



ELSEVIER

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

journal homepage: [www.elsevier.com/locate/jval](http://www.elsevier.com/locate/jval)

## SYSTEMATIC REVIEWS

## How Should We Deal with Patient Heterogeneity in Economic Evaluation: A Systematic Review of National Pharmacoeconomic Guidelines

Bram L.T. Ramaekers, MSc<sup>1,2,\*</sup>, Manuela A. Joore, PhD<sup>2</sup>, Janneke P.C. Grutters, PhD<sup>3</sup>

<sup>1</sup>Department of Health Services Research, Maastricht University, Maastricht, The Netherlands; <sup>2</sup>Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Center, Maastricht, The Netherlands; <sup>3</sup>Department for Health Evidence & Operating Rooms, University Medical Center, St. Radboud, Nijmegen, The Netherlands

## ABSTRACT

**Objective:** To review and analyze recommendations from national pharmacoeconomic guidelines with regard to acknowledging patient heterogeneity in economic evaluations. **Methods:** National pharmacoeconomic guidelines were obtained through the ISPOR Web site. Guidance was extracted by using a developed data extraction sheet. Extracted data were divided into subcategories on the basis of consensus meetings. **Results:** Of the 26 included guidelines, 20 (77%) advised to identify patient heterogeneity. Most guidelines (77%) provided general methodological advice to acknowledge patient heterogeneity, including justifications for distinguishing subgroups (65%), prespecification of subgroups (42%), or methodology to acknowledge patient heterogeneity (77%). Stratified analysis of cost-effectiveness was most commonly advised (20 guidelines; 77%); however, guidance on the specific application of methods was scarce (9 guidelines; 34%) and generally limited if provided. Guidance to present patient heterogeneity was provided by 15 guidelines (58%), most prominently to describe the definition (31%) and justification (31%) of subgroups. **Conclusions:** The majority of national

pharmacoeconomic guidelines provide guidance on acknowledging patient heterogeneity in economic evaluations. However, because guidance is mostly not specific, its usefulness is limited. This may reflect that the importance of acknowledging patient heterogeneity is usually recognized while there is a lack of consensus on specific methods to acknowledge patient heterogeneity. We advise the further development of national pharmacoeconomic guidelines to provide specific guidance on the identification of patient heterogeneity, methods to acknowledge it, and presenting the results. We present a checklist that can assist in formulating these recommendations. This could facilitate the systematic and transparent handling of patient heterogeneity in economic evaluations worldwide.

**Keywords:** economic evaluation, national pharmacoeconomic guideline, patient heterogeneity, systematic review.

Copyright © 2013, International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Published by Elsevier Inc.

### Introduction

Considering the rapidly increasing health care costs and the finite amount of available resources, the criteria to grant reimbursement to new treatments have become more restricted. These reimbursement decisions are often made for groups of patients. A more individualized approach for the allocation of available resources, that is, providing treatment reimbursement for subgroups of patients, however, has the potential to increase population health gains [1–4]. Acknowledging patient heterogeneity in reimbursement decisions may lead to more efficient health care if these reimbursement decisions are based on cost-effectiveness [5]. As economic evaluations are frequently used to estimate cost-effectiveness and support reimbursement decision making [6], it is essential that patient heterogeneity be incorporated in economic evaluations. Although there is consensus on

its importance [7], patient heterogeneity is frequently neglected in economic evaluations [8].

Patient heterogeneity might be neglected because subgroup policy sometimes is controversial due to ethical concerns. This may lead to equity constraints, where the use of certain characteristics is considered unacceptable to determine which subgroups have access to a technology. The acknowledgment of patient heterogeneity in economic evaluations also seems to be hampered by a lack of clarity on when and how this should be done [2,9]. In this respect, there is an important role for national pharmacoeconomic guidelines. National pharmacoeconomic guidelines provide essential guidance how economic evaluations, with the purpose to support reimbursements decision making, should be performed within a jurisdiction. The objective of this study was therefore to review and analyze recommendations from national pharmacoeconomic guidelines with

This article was discussed in part during the lowlands Health Economists' Study Group (May 24–25, 2012, Almen), at the Health Technology Assessment International conference (June 25–27, 2012, Bilbao), and at the European Conference on Health Economics (July 18–21, 2012, Zürich).

\* Address correspondence to: Bram L.T. Ramaekers, P.O. Box 5800, 6202 AZ Maastricht, The Netherlands.

E-mail: [bram.ramaekers@mumc.nl](mailto:bram.ramaekers@mumc.nl).

1098-3015/\$36.00 – see front matter Copyright © 2013, International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

Published by Elsevier Inc.

<http://dx.doi.org/10.1016/j.jval.2013.02.013>

regard to acknowledging patient heterogeneity in economic evaluations.

## Methods

### Definition of Patient Heterogeneity

Patient heterogeneity was defined as the part of the natural variation between patients (variability) that can be attributed to characteristics of those patients [6,9,10]. This was differentiated from treatment variability (differences in the nature of the treatment), differences between geographical regions that may impact cost-effectiveness, and statistical heterogeneity. These concepts relate more to the generalizability of cost-effectiveness results [9,11] and variation in outcomes between studies (e.g., included in a meta-analysis) and are beyond the scope of this review.

Characteristics that potentially explain patient heterogeneity include demographics (e.g., age, sex, and income), preferences (e.g., attitude, beliefs, and risk tolerance), and/or clinical characteristics (e.g., disease severity, disease history, and genetic profile) [9]. These sources of patient heterogeneity may have an impact on different input parameters used in an economic evaluation: baseline risks, relative treatment effects, health state utility, and resource utilization [9]. Differences in unit costs are more likely a result of differences between geographical regions and are thus not considered in this review [9,12].

### Search Strategy and Data Extraction

Consistent with previous reviews of national pharmacoeconomic guidelines [12,13], national pharmacoeconomic guidelines were obtained through the link provided on the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Web site ([www.ispor.org](http://www.ispor.org)) [14] and retrieved from the Web site of the guideline agencies. This was done to ensure that the most recent versions were retrieved. The ISPOR Web site was considered a reliable and valid source because the overview of national pharmacoeconomic guidelines is based on contacts with experts from approximately 60 countries from around the world [12]. Guidelines were included if they were available in English. To systematically extract relevant guidance, we used a data extraction sheet (see Appendix 1 in Supplemental Materials found at <http://dx.doi.org/10.1016/j.jval.2013.02.013>) containing the following categories:

1. Acknowledgment of patient heterogeneity: whether guidelines advised to identify patient heterogeneity and whether a distinction is made between different inputs of an economic evaluation: 1) baseline risk, 2) relative treatment effect, 3) health state utility, and 4) resource utilization.
2. Methodology to acknowledge patient heterogeneity: whether guidelines advised methodology to acknowledge patient heterogeneity. This contains guidance whether to justify for acknowledging patient heterogeneity (including equity constraints), guidance whether to a priori prespecify potential sources of patient heterogeneity, general methods, and the specific application of methods to acknowledge patient heterogeneity.
3. Presentation of patient heterogeneity: whether guidelines advised what should be presented when acknowledging patient heterogeneity.

Data were extracted and categorized (into the above-mentioned categories) by one author (B.R.). Extracted data from all guidelines were divided into subcategories. If the classification of guidance was ambiguous, it was independently judged by the

other authors (J.G. and M.J.). Possible discrepancies were discussed to reach consensus.

## Results

In total 33 guidelines were retrieved. Seven guidelines were excluded because they were not available in English [15–21]. This accumulated to 26 included guidelines, published between 1997 and 2012 [22–47].

### Acknowledgment of Patient Heterogeneity

Most guidelines (20; 77%) advise to identify patient heterogeneity in general [22–41]. Thirteen guidelines (50%) explicitly consider it relevant to identify the impact of patient heterogeneity on effects in general (irrespective of whether it has an impact on the baseline risk and/or treatment effect) [22–25,27,29,30,32,34–36,38,40]. Seven guidelines (27%) specify this into differences in baseline risk and treatment effect and consider them both as relevant [22–25,30,32,36]. In addition, four guidelines consider it relevant to reflect the impact of patient heterogeneity on health state utility [24,27,30,34]. Nine guidelines (35%) consider differences in resource utilization as relevant input to acknowledge patient heterogeneity [23–25,29,30,34,36,38,40]. None of the guidelines advise not to identify patient heterogeneity in any of these four key inputs of an economic evaluation.

### Methodology to Acknowledge Patient Heterogeneity in Economic Evaluations

Methodological guidance on acknowledging patient heterogeneity is provided by 20 guidelines (77%) [22–41].

#### Arguments to justify acknowledging patient heterogeneity in economic evaluations

Arguments to justify acknowledging patient heterogeneity are required by 17 guidelines (65%) [22–27,29,30,32–37,39–41]. Only the England & Wales guideline [25] lists equity constraints (Table 1). Instead of neglecting subgroups based on a particular equity point of view, the Canadian guideline [24] proposes to calculate the opportunity costs of equity concerns by using the framework proposed by Coyle et al. [1]. These opportunity costs can be interpreted as the costs of neglecting subgroups based on grounds of equity. Hence, this framework aims to inform the trade-off between equity and efficiency [1]. In addition, the German guideline states that only those subgroups should be addressed for which an additional benefit or lesser harm was established [28].

#### Specification of potential sources of patient heterogeneity

Eight guidelines (31%) [22,24,25,29,30,32,35,37] advise to prespecify potential sources of patient heterogeneity (Table 1). The French guideline considers post hoc multivariate analysis acceptable to explore patient heterogeneity [27]. Post hoc analysis is allowed under certain conditions by eight guidelines (31%): only for differences in costs [23], with (strong) justification [24,36] and/or if interpreted as explorative [23], with caution [22,30,32], or hypothesis generating [24,35].

#### How to acknowledge patient heterogeneity

Most guidelines (20; 77%) provide general advice how to acknowledge patient heterogeneity [22–41]. Stratified analysis is the most commonly advised method [22–41]. The French, German, and Scottish guidelines generally advise the use of decision analytic modeling [27,28,36]. Furthermore, sensitivity and/or scenario analyses are advised by the guidelines from Australia, Canada, and England & Wales [22,24,25]. Although most guidelines

Download English Version:

<https://daneshyari.com/en/article/987531>

Download Persian Version:

<https://daneshyari.com/article/987531>

[Daneshyari.com](https://daneshyari.com)