ORIGINAL RESEARCH ARTICLE

Drug Saf 2011; 34 (8): 683-690
0114-5916/11/0008-0683/$49.95/0

Clarity and Applicability of Drug-Drug Interaction Management Guidelines

A Systematic Appraisal by General Practitioners and Community Pharmacists in the Netherlands

Annemieke Floor-Schreudering,[1] *Peter A.G.M. De Smet*,[2,3] *Henk Buurma*,[1] *Sonia Amini*[1] and *Marcel L. Bouvy*[1,4]

1 SIR Institute for Pharmacy Practice and Policy, Leiden, the Netherlands
2 Department of Clinical Pharmacy and IQ Healthcare, University Medical Centre St Radboud, Nijmegen, the Netherlands
3 Scientific Institute of Dutch Pharmacists (WINAp), The Hague, the Netherlands
4 Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, the Netherlands

Abstract

Background: Despite the availability and daily use of computerized drug-drug interaction surveillance systems, exposure to potentially relevant drug-drug interactions (DDIs) continues. DDI management guidelines are often inadequate and clear management options are lacking, which attributes to overriding of DDI signals. Although general criteria for the development and reporting of high-quality clinical practice guidelines have been identified, it appears these have not yet been applied to DDI management guidelines.

Objectives: The aim of the study was to assess the clarity and applicability of guidelines for the management of potentially harmful DDIs.

Methods: We selected 13 DDIs that are potentially harmful for patients and frequently occur in community pharmacy practice in the Netherlands. The clarity and applicability of the management guidelines of these DDIs were appraised using the appropriate two domains – 'Clarity and presentation' and 'Applicability', of the validated Appraisal of Guidelines for Research and Evaluation (AGREE) Instrument. The appraisal was performed by 12 community pharmacists and 12 general practitioners. The standardized domain scores and mean item scores for 'Clarity and presentation' and 'Applicability' were compared.

Results: All DDI management guidelines were generally found to score well on 'Clarity and presentation', but poorly with respect to 'Applicability' (standardized domain scores 68.0 vs 26.1%). Within the domain 'Clarity and presentation', the item 'tools for application' received the lowest scores. Within the domain 'Applicability', cost implications, organizational barriers and key review criteria were all poorly documented. All guidelines presented non-directive advice using words such as 'consider' and 'regularly'.

Conclusions: Developers of DDI management guidelines should take the appropriate domains of the AGREE Instrument into consideration in their development processes. The applicability of DDI management guidelines should be pretested before publishing. To improve guideline quality, more attention should particularly be paid to the available tools for applications and cost implications.

Background

Despite the extensive use of computerized drug-drug interaction surveillance systems (CIS), exposure to potentially relevant drug-drug interactions (DDIs) continues.[1-3] In current practice, many physicians and pharmacists are overwhelmed by alerts of DDIs with questionable or unclear clinical significance because of a lack of specificity of their surveillance system.[4] Therefore, they frequently override alerts, a phenomenon often described as alert fatigue.[5-7] On the other hand, they experience that their systems sometimes neglect relevant DDIs and/or do not adjust for identifiable patient-related risk factors.[7-11] Moreover, professionals complain that information about strategies to prevent patient harm, such as non-interacting alternative therapies or specific advice for dose adjustment, is sometimes lacking in DDI guidelines (e.g. diuretics and NSAIDs, simvastatin and diltiazem).[12,13] In agreement, Hansten[14] observed that current DDI management guidelines are often inadequate and should have clear management options. These shortcomings stimulated Van Roon et al.[15] to develop a procedure for the structured assessment of DDIs. Clinically relevant DDIs should be presented with appropriate information on the relevance for individual patients and with a clear proposal for potential interventions.

Clear and specific recommendations are associated with better compliance with clinical guidelines.[16] Preferably, these recommendations should contain concrete and precise descriptions of the appropriate management and require few new skills and/or organizational changes.[17-19] Criteria for the development and reporting of high-quality clinical practice guidelines have been identified by the Appraisal of Guidelines for Research and Evaluation (AGREE) Collaboration. This collaboration developed and validated the AGREE Instrument (http://www.agreetrust.org/).[20] This has become a widely used assessment instrument that has been proven reliable and valid for various clinical practice guidelines,[21-23] and has been applied to all kinds of clinical guidelines.[24-29] However, to the best of our knowledge these have not yet been used to assess the quality of reporting in DDI management guidelines. Therefore, the objective of this study was to assess the clarity and applicability of guidelines for the management of potentially harmful drug interactions.

Methods

Selection of Interactions

We selected 13 DDIs that are potentially harmful for patients and frequently occur in daily clinical practice (table I). The latter criterion was based on the most frequently encountered DDI alerts in the Netherlands that were identified by Buurma et al.[4] To fulfil the former criterion, there had to be evidence from controlled, published, interaction studies in patients or healthy volunteers, and the potential adverse reaction had to be considered as clinically relevant.[15]

Drug-Drug Interaction (DDI) Management Guidelines

In the Netherlands there are two sets of DDI management guidelines that are integrated in different types of CIS. One set is maintained by a working group of the Scientific Institute of Dutch Pharmacists (WINAp) and the other set by a working group of the Health Base Foundation (SHB).[15,30,31]

Hard copies of the entire management guidelines of all selected DDIs (2×13) were available.

Assessment of the DDI Management Guidelines

To assess the clarity and applicability of these DDI management guidelines we used the appro-

Table I. Appraisal of Guidelines for Research and Evaluation (AGREE) domain scores of the drug-drug interaction (DDI) management guidelines

DDI management guidelines	'Clarity and presentation' (%)[a]	'Applicability' (%)[a]
Renin-angiotensin system inhibitors and diuretics	83.2	33.7
NSAIDs and renin-angiotensin system inhibitors	75.0	19.5
Diuretics and NSAIDs	74.1	35.0
β-Adrenoceptor antagonists (β-blockers) and NSAIDs	68.9	14.5
Non-selective β-blockers and β-adrenoceptor agonists	68.3	30.7
Coumarin anticoagulants and NSAIDs	68.1	26.7
Corticosteroids and NSAIDs	67.4	32.0
Simvastatin/atorvastatin and diltiazem/verapamil	66.8	22.4
NSAIDs (excluding selective COX-2 inhibitors) and SSRIs	66.3	20.3
Levothyroxine and iron	65.8	25.2
Coumarin anticoagulants and antibacterials	65.3	31.5
Methotrexate and NSAIDs/salicylates	59.3	21.7
Calcium channel antagonists and β-blockers	55.9	26.5
Overall score (%)	**68.0**	**26.1**

a [(Score obtained – minimum score possible)/(maximum score possible – minimum score possible)] × 100.

COX = cyclo-oxygenase; **SSRIs** = selective serotonin reuptake inhibitors.

priate domains of the validated AGREE Instrument.[20] The entire guidelines were assessed on the domains 'Clarity and presentation' and 'Applicability', comprising 7 of the 23 AGREE items (see figure 1). Scoring of each item was performed according to the AGREE Instrument, on a 4-point Likert scale: 1 = strongly disagree, 2 = disagree, 3 = agree and 4 = strongly agree. As the AGREE Collaboration recommends a minimum number of four appraisers for a reliable assessment,[20] and as we did not know whether different types of healthcare provider would produce different results or not, each guideline was independently assessed by four community pharmacists and four general practitioners who were randomly selected from a pool of 12 community pharmacists and 12 general practitioners. All selected healthcare providers were known by the researchers and used DDI management guidelines in daily practice. The appraisal was individually performed and scores and comments were returned to the researchers by e-mail or posted mail.

Data Analyses

Mean item scores and standardized domain scores for the two domains ('Clarity and presentation' and 'Applicability') were calculated according to the instructions of the AGREE Instrument. Standardized domain scores were calculated by summing the scores given by the appraisers and standardizing them as a percentage of the maximum possible score for that domain (equation 1):

$$\frac{\text{Score obtained} - \text{minimum score possible}}{\text{Maximum score possible} - \text{minimum score possible}} \times 100 \quad \text{(Eq. 1)}$$

A majority of item scores of 3 or 4 and standardized domain scores above 60% indicate good quality within the domain, equal numbers of item scores of 3 or 4 and 1 or 2 and standardized domain scores between 30% and 60% indicate moderate quality, and a majority of item scores of 1 or 2 and standardized domain scores below 30% indicate poor quality within the domain.

The standardized domain scores and mean item scores of the DDI management guidelines were compared between SHB and WINAp and between general practitioners and community pharmacists using mixed-model analyses. The intraclass correlation coefficients (ICCs) were calculated for each item and the two domains to assess appraiser reliability.[20,21] A one-way random effects model was used as pairs of appraisers were randomly selected from our pool of community pharmacists and general practitioners. The level of significance for all analyses was set at

Domain 'Clarity and presentation'
Item 1. The recommendations are specific and unambiguous
A recommendation should provide a concrete and precise description of which management is appropriate in which situation and in what patient group, as permitted by the body of evidence. An example of a specific recommendation is: inform anticoagulation clinic on start of antibacterial

Item 2. The different options for management of the condition are clearly presented
For some recommendations, different management options might be considered. These alternatives should be clearly presented in the guideline. An example of a specific recommendation with management options for the interaction between NSAIDs and renin-angiotensin system inhibitors is:
a. in case of short use of NSAIDs for hypertension: no action;
b. in case of long use of NSAIDs for hypertension: monitor blood pressure frequently;
c. in case of heart failure: consider replacement of NSAID by paracetamol (acetaminophen);
d. when NSAIDs are not replaced by paracetamol in a patient with heart failure, instruct patient to contact physician in case heart failure symptoms increase

Item 3. Key recommendations are easily identifiable
Users should be able to find the most relevant recommendations easily. These recommendations address the main clinical questions that have been covered by the guideline. They can be identified in different ways. For example, they can be summarized in a box, typed in bold, underlined or presented as flow charts or algorithms

Item 4. The guideline is supported with tools for application
For a guideline to be effective it needs to be disseminated and implemented with additional materials. These may include, for example, a summary document, a quick reference guide, educational tools, patient leaflets and/or computer support. Such a tool should be provided with the guideline

Domain 'Applicability'
Item 5. The potential organizational barriers in applying the recommendations have been discussed
Applying recommendations may require changes in the current organization of care within a service or a clinic. These changes may be a barrier to using the recommendations in daily practice and should be discussed in the guideline. For example, a DDI management guideline may recommend monitoring of serum drug levels

Item 6. The potential cost implications of applying the recommendations have been considered
The recommendations may require additional resources in order to be applied. For example, there may be a need for more specialized staff, new equipment and expensive drug treatment. These may have cost implications for healthcare budgets. There should be a discussion of the potential impact on resources in the guideline. For example, resource implications of monitoring or adding a specific drug to the therapy

Item 7. The guideline presents key review criteria for monitoring and/or audit purposes
Measuring adherence to a guideline can enhance its use. This requires clearly defined review criteria that are derived from the key recommendations in the guideline. These should be presented. Examples of review criteria are:
• the HbA_{1c} should be <8.0%;
• the level of diastolic blood pressure should be <95 mmHg

Fig. 1. Appraisal of Guidelines for Research and Evaluation (AGREE) items that have been assessed. **HbA_{1c}** = glycosylated haemoglobin.

$p < 0.05$. All statistical analyses were performed using SPSS 16.0 (SPSS Inc, Chicago, IL, USA) and SAS software version 9.0 (SAS, Cary, NC, USA).

Results

There was no significant difference in the assessment of the quality of the DDI management guidelines between the type of appraiser, with the exception of the significantly higher scores provided by community pharmacists for item 4 (tools for application: 2.8 vs 2.2; $p = 0.007$ compared with general practitioners.

Quality of Guidelines

Most of the guidelines (21 of 26) were rated good quality for the domain 'Clarity and presentation' (standardized domain scores of 65.3–83.2%). However, the domain 'Applicability' performed poorly for more than half of the guidelines (16 of 26) [standardized domain scores of 14.5–26.7%; table I].

The analyses revealed the mean score across all 26 guidelines (2 × 13) was low for items 5 (organizational barriers: 2.2), 6 (cost implications: 1.2) and 7 (key review criteria: 1.9), indicating the guidelines performed poorly for these items (table II).

For item 6 'cost implications', several appraisers reported that they could not find any discussion on (additional) resources required for the recommendations, except for the reporting of an increased risk of hospitalization in case a specific DDI was not prevented.

The guidelines produced a moderate score for item 4 (tools for application: 2.5), whereas items 1–3 in the domain 'Clarity and presentation' scored good quality (specific and unambiguous: 3.2; clearly presented options: 3.2; identifiable key recommendations: 3.3).

Several appraisers mentioned the guidelines used non-directive advice, using words such as 'it is to be recommended', 'consider' and 'regularly'. Moreover, they reported that risk factors and patient modifiers were not always presented clearly in the management options.

Quality of Guidelines According to Type of Working Group

There was no difference in scores between SHB and WINAp guidelines for the domain 'Applicability'.

SHB guidelines had significantly higher scores for the domain 'Clarity and presentation' (70.4 vs 65.7%; $p = 0.031$), as well as significantly higher scores for item 3 (identifiable key recommendations; 3.7 vs 2.9; $p < 0.0001$). According to several appraisers 'key recommendations' were most easily identifiable in SHB guidelines since they were presented in a text box.

WINAp guidelines had significantly higher scores for item 4 (tools for application: 2.7 vs 2.3; $p = 0.0002$) [table II].

Data Validation

The ICCs indicate moderate reliability for the domain 'Clarity and presentation' (ICC = 0.49) and low reliability for the domain 'Applicability' (ICC = 0.28). For items 1–7 (figure 1), the ICCs were 0.19, 0.36, 0.73, 0.66, 0.00, 0.09 and 0.40, respectively.

Discussion

All DDI management guidelines had moderate to good quality within the domain 'Clarity and presentation', but had poor to moderate quality with respect to the domain 'Applicability'.

Other studies that have used the AGREE Instrument to assess guideline quality obtained si-

Table II. Comparison of mean item scores of the drug-drug interaction (DDI) management guidelines for Scientific Institute of Dutch Pharmacists (WINAp) and Health Base Foundation (SHB)

Domain[a]	Mean[b]	Range[c]	Mean[b]		p-Value
			WINAp	SHB	
Clarity and presentation					
1. Specific and unambiguous	3.2	2.9–3.7	3.2	3.1	0.659
2. Clearly presented options	3.2	2.4–3.6	3.1	3.3	0.084
3. Identifiable key recommendations	3.3	3.0–3.6	2.9	3.7	<0.0001
4. Tools for applications	2.5	1.9–3.3	2.7	2.3	0.0002
Applicability					
5. Organizational barriers	2.2	1.8–2.6	2.2	2.2	0.842
6. Cost implications	1.2	1.1–1.6	1.2	1.3	0.561
7. Key review criteria	1.9	1.3–2.4	1.9	1.9	1.000

a For further details on domains 1–7 see figure 1.

b Item score: maximum = 4; minimum = 1.

c Range of the mean item scores of the assessed DDI management guidelines.

milar results; the domain 'Clarity and presentation' received higher scores than 'Applicability'.[22-25]

Domain 'Clarity and Presentation'

Within the domain 'Clarity and presentation', the item 'tools for application' received the lowest scores. Patient leaflets, computer support and summary documents were often not reported in the guidelines, although they were available for most guidelines. The quality of guidelines could be improved by systematically referring to the available tools for applications.

Most of the guidelines scored well on the item 'recommendations are specific and unambiguous'. Most obviously, the appraisers observed that guidelines used non-directive advice, using words such as 'it is to be recommended', 'consider' and 'regularly'. The GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system[32] recommends that guideline panels systematically apply such terminology (e.g. 'it is to be recommended', 'consider') in order to differentiate between the strength of recommendations.[33] However, the appraisers did not recognize these wordings in the guidelines as part of a systematic terminology. Clearly there is a need to explain how to interpret this terminology.

Guideline users might be able to find the most relevant recommendations more easily when key recommendations are presented as boxed text. In addition, management options should clearly present risk factors and patient modifiers.

Domain 'Applicability'

DDI management guidelines scored lowest on the item 'cost implications'. There should be a discussion of the potential impact on costs in the guidelines. Cost effectiveness of recommendations should be addressed.

Most of the guidelines failed to discuss key review criteria that could be used to measure the adherence to a guideline. Although some guidelines reported which biomarkers should be monitored (e.g. blood pressure, International Normalized Ratio, serum drug level and potassium level), the consequences of changes in biomarkers remained mostly unreported.

Most of the guidelines were poorly documented with respect to organizational barriers. How to monitor and who needs to monitor was mostly unclear and information exchange between healthcare providers was rarely advised.

The low score on the domain 'Applicability' suggests there are still numerous barriers to the implementation of DDI management guidelines.[19,34] Enhanced compliance with guidelines and significant improvements in clinical care could be achieved when guideline developers pay attention to these barriers from the beginning of the guideline development process.[35]

Limitations

There are some limitations to this study. First, the AGREE Instrument has primarily been developed to appraise the quality of disease-specific clinical guidelines;[20] however, we believe that similar quality principles are relevant for DDI management guidelines. This assumption seems acceptable as the AGREE Instrument has also been used successfully in other areas.[22,24,25]

Another potential limitation is that the guidelines assessed in our study may not be representative for all DDI management guidelines. As we appraised guidelines for frequently occurring DDIs with the highest level of evidence and potentially clinically relevant adverse events resulting from the DDI, it is most likely that our selection has relatively good recommendations, and guidelines in general might have even more problems.

The appraisers may have had a preference for the set of DDI management guidelines (WINAp or SHB), which they used in their clinical practice. We have analysed this potential bias and found no substantial influence on the results.

There is always potential for lack of reliability among appraisers when using the AGREE Instrument. We aimed to minimize this by providing a training manual that included examples of DDI management guidelines, which has been pretested, and the appraisers could contact the researchers by e-mail or phone for help. Moreover, we used two panels of four appraisers (i.e. four general practitioners and four community pharmacists) for each guideline, which was double the

number advised by the AGREE Collaboration (i.e. eight appraisers instead of four).[20,36]

The ICCs for the two domains were lower than reported in the AGREE validation study[20] and by Gorman et al.,[22] which reflects a lower degree of reliability among the appraisers. As for some items, the information provided in the guidelines was incomplete or even completely missing; therefore, appraisers might have relied on their clinical expertise. Although all appraisers used the guidelines in their practice, we did not ascertain whether appraisers were clinical experts in the therapeutic areas covered by all 13 guidelines. Thus, low reliability may relate to differences in the level of clinical expertise of the appraisers.

Poor reliability was evident for the domain 'Applicability'. Appraisers might have had difficulties interpreting these items because of the lack of consensus about the meaning of these items in DDI management guidelines. Apparently, the pretested training manual and phone and e-mail help service were not sufficient for all appraisers.

There is a clear need for the comprehensive assessment of the quality of DDI management guidelines. A structured procedure for assessing the clinical relevance of DDIs has been proposed[15] but this is not sufficient since the quality of the clinical content of guidelines does not necessarily correspond to AGREE quality scores, which focus on the methods used for developing the guideline and the quality of reporting.[37,38] Consequently, the quality of DDI management guidelines should also be appraised by applying the appropriate domains of the AGREE instrument, in particular 'Clarity and Presentation' and 'Applicability'. However, in addition to a pretested training manual and help service, thorough training, with instructions on how to interpret items, is required when the AGREE instrument is used for this particular purpose.

Conclusions

The selected management guidelines of DDIs that are potentially harmful for patients and frequently occur in community pharmacy practice were found to have good 'Clarity and presentation' but poor 'Applicability'. To improve guideline quality, more attention should particularly be paid to available tools for applications and cost implications.

Developers of DDI management guidelines should take the appropriate domains of the AGREE instrument into consideration in their development processes.

The applicability of DDI management guidelines should be pretested before publishing. There should also be a monitoring system in place to check, after dissemination, whether the guidelines offer the intended high quality in daily practice.

Acknowledgements

We would very much like to thank all general practitioners and community pharmacists who participated in this study. Special thanks to Jan Mulder and Svetlana Belitzer for their advice on the statistical analysis of the data.

No sources of funding were used to conduct this study or prepare this manuscript. The authors have no conflicts of interest that are directly relevant to the content of this study. All authors met the criteria for authorship, and read and approved the final version of the manuscript.

References

1. Juurlink DN, Mamdani M, Kopp A, et al. Drug-drug interactions among elderly patients hospitalized for drug toxicity. JAMA 2003 Apr 2; 289 (13): 1652-8
2. Malone DC, Abarca J, Skrepnek GH, et al. Pharmacist workload and pharmacy characteristics associated with the dispensing of potentially clinically important drug-drug interactions. Med Care 2007 May; 45 (5): 456-62
3. Merlo J, Liedholm H, Lindblad U, et al. Prescriptions with potential drug interactions dispensed at Swedish pharmacies in January 1999: cross sectional study. BMJ 2001 Aug 25; 323 (7310): 427-8
4. Buurma H, De Smet P, Egberts A. Clinical risk management in Dutch community pharmacies: the case of drug-drug interactions. Drug Saf 2006; 29 (8): 723-32
5. Van der Sijs H, Aarts J, Vulto A, et al. Overriding of drug safety alerts in computerized physician order entry. J Am Med Inform Assoc 2006 Mar-Apr; 13 (2): 138-47
6. Weingart SN, Toth M, Sands DZ, et al. Physicians' decisions to override computerized drug alerts in primary care. Arch Intern Med 2003 Nov 24; 163 (21): 2625-31
7. Murphy JE, Forrey RA, Desiraju U. Community pharmacists' responses to drug-drug interaction alerts. Am J Health Syst Pharm 2004 Jul 15; 61 (14): 1484-7
8. Buurma H, de Smet P, van den Hoff O, et al. Nature, frequency and determinants of prescription modifications in Dutch community pharmacies. Br J Clin Pharmacol 2001 Jul; 52 (1): 85-91
9. Abarca J, Colon LR, Wang VS, et al. Evaluation of the performance of drug-drug interaction screening software in

community and hospital pharmacies. J Manag Care Pharm 2006 Jun; 12 (5): 383-9

10. Becker M, Kallewaard M, Caspers P, et al. Potential determinants of drug-drug interaction associated dispensing in community pharmacies. Drug Saf 2005; 28 (5): 371-8
11. Gaikwad R, Sketris I, Shepherd M, et al. Evaluation of accuracy of drug interaction alerts triggered by two electronic medical record systems in primary healthcare. Health Informatics J 2007 Sep; 13 (3): 163-77
12. Indermitte J, Erba L, Beutler M, et al. Management of potential drug interactions in community pharmacies: a questionnaire-based survey in Switzerland. Eur J Clin Pharmacol 2007 Mar; 63 (3): 297-305
13. Bergk V, Gasse C, Schnell R, et al. Requirements for a successful implementation of drug interaction information systems in general practice: results of a questionnaire survey in Germany. Eur J Clin Pharmacol 2004 Oct; 60 (8): 595-602
14. Hansten PD. Drug interaction management. Pharm World Sci 2003 Jun; 25 (3): 94-7
15. Van Roon EN, Flikweert S, le Comte M, et al. Clinical relevance of drug-drug interactions: a structured assessment procedure. Drug Saf 2005; 28 (12): 1131-9
16. Grol R, Dalhuijsen J, Thomas S, et al. Attributes of clinical guidelines that influence use of guidelines in general practice: observational study. BMJ 1998 Sep 26; 317 (7162): 858-61
17. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet 2003 Oct 11; 362 (9391): 1225-30
18. Burgers JS, Grol RP, Zaat JO, et al. Characteristics of effective clinical guidelines for general practice. Br J Gen Pract 2003 Jan; 53 (486): 15-9
19. Buurma H, Schalekamp T, Egberts AC, et al. Compliance with national guidelines for the management of drug-drug interactions in Dutch community pharmacies. Ann Pharmacother 2007 Dec; 41 (12): 2024-31
20. The AGREE Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care 2003 Feb; 12 (1): 18-23
21. MacDermid JC, Brooks D, Solway S, et al. Reliability and validity of the AGREE instrument used by physical therapists in assessment of clinical practice guidelines. BMC Health Serv Res 2005 Mar 2; 5 (1): 18
22. Gorman SK, Chung MH, Slavik RS, et al. A critical appraisal of the quality of critical care pharmacotherapy clinical practice guidelines and their strength of recommendations. Intensive Care Med 2010 Oct; 36 (10): 1798-801
23. Burgers JS, Fervers B, Haugh M, et al. International assessment of the quality of clinical practice guidelines in oncology using the Appraisal of Guidelines and Research and Evaluation Instrument. J Clin Oncol 2004 May 15; 22 (10): 2000-7
24. Wilting I, Egberts AC, Heerdink ER, et al. Evaluation of available treatment guidelines for the management of lithium intoxication. Ther Drug Monit 2009 Apr; 31 (2): 247-60
25. Kinnunen-Amoroso M, Pasternack I, Mattila S, et al. Evaluation of the practice guidelines of Finnish Institute of Occupational Health with AGREE instrument. Ind Health 2009 Dec; 47 (6): 689-93
26. McNair RP, Hegarty K. Guidelines for the primary care of lesbian, gay, and bisexual people: a systematic review. Ann Fam Med 2010 Nov-Dec; 8 (6): 533-41
27. Faggion Jr CM. Clinician assessment of guidelines that support common dental procedures. J Evid Based Dent Pract 2008 Mar; 8 (1): 1-7
28. Van Diermen DE, Aartman IH, Baart JA, et al. Dental management of patients using antithrombotic drugs: critical appraisal of existing guidelines. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009 May; 107 (5): 616-24
29. Potting C, Mistiaen P, Poot E, et al. A review of quality assessment of the methodology used in guidelines and systematic reviews on oral mucositis. J Clin Nurs 2009 Jan; 18 (1): 3-12
30. Royal Dutch Association for the Advancement of Pharmacy. The G-standard: structure, safety assessment and decision support [online]. Available from URL: http://www.knmp.nl/vakinhoud/farmacotherapie/g-standaard/the-g-standaard-the-medicines-standard-in-healthcare [Accessed 2008 Dec 10]
31. Medication surveillance commentaries 2008-2009 [in Dutch]. Houten: Health Base Foundation, 2008
32. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008 Apr 26; 336 (7650): 924-6
33. Guyatt GH, Cook DJ, Jaeschke R, et al. Grades of recommendation for antithrombotic agents: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th ed.). Chest 2008 Jun; 133 (6 Suppl.): 123-31S
34. Nuckols TK, Lim YW, Wynn BO, et al. Rigorous development does not ensure that guidelines are acceptable to a panel of knowledgeable providers. J Gen Intern Med 2008 Jan; 23 (1): 37-44
35. Ray-Coquard I, Philip T, de Laroche G, et al. A controlled ''before-after'' study: impact of a clinical guidelines programme and regional cancer network organization on medical practice. Br J Cancer 2002 Feb 1; 86 (3): 313-21
36. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull 1979 Mar; 86 (2): 420-8
37. Burgers JS. Guideline quality and guideline content: are they related? Clin Chem 2006 Jan; 52 (1): 3-4
38. Watine J, Friedberg B, Nagy E, et al. Conflict between guideline methodologic quality and recommendation validity: a potential problem for practitioners. Clin Chem 2006 Jan; 52 (1): 65-72

Correspondence: Mrs *Annemieke Floor-Schreudering*, SIR Institute for Pharmacy Practice and Policy, Theda Mansholtstraat 5B, 2331 JE Leiden, the Netherlands.
E-mail: a.floor@stevenshof.nl