaluation of rituximab added to fludarabine plus cyclophosphamide versus fludarabine plus cyclophosphamide for the treatment of chronic lymphocytic leukemia]. [Article in Spanish]. *Gac Sanit.* 2011 *25*(4): 274-281. Spanish.
10. Hornberger J, Reyes C, Shewade A, Lerner S, Friedmann M, Han L, Gutierrez H, Satram-Hoang S, Keating MJ. Cost-effectiveness of adding rituximab to fludarabine and cyclophosphamide for the treatment of previously untreated chronic lymphocytic leukemia. Leuk Lymphoma. 2012; 53(2): 225-234.
11. Main C, Pitt M, Moxham T, Stein K. The clinical effectiveness and cost-effectiveness of rituximab for the first-line treatment of chronic lymphocytic leukaemia: an evidence review of the submission from Roche. Health Technol Assess. 2010; 14(Suppl. 2): 27-32.
12. World Health Organization. Cost effectiveness and strategic planning (WHO-CHOICE). Cost-effectiveness thresholds. Available from http://www.who.int/choice/costs/CER_thresholds/en/. [Assessed 20 October 2014].
13. GDP per capita (current US$). World Bank national accounts data, and OECD National Accounts data files Available from http://data.worldbank.org/indicator/NY.GDP.PCAP.CD. [Assessed 20 October 2014].
14. Severens JL, Milne RJ. Discounting health outcome in economic evaluation; the ongoing debate. Value in Health. 2004; 7(4): 397-401.

15. Drummond M, Barbieri M, Cook J, Glick HA, Lis J, Malik F, Reed SD, Rutten F, Sculpher M, Severens J.. Transferability of Economic Evaluations Across Jurisdictions: ISPOR Good Research Practices Task Force Report. Value in Health. 2008; 8: 1098-3015.

16. Indexes of of consumption prices for the separate groups of goods and services (related to the previous month) Ukrainian state statistics department. Available from http://www.km.ukrstat.gov.ua/ukr/statinf/ct/isc_pm13.htm. [Assessed 20 October 2014].

17. Beusterien KM, Davies J, Leach M, Meiklejohn D, Grinspan JL, O'Toole A, Bramham-Jones S. Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. Health Qual Life Outcomes. 2010; 8(50).

18. State Committee of Statistics of Ukraine. [Social protection of the population of Ukraine. The compendium of statistics]. Kyiv, 2011. P119. Ukrainian.

19. Actuarial life table. Period life table, 2010. Official social security website. Available from: http://www.ssa.gov/oact/STATS/table4c6.html [Assessed 14 October 2014].

Chapter 9

General Discussion

Health Technology Assessment (HTA) approaches with a focus on economic evaluations have become important in evidence-based decision making in healthcare. [1-3]. In view of the growing number of new technologies, the comprehensiveness of health economic studies in general, and the limited capacity of HTA bodies, the transferability of such economic evaluations from other jurisdictions is considered an important issue to be addressed [4-11]. This issue has not yet been addressed, however, for the Central and Eastern European (CEE) and former Soviet countries. This thesis, therefore, investigated aspects of transferability of economic studies and their components to the countries of the CEE region and former Soviet Union with no established centralized HTA agency, using Ukraine as a main example.

In part 1 of the dissertation the use and transferability of economic evaluations to CEE and former Soviet countries were investigated by means of experts' interviews and a systematic review of economic evaluations. Practical economic studies conducted for healthcare settings of CEE and former Soviet countries (primarily Ukraine) are presented in part 2 (chapters 3-8). In this chapter, the main findings of the thesis, recommendations for improving transferability of economic evaluations to CEE and former Soviet countries and further research possibilities are presented.

Main findings and their implications

Box 1. Main findings

- There are barriers to the use of economic evaluations in healthcare decision making, related to low HTA capacity
- Transferability issues are known and considered important in the countries studied, but have not yet gained the attention they deserve
- The degree of transferability of economic evaluations conducted in healthcare settings of CEE and former Soviet countries is limited
- Variations in unit cost, resource use and baseline risk could have a significant impact on the results of economic studies, thereby rendering them non-generalizable
- Transferability of technologies' efficacy and patients' preferences should be assessed for each case separately and may be generalizable

Use of economic evaluations and need for transferability in CEE and former Soviet countries

While scope of impact of the cost-effectiveness criterion on the decision-making process differs from country to country [3, 12], it appears from chapter 2 that economic evaluations can be an additional tool for state reimbursement decisions – even in countries without a formal HTA agency. While other factors (for example, budget impact) may be predominant in middle-income countries, comparative economic studies may be accepted under the following conditions: (1) The methodology is considered relevant (technology, comparators, population) and of high quality; (2) Experts or decision makers perceive the study to be reliable (i.e., "free of bias"), which corresponds to observations from other jurisdictions [13].

Setting out to implement an HTA approach, CEE and former Soviet countries already are facing a number of barriers, primarily related to low HTA capacity (including budget, manpower and data constraints) and to the decision-making process itself. Although capacity building should be addressed before implementing an HTA system [14], some countries follow an alternative approach, using HTA without having built more capacity and without strict priority settings. This approach slows down the development of the system and may lead to incorrect decisions and, therefore, to a waste of resources.

Figure 9.1 nicely illustrates that even though the basis for a reimbursement decision may not yet be clear [13], HTA capacity is a requirement for any HTA-based decision. At the same time, reimbursement decisions may be argued on the grounds of factors such as the importance of the submitted HTA report to the decision makers (thus, a formal or advisory role of HTA, belief in the evidence provided, educational level of the decision makers), health priority of the technology, budget availability, and transparency of the decision-making process (including rationality in the decision making, personal opinion and conflict of interest). Consequently, if the role of HTA in budget allocation is not defined, as is the case in many countries [5], low HTA capacity results in a limited added value of the submitted HTA reports in reimbursement decisions. As a result, the producers of medical technologies are not motivated to invest in budget-consuming submissions, especially under conditions of limited or unsecured financing.

HTA manpower is scarce in many middle-income jurisdictions [6], and educational programs in HTA and economic evaluations are highly needed there (chapter 2). It is unfortunate, however, that many countries of the study region have not the means to widely finance educational programs. On the other hand, in those countries that can afford this, we often see a brain drain from state regulatory committees to the private sector [17].

Besides manpower, financial issues have a major impact on the use of economic evaluations and HTA development in most countries, including countries of the European Union [15, 17].

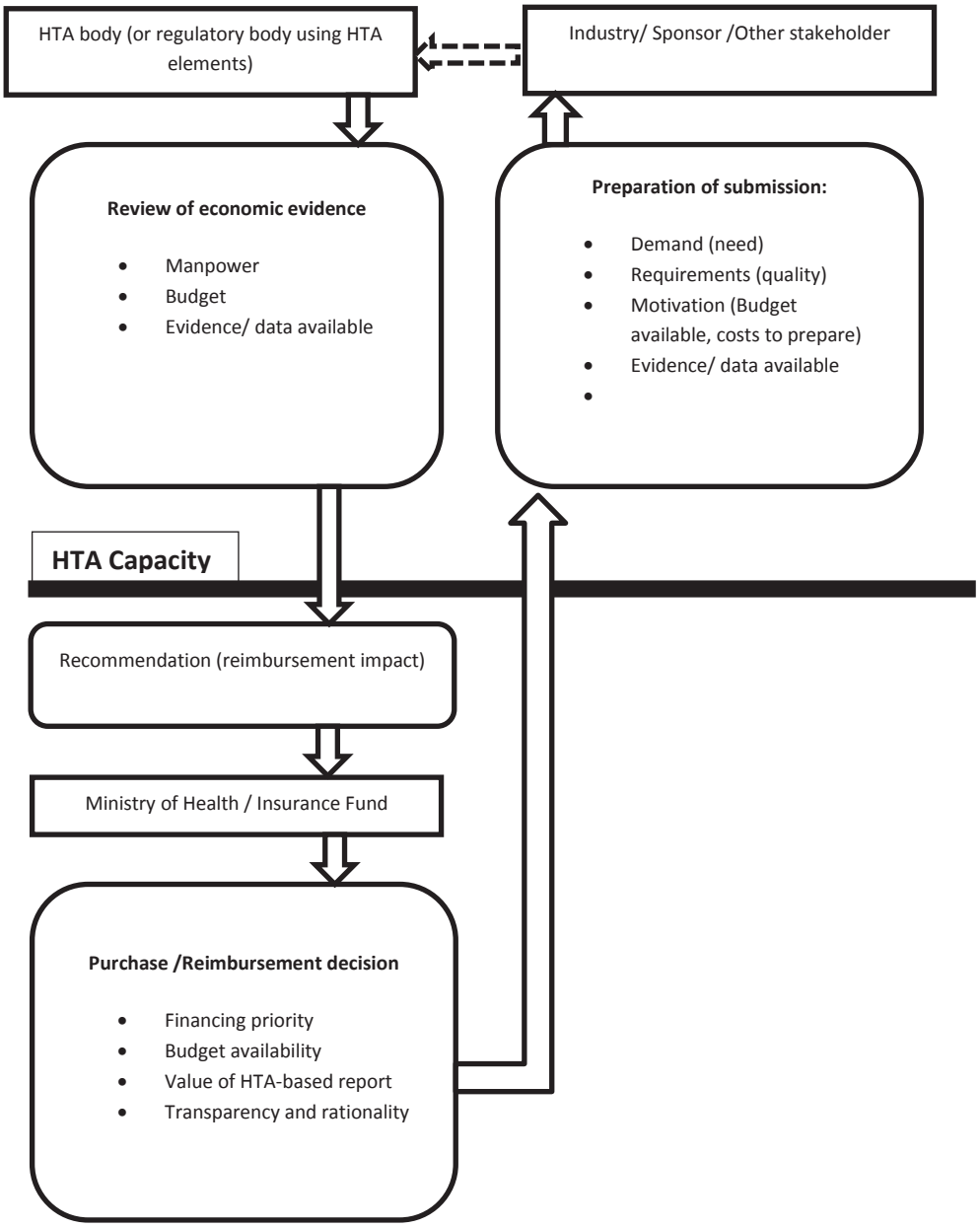

Figure 9.1 Use of health technology assessment elements/ economic evaluations in countries with no obligatory single HTA process

Additionally, a lack of data on both costs and outcomes influences both the methodology of economic evaluations and experts' requirements for submitting economic evidence (chapters 2, 3). These requirements for high–quality, unbiased submissions become more critical if not enough expertise is available [3], which currently seems to be the case in CEE and former Soviet countries (chapter 2).

Because of the barriers indicated above, generalizability or simple transferability adjustments of economic evaluations may be the only way to include economic considerations in the decision-making process in many CEE and former Soviet countries (chapters 2, 3). Meanwhile, generalizing economic evaluations from neighboring countries is not possible, and due to significant differences in healthcare practices, system structures and financing, the transferability of studies between different geographic regions is even more limited.

Chapter 3 makes clear that only very few transparently reported economic evaluations for healthcare settings of CEE and former Soviet countries have been published; most economic evaluations originate from North America (Canada and the USA) and Western and Northern Europe [17]. This seems to be the cause of a paradoxical situation: knowing about transferability issues, HTA-related bodies use published economic evidence conducted in other jurisdictions which are often not comparable with the own jurisdiction.

Previous research has also addressed this limited generalizability as a result of variability in health and economic indicators [10, 20]. Even for economically comparable Western European countries, such as the UK and France, it was found difficult to generalize economic evaluations [21].

Being a first knock-out criterion for transferability [6], the quality of economic evaluations is an issue of concern for decision makers in CEE and former Soviet countries (chapter 2), similar to other geographic jurisdictions [3]. Nevertheless, as described in chapter 3, both quality and transparency of evaluations conducted in healthcare settings of CEE and former Soviet countries are frequently insufficient. Furthermore, they often lack a stated perspective and a clear cost description and fail to fully address uncertainty. Additionally, piggy-backed economic studies are usually based on small, local trials rather than on multicenter trials, so the small sample sizes limit generalizability of the results due to low statistical power. Most economic evaluations conducted in the study region did not discuss the transferability of their studies' results to other jurisdictions, nor did they define critical influential parameters and their threshold values. As such, the transferability of trial- and model-based studies to other jurisdictions is complicated [21-23].

Practical application of transferability principles and transferability of input parameters by major data categories

While the generalizability of economic evaluations within the CEE region and former Soviet Union is without validity problems, certain input parameters possess a different level of transferability [24]. The most difficult to transfer are costs and prices, baseline risk and treatment effect, in contrast to treatment adherence and utility values, which are considered of less importance. Costs are not considered to be generalizable parameters and are almost always locally adapted in published studies from this region.

The following factors may limit the degree of cost generalization from the other jurisdictions: 1) the cost components of one unit differ between jurisdictions; 2) the cost of individual units may be different and not be proportional to the purchasing index or GDP per capita; 3) market differences may result in cost variations. As an example, the hospitalization costs in Ukraine from a state or healthcare perspective frequently include diagnostics, “hotel services,” and administration and medical care costs; at the same time unit costs in most of the countries with reimbursement system are defined by diagnostic-related groups (chapter 3). Not only cost components themselves, but also their relative values can differ. Chapters 4, 5, 6 and 8 demonstrate a significant difference between the costs of therapy and medical care (hospitalization or ambulatory visits), culminating in non-comparability of the results between Ukraine and high-income markets.

While pharmaceutical markets in many Western European countries have rigid pricing regulations, primary out-of-pocket markets in former Soviet countries are frequently missing price-entry schemes for generic products. As a result, there is a considerable variety in drug costs (chapters 5 and 8), which, depending on the technology, may have an impact on the results of economic evaluations.

Resource utilization between countries may vary for both inpatient and outpatient visits (chapters 4-8), dependent on parameters such as normative recommendations by the Ministry of Health, clinical guidelines, current clinical practice, and population characteristics (e.g., age/gender, education level, share of internet users among patients). For example, in contrast to Western European and North American countries, Ukrainian type 2 diabetes patients are seen by specialists (endocrinologists) and not by primary care specialists or nurses (chapter 6), and Ukrainian clinical guidelines on hematologic malignancies provide additional treatment options under conditions of limited availability of financing (chapter 4). Because of the impact of health economic indicators (chapter 1), resource utilization may be a critical parameter for both non-comparative (chapters 4, 5) and comparative (chapter 8) economic evaluations.

Baseline risk is a parameter that widely varies between different jurisdictions [2,24]. While the risk of future events of interest without treatment may vary more for preventive technologies, case-mix characteristics may significantly impact the results of economic studies. Chapter 5 makes clear the baseline risk of the success of an IVF

procedure (which is primarily dependent on mother's age) and the protocols followed in the particular jurisdiction/clinic have a defining impact on the resultant net present value from the population born. Similarly, population mortality among the general population has an additional impact on the results of economic studies (chapters 5 and 8). Diversity of case-mix characteristics (e.g., gender distribution, age at diagnosis, body mass index) may affect cost-effectiveness results because of the impact of these characteristics on cohort life duration, higher income/costs associated with the particular gender group, or differences in drug doses received (chapters 5, 6, and 8).

Relative risk reduction or treatment effect is considered to be an easily transferable parameter both by pharmacoeconomic guidelines [24] and by CEE reimbursement experts. As shown in Chapters 6 and 8 for certain disease areas, using the transferred treatment effect may be beneficial for economic studies conducted in the CEE region and former Soviet Union as an opportunity: 1) to increase power in a study and to assess the generalizable treatment effect; 2) to compare with a wider number of alternatives; 3) to avoid trial costs; and 4) to have evidence available within a shorter time span [20, 24, 25].

Despite evidence of differences in utilities between populations [2, 24, 26], country-specific utility weights are not of major interest for decision makers in CEE and former Soviet countries, and are rarely used in relevant published studies (chapters 2, 3). While transferability of utility parameters is disease specific and should be assessed on an individual basis, in a qualitative study on type 2 diabetes patients, patients' perception of the disease state did not differ between Ukrainian and Western-European populations (chapter 7).

Recommendations and policy implication

Box 2. Recommendations and policy implication

- Address barriers related to decision making process and limited HTA capacity
- Develop pharmacoeconomic guidelines related to the local context and requirements
- Adapt a standardized approach to simplify transferability assessment process
- Define priorities for HTA evaluations
- Provide incentives to improve quality and transparency of economic evaluations

Barriers to address

Governmental bodies of countries wishing to enhance utilization of HTA in healthcare decision making should at least address the following barriers: 1) non-transparency of the decision-making process and the limited value of economic evaluations perceived by decision makers; 2) limited capacity of HTA bodies and insufficient education of experts; and 3) insufficient or low quality input data and a numerous assumptions in economic models. Subjective individual experts' perception – that is primarily based on education – potentially may have a significant impact on both acceptability and transferability judgments. The major HTA capacity issues, such as experts' education, budget allocation and data access, should be addressed prior to the establishment of a single HTA body.

Guidelines to develop

Guidelines on the use of, or on performing economic evaluations for CEE and former Soviet countries should include limitations and approaches related to the local context (such as dealing with lack of data), requirements for quality and transparency (e.g., inputs and methods presentation, addressing uncertainty and data heterogeneity, threshold evaluation) and addressing of transferability. Although guidelines in many countries recommend using the societal perspective [27], in view of data constraints this approach should be reconsidered in countries of the CEE region and former Soviet Union which are in the process of implementing or have recently implemented single HTA agencies.

Transferability to adapt

The centralized or governmental HTA bodies of CEE and former Soviet countries should focus on a standardized approach for simple transferability of economic evaluations in order to avoid budget and manpower constraints and provide rational decisions. Moreover, the requirements and needs for local data should be strongly adjusted. When the model from the reference country is of appropriate quality and includes relevant study technology and comparators, and both jurisdictions have similar healthcare structures and disease incidence/prevalence, simple adaptation (costs, resource use, baseline risk) is recommended.

Priorities to apply

Taking into account that HTA resources are limited, HTA research priorities should be defined by a country payer. To define if a high-cost technology is a priority for HTA, reimbursement decisions from HTA-developed jurisdictions and their economic backgrounds can be used to filter non-efficient technologies.

Stakeholders to involve

Stakeholders' opinions on methodology and data transferability were gathered implicitly during group meetings or face-to-face interviews before the start of each study presented in Part 2. Obviously, relevant stakeholders should be involved explicitly to improve the quality, the transparency and the transferability, and thus to improve the use of economic evaluations in healthcare decision making of CEE and former Soviet countries. As such, policy makers should provide clear incentives to research payers/sponsors (often the producer of a medical technology) and researchers. Therefore, applying the CHEERS statement [28] is strongly recommended.

Unaddressed issues and possibilities for future research

In this work we analyzed transferability of economic evaluations and their components to CEE and former Soviet countries without an established centralized HTA agency. The following aspects, not addressed in this dissertation, may be of interest for future research:

Priorities for economic evaluations conducted for healthcare settings of CEE and former Soviet countries

As indicated in chapter 3, economic evaluations conducted for healthcare settings of CEE and former Soviet countries may be fund driven and, therefore, at risk of being unrelated to the priorities of decision makers. Because these priorities may be assessed indirectly (for example, by budget allocations), systematizing this evidence may be useful for future studies.

Impact of evidence on reimbursement decisions in CEE and former Soviet countries

The research presented in this dissertation allowed conclusions to be drawn regarding the use of economic evaluations in the healthcare decision making processes of CEE and former Soviet countries. However, the scope of impact of economic studies as well as the background impact of other evidence and factors is not known.

Quality of local language publications in CEE and former Soviet countries

To our knowledge there are no studies assessing quality of local-language publications with the use of quality checklists. This may be attributed, in part, to language barriers and conflicts of interest.

Variations in cost-effectiveness ratios depending on country characteristics

Differences in costs, resource use, and baseline risks in lower- and higher-income countries suggest possible higher ICER for expensive innovative treatments in CEE and former Soviet countries. However, more evidence is needed before we can draw valid conclusions regarding possible dependence of ICER expectations on average country values for the data categories.

Difference in utility values for CEE and former Soviet countries and countries with frequently referenced utility sets

As stated above, transferability of utility values is not an issue of importance for researchers and decision makers in CEE and former Soviet countries. At the same time, the failure to address variations in utilities between different populations may be attributable to insufficient knowledge of their values.

General conclusion

If HTA capacity – defined here as budget, knowledge, manpower and data quality constraints – in low and middle income countries in central and eastern Europe is limited, transferability and priority settings should be the major issues to be diagnosed prior to implementing an explicit HTA process. While it is not possible to generalize the results of economic evaluations, certain input parameters may be transferable between jurisdictions. Transferability of input data should be assessed individually for each case to define which parameters are important to localize. Possible variations in the values of model parameters should be addressed accordingly. In sum, it can be said that geographic transferability of economic evaluations is a necessity for CEE and former Soviet countries.

References

1. Drummond M. An Introduction to Health Economics. Brookwood, Surrey, UK: Brookwood Medical Publications; 1995.
2. Barbieri M, Drummond M, Rutten F, Cook J, Glick HA, Lis J, Reed SD, Sculpher M, Severens JL. What Do International Pharmacoeconomic Guidelines Say about Economic Data Transferability? Value in Health. 2010; 10: 1098-3015.
3. Sorenson C, Drummond M, Kristensen FB, Busse R. How can the impact of health technology assessments be enhanced? Health systems and policy analysis, World Health Organization, Copenhagen, Denmark; 2008.
4. Knies S. Transparency of transferability. Diagnosing international aspects of economic evaluations of health care technologies. Maastricht University: Maastricht. 2011; p.136.
5. Goeree R, He J, O'Reilly D, Tarride JE, Xie F, Lim M, Burke N. Transferability of health technology assessments and economic evaluations: a systematic review of approaches for assessment and application. Clinicoecon Outcomes Res. 2011; 3: 89-104.
6. Welte R, Feenstra T, Jager H, Leidl R. A decision chart for assessing and improving the transferability of economic evaluation results between countries. Pharmacoeconomics. 2004; 22(13): 857-76.
7. Antonanzas F, Rodriguez-Ibeas R, Juarez C, Hutter F, Lorente R, Pinillos M. Transferability indices for health economic evaluations: methods and applications. Health Econ. 2009; 18: 629–643.
8. Essers BA, Seferina SC, Tjan-Heijnen VC, Severens JL, Novák A, Pompen M, Oron UH, Joore MA. Transferability of model-based economic evaluations: the case of trastuzumab for the adjuvant treatment of HER2-positive early breast cancer in the Netherlands. Value Health. 2010; 13: 375-380.
9. Goeree R, Burke N, O'Reilly D, Manca A, Blackhouse G, Tarride JE. Transferability of economic evaluations: approaches and factors to consider when using results from one geographic area for another. Curr Med Res Opin. 2007; 23: 671-682.
10. Knies S, Ament AJ, Evers SM, Severens JL. The transferability of economic evaluations:testing the model of Welte. Value Health. 2009; 12: 730-738.
11. EUnetHTA Work Package 8. EUnetHTA Handbook on Health Technology Assessment Capacity Building. Catalan Agency for Health Technology Assessment and Research. Catalan Health Service. Department of Health Autonomous Government of Catalonia Barcelona, Spain;2008.
12. World Health Organization. Cost effectiveness and strategic planning (WHO-CHOICE). Cost-effectiveness thresholds. Available from http://www.who.int/choice/costs/CER_thresholds/en/. [Assessed 20 October 2014].
13. Erntoft S. Pharmaceutical Priority Setting and the Use of Health Economic Evaluations: A Systematic Literature Review. Value in Health. 2011; 14: 587-599.
14. Martelli F, La Torre G, Di Ghionno E, Staniscia T, Neroni M, Cicchetti A, Von Bremen K, Ricciardi W; NI-HTA Collaborative Group. Health technology assessment agencies: an international overview of organizational aspects. Int J Technol Assess Health Care. 2007; 23(4): 414-24.
15. Kolasa K, Kalo Z, Zah V, Dolezal T. Role of health technology assessment in the process of implementation of the EU Transparency Directive: relevant experience from Central Eastern European countries. Expert Rev. Pharmacoecon. Outcomes Res. 2012; 12: 283-287.
16. Gulacsi L, Orlewska E, Pe´ntek M. Health economics and health technology assessment in Central and Eastern Europe: a dose of reality. Eur J Health Econ. 2012; 13: 525–531.
17. Report on the public consultation on the modalities of stakeholder consultation in the future Health Technology Assessment Network. European Commission health and consumers directorate-general; 2012.
18. Danko D. Health technology assessment in middle-income countries: recommendations for a balanced assessment system. J. Mark. Access & Health Policy. 2014; 2:1-10.

19. Kaló Z, Bodrogi J, Boncz I, Dózsa C, Jona G, Kövi R, Pásztélyi Z, Sinkovits B. Capacity Building for HTA Implementation in Middle-Income Countries: The Case of Hungary. Value Health Reg. Issues.2013;2:264 – 266.

20. Sculpher MJ, Pang FS, Manca A, Drummond MF, Golder S, Urdahl H, Davies LM, Eastwood A. Generalisability in economic evaluation studies in healthcare: a review and case studies. Health Technology Assessment. 2004; 8: 1-213.

21. Boulenger S, Nixon J, Drummond M, Ulmann P, Rice S, de Pouvourville G. Can economic evaluations be made more transferable? Eur J Health Econ. 2005; 6(4): 334-46.

22. McGhan WF, Al M, Doshi JA, Kamae I, Marx SE, Rindress D. The ISPOR Good Practices for Quality Improvement of Cost-Effectiveness Research Task Force Report. Value Health. 2009;12:1086-99.

23. Hay JW, Smeeding J, Carroll NV, Drummond M, Garrison LP, Mansley EC, Mullins CD, Mycka JM, Seal B, Shi L. Good Research Practices for Measuring Drug Costs in Cost Effectiveness Analyses: Issues and Recommendations: The ISPOR Drug Cost Task Force Report—Part I Value Health. 2010;13:3-7.

24. Drummond M, Barbieri M, Cook J, Glick HA, Lis J, Malik F, Reed SD, Rutten F, Sculpher M, Severens J. Transferability of Economic Evaluations Across Jurisdictions: ISPOR Good Research Practices Task Force Report. Value in Health. 2008; 8: 1098-3015.

25. Berger ML, Dreyer N, Anderson F, Towse A, Sedrakyan A, Normand SL., Prospective observational studies to assess comparative effectiveness: the ISPOR good research practices task force report. Value Health. 2012; 15(2):217-30.

26. Knies S, Evers S, Candel MJJM, Severens JL, Ament AJHA. Utilities of the EQ-5D: transferable or not? Pharmacoeconomics. 2009; 27(9): 767-779.

27. Garrison LP, Mansley EC, Abbott TA, Bresnahan BW, Hay JW, Smeeding J. Good research practices for measuring drug costs in cost-effectiveness analyses: a societal perspective: the ISPOR Drug Cost Task Force report--Part II. Value Health. 2010;13(1):8-13.

28. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, Augustovski F, Briggs AH, Mauskopf J, Loder E. CHEERS Task Force. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. BMJ. 2013;346.

Summaries

Summary

Despite that the transferability of economic evaluations is a widely discussed topic, it was until recently only limitedly explored in the region of Central and Eastern European (CEE) and former Soviet countries.

In part 1 of the thesis the use of economic studies in healthcare decision making and the current need for transferability of economic evaluation studies in the study region are presented. In chapter 2, presenting the results of a qualitative assessment of the opinion of experts, it becomes clear that economic studies are not always formally used in healthcare decision making in the CEE region. As stated, their acceptance depends upon the perspective of the study, perceived quality, the methodology used, costs source and assessment method, reliability of the study and population characteristics. Even though economic studies are not considered to be generalizable from one jurisdiction to another, foreign evidence still may be used for local decisions. Because similarities in healthcare systems and practices are considered important by the experts, along with costs and countries' comparative economic development, perspective of the study, and disease epidemiology, transferability of studies within one geographic region may be simpler than across regions.

Chapter 3 describes the characteristics of published economic evaluations from CEE and former Soviet countries, retrieved by a systematic literature search. Using Drummond's checklist it was concluded that items such as perspective stated, relevant costs included, costs measured accurately in appropriate units, outcomes and costs valued credibly, and uncertainty addressed were the least frequently and not transparently addressed parameters. Even though studies frequently generalized clinical effect and utilities from other populations, limitations of using foreign data were rarely discussed. Additionally, transferability of the results was not sufficiently discussed in the published economic studies. The transferability of studies to other jurisdictions may be simplified if input uncertainty and data transferability are comprehensively addressed and the transparency of reporting is improved.

Decision makers' methodology requirements and data availability are two important factors influencing the transferability of economic evaluations. In part 2 of the thesis basing the study design on the assessed preferences of the decision makers and on the data available, transferability principles are applied (chapters 4-8).

As can be seen from chapter 4, the costs for the treatment of chronic lymphocytic leukemia (CLL) in Ukraine may significantly vary even between comparable specialized institutions. While the major costs are related to drug treatment, many patients in Ukraine pay out of pocket for in-hospital drugs, and so these costs become an economic burden for an individual patient. While drug therapy is a main driver of CLL treatment costs not only in Ukraine, in the structure of total CLL treatment costs medical care remains as non-

influential component what differs from such economically developed countries as the USA and Germany.

In chapter 5 net lifetime tax revenues of a population received via in-vitro fertilization (IVF) in Ukraine, Belarus, and Kazakhstan were calculated. As described in the chapter, financing IVF may be a positive financial return even in lower-income countries with state-financed healthcare systems such as Ukraine, Belarus, and Kazakhstan. Some parameters, such as the "deliveries per cycle after IVF" are country-specific and have a defining impact on the results of the economic analysis, and so have a limited generalizability. Additionally, it was noted that return of investment into IVF may not be directly proportional to economic indicators, as GDP per capita in the country, being dependent on many parameters, such as societal guarantees to population provided by state and taxation rates.

Chapter 6 presents a comparative cost study of the use of pegylated interferons (Peg-α-2b and Peg-α-2a) as a treatment for genotype 1 chronic hepatitis C. The clinical outcomes (sustained virologic response and patients' follow-up on the therapy) were generalized from other populations by using data of an American multicentre randomized controlled trial, while in the base-case scenario the cost data were specific for the Ukraine population. For patients with an average body weight, a small cost saving with Peg-α-2b treatment is observed from both a patient and a healthcare perspective. With the adjustment to reflect an average body weight in Ukraine, the difference in costs per patient and costs per sustained virologic response in favor of Peg-α-2b was slightly higher, but without a significant impact on the study's conclusion.

In chapter 7 a qualitative study on the preferences and perceptions of Ukrainian type 2 diabetes patients experiencing hypoglycemia is presented. From the results of three focus groups with in total 26 patients it was concluded that the adaptation of Ukrainian patients to potential episodes of hypoglycemia is similar to observations made in other countries. In contrast to some other economically developed countries, Ukrainian patients older than 40 years receive information on disease management majorly from endocrinologists, and rarely use Internet resources on diabetes management. This fact should be accounted in disease management studies as well as in relevant economic evaluations.

Chapter 8 presents the results of a cost-effectiveness analysis of the use of rituximab in the treatment of CLL in previously non-treated and relapsed/refractory patients in Ukraine. The incremental cost-effectiveness ratio (ICER) of adding rituximab to the fludarabine and cyclophosphamide scheme (FCR versus FC) is $8,704 per quality-adjusted life year gained for treatment-naive patients and $11,056 for refractory/relapsed patients. The transferability of clinical outcomes, overall and progression-free survival was assessed by modifying the trial data to the lower life expectancy of the general population in Ukraine. In this case the ICER for treatment-naive patients was higher than $13,000, which

is three times higher than the current gross domestic product per capita in Ukraine. Sensitivity analyses have shown a high impact of rituximab costs and a moderate impact of differences in utilities on the ICER. Population characteristics and unit costs have a significant impact on the study result.

The main findings, presented in chapter 9, suggests that the use of economic evaluations in healthcare decision making faces barriers related to the low health technology assessment (HTA) capacity. Despite that transferability of economic evaluations conducted in health care settings of CEE and former Soviet countries is limited and rarely applied; the principle of transferring data is familiar in the countries studied. While variations in some of the parameters, such as unit cost, resource use, and baseline risk cause non-generalizability of the results, efficacy and patients' preferences may be generalizable in some cases.

The recommendations of chapter 9 regarding improvement of the use of economic evaluations in healthcare decision making are the following: to address barriers related to decision making process and limited HTA capacity, to develop HTA and health economic guidelines, to standardize the approach for transferability, to define HTA priorities, and to provide incentives for improving the quality of studies.

This dissertation concludes that geographic transferability of economic evaluations is necessary for CEE and former Soviet countries.

Nederlandse samenvatting

Ondanks dat de transferabiliteit van economische evaluaties wereldwijd een veel besproken onderwerp is, was het tot kort een weinig besproken onderwerp in de regio van Centraal- en Oost-Europa en de voormalige Sovjet landen.

In deel 1 van het proefschrift wordt het gebruik van economische studies voor besluitvorming in de gezondheidszorg en het huidig gebruik van het concept transferabiliteit van economische evaluaties in de regio beschreven. Hoofdstuk 2 laat de resultaten zien van interviews met experts uit de regio. Hieruit blijkt dat economische studies vaak geen formele status hebben in het besluitvormingsproces. Daarnaast bleek dat de acceptatie van economische studies af hangt van een aantal factoren zoals het perspectief van de studie, kwaliteit van de studie, gebruikte methodologie, kostenbron en beoordelingsmethode, betrouwbaarheid van de studie en populatiekenmerken. Hoewel economische studies niet als generaliseerbaar worden beschouwd, wordt buitenlandse data toch geregeld gebruikt voor lokale besluiten. Omdat overeenkomsten in zorgsystemen en behandelpraktijk, naast vergelijkbare kosten, economische ontwikkeling van het desbetreffende land, studieperspectief en epidemiologie van de ziekte, belangrijk wordt gevonden door de experts is de transferabiliteit van studies binnen een geografische regio waarschijnlijk makkelijker dan tussen verschillende regio's.

Hoofdstuk 3 beschrijft de studiekenmerken van gepubliceerde Engelstalige economische evaluaties uit Centraal- en Oost-Europa en voormalige Sovjet landen. Met behulp van de checklist van Drummond et al. kon worden geconcludeerd dat items als perspectief, inclusie van relevante kosten, accurate meting van kosten, geloofwaardige waardering van uitkomsten en kosten, en beschrijving van de onzekerheid het minst vaak en niet transparant waren beschreven. Hoewel de studies vaak klinische effecten en utiliteiten uit andere landen gebruikten werden de beperkingen van het gebruik van buitenlandse data in slechts een beperkt aantal studies besproken. Daarnaast werd de transferabiliteit van de studieresultaten niet genoeg bediscussieerd in de gepubliceerde economische studies. De transferabiliteit van studies naar andere jurisdicties kan worden vereenvoudigd als de onzekerheid rondom de data en de transferabiliteit van de data duidelijk wordt besproken en als de transparantie van de rapportage verbeterd.

Methodologische vereisten van beleidsmakers en de beschikbaarheid van data zijn twee belangrijke factoren die de transferabiliteit van economische evaluaties beïnvloeden. In deel 2 van het proefschrift worden de transferabiliteit principes toegepast in samenhang met de door beleidsmakers geprefereerde studieopzet en de beschikbaarheid van data (hoofdstukken 4-8).

Zoals te zien is in hoofdstuk 4, zijn er significante verschillen in Oekraïne tussen de gespecialiseerde instellingen in de behandelkosten van chronische lymfatische

leukemie (CLL). Het grootste deel van de kosten zijn gerelateerd aan geneesmiddelen en aangezien veel patiënten in Oekraïne zelf moeten betalen voor ziekenhuisgeneesmiddelen zijn deze kosten een financiële last voor een individuele patiënt. Niet alleen in Oekraïne vormen de kosten van geneesmiddelen een substantieel deel van de totale behandelkosten van CLL, maar in tegenstelling tot de Verenigde Staten en Duitsland zijn de kosten van de medische of ziekenhuiszorg in Oekraïne relatief laag.

In hoofdstuk 5 zijn de netto levenslange belastingopbrengsten van een populatie geboren met behulp van in-vitro fertilisatie (IVF) in Oekraïne, Wit-Rusland en Kazakstan berekend. Het financieren van IVF zorgt voor een positieve financiële opbrengst zelfs in lagerinkomen landen met staatsgefinancierde zorgsystemen zoals in Oekraïne, Wit-Rusland en Kazakstan. Uit de resultaten bleek dat sommige parameters zoals 'aantal bevallingen per IVF-cyclus' landspecifiek zijn en een belangrijke impact hebben op de resultaten van de economische analyse. Daarom zijn deze parameters maar beperkt generaliseerbaar. Daarnaast bleek dat het investeringsrendement in IVF niet proportioneel gerelateerd is aan economische indicatoren zoals het bruto binnenlands product van een land. Dit kan verklaard worden door middel van parameters zoals sociale garanties van de staat aan de bevolking en de verwachte belastingopbrengsten.

Hoofdstuk 6 bevat een vergelijkende kostenstudie naar het gebruik van pegylated interferon (Peg-α-2b en Peg-α-2a) voor de behandeling van genotype 1 chronische hepatitis C. De klinische uitkomsten (sustained virologic response/SVR en therapietrouw van de patiënt) zijn gegeneraliseerd vanuit de Verenigde Staten door gebruik te maken van een Amerikaanse gerandomiseerde multicenter studie, waarbij in de base-case scenario alleen de kostendata specifiek voor de Oekraïense populatie waren. Bij patiënten met een gemiddeld lichaamsgewicht is er vanuit zowel het patiëntenperspectief als vanuit het gezondheidszorgperspectief een kleine kostenbesparing te zien bij behandeling met Peg-α-2a. Echter als het gemiddelde lichaamsgewicht uit de studie wordt aangepast aan het gemiddelde in Oekraïne was het verschil in kosten per patiënt en per SVR in het voordeel van Peg-α-2b.

In hoofdstuk 7 wordt een kwalitatieve studie naar de preferenties en percepties van Oekraïense diabetes type 2 patiënten met ervaringen met hypoglykemie gepresenteerd. Uit de resultaten van drie focusgroepen met in totaal 26 patiënten kan worden geconcludeerd dat de aanpassing van Oekraïense patiënten naar potentiële episodes van hypoglykemie vergelijkbaar is met gedane observaties in andere landen. In tegenstelling tot een aantal economisch ontwikkelde landen, krijgen Oekraïense patiënten ouder dan 40 jaar vooral informatie van de endocrinoloog over disease management en gebruiken ze amper het Internet voor het vinden van informatie. Dit resultaat moet worden meegenomen in disease management studies en ook in de relevante economische evaluaties.

Hoofdstuk 8 laat de resultaten van een kosteneffectiviteitstudie zien naar het gebruik van rituximab in de behandeling van CLL bij behandelnaïeve en relapsed/refractair patiënten in Oekraïne. De incrementele kosteneffectiviteitsratio (ICER) van het toevoegen van rituximab aan een behandelschema met fludarabine en cyclofosfamide (FCR versus FC) is $8.704 per QALY (voor kwaliteit van leven gecorrigeerde levensjaren) voor behandelnaïeve patiënten en $11,056 voor relapsed/refractair patiënten. De transferabiliteit van de klinische uitkomsten, algehele en progressievrije overleving is beoordeeld door het aanpassen van de studiedata aan de lagere levensverwachting van de algemene bevolking in Oekraïne. In dit geval werd de ICER voor behandel-naïeve patiënten hoger dan $13.000, wat drie keer hoger is dan het huidige bruto binnenlands product per hoofd van de bevolking in Oekraïne. Gevoeligheidsanalyses laten daarnaast een grote impact van de kosten van rituximab op de ICER zien en een matige impact van verschillen in utiliteiten. Verder hebben ook populatiekenmerken en prijzen een significante impact op de resultaten.

De belangrijkste resultaten, zoals te zien in hoofdstuk 9, suggereren dat voor dat economische evaluaties in de besluitvorming gebruikt kunnen worden een aantal barrières gerelateerd aan de beperkte capaciteit voor Health Technology Assessment (HTA) in Centraal- en Oost Europa en voormalige Sovjet landen moeten worden overwonnen. Ondanks dat transferabiliteit van economische evaluaties uit Centraal- en Oost-Europa en voormalige Sovjet landen beperkt is en amper wordt toegepast; zijn de principes achter transferabiliteit bekend in deze landen. Hoewel variabiliteit in parameters zoals prijzen, zorggebruik en baseline risico ervoor zorgen dat de resultaten niet generaliseerbaar zijn, zijn data gerelateerd aan efficacy en patiëntenpreferenties in sommige gevallen wel generaliseerbaar. De hierop volgende aanbevelingen in hoofdstuk 9 zijn als volgt: opheffen van barrières gerelateerd aan het besluitvormingsproces en de beperkte HTA capaciteit; ontwikkel richtlijnen voor economische evaluaties en HTA-studies, standaardiseer de benadering van transferabiliteit, definieer prioriteiten voor HTA-studies en introduceer prikkels om de kwaliteit van studies te verbeteren.

De conclusie van dit proefschrift is de geografische transferabiliteit van economische evaluaties noodzakelijk is voor Centraal-en Oost-Europa en voormalige Sovjet landen.

Резюме

Несмотря на то что переносимость экономических оценок - широко обсуждаемая тема, до недавнего времени она изучалась только ограниченно в Центральном и Восточно-Европейском регионе (ЦВЕ) и странах бывшего Советского Союза.

В части 1 данной диссертации показано использование экономических исследований в принятии решений в здравоохранении и существующая потребность в переносимости их результатов в данном регионе. В главе 2, представляющей результаты качественной оценки мнения экспертов, становится понятно, что экономические исследования не всегда используются формально в принятии решений здравоохранения ЦВЕ региона. Как продемонстрировано, их использование зависит от перспективы исследования, восприятия качества, методологии, источников затрат и методов оценки, надежности исследования и характеристики популяции. Хотя результаты экономического анализа не считаются переносимыми с одной территории на другую, иностранные исследования могут использоваться в принятии локальных решений. Поскольку, согласно экспертному мнению, близость систем здравоохранения и клинических практик являются важными параметрами, также, как и затраты, относительное экономическое развитие страны, перспектива исследования и эпидемиология заболевания, переносимость исследований между странами одного географического региона может быть проще, чем между разными регионами.

Глава 3 описывает характеристики опубликованных экономических оценок из стран ЦВЕ и бывшего Советского Союза, полученных методом систематического поиска литературы. Используя контрольный перечень Драммонда, был сделан вывод, что четкое обозначение перспективы, обоснованность выбора затрат и их точное измерение, надежность оценки затрат и эффективности, и анализ сомнительности полученных результатов, - являются наименее часто и открыто рассмотренными параметрами. Хотя показатели клинической эффективности и утилитарности часто обобщались из других популяций, ограничения относительно использования иностранных данных в исследованиях обсуждались редко. Кроме того, переносимость полученных результатов была описана не достаточно в опубликованных экономических исследованиях. Переносимость исследований между странами может быть упрощена, если неточности вводных параметров и переносимости данных, всесторонне учтены, а также если четкость информации в публикациях будет улучшена.

Требования лиц, принимающих решения, к методологии и доступность данных являются двумя важными факторами, влияющими на переносимость экономических оценок. В части 2 этой диссертации, основывая дизайн исследований на

предпочтениях лиц, принимающих решения, и доступных данных, нами были использованы принципы переносимости (главы 4-8).

Как можно увидеть из главы 4, затраты на лечение хронической лимфоцитарной лейкемии (ХЛЛ) в Украине могут существенно меняться даже между сравнимыми специализированными учреждениями. Хотя основные затраты лечения связаны с лекарственной терапией, многие украинские пациенты покрывают их самостоятельно, что может стать экономическим бременем для некоторых из них. Лекарственная терапия является основным драйвером затрат на лечение ХЛЛ не только в Украине. Тем не менее, в отличие от таких экономически развитых стран как США и Германия, медицинская помощь не является существенным компонентом в структуре общих затрат на ХЛЛ.

В главе 5 была рассчитана чистая пожизненная налоговая прибыль населения Украины, Республик Беларусь и Казахстана, полученная с помощью экстракорпорального оплодотворения (ЭКО). Как описано в данной главе, финансирование ЭКО может быть прибыльным государственным финансовым вложением даже в странах с невысоким доходом, такими как Украина, Республики Беларусь и Казахстан. Некоторые параметры, такие как «количество живорожденных на цикл как результат ЭКО», являются индивидуальными для страны и могут иметь определяющий эффект на результаты экономического анализа, а значит низкую обобщаемость. Дополнительно было отмечено, что возвращение инвестиций в ЭКО может не быть прямо пропорциональным экономическим показателям страны, таким как ВВП на душу населения, так как зависит от многих параметров, например, социальных гарантий и налоговых ставок.

В главе 6 представлено сравнительное исследование затрат, связанных с лечением пегиллированными интерферонами (Пег-α-2b и Пег-α-2a) гепатита С 1-го генотипа. Клинический результат (стойкий вирусологический ответ и соблюдение пациентами режима терапии) были обобщены из другой популяции, используя данные многоцентрового рандомизированного контролируемого исследования в США, в то время как затраты были специфическими для украинского населения в основном сценарии. Для пациента со средним весом тела небольшая экономия затрат как с перспективы пациента, так и сектора здравоохранения, наблюдалась при лечении Пег-α-2b. При корректировке для отображения среднего веса тела пациента в Украине, разница в затратах на пациента и в затратах на один стойкий вирусологический ответ в пользу Пег-α-2b стала несколько больше, но без существенного влияния на выводы исследования.

В главе 7 представлено качественное исследование предпочтений и восприятия заболевания украинскими пациентами с диабетом 2 го типа, которые испытывают гипогликемию. По результатам трех фокус-групп с общим количеством 26 пациентов был сделан вывод, что адаптация украинских пациентов к возможным эпизодам

гипогликемии является близкой к результатам, полученным в других странах. В отличие от других экономически развитых стран, украинские пациенты старше 40 лет получают информацию о контроле заболевания в большинстве случаев от эндокринологов и редко используют специализированные Интернет ресурсы. Эти данные должны быть приняты во внимание в исследованиях по контролю заболевания, а также в соответствующих экономических исследованиях.

Глава 8 представляет результаты анализа затраты - эффективность применения ритуксимаба в лечении ХЛЛ у украинских пациентов ранее не получавших терапию и пациентов без ответа на терапию / с рецидивами. Относительная добавочная стоимость/эффективность (ICER) ритуксимаба в схемме с флудурабином и циклофосфамидом (ФЦР против ФЦ) составляет $8,704 за один год жизни стандартизированный с качеством для пациентов ранее не получавших терапию и $11,056 для пациентов без ответа на терапию / с рецидивами. Переносимость клинических результатов была оценена путем изменения данных клинического исследования (общей выживаемости и выживаемости без прогресса) на более низкую ожидаемую продолжительность жизни среди населения Украины. В этом случае ICER для пациентов, ранее не получавших терапию, составил более $13,000, что в три раза выше за ВВП на душу населения в Украине. Анализ чувствительности показал значительное влияние стоимости ритуксимаба и посредственное влияние разницы в показателях утилитарности на значение ICER. Характеристики населения и стоимость отдельных вводных параметров существенно влияют на результаты исследования.

Основные результаты, представленные в главе 9, предполагают, что использование экономических оценок в принятии решений в здравоохранении сталкивается с барьером низкой пропускной способности оценки медицинских технологий (ОМТ). Не смотря на то что переносимость экономических оценок, проводимых в структурах здравоохранения ЦВЕ и странах бывшего Советского Союза, ограничена и редко применяется, принципы переносимости данных известны в исследованных странах. Хотя вариации некоторых параметров, таких как стоимость, использование ресурсов и базовый риск создают не переносимость результатов, клиническая эффективность и предпочтения пациентов (например, следование режиму терапии) могут обобщаться в некоторых случаях.

Следующие рекомендации обозначены в разделе 9 относительно улучшения использования экономических оценок в принятии решений в здравоохранении: учесть барьеры, связанные с процессом принятия решений и ограниченной пропускной способностью ОМТ, разработать руководства по экономическим оценкам и ОМТ, стандартизировать подход к переносимости экономического анализа, определить приоритеты ОМТ, предоставить стимулы улучшения качества исследований.

Как показано в данной диссертации, географическая переносимость экономических оценок является необходимостью для ЦВЕ и стран бывшего Советского Союза.

Стислий зміст

Не дивлячись на широке обговорення потреби у переносимості економічних оцінок, до даного часу ця тема вивчалась лише обмежено у Центральному та Східно-Європейському регіоні (ЦСЄ) та країнах колишнього Радянського Союзу.

В частині 1 даної дисертації показане використання економічних досліджень у прийнятті рішень у охороні здоров'я, а також існуюча потреба у їх переносимості. В главі 2, в якій представлено результати якісної оцінки експертної думки, стає зрозуміло, що економічні дослідження не завжди використовуються формально у ЦСЄ з метою прийняття рішень у охороні здоров'я. Як було продемонстровано, вплив економічних досліджень на рішення залежить від перспективи дослідження, якості дослідження, методології, що було використана, джерел витрат та методів оцінки, суб'єктивного сприйняття надійності дослідження та характеристик популяції.

Хоча результати економічного аналізу не вважаються переносимими з однієї території на іншу, іноземні дослідження можуть використовуватись у прийнятті локальних рішень. Враховуючи що, згідно експертної думки, схожість систем охорони здоров'я та клінічних практик є важливими параметрами, так само як і вартість, відносний економічний розвиток країни, перспектива дослідження та епідеміологія захворювання, переносимість досліджень між країнами одного географічного регіону може бути простіше, ніж між різними регіонами.

Глава 3 описує характеристики опублікованих економічних оцінок з ЦСЄ та країн колишнього Радянського Союзу, знайдених у базах даних методом систематичного пошуку літератури. Використовуючи контрольний перелік Драммонда, було зроблено висновок, що чітке визначення перспективи, правильність вибору витрат, чіткість виміру витрат у відповідних одиницях, достовірність оцінки витрат та ефективності, та аналіз сумнівності отриманих результатів, - є найменш часто та відкрито представленими параметрами.

Хоча в дослідженнях показники клінічного ефекту та утилітарності часто узагальнюються з інших популяцій, обмеження стосовно використання іноземних даних зазначаються рідко. До того ж переносимість отриманих результатів не достатньо розглядалась у опублікованих економічних дослідженнях. Переносимість економічних досліджень між країнами може бути спрощена, якщо варіабельність вхідних параметрів моделі є врахованою, а також якщо чіткість представлення методології та результатів досліджень у публікаціях буде покращено.

Вимоги осіб, що приймають рішення, до методології та доступність даних є двома важливими факторами, що впливають на переносимість економічних оцінок. В частині 2 цієї дисертації, враховуючи при виборі дизайну досліджень думку осіб, що приймають рішення, та доступність даних, нами було використано принципи переносимості (глави 4-8).

Як можна побачити із глави 4, витрати на лікування хронічної лімфоцитарної лейкемії (ХЛЛ) в Україні можуть суттєво відрізнятись навіть серед спеціалізованих закладів. В той час як основні витрати на лікування є пов'язаними із терапією лікарськими засобами, багато українських пацієнтів покривають ці витрати самостійно, що стає економічним тягарем для деяких із них. Терапія лікарськими препаратами є основною складовою витрат на лікування ХЛЛ не лише в Україні. Тим не менш, на відміну від таких економічно розвинутих країн як США та Німеччина, медична допомога не є суттєвим компонентом в структурі загальних витрат на ХЛЛ.

У главі 5 було розраховано пожиттєвий податковий прибуток населення України, республік Білорусь та Казахстан, що було отримано за допомогою екстракорпорального оплодотворення (ЕКО). Як було описано у даній главі, фінансування ЕКО може бути прибутковим вкладом навіть у країнах із не високим доходом та системами охорони здоров'я, що фінансуються державою, такими як Україна, республіки Білорусь та Казахстан. Деякі параметри, такі як «кількість живонароджених на цикл ЕКО» є специфічними для країни та можуть мати визначальний вплив на результати економічного аналізу, а отже і низьку здатність до узагальнення. Додатково було відмічено, що повернення інвестицій у ЕКО може не бути прямопропорційним економічним показникам країни, таким як ВВП на душу населення, так як залежить від багатьох параметрів, таких як соціальні гарантії та податкові ставки.

Глава 6 представляє порівняльне дослідження витрат, що пов'язані із лікуванням пегильованими інтерферонами (Пег- α-2b та Пег-α-2a) гепатиту С 1-го генотипу. У базовому сценарії клінічний результат (стійка вірусологічна відповідь та слідування пацінтами режиму терапії) було узагальнено з інших популяцій використовуючи данні багатоцентрового рандомізованого контрольованого клінічного дослідження із США, в той час як витрати були специфічними для українського населення. Для пацієнта із середньою вагою тіла, не значна економія витрат з перспективи як пацієнта, так і сектору охорони здоров'я, спостерігалась при лікуванні Пег- α-2b. При корекції даних для відображення середньої ваги тіла пацієнта в Україні, різниця у витратах на пацієнта та витратах на одну стійку вірусологічну відповідь на користь Пег- α-2b стала дещо більшою, проте без суттєвого впливу на результати дослідження.

У главі 7 представлено якісне дослідження контрою та сприйняття захворювання українськими пацієнтами із цукровим діабетом 2го типу, що страждають на гіпоглікемію. По результатам трьох фокус-груп із загальною кількістю у 26 пацієнтів було зроблено висновок, що адаптація українських пацієнтів до можливих випадків гіпоглікемії є близькою до результатів, одержаних в інших дослідженнях. На відміну від інших економічно розвинутих країн, українські пацієнти старше 40 років отримують інформацію щодо контролю захворювання переважно від

ендокринологів, та рідко використовують спеціалізовані Інтернет ресурси. Ці дані мають бути прийняті до уваги у дослідженнях із контролю захворювання, а також у відповідних економічних дослідженнях.

Глава 8 представляє результати аналізу витарти-ефективність використання ритуксимабу у лікуванні ХЛЛ у українських пацієнтів, що раніше не отримували терапію, або що не мають відповіді на попередню терапію / з рецидивами. Відносна додаткова вартість /ефективність ритуксимабу (ICER) у схемі з флударабіном та циклофосфамідом (ФЦР проти ФЦ) складає $8,704 за один рік життя стандартизованого із якістю для пацієнтів, що раніше не отримували терапію, та $11,056 для пацієнтів що не мають відповіді на попередню терапію / з рецидивами. Переносимість клінічних результатів було оцінено шляхом зміни даних клінічного дослідження (загальне виживання та виживання без прогресування захворювання) із врахуванням більш низької очикуваної продовжуваності життя серед населення України.

В цьому випадку ICER для пацієнтів, що раніше не отримували терапію, склала $13,000, що у три рази більше за існуючий ВВП на душу населення в Україні. Аналіз чутливості результатів показав суттєвий вплив вартості ритуксимабу та опосередкований вплив різниці у значеннях утилітарності на значення ICER. Характеристики населення та вартість суттєво впливають на результати дослідження.

Основні результати, представлені у главі 9, показують, що використання економічних оцінок у прийнятті рішень у охороні здоров'я зтикається з бар'єрами, що пов'язані з низькою пропускною здатністю оцінки медичних технологій (ОМТ). Не дивлячись на те, що переносимість економічних оцінок, що проводяться у структурах ЦСЄ та країнах колишнього Радянського Союзу, обмежена та рідко застосовується, принципи переносимості даних є відомими в досліджуваних країнах. Хоча варіації деяких параметрів, таких як вартість одиниці товару/ послуги, використанні ресурси, та базовий ризик, створюють неможливість узагальнення результатів, клінічна ефективність та уподобання пацієнтів (наприклад, слідування режиму терапії) можуть узагальнюватись у деяких випадках.

Наступні рекомендації було обозначено у главі 9 стосовно покращення використання економічних оцінок у прийнятті рішень у охороні здоров'я: прийняти до уваги бар'єри, що є пов'язаними з процесом прийняття рішення та обмеженною пропускною здатністю ОМТ, розробити керівництва з економічних оцінок та ОМТ, стандартизувати підхід до переносимості економічного аналізу, визначити пріорітети ОМТ, надати стимули покращення якості дослідження.

Як було показано у даній дисертації, географічна переносимість економінчих оцінок є необхідністю для ЦСЄ та країн колишнього Радянського Союзу.

Acknowledgement

To my dearest research supervisors from Erasmus University of Rotterdam, Prof. Hans Severens and Dr. Saskia Knies, this thesis would not be possible to prepare without your professional guidance and kind support in each step of the execution. You are simply great – it is difficult to say more than this. You both had a tremendous impact on my life from a very broad professional perspective: to define life and career horizons, to apply a constant quality benchmark, to think step ahead, and (importantly) to improve agenda-planning skills.

Dear Hans, I believe that meeting you at the University Clinic in 2007 and being the only Master student whose thesis you supervised that year was the best luck of all time. All the past eight years, it has been a great pleasure and a huge professional benefit to work with you on all the numerous projects, organized trainings and seminars and, of course, research. Your great ability to see instantly to the core of an issue, incredible working productivity and inspirational enthusiasm always thrilled me. From the time we first met you remain as my favorite teacher and a vivid example of the type of person and achievements I would be proud one day to reach.

Dear Saskia, it goes without saying that your joining the work on this dissertation made a dramatic improvement in its development and quality of execution. It was your supervision that allowed keeping the work on schedule. I am very grateful to you for raising multiple questions and shaping the incomplete writing pieces, for reviewing my manuscript drafts, for helping with Dutch translations and for supporting the numerous research ideas with unending energy. Thinking back on our previous years of collaboration, I need to say that it was a great combination of work and fun, and I will look forward to working with you more in the future.

I am very much grateful to the person who first involved me into post-graduate research, my second supervisor, prof. Olha Zalis'ka. As Head of Department of Management and Economy of Pharmacy and Medicine Technology, Danylo Halytsky Lviv National Medical University (Ukraine), Olha was the first who saw in me a potential researcher and proposed to write a PhD thesis under her supervision. I am very grateful for the faith you had in me, for your leadership throughout the whole period of thesis preparation and for support in research initiation.

I would also like to express gratitude to all the coauthors of my publications, with special appreciation to Prof. Zoltan Kalo (Department of Health Policy and Health Economics, Faculty of Social Sciences, Eötvös Loránd University), Isaac Corro Ramos and Maiwenn All from Erasmus University of Rotterdam. And, of course, I express a sincere gratitude to all of the employees of the Section of Health Economics and Health Technology Assessment of iBMG, who challenged and supported this dissertation, with

special appreciation to Liza Moreira. Dear Liza, being at a distance and without your “hands” and kind help I would never be able to reach the thesis defense.

I want to give thanks to all the members of the evaluation committee for the time they devoted: Prof. W.B.F. Brouwer, Prof. C.A. Uyl - de Groot, Prof. L. Gulasci PhD (Corvinus University, Hungary). I very much appreciate the time you gave, and the inputs and comments you provided regarding my thesis, which certainly will serve to improve both the current and future research projects.

I would also like to thank to my peer-colleagues, friends and family members, who not only verbally supported me through these years, but also provided technical inputs with resources, data sources, validations, experts’ contacts and more. To Carter Mandrik, Yulia Radich, Tetiana Melnichuk, Marina Zhukova, Olena Doroshenko, Tetiana Zlotnik, thank you much for your wonderful help! And of course, many thanks to my parents who always believed in me and who supported all the choices I have made in my life.

Curriculum vitae

Olena Mandrik was born in Kyiv, Ukraine on July 10, 1983. In 2005 she received a Bachelor and Specialist Degree in Biotechnology and Pharmaceutical Production (National University of Food technologies). In 2008 Olena simultaneously graduated from two Universities, National University “Kyiv-Mohyla Academy” (Management of Organizations), and Maastricht University (Public Health) with Master degrees.

Before joining a Master program in the Netherlands, Olena was involved in research in Ukraine at the Institute of Microbiology (2003-2005), Institute of Experimental Pathology, Oncology and Radiobiology (February 2005- July 2005), Medved’s Institute of Ecohygiene and Toxicology (August 2005-September 2006), and as clinical research associate at SPRI Clinical Trials (November 06 – August 2007).

In 2008 Olena became a PhD candidate at Lviv Medical University (chair Pharmacology and Pharmacoeconomics) in Ukraine. The next year Olena joined a distant PhD program at Erasmus University, the Netherlands. In 2010-2011 Olena was involved as a part-time lecturer at the School of Public Health, National University Kiev-Mohyla Academy, Ukraine. In the academic year 2012 Olena was a guest lecturer at Bogomolets National Medical University. In 2013 Olena received a PhD degree at Lviv Medical University, Ukraine, after defending her thesis titled “Economic studies on hematologic malignancies in Ukraine”.

Simultaneously with working on academia research Olena was employed in pharmaceutical companies as a Pharmacoeconomic Manager in Janssen-Cilag, Ukraine (Oct 2008-Feb 2010) and MSD Ukraine (Apr 2011-Aug 2013), Market Access Manager in MSD Ukraine (Aug 2013-Apr 2014), and Head of Market Access in Sanofi Ukraine (July 2014 – April 2015).

Publications

Mandrik O, Knies S, Kalo Z, Severens JL. Exploring expert opinions regarding use and transferability of economic evaluations in Central and Eastern Europe and former Soviet countries. Submitted, under review.

Mandrik O, Knies S, Kalo Z, Severens JL. Transferability issues addressed in economic evaluations. A systematic review of studies from Central and Eastern European and former Soviet countries. Submitted, under review.

Mandrik O, Knies S, Severens JL. Economic value of in-vitro fertilization in Ukraine, Belarus, and Kazakhstan. Accepted to ClinicoEconomics and Outcomes Research.

Mandrik O, Carro Ramos I, Knies S, Al M., Severens JL. Cost-Effectiveness of Adding Rituximab to Fludarabine and Cyclophosphamide for Treatment of Chronic Lymphocytic Leukemia in Ukraine. Accepted to Cancer Management and Research**.**

Mandrik O, Knies S, Golubovska O, Duda O, Dudar L, Fedorchenko S, Zalis'ka O, Severens JL. Cost comparison of treating chronic hepatitis C genotype one with pegylated interferons in Ukraine. Open Med. 2015; 10: 25-33.

Mandrik O, Severens JL, Doroshenko O, Pan'kiv V, Kravchun N, Vlasenko M, Hulchiy M, Baljuk M, Komisarenko Y, Martsynik E, Sokolova L, Zalis'ka O, Mankovsky B. Impact of hypoglycemia on daily life of type 2 diabetes patients in Ukraine. Multidisciplinary Health Care. 2013; 6: 249-257.

Mandrik O, Carro Ramos I, Zalis'ka O, Gaysenko A, Severens JL. Cost for Treatment of Chronic Lymphocytic Leukemia in Specialized Institutions of Ukraine. Value in Health Regional Issues. 2013; 3: 205-209.

Mandrik O, Zalis'ka O, Severens JL. Cost of treating lymphoproliferative disorders in Ukraine: a pilot evaluation / // Medical technologies. Assessment and choice. Moscow. Special Issue. 2012; 73-76.

Oral Presentations

Mandrik O. Pharmacoeconomic Evaluation of Medical Technologies applied to the inpatients in Ukraine. 14-th ISPOR European Congress. 5-8 November 2011. Madrid, Spain.

Poster presentations

Mandrik O, Knies S, Kalo Z, Severens JL. Transferability of economic evaluations to Central and Eastern European and former Soviet countries. ISPOR 17th Annual European Congress. Amsterdam, the Netherlands. November, 2014. Value in Health. 2014; 17(7): 443-444.

Mandrik O, Knies S, Kalo Z, Severens JL. Use and transferability of economic evaluations in the countries of the Central and Eastern Europe. 15th Biennial European Meeting of the Society for Medical Decision Making. Antwerp, Belgium. June 8-10, 2014.

Mandrik O, Knies S, Zalis'ka O, Severens JL. Economic benefits of subsidizing in-vitro fertilization from the government perspective in Belarus, Kazakhstan, and Ukraine. Strategic Medical Decision Making Annual Meeting. the USA. October 22, 2013.

Mandrik O, Zalis'ka O, Severens JL. Cost-effectiveness analysis of rituximab use in treatment of chronic lymphocytic leukemia in Ukraine. ISPOR 17th Annual International meeting. 2-6 June 2012. Washington, USA. Value in Health. 2012; 15(4): 221.

Mandrik O, Zalis'ka O, Severens JL. How much price component is accounted for in state drugs purchase decisions in ukranian oncology? Abstracts 15-th ISPOR European Congress. 3-7 November Berlin, Germany. Value in Health. 2012; 15(7): 428.

Mandrik O, Severens JL, Zalis'ka O, Doroshenko O. Analysis of factors influencing drugs prescription decision making in Ukraine. ISPOR 17th Annual International meeting. 2-6 June 2012, Washington. Value in Health. 2012; 15(4):28.

Mandrik O, Zalis'ka O. The relationship of age and sex with cost of treatment for chronic lymphocytic leukemia in Ukraine. Value in Health. 2011; 14 (3): 163.

Mandrik O, Zalis'ka O, Severens JL. Cost of multiple myeloma in Ukraine. 14-th ISPOR European Congress. 5-8 November 2011. Madrid, Spain.Value in Health. 2011; 14 (7): 444.

Mandrik O, Zalis'ka O, Severens JL. The relationship of age and sex with cost of treatment for chronic lymphocytic leukemia in Ukraine. ISPOR 16th Annual International Meeting. June 2-6, Baltimore, USA. Value in Health. 2011; 14(3): 163.

Mandrik O, Zalis'ka O. Pharmacoeconomics of innovative medicines for treatment in Ukraine. 13-th ISPOR European Congress.– 6-9 November Prague, Czech Republic. Value of Health. 2010; 13(7): 400.

Pariy V, Stepanenko A, Mandrik O, Zalis'ka O. Priority setting for health technology assessment in Ukraine. ISPOR 17th Annual International meeting, 2-6 June 2012.Washington, USA. 2012. Value in Health. 2012; 15(4): 32.

Tolubaiev V, Zalis'ka O, Mandrik O, Majnych J. Analysis of formulary lists for veterans and Chernobyl victims in Ukraine. ISPOR 17th Annual International Meeting. June 2-6, Washington, DC, USA. Value in Health. 2012; 15(4);18.

Supplementary Training

Short course "Evidence synthesis for the decision making". Strategic Medical Decision Making Annual Meeting. the USA. October, 2013.

"Bench, Bedside and Beyond: Medical Decision Making and Public Policy", October, 2013

Short course "An introduction to compartmental Models". 14th Biennial European Meeting of the Society for Medical Decision Making, Oslo, Norway, June 10 -12, 2012

Short course "Economic modeling in infectious diseases" on 14th Biennial European Meeting of the Society for Medical Decision Making, Oslo, Norway, June 10 -12, 2012

Short course "Pharmacoeconomic Modeling – Applications" ISPOR 14th Annual European Congress, November, 2011, Spain

Short course "Introduction to modeling" ISPOR 14th Annual European Congress, November, 2011, Spain.

Short course "Discrete Event Simulation for Economic Analyses" ISPOR Annual Meeting, May, 2011, Baltimore, MD, USA

Summer School "Health Care & Social System". The European Forum Alpbach and the Vienna School of Clinical Research, 14-21 August, 2008. Alpbach, Austria.

Pharma school training. June, 2007. Kyiv, Ukraine.

Training on projects' quality and patients' rights protection. May, 2007. Prague, Check Republic.

Workshop "Project management skills". March, 2007. Battle, the Great Britain.

Other research projects

Economic burden and quality of life of patients with diabetes in Ukraine (protocol writing, primary and secondary data analysis, statistical analysis, report writing).

Treatment satisfaction and quality of life of patients with hip and knee osteoarthritis (protocol and statistical plan development).

Economic burden of the diseases related to HPV infection (protocol writing, data analysis, report preparation).

Cost-effectiveness analyses of antibiotic therapy use in treatment of 1) nosocomial pneumonia, 2) urinary tract infection , 3) intra-abdominal infections.

Cost-effectiveness analysis in use of antipsychotic drugs for treatment of schizophrenia.

Analysis of the political and health care environment in Ukraine; developing ways for improvement in access to treatment.

Impact of health technology assessment on pharmaceuticals appraisal process (qualitative study conducted in the health care settings of the Netherlands and Ukraine).

Scholarships and Scientific Event Organization

Open Society Institute, Academic Fellowship Program scholarship (2010-2011).

International congress “Health technology assessment in antibacterial therapy”. Kyiv, Ukraine. September, 2011 (financed by a pharmaceutical company).

Educational seminar in the Ministry of Health on the topic “Health technology assessment in health care decision making” (financed by MATRA grant, the Netherlands). September, 2009.

MTEC-scholarship for getting Master Degree at Maastricht University, the Netherlands (2007- 2008).

Personal

Languages: Ukrainian (native), Russian (native), English (fluent), German (beginner)