University of Groningen

Reimbursement of Targeted Cancer Therapies Within 3 Different European Health Care Systems

Mihajlović, Jovan; Dolk, Christiaan; Tolley, Keith; Simoens, Steven; Postma, Maarten J.

Published in:
Clinical Therapeutics

DOI:
[10.1016/j.clinthera.2014.12.005](https://doi.org/10.1016/j.clinthera.2014.12.005)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2015

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Mihajlović, J., Dolk, C., Tolley, K., Simoens, S., & Postma, M. J. (2015). Reimbursement of Targeted Cancer Therapies Within 3 Different European Health Care Systems. *Clinical Therapeutics*, 37(2), 474-480. <https://doi.org/10.1016/j.clinthera.2014.12.005>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Reimbursement of Targeted Cancer Therapies Within 3 Different European Health Care Systems

Jovan Mihajlović, MSc^{1,2}; Christiaan Dolk, MSc¹; Keith Tolley, PhD³; Steven Simoons, PhD⁴; and Maarten J. Postma, PhD¹

¹Unit of PharmacoEpidemiology & PharmacoEconomics (PE2), Department of Pharmacy, University of Groningen, Groningen, the Netherlands; ²Mihajlović Health Analytics, Novi Sad, Serbia; ³Tolley Health Economics Ltd, Buxton, United Kingdom; and ⁴Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium

ABSTRACT

Purpose: Targeted cancer therapies (TCTs) are drugs that specifically act on molecular targets within the cancer cell, causing its regression and/or destruction. Although TCTs offer clinically important gains in survival in one of the most challenging therapeutic areas, these gains are followed by considerable increases in health care expenditures. The aim of this study was to identify differences in the recommendations for TCTs in 3 European health care systems (Serbian, Scottish, and Dutch) and to examine the role of pharmacoeconomic (PE) assessments in such recommendations.

Methods: A list of currently approved TCTs cited from the European Medicines Agency was cross-referenced with drug reimbursement reports issued by the National Health Insurance Fund for Serbia, the Scottish Medicines Consortium for Scotland, and the National Health Institute for the Netherlands. The following key variables were gathered from the reports: drug indication, registration status, reimbursement status, and outcome of the PE evaluation.

Findings: There were 41 TCTs approved by the European Medicines Agency for 70 cancer indications. Of the total number of TCT indications, 20 were reimbursed in Serbia, and 25 are still without a decision from the national agency. The remaining TCT indications (n = 25) are not registered in Serbia. None of the submissions or the PE analyses were publicly available. The Scottish Medicines Consortium positively assessed 26 TCT indications and rejected 30. All appraisals were published, and the majority contained full PE assessments. Finally, the Dutch agency accepted 60 TCT indications and disapproved the use of 1. The majority of reimbursed drugs were

exempted from PE evaluation in accordance with 2 recent policies regarding expensive hospital drugs.

Implications: In the 3 examined health care systems, the reimbursement status of the TCTs differed significantly. Level of PE application within the TCT evaluation procedures seemed to largely affect the final reimbursement decisions. Although, there are special policies in the Netherlands that enabled fast access for 98% of the TCTs that applied for reimbursement, a clear definition of cost-effectiveness threshold and strict requirements for full cost utility assessments in Scotland led to acceptance of only 46% of the TCT submissions. More precise PE guidelines must still be designed for TCT reimbursement in Serbia. Guidelines must account for specific epidemic and economic conditions of the country and could build on the experiences of Scotland and the Netherlands. (*Clin Ther.* 2015;37:474–480) © 2015 Elsevier HS Journals, Inc. All rights reserved.

Key words: health care policy, Europe, pharmacoeconomics, reimbursement, Serbia, targeted cancer therapy.

INTRODUCTION

Targeted cancer therapies (TCTs) are drugs that interfere with specific predefined molecular targets involved in cancer cell growth and survival. These targets, however, must be clearly identified, either

17th Annual European Congress of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR); 8–12th November 2014, Amsterdam, the Netherlands.

Accepted for publication December 9, 2014.

<http://dx.doi.org/10.1016/j.clinthera.2014.12.005>

0149-2918/\$ - see front matter

© 2015 Elsevier HS Journals, Inc. All rights reserved.

quantitatively or qualitatively, and a correlation exists between their presence and the clinical effectiveness of the TCT.¹ Selectiveness for processes within the cancer cells is what distinguishes TCTs from traditional chemotherapies. This selectiveness provides TCTs with the potential for improved effectiveness, with fewer severe adverse events, than conventional chemotherapy regimens.

Dozens of TCTs have been licensed worldwide since the first market authorization of rituximab that occurred in the late 1990s.² The total number of TCTs in 2010 was 22; only 4 years later, 44 registered targeted therapies have been issued for oncologic indications by the European Medicines Agency (EMA) and/or the US Food and Drug Administration.^{3–5} By revenue, these drugs comprise the biggest and fastest growing part of oncologic therapeutics, which is the most dominant therapeutic group on the global pharmaceutical market.^{3,6}

Although TCTs produce clinically important gains in survival and/or quality of life within the indications that had not seen any improvements previously, they also come at considerable cost.⁷ Different policies in drug pricing and reimbursement among European countries that were applied to address this issue resulted in significant imbalances in access to the TCTs. In particular, cost utility analysis (CUA) seemed to be an influential element in the assessments of new oncologic drugs.⁸ To illustrate the variety of approaches and its effect on TCT reimbursement, the present study examined 3 distinctive health care systems in Europe (Serbian, Scottish, and Dutch).

The main principles for drug reimbursement in Serbia are defined within the rule book issued by the government and incorporated into practice by the National Health Insurance Fund (in Serbian, Republički fond za zdravstveno osiguranje [RFZO]).⁹ In accordance with this regulation, assessments are performed by the RFZO committees, and all drugs that attain a positive decision can be placed on the 5 reimbursement lists, which mostly differ in dispensability, level of patients' copayment, and potential prescription restrictions. Together with the common requests for clinical efficacy, the CUA and budget impact analysis (BIA) are obligatory parts of a submission process. However, other than basic definitions of the CUA and BIA, more details of what they should include or specification of a cost-effectiveness threshold were not provided. Furthermore, the RFZO

does not consider TCTs, or any other therapeutic group, separately from the general policy. Decisions are made publicly and are available from the reimbursement lists,¹⁰ but they do not contain submission files or respective evaluations.

In Scotland, drug assessments are performed by the Scottish Medicines Consortium (SMC), a committee that advises local boards of the National Health Service on the use and reimbursement of newly licensed drugs.¹¹ A standard SMC assessment examines a drug's clinical efficacy and cost-effectiveness and can engage the manufacturer, clinical experts, and patient groups within the process. Consequently, detailed reports are produced and published at the SMC site. A drug is generally considered cost-effective if its incremental cost-effectiveness ratio (ICER) is below £20,000 per quality-adjusted life-year (QALY) and not cost-effective if the ratio is over the threshold of £30,000/QALY.¹² Drugs with the ICER between 2 cited values can be regarded as cost-effective if they offer significant benefit compared with the standard treatment. Although there are no exemptions from the regular procedure for a particular therapeutic group or patient population, the SMC recognizes certain decision modifiers that can enable a positive recommendation despite relatively high and otherwise unacceptable cost-effectiveness ratios.¹³ Decision modifiers potentially ascribed to TCTs are: substantial improvement in the survival or quality of life, absence of any therapeutic alternative, and additional benefit for specific subgroups of patients.

Finally, in the Netherlands, the National Health Institute (in Dutch, Zorginstituut Nederland [ZiNL]; formerly known as College voor Zorgverzekeringen [CvZ]) conducts assessments of drugs and suggests their reimbursement status to the Ministry of Health, which generally follows the advice. In deciding on a manufacturer's submission, CvZ/ZiNL evaluates a drug's clinical value, cost-effectiveness, and budget impact.¹⁴ Although a cost-effectiveness threshold is not predetermined, a pharmacoeconomic (PE) assessment can influence the final reimbursement decision. In addition to the general reimbursement procedure, 2 recent policies with several updated versions may be applied to the TCT reimbursement. As of 2002, the Policy Rule for Expensive Hospital and Orphan Drugs (PREHO) supports supplemental financing of hospitals

for use of expensive and orphan drugs.¹⁵ The regulation that replaced it in January 2012 (and which is currently active) allows fast access to an even broader group of medicines.¹⁶ More precisely, the updated fast-access PREHO (UFAP) is intended for conditional reimbursement of clinically effective hospital drugs with a yearly cost per patient of more than €10,000 and a total budget impact of more than €2.5 million. In 2015, the limit of €10,000 within the current policy will be removed, thus allowing even cheaper hospital drugs to be considered through the UFAP.¹⁷ Drugs that the PREHO and UFAP policies refer to are guaranteed fast access after proving the additional clinical value, while cost effectiveness evaluation could be initially averted. However, this kind of reimbursement is conditional with obligatory reassessment that is to start within four years after initial approval and include the real-world economic and clinical data for full pharmacoeconomic assessment.

The aim of the present work was to identify differences in the reimbursement status of TCTs in 3 European health care systems (ie, Serbian, Scottish, Dutch). We focused on the role of PE assessment within the reimbursement procedures. The study also offers illustrative examples of distinctive health care policies and their relation to the TCT market access.

MATERIALS AND METHODS

To introduce the main characteristics of the respective health care systems, we first present a number of structural parameters for Serbia, Scotland, and the Netherlands. These include: population (total number, annual growth, and age structure), cancer epidemiology (absolute annual number of new cancer cases and deaths, ratio of cancer deaths and new cancer cases), and basic health care funding parameters (total gross domestic product [GDP], GDP per capita, total health care expenditure, health care expenditure per capita, and predominant source of health care funding). The official statistical data of the Serbian, Scottish, and Dutch governments were used.^{18–23} All parameters were gathered for the latest available years, with the exception of population figures, which were all set to the same year (2013).

Second, a list of currently approved TCTs and therapeutic indications was formed from the available databases of the EMA.²⁴ New oncologic drugs that do not explicitly comply with the concept of TCTs, such

as new hormonal oncologic therapies (eg, abiraterone acetate) or new chemotherapies (eg, cabazitaxel, pemetrexed), were not included in the list. The same TCT could have been registered for >1 indication. The list of TCTs and approved therapeutic indications was then cross-referenced with the drug reimbursement lists and reports issued by the RFZO for Serbia, the SMC for Scotland, and the CvZ/ZiNL for the Netherlands as of August 15, 2014.^{9,10,14} The following variables were gathered from cited sources: reimbursement status, type of PE assessment, and outcomes of such an assessment if available in terms of ICERs or cost per patient. For the Netherlands, due to specificity of granted reimbursement statuses that are frequently conditional and require future reassessments, we included additional sources from CvZ/ZiN²⁵ to differentiate between reimbursed TCTs that need reassessment and TCTs that do not need reassessment.

RESULTS

Table 1 presents population, cancer epidemiology, and health care funding parameters in Serbia, Scotland, and the Netherlands. The Serbian population is the only one with a negative annual growth (−4.8%) and the relatively highest proportion of population aged > 65 years (17.3%). Furthermore, the ratio of annual cancer deaths and cancer cases is the highest in Serbia (0.58), followed by the Netherlands (0.43) and Scotland (0.38). In terms of the economy, the Scottish and Dutch economies are producing comparable GDP per capita (€32,443 and €38,315, respectively), whereas the GDP per capita in Serbia is much lower (€4464). Correspondingly, investments in health care are €3095, €2387, and €282 per capita for the Netherlands, Scotland, and Serbia, respectively.

An overview of the different reimbursement statuses and approaches in PE assessment of all EMA-registered TCTs in Serbia, Scotland, and the Netherlands is reported in **Supplemental Table 1** in the online version at <http://dx.doi.org/10.1016/j.clinthera.2014.12.005>. As of August 15, 2014, there were 41 TCTs registered, and these drugs referred to 70 TCT indications with marketing authorization by the EMA. Of the total number of TCT indications issued by EMA for Serbia, 20 (29%) are reimbursed (total of 11 TCT drugs). As many as 25 TCT indications (36%) are still not registered by regulatory authorities in Serbia and therefore could not have had an

Table I. Population, cancer epidemiology, and health care funding parameters in Serbia, Scotland, and the Netherlands.

	Serbia	Scotland	The Netherlands	Source
Population				
Total population	7,164,132	5,327,700	16,778,025	18, 20, 22*
Annual population growth	-4.8%	2.7%	2.8%	18, 20, 22
Proportion of population aged 0–14 y	14.40%	16.10%	17.00%	18, 20, 22
Proportion of population aged 15–64 y	68.30%	67.20%	67.40%	18, 20, 22
Proportion of population aged > 65 y	17.30%	16.70%	15.60%	18, 20, 22
Cancer epidemiology				
Annual no. of registered cancer cases	36,308	41,322	101,210	19, 20, 23
Annual no. of cancer deaths	21,069	15,864	43,666	19, 20, 23
Ratio cancer deaths/new cancer cases	0.58	0.38	0.43	
Health care funding				
GDP (in million)	€31,980	€172,849	€642,851	18, 21, 22
GDP per capita	€4464	€32,443	€38,315	
Total health care expenditure (in million)	€2,018	€12,720	€51,926	18, 21, 22
Health care expenditure per capita	€282	€2387	€3095	
Predominant source of health care funding	Obligatory insurance	Regular taxation	Obligatory insurance	18, 21, 22

GDP = gross domestic product.

*Total population is set for the year 2013 in all countries; all other data are the latest possible.

application for reimbursement. For the same number of indications ($n = 25$ [36%]), there are no available information on the reimbursement status. Although registered, these drugs are either not yet submitted, are currently under consideration, or were rejected in the past. None of the reviewed indications and TCTs had publicly available PE assessment reports.

The SMC gave positive recommendations for 26 TCT indications (37%) and rejected 30 (43%). Most of the negative decisions were related to the submitted applications of manufacturers ($n = 18$ [26%]), whereas the SMC also gave short negative appraisals in the absence of manufacturers' submissions ($n = 12$ [17%]). The manufacturers did not submit reimbursement applications for the rest of the TCT indications ($n = 14$ [20%]); none of these were probably considered by the SMC. Regarding the PE assessment, it should be noted that 42 TCT indications were followed with a full CUA (or cost-minimization analysis if appropriate) and BIA reports of the total 44

submissions. Focusing on the outcomes of PE assessments, ICERs varied from £1790/QALY to £376,475/QALY as estimated by the manufacturers. Among the approved TCT indications, ICERs varied from £1790/QALY to £56,343/QALY, and only 5 of 26 positive recommendations were given to the TCTs with an ICER higher than £30,000/QALY. Conversely, TCT indications that gained negative recommendations corresponded with ICERs from £22,445/QALY to £376,475/QALY and only in 2 of 18 of these cases were the manufacturers' estimates of ICER below £30,000/QALY. Finally, decision modifiers were applied in the assessments of 7 TCT indications, and they contributed to the positive decision in 6 submissions.

Within the Dutch health care system, TCT indications were awarded with an initial positive reimbursement by CvZ/ZiNL in 60 cases (86%). Notably, only 1 TCT indication has been explicitly rejected by CvZ/ZiNL (1%); the remaining 9 (13%) were not reimbursed, and it is unknown if (or when) the

manufacturers submitted reimbursement records for these TCT indications. Among the 60 initial approvals, 22 TCT indications (31%) have been accepted conditionally, and reassessment is needed with real-world data and full PE assessment. However, up to the cutoff date of the present study, only 1 drug (trastuzumab) appeared with the reassessment report, and the outcome of its reassessment was positive.²⁶ Of the 22 conditionally approved drugs, 15 have been accepted within earlier PREHOs and 7 within new UFAPs. All other accepted TCT indications ($n = 38$ [54%]) do not currently require reassessment. They have varying reasons for exemption from the reassessment and thus from the PE evaluation; 16 were previously accepted within a regular extramural reimbursement system (reference pricing system) and therefore do not require reassessment. Orphan drug designation was allowed for 10 of these TCT indications, and an earlier PREHO did not require reassessment for orphan drugs. Budget impact below €2.5 million was the reason for 9 TCT indications to be exempted from reassessment, as long as this annual limit is not crossed. Lastly, only 3 TCTs are still initially assessed, and requirement for reassessment is not yet known. As for PE assessments, although accepted TCT indications ($n = 60$) could have been exempted from full PE assessment in compliance with the applied policies, 15 of them estimated cost per some unit of time; 10 submitted full CUAs with ICERs as the outcome. Reported ICERs differed significantly, ranging from €6412/QALY to €164,262/QALY.

DISCUSSION

The present study analyzed differences in the reimbursement status of TCTs in the diverse health care systems of Serbia, Scotland, and the Netherlands. We examined the impact of the respective national approaches and special policies applied in PE assessment of TCTs on the final reimbursement decisions. Serbia, Scotland, and the Netherlands are European health care systems with varying characteristics of population size and composition, epidemiology, and economic parameters. As expected, significant inequalities were noted in the various TCT reimbursement statuses.

Reimbursement in Serbia and Scotland was granted to 20 and 26 TCT indications, respectively; in the Netherlands, the number of reimbursed TCT indications was >2-fold higher (ie, 60). Because of a lack of

data, we could not identify the reasons or the values ascribed to PE assessments in the Serbian reimbursement system. On the contrary, it is clear that differences observed between Scotland and the Netherlands could be at least partially explained by the different application of the PE evaluation. Requirements of the SMC for full CUA for any therapy regardless of its novelty or the seriousness of the disease being treated led to this being an inevitable part of 95% of submissions for the TCT indications. The existence of a clearly defined cost-effectiveness threshold, with drugs considered cost ineffective if their ICER was higher than £30,000/QALY, seemed to contribute to the negative SMC recommendation in 89% (16 of 18) of the manufacturer submissions. Among accepted submissions, 80% had an ICER below that very same threshold. As for the Netherlands (a country with an economic background comparable to Scotland), the previous PREHO and current UFAP allow adoption of expensive drugs with no initial examination of their PE value. Notably, only 1 submission of the 61 TCT indications was explicitly rejected for reimbursement in the Netherlands.

Our comparison between Scotland and the Netherlands is in line with a previous article on the subject of orphan drugs.²⁷ Major conclusions on that subject have not changed and have been strengthened by the present analysis. We included Serbia in the comparative approach, with the potential to draw on findings in Scotland and the Netherlands, to assist in the Serbian development of the reimbursement process.

We believe that PE assessments should consistently be one of the determining factors in decisions on TCT funding in all countries considered and beyond. It is important, however, to understand that designing regular CUAs presents a challenging task, in particular if patient groups are small or limited information from clinical trials is available. This is often the case with TCTs, and extrapolations are required that bring uncertainties in CUAs. In addition, PE assessments should not be the only decisive factor; other factors should be considered in an integrative approach. Currently, Scotland and the Netherlands seem to reflect the extremes of the options, with PE assessments strictly applied in Scotland (and therefore potentially decisive) and relatively loosely applied in the Netherlands. It should be noted that the postponing of PE assessment in the Netherlands is deliberately

chosen with the purpose of obtaining fast access for clinically effective new drugs and gaining sufficient real-world evidence with which future PE assessments will be conducted. Serbia could draw on these variations and develop an approach in between, taken the best of both countries. Obviously, with its different demographic characteristics, epidemiology, and economics, Serbia must adopt a policy designed to its specific circumstances. In general, policies for reimbursement of new expensive drugs in terminal phases of diseases that come with increments in survival, such as TCTs, are constantly changing and their outcomes are being reassessed. It remains debatable whether the PE values of these drugs should be evaluated with the same approach as in general.^{28–30}

The present review had several limitations. First, and most importantly, we were limited with data accessibility in our choice of countries for comparison. Although data on reimbursement decisions and PE assessment are broadly available in various countries, linguistic barriers prevented us choosing from all European countries. We limited our comparison to the countries of our origin, for which we could guarantee the highest level of data access. Second, the purpose of our comparison (to illustrate diversities of existing European systems from the perspective of TCT reimbursement) was demanding. Without an exact knowledge of all European health care systems, we cannot claim that all important differences were grasped. However, we believe that Serbia, Scotland, and the Netherlands are typical examples of: (1) a health care system from southeastern Europe with PE assessments not fully implemented and health care expenditures per capita far below the European average; (2) a British health care system, renowned for its thorough PE assessments, with approximately average expenditures in health care in Europe; and (3) 1 of the most frequently changing systems, with health care expenditures far above the European average and a specific role of PE evaluation. Hopefully, these specific features enabled us to sufficiently illustrate differences in findings.

CONCLUSIONS

The reimbursement status of TCTs differed considerably in the 3 examined health care systems. Requirements and interpretation of cost-effectiveness assessments and the level of its application affect final reimbursement decisions. Within the systems under comparison, the Netherlands applies special approaches for expensive and orphan drugs, which postponed the

PE analyses and resulted in the highest proportion of reimbursed TCTs. In Scotland, exemptions from standard PE analyses are not acceptable, which led to considerably lower numbers of reimbursed TCTs, comparable to that found in Serbia. Serbian health care authorities currently offer the least information on the process of drug reimbursement assessments, and PE analyses are still to be fully implemented within this system. Serbia could draw on the experiences reported here for the other countries.

ACKNOWLEDGMENTS

Mr. Mihajlović and Mr. Dolk participated in the acquisition and interpretation of data and drafted the initial version of the manuscript; Dr. Tolley and Dr. Simoons participated in the interpretation of data; and Dr. Postma participated in the analysis and interpretation of data and drafted the initial version of the manuscript. All authors approved the final version of the manuscript as submitted.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

SUPPLEMENTAL MATERIALS

Supplementary material cited in this article is available online at <http://dx.doi.org/10.1016/j.clinthera.2014.12.005>.

REFERENCES

1. Ross JS, Schenkein DP, Pietrusko R, et al. Targeted therapies for cancer 2004. *Am J Clin Pathol*. 2004;122:598–609.
2. Grillo-López J, White C, Dallaire BK, et al. Rituximab: the first monoclonal antibody approved for the treatment of lymphoma. *Curr Pharm Biotechnol*. 2000;1:1–9.
3. Aggarwal S. Targeted cancer therapies. *Nat Rev Drug Discov*. 2010;9:427–428.
4. Database of European Medicines Agency. <http://www.ema.europa.eu/ema/>. Accessed August 15, 2014.
5. Database of Food and Drug Administration. <http://www.fda.gov/>. Accessed August 15, 2014.
6. IMS International. Cancer drug innovation surges as cost growth moderates; Report summary. <http://www.imshealth.com/>. Accessed August 15, 2014.
7. Aggarwal A, Sullivan R. Affordability of cancer care in the United Kingdom – Is it time to introduce user charges? *J Cancer Policy*. 2014;2:31–39.
8. Wilking N, Jönsson B. A pan-European comparison regarding patient access to cancer drugs. *Karolinska*

Institutet in collaboration with Stockholm School of Economics Stockholm, Sweden. 2005.

9. National Health Insurance Fund (RFZO). The rule book on criteria for drugs' reimbursement. [in Serbian]. http://www.rfzo.rs/download/pravilnici/lekovi/Pravilnik_kriterijumima_24042014.pdf. Accessed August 15, 2014.
10. National Health Insurance Fund (RFZO). Reimbursement lists [in Serbian]. <http://www.rfzo.rs/index.php/lekovi-actual56/lista-lekova-05022014>. Accessed August 15, 2014.
11. Scottish Medicines Consortium (SMC). Home page. <https://www.scottishmedicines.org.uk/Home>. Accessed August 15, 2014.
12. Scottish Medicines Consortium (SMC). Policy statements, a guide to quality adjusted life years. http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/A_Guide_to_Quality_Adjusted_Life_Years. Accessed August 15, 2014.
13. Scottish Medicines Consortium (SMC). Policy statements, modifiers used in appraising new medicines. https://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/SMC_Modifiers_used_in_Appraising_New_Medicines. Accessed August 15, 2014.
14. National Health Institute of the Netherlands (ZiNL). Home page [In Dutch]. <http://www.zorginstituutnederland.nl/>. Accessed August 15, 2014.
15. Danish Ministry of Health and Prevention. Analysis of hospital pharmaceuticals: Country report - the Netherlands. http://www.sum.dk/Aktuelt/Publikationer/~media/Filer%20-%20Publikationer_i_pdf/2009/Landerapport%20Nederlandene%20sygehusmedicin.ashx. Accessed August 15, 2014.
16. National Health Institute of the Netherlands (ZiNL). Voorwaardelijke toelating/financiering van zorg. [In Dutch]. <http://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/rapporten-en-standpunten/2012/1204-voorwaardelijke-toelating-financiering-van-zorg/Voorwaardelijke+toelating-financiering+van+zorg.pdf>. Accessed August 15, 2014.
17. The Dutch Healthcare Council. Bekostiging van add-on geneesmiddelen eenvoudiger per 2015 [In Dutch]. <http://www.nza.nl/zorgonderwerpen/zorgonderwerpen/ziekenhuiszorg/nieuws/Bekostiging-van-add-on-geneesmiddelen-eenvoudiger-per-2015/>. Accessed November 25, 2014.
18. Statistical Office of the Republic of Serbia. <http://webzrs.stat.gov.rs/WebSite/>. Accessed August 15, 2014.
19. Institute of Public Health of Serbia "Dr Milan Jovanović Batut". <http://www.batut.org.rs/index.php?lang=2>. Accessed August 15, 2014.
20. Scottish Government, National Statistics. <http://www.scotland.gov.uk/Topics/Statistics/About>. Accessed August 15, 2014.
21. Information Services Division of the NHS National Services Scotland. <http://www.isdscotland.org/index.asp>. Accessed August 15, 2014.
22. Statistics Netherlands. <http://statline.cbs.nl/statweb/?LA=en>. Accessed August 15, 2014.
23. The Netherlands Cancer Registry. <http://www.dutchcancerfigures.nl/>. Accessed August 15, 2014.
24. The European Medicines Agency. Medicines database. http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/medicines/medicines_landing_page.jsp&mid=. Accessed August 15, 2014.
25. National Health Institute of the Netherlands (ZiNL). VOORWAARDELIIK GEFINANCIERDE SPECIALISTISCHE GENEESMIDDELEN. 9th of October, 2014. [In Dutch]: <https://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/rubrieken/pakket/consultaties/1410-voorwaardelijk-gefinancierde-specialistische-geneesmiddelen/Voorwaardelijk+gefinancierde+specialistische+geneesmiddelen.pdf>. Accessed November 25, 2014.
26. <http://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/pakket/adviescommissie-pakket/adviescommissie-pakket/adviescommissie-pakket/zinl%3Aparagraaf%5B3%5D/zinl%3Adocument%5B%25D/1408-acp-stukken-ter-kennisneming>. Accessed August 15, 2014.
27. Vegter S, Rozenbaum MH, Postema R, et al. Review of regulatory recommendations for orphan drug submissions in the Netherlands and Scotland: Focus on the underlying pharmacoeconomic evaluations. *Clin Ther.* 2010;32:1651-1661.
28. Raftery J. NICE and the challenge of cancer drugs. *BMJ.* 2009;338:b67.
29. Rawlins MD, Chalkidou K. The opportunity cost of cancer care: a statement from NICE. *Lancet Oncol.* 2011;12:931-932. [http://dx.doi.org/10.1016/S1470-2045\(11\)70218-2](http://dx.doi.org/10.1016/S1470-2045(11)70218-2).
30. Kantarjian HM, Fojo T, Mathisen M. Cancer drugs in the United States: Justum pretium—the just price. *J Clin Oncol.* 2013;31:3600-3604.

Address correspondence to: Jovan Mihajlović, MSc, Antonius Deusin-
glaan 1, 9713, AV Groningen, the Netherlands. E-mail: jovan@miha.rs