PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	What drives the prescribing of growth hormone preparations in England? Prices versus patient preferences
AUTHORS	Chapman, Stephen; Fitzpatrick, Raymond; Aladul, Mohammed

VERSION 1 - REVIEW

REVIEWER	David Ridley Duke University USA
REVIEW RETURNED	10-Sep-2016

GENERAL COMMENTS	Summary The authors examined the UK market for human growth hormone products using price and quantity data from 2011 through 2015. For the primary care setting they used data from the NHS, and for the secondary setting they used data from the DEFINE database. They found that "the price of growth hormone products was not the key factor influencing prescribing... The main driver ... was the ease of use." Comments 1. The authors conclude that price is not an important factor based on correlations, but these are problematic. Quantity depends on quality (ease of use) and price, but price also depends on quality. This can be written as quantity = f(quality(price), price). To accurately estimate the effect of price independent of quality, the authors need something exogenous that drives price but not quality. Possibilities include a change in manufacturing cost or a change in reimbursement or copayment set by the government. Essentially, this would offer an instrumental variable. The authors might not choose to perform such an analysis but they should at least acknowledge the problem that price is unlikely to be set independently of ease of use, and thus it is difficult to measure the effect of price on quantity. 2. A figure might be helpful for illustrating the main result: that quantity depends on quality (ease of use) not price. For example, price could be on the horizontal axis, quantity on the vertical, and quality as the shape of the point -- easy to use represented as a circle and inconvenient as a square. 3. More broadly, the authors should make a stronger case for why the results are interesting, surprising, and/or important. 4. The authors should write more about why the differences between

	primary and secondary care are interesting. 5. The authors should consider citing the economics literature on biosimilars. I believe that the earliest study of biosimilars in economics was Grabowski et al. (2007). More recently, Scott Morton et al. (2016) have a useful paper. Grabowski et al., "Entry and Competition in Generic Biologics", Managerial and Decision Economics, 2007. Scott Morton et al., "The Impact of the Entry of Biosimilars: Evidence from Europe", Harvard Business School, http://www.hbs.edu/faculty/Pages/item.aspx?num=51309

REVIEWER	Simit Doshi, MD, MPH and Jay Wish, MD Indiana University, USA
REVIEW RETURNED	09-Oct-2016

GENERAL COMMENTS	The authors present a longitudinal observational study or prescribing trends for growth hormone preparations in England over 5 years with the aim to determine drivers of prescribing practices. Following are some of concerns: Title: The study looks only at growth hormone and may not necessarily be applicable to all biosimilars. Consider revising title to reflect this eg. “What drives the prescribing of growth hormone in England?” OR Consider adding data to suggest that prescribing patterns and use of GH may be a good surrogate for biosimilars in general. Page 4: line 10. It is unclear when the price drop occurred. Was it a gradual decrease to 25% or was it reduced at one point of time. How much time was provided following the price change to observe for change in prescribing practice? Page 4: line 49 Comparison is provided for 2nd quarter of 2011 and last quarter of 2015. The regression analysis uses these 2 time points. Figure 1. does not suggest any major change in utilization of growth hormone in primary care. Eg the fourth quarter of 2013 and second quarter of 2015 visually show same or higher utilization of biosimilars so the conclusion that a statistically significant reduction occurred between 2011 and 2015 may not be completely valid. Page 4: line 50. Paper does not fully explain the reason for the pattern of use at the outset. Agents that are highest priced dominate the market share. Is this because of easier availability, marketing practices, side effect profile or other reasons? These data suggest that product price is not driving utilization to begin with and a longitudinal analysis seems unnecessary for such a conclusion. This may also reflect that some confounding variable may have been missed when looking at prescribing patterns since the most widely used product is not a ready-to-use product either Page 4: line 51. It is also not clear why ready-to-use agents were not more popular in 2011. They are equal or lower priced than the alternatives requiring reconstitution.

REVIEWER	Jorge Mestre-Ferrandiz Office of Health Economics, UK The Office of Health Economics receives a programme research grant from the Association of the British POharmaceutical Industry. No

	separate funding was received to review this paper. I am an employee of the OHE. I, as part of the Office of Health Economics, received a research grant from Amgen to run a workshop on biosimilars and health technology assessment, and have previously received consulting funding from both innovator and biosimilar companies
REVIEW RETURNED	19-Oct-2016

GENERAL COMMENTS	The paper is very interesting and provides evidence on the evolution of growth hormone preparations in England between April 2011 and December 2015. The key result is that prices seems not to be the key driver influencing prescribing, but rather that patient preferences are. General comments: Title: the title is too broad, as looking at one therapy area, where indeed there is a biosimilar since 2006. I would change to something like: “What drives the prescribing of growth hormone preparations in England? Prices versus patient preferences” The authors should provide their a-priori hypothesis i.e. whether they think price will, or will not, be a key driver in influencing prescribing of growth hormone preparation. There are currently many more biosimilars available in other therapy areas (EPOs, G-CSFs and more recently infliximab). The literature is very clear to suggest that it is difficult to generalise across therapy areas with biosimilars, and indeed, across countries. I suggest that the authors need to make this point, and as they rightly point out, their analysis is focused on one therapy area, which is very different to the other therapy areas mentioned above. I would suggest authors highlight briefly the differences between growth hormone preparations and other areas with biosimilars (possibly in the Introduction section) – see references below. The authors should make it very clear the “level” of prices used i.e. are they “list” prices or “net” prices (which will take into account any discounts/rebates). I suspect they will be “list” prices. Specific comments Abstract. I would add when biosimilar entered. Possibly refer about the two “types” of preparations: ready to use and requiring constitution Introduction Page 2 Line 50: “Biological medicines are expensive”: possibly change to “tend to be” and make clear we are talking about treatment cost per patient? Page 3, line 32: “It is not clear whether this is universally applicable”: what is “this”? State (if information is available) the share of the total medicines bill accounted for by human growth hormones. Authors should point out that biosimilars are not the same as generics. This has been acknowledged by EMA, for instance. Other references: Mestre-Ferrandiz J, Towse A, Berdud M. Biosimilars: how can payers get long-term savings? Pharmacoeconomics. 2016;34(6):609-16. Aitken M. Delivering on the potential of biosimilar medicines. The role of functioning competitive markets. 2016. IMS Institute for

	Healthcare Informatics Updated IMS report published in June 2016: http://ec.europa.eu/growth/tools-databases/newsroom/cf/itemdetail.cfm?item_type=251&lang=en&item_id=8854 Policy requirements for a sustainable biosimilar market – Simon-Kucher (2016): http://www.medicinesforeurope.com/2016/09/19/policy-requirements-for-a-sustainable-biosimilar-market-simon-kucher-2016/ [although growth hormones not included] Methods Page 3, line 48: Explain what is meant by "2U" DEFINE database: what is its market coverage? Clarify "level" of prices: list vs net. See point above Would be helpful to have a description about the two "types" of preparations, ready to use vs requiring constitution, and summarise in a table which presentation falls under which category. Statistical analysis: might be worth offering a rationale why the linear regression analysis is the correct approach Results Table 1: I assume prices are in £s? Would be very helpful to: • Identify when the price changes actually happened, and in what order i.e. were they simultaneous or sequential? • Understand, if possible, why prices are different between primary and secondary care • Understand whether treatment with growth hormone preparations starts in primary or secondary care, and whether there has been a change in treatment pathways that can also explain the changes in overall utilisation between primary and secondary care Discussion Page 5, lines 43 – 45:"At the same time ,…, still respecting the patient's choice". I understand that the objective of the paper is NOT to look at what influences prescribing in England/UK more generally, but some useful references looking at this issue include: • Karlsberg Schaffer, S., Sussex, J. and Feng, Y. 2015. Incentives to follow Best Practice in Health Care. OHE Briefing (https://www.ohe.org/publications/incentives-follow-best-practice-health-care) • Karlsberg Schaffer, S., Sussex, J., Hughes, D. and Devlin, N., 2016. Opportunity costs and local health service spending decisions: a qualitative study from Wales. BMC Health Services Research, 16(1). • Karlsberg Schaffer, S., Sussex, J., Devlin, N. and Walker, A., 2015. Local health care expenditure plans and their opportunity costs. Health Policy, 119(9), pp.1237-1244. Page 5, line 47: unfinished sentence Page 6, line 5: "for dose preparation by patients": would be helpful to understand what patients need to do for the reconstitution process Page 6, Lines 19-20: might be worth pointing out that Omnitrope Cart is actually the cheapest option Page 6, line 46: "This study is the first to show": too strong

	language. Before authors have used “this indicates…” (line 37) Page 6, lines 49-50: which biosimilar are you referring to? Limitations: I would add level of prices if prices are at “list” rather than “net” Conclusion Page 7, line 8: “This study has demonstrated”: again, possibly too strong language (see comment above)

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name
David Ridley

Institution and Country
Duke University
USA

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below
SummaryThe authors examined the UK market for human growth hormone products using price and quantity data from 2011 through 2015. For the primary care setting they used data from the NHS, and for the secondary setting they used data from the DEFINE database. They found that "the price of growth hormone products was not the key factor influencing prescribing... The main driver ... was the ease of use."

Comments

1. The authors conclude that price is not an important factor based on correlations, but these are problematic. Quantity depends on quality (ease of use) and price, but price also depends on quality. This can be written as quantity = f(quality(price), price). To accurately estimate the effect of price independent of quality, the authors need something exogenous that drives price but not quality. Possibilities include a change in manufacturing cost or a change in reimbursement or copayment set by the government. Essentially, this would offer an instrumental variable. The authors might not choose to perform such an analysis but they should at least acknowledge the problem that price is unlikely to be set independently of ease of use, and thus it is difficult to measure the effect of price on quantity.

Response to reviewer. We have amended Table 1 to show the exact time points when prices have changed. In the NHS the basic price is agreed with the government and is not directly related to quality. Prices in secondary care are negotiated through regional contracting as we describe later in response to comment 4.

2. A figure might be helpful for illustrating the main result: that quantity depends on quality (ease of use) not price. For example, price could be on the horizontal axis, quantity on the vertical, and quality as the shape of the point -- easy to use represented as a circle and inconvenient as a square.

Response to reviewer. We have included two further figures (figures 4, and 5) showing the change in

utilisation versus cost in both primary and secondary care as suggested by reviewer 1. We have also included additional narrative relating to figures 4 and 5.

3. More broadly, the authors should make a stronger case for why the results are interesting, surprising, and/or important.

Response to reviewer
We have amended paragraph 6 in the discussion to make a stronger case for why the results are interesting, and the implications for policy makers and budget managers.

4. The authors should write more about why the differences between primary and secondary care are interesting.

Response to reviewer. We have amended paragraph 2 in the methods and paragraph 7 of the discussion to explain the different pricing systems in primary and secondary care which make the results interesting.

5. The authors should consider citing the economics literature on biosimilars. I believe that the earliest study of biosimilars in economics was Grabowski et al. (2007). More recently, Scott Morton et al. (2016) have a useful paper.
Grabowski et al., "Entry and Competition in Generic Biologics", Managerial and Decision Economics, 2007.
Scott Morton et al., "The Impact of the Entry of Biosimilars: Evidence from Europe", Harvard Business School, http://www.hbs.edu/faculty/Pages/item.aspx?num=51309

Response to reviewer. We have cited Grabowski et al. paper.

Reviewer: 2

Reviewer Name
Simit Doshi, MD, MPH and Jay Wish, MD

Institution and Country
Indiana University, USA

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below
The authors present a longitudinal observational study or prescribing trends for growth hormone preparations in England over 5 years with the aim to determine drivers of prescribing practices.
Following are some of concerns:
Title: The study looks only at growth hormone and may not necessarily be applicable to all biosimilars. Consider revising title to reflect this eg. “What drives the prescribing of growth hormone in England?”
OR
Consider adding data to suggest that prescribing patterns and use of GH may be a good surrogate for biosimilars in general.

Response to reviewer. This a good point and we have amended the title accordingly. We do not believe we should extrapolate of use of growth hormone to biosimilars in general since it is clear from our results that the formulation and patient/prescriber preferences influence use. This may not be the

case for other biosimilars where there are no such formulation differences.

Page 4: line 10. It is unclear when the price drop occurred. Was it a gradual decrease to 25% or was it reduced at one point of time. How much time was provided following the price change to observe for change in prescribing practice?

Response to reviewer. We have amended table 1 to include price by year which shows clearly the year any price change occurred.

Page 4: line 49 Comparison is provided for 2nd quarter of 2011 and last quarter of 2015. The regression analysis uses these 2 time points. Figure 1. does not suggest any major change in utilization of growth hormone in primary care. Eg the fourth quarter of 2013 and second quarter of 2015 visually show same or higher utilization of biosimilars so the conclusion that a statistically significant reduction occurred between 2011 and 2015 may not be completely valid.

Response to reviewer. Whilst there is no major change figure 1 suggests an overall gradual decline in use despite the two spikes in Q4 2013 and Q2 2015. The linear regression analysis supports this.

Page 4: line 50. Paper does not fully explain the reason for the pattern of use at the outset. Agents that are highest priced dominate the market share. Is this because of easier availability, marketing practices, side effect profile or other reasons? These data suggest that product price is not driving utilization to begin with and a longitudinal analysis seems unnecessary for such a conclusion. This may also reflect that some confounding variable may have been missed when looking at prescribing patterns since the most widely used product is not a ready-to-use product either
Page 4: line 51. It is also not clear why ready-to-use agents were not more popular in 2011. They are equal or lower priced than the alternatives requiring reconstitution.

Response to reviewer. We have expanded paragraph 9 of the discussion relating to the pattern of use in figure 3 highlighting the date of launch of the ready to use agents which answers this point.
Reviewer: 3

Reviewer Name
Jorge Mestre-Ferrandiz

Institution and Country
Office of Health Economics, UK

Please state any competing interests or state ‘None declared’:
The Office of Health Economics receives a programme research grant
from the Association of the British Pharmaceutical Industry. No separate funding was received to review this paper. I am an employee of the OHE.
I, as part of the Office of Health Economics,
received a research grant from Amgen to run a workshop on biosimilars and health technology assessment, and have previously received consulting funding from both innovator and biosimilar companies

Please leave your comments for the authors below
The paper is very interesting and provides evidence on the evolution of growth hormone preparations in England between April 2011 and December 2015. The key result is that prices seems not to be the key driver influencing prescribing, but rather that patient preferences are.

General comments:

Title: the title is too broad, as looking at one therapy area, where indeed there is a biosimilar since 2006. I would change to something like: “What drives the prescribing of growth hormone preparations in England? Prices versus patient preferences”

Response to reviewer. Good point we have amended the title accordingly.

The authors should provide their a-priori hypothesis i.e. whether they think price will, or will not, be a key driver in influencing prescribing of growth hormone preparation.

Response to reviewer. We have included an ‘A priori hypothesis’ in the final paragraph of the introduction.

There are currently many more biosimilars available in other therapy areas (EPOs, G-CSFs and more recently infliximab). The literature is very clear to suggest that it is difficult to generalise across therapy areas with biosimilars, and indeed, across countries. I suggest that the authors need to make this point, and as they rightly point out, their analysis is focused on one therapy area, which is very different to the other therapy areas mentioned above. I would suggest authors highlight briefly the differences between growth hormone preparations and other areas with biosimilars (possibly in the Introduction section) – see references below.

Response to reviewer. We have amended the title to reflect that this study is about growth hormone and its biosimilar. We do not believe we should extrapolate of use of growth hormone to biosimilars in general since it is clear from our results that the formulation and patient/prescriber preferences influence use. This may not be the case for other biosimilars where there are no such formulation differences. We have made this point in an amended paragraph 4 of the introduction.

Specific comments

Abstract. I would add when biosimilar entered. Possibly refer about the two “types” of preparations: ready to use and requiring constitution.

Response to reviewer. We have amended the objective in the abstract to make specific reference to the date of the introduction of biosimilar growth hormone.

Introduction
Page 2 Line 50: “Biological medicines are expensive”: possibly change to “tend to be” and make clear we are talking about treatment cost per patient?

Response to reviewer. We have amended this sentence accordingly and made it clear in the following sentence that we are talking about treatment cost per patient.

Page 3, line 32: “It is not clear whether this is universally applicable”: what is “this”?

Response to reviewer. Good point. We have amended the penultimate paragraph of the introduction to make this clearer.

State (if information is available) the share of the total medicines bill accounted for by human growth hormones.

Response to reviewer. We have added this information at the end of paragraph 3 of the introduction.

Authors should point out that biosimilars are not the same as generics. This has been acknowledged by EMA, for instance.

Response to reviewer. We have added this point at the beginning of paragraph 4 of the introduction.

Other references:
Mestre-Ferrandiz J, Towse A, Berdud M. Biosimilars: how can payers get long-term savings? Pharmacoeconomics. 2016;34(6):609-16.
Aitken M. Delivering on the potential of biosimilar medicines. The role of functioning competitive markets. 2016. IMS Institute for Healthcare Informatics
Updated IMS report published in June 2016: http://ec.europa.eu/growth/tools-databases/newsroom/cf/itemdetail.cfm?item_type=251&lang=en&item_id=8854
Policy requirements for a sustainable biosimilar market – Simon-Kucher (2016): http://www.medicinesforeurope.com/2016/09/19/policy-requirements-for-a-sustainable-biosimilar-market-simon-kucher-2016/ [although growth hormones not included]

Response to reviewer. We have cited Mestre-Ferrandiz et al., paper.

Methods

Page 3, line 48: Explain what is meant by “2U”

Response to reviewer. We have changed this to international units.

DEFINE database: what is its market coverage?

Response to reviewer. We have added the coverage of Define (90%) in paragraph 1 of the methods.

Clarify “level” of prices: list vs net. See point above

Response to reviewer. We have amended paragraph 2 in the methods and paragraph 7 of the discussion to explain the different pricing systems in primary and secondary care which make the results interesting.

Would be helpful to have a description about the two “types” of preparations, ready to use vs requiring constitution, and summarise in a table which presentation falls under which category.

Response to reviewer. We have added a table (table 2) which describes the characteristics of the different preparations.

Statistical analysis: might be worth offering a rationale why the linear regression analysis is the correct approach.

Response to reviewer. We have added an addition sentence at the beginning of the statistical analysis section to explain the rationale for the use of linear regression. We also make the point in the study limitations section why segmented regression of interrupted time series analysis was not used.

Results
Table 1: I assume prices are in £s?

Response to reviewer. Yes as we stated in the methods section. We have also amended the title of table 1 to make this explicit.

Would be very helpful to:
• Identify when the price changes actually happened, and in what order i.e. were they simultaneous or sequential?

Response to reviewer. Table 1 has been amended to show this.

• Understand, if possible, why prices are different between primary and secondary care.

Response to reviewer. We have amended paragraph 2 in the methods and paragraph 7 of the discussion to explain the different pricing systems in primary and secondary care which make the results interesting.

• Understand whether treatment with growth hormone preparations starts in primary or secondary care, and whether there has been a change in treatment pathways that can also explain the changes in overall utilisation between primary and secondary care.

Response to reviewer. The clinical pathway for the initiation and maintenance of growth hormone is explained in a new paragraph 2 of the discussion.

Discussion

Page 5, lines 43 – 45:"At the same time ,…, still respecting the patient's choice". I understand that the objective of the paper is NOT to look at what influences prescribing in England/UK more generally, but some useful references looking at this issue include:
• Karlsberg Schaffer, S., Sussex, J. and Feng, Y. 2015. Incentives to follow Best Practice in Health Care. OHE Briefing (https://www.ohe.org/publications/incentives-follow-best-practice-health-care)
• Karlsberg Schaffer, S., Sussex, J., Hughes, D. and Devlin, N., 2016. Opportunity costs and local health service spending decisions: a qualitative study from Wales. BMC Health Services Research, 16(1).
• Karlsberg Schaffer, S., Sussex, J., Devlin, N. and Walker, A., 2015. Local health care expenditure plans and their opportunity costs. Health Policy, 119(9), pp.1237-1244.

Response to reviewer. Thank you for identifying these references we have expanded paragraph 1 of the discussion to cover the point made in these references.

Page 5, line 47: unfinished sentence.

Response to reviewer. Sentence amended accordingly.

Page 6, line 5: "for dose preparation by patients": would be helpful to understand what patients need to do for the reconstitution process.

Response to reviewer. We have added more detail around the reconstitution process in paragraph 4 of the discussion.

Page 6, Lines 19-20: might be worth pointing out that Omnitrope Cart is actually the cheapest option.

Response to reviewer. We have amended paragraph 7 of the discussion to highlight this point.

Page 6, line 46: “This study is the first to show”: too strong language. Before authors have used “this indicates…” (line 37)

Response to reviewer. We have amended this sentence.

Page 6, lines 49-50: which biosimilar are you referring to?

Response to reviewer. We have amended this sentence to make clear we are referring to growth hormone biosimilar.

Limitations: I would add level of prices if prices are at “list” rather than “net”

Response to reviewer. Prices in primary care are list prices which are the price the community pharmacy is reimbursed by the government, and the hospital prices are the actual price paid as explained in a revised final paragraph of the data sources section of the methods. We do not think this is a limitation since in effect both prices are what the payer pays.

Conclusion

Page 7, line 8: “This study has demonstrated”: again, possibly too strong language (see comment above).

Response to reviewer. We have amended the first sentence of the conclusion using ‘suggests’ rather than ‘demonstrated’

VERSION 2 – REVIEW

REVIEWER	David Ridley Duke University USA
REVIEW RETURNED	13-Jan-2017

GENERAL COMMENTS	Thank you for the opportunity to review the revision of the paper. My sense is that the authors have been very responsive to the reviewers’ concerns. I have two remaining, related concerns: 1) I’m not able to view the revised figures because they are so small. These figures (especially Figures 4 and 5) are important to my question about the relationship between quality, quantity, and price in #2 below. 2) My primary concern is that both quantity and price might be related to unobserved quality. Quantity = f(price(quality), quality). The authors argue that “In the NHS the basic price is agreed with the government and is not directly related to quality.” This surprises me. Perhaps the authors can provide a quote from NIH documents (or other evidence) in support of this claim.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name
David Ridley

Institution and Country
Duke University
USA

1) I'm not able to view the revised figures because they are so small. These figures (especially Figures 4 and 5) are important to my question about the relationship between quality, quantity, and price in #2 below.
Response to reviewer. Further copies of the figures are appended

2) My primary concern is that both quantity and price might be related to unobserved quality. Quantity = f(price(quality), quality). The authors argue that "In the NHS the basic price is agreed with the government and is not directly related to quality." This surprises me. Perhaps the authors can provide a quote from NIH documents (or other evidence) in support of this claim.
Response to reviewer.
In the U.K. the price of branded medicines is agreed between the pharmaceutical industry and the Department of Health which is department within the U.K. government. The strategies of price fixing in Europe is described in (Ess et al., 2003). An extract from this paper is quoted here. The fourth strategy 'Contribution of Pharmaceuticals to the Economy' is used in the U.K. and is called the Pharmaceutical price regulation Scheme (PPRS), and as the article describes has been used in the U.K since 1957. Basically the price is agreed nationally between the pharmaceutical company and the department of health together with the target profit margin the pharmaceutical company is allowed to make. The aim is to ensure the National Health Service does not pay too much for medicines but at the same time the pharmaceutical industry makes reasonable profits since it is recognised this contributes to the U.K. economy.
'Although price fixing causes distortions in private markets, it is applied to pharmaceuticals in the majority of European countries. In the late 1980s, manufacturers were free to set prices in only three countries: Germany, Denmark, and The Netherlands.
Strategies used in price fixing vary, but most countries use a combination of the following criteria:
• The therapeutic value of the drug. Methods used to determine this vary from country to country. Some countries (e.g. Belgium, France, Italy, and Sweden) require cost-effectiveness studies in their New Drug Applications.
• Reference to existing products. Several countries refer to such comparisons. In Belgium, prices are based on improvement over existing products. In France, final prices are the result of negotiations with pharmaceutical companies, which take into account similar products.
• Reference to international comparisons. Most countries take into account prices charged for the same product in other countries, e.g. Canada. This further contributes to a more unified world pharmaceutical market than would result from the autonomous operation of fragmented national markets. Price differences do exist, but they are smaller than expected based on other products.
• The contribution of the pharmaceuticals to the economy. This applies in Belgium, Spain, and the UK. The extent to which such practices are also followed implicitly in other countries remains unknown.'

Reference: Ess, S. M., Schneeweiss, S., & Szucs, T. D. (2003). European healthcare policies for controlling drug expenditure. Pharmacoeconomics, 21(2), 89-103.