



**Universiteit
Leiden**
The Netherlands

Development and implementation of guidelines in allergic rhinitis - an ARIA-GA2LEN paper

Bousquet, J.; Schunemann, H.J.; Zuberbier, T.; Bachert, C.; Baena-Cagnani, C.E.; Bousquet, P.J.; ... ; WHO Collaborating Ctr Asthma Rhini

Citation

Bousquet, J., Schunemann, H. J., Zuberbier, T., Bachert, C., Baena-Cagnani, C. E., Bousquet, P. J., ... Zhong, N. (2010). Development and implementation of guidelines in allergic rhinitis - an ARIA-GA2LEN paper. *Allergy*, 65(10), 1212-1221.
doi:10.1111/j.1398-9995.2010.02439.x

Version: Not Applicable (or Unknown)
License: [Leiden University Non-exclusive license](#)
Downloaded from: <https://hdl.handle.net/1887/117589>

Note: To cite this publication please use the final published version (if applicable).

Development and implementation of guidelines in allergic rhinitis – an ARIA-GA²LEN paper

J. Bousquet^{1*}, H. J. Schünemann², T. Zuberbier^{3*}, C. Bachert^{4*}, C. E. Baena-Cagnani⁵, P. J. Bousquet^{6*}, J. Brozek², G. W. Canonica^{7*}, T. B. Casale⁸, P. Demoly^{9*}, R. Gerth van Wijk^{10*}, K. Ohta¹¹, E. D. Bateman¹², M. Calderon^{13*}, A. A. Cruz¹⁴, W. K. Dolen¹⁵, J. Haughney¹⁶, R. F. Lockey¹⁷, J. Lötvald^{18*}, P. O'Byrne¹⁹, O. Spranger^{20*}, A. Togias²¹, S. Bonini^{22*}, L. P. Boulet²³, P. Camargos²⁴, K. H. Carlsen^{25*}, N. H. Chavannes^{26*}, L. Delgado^{27*}, S. R. Durham^{28*}, W. J. Fokkens^{29*}, J. Fonseca^{30*}, T. Haahtela^{31*}, O. Kalayci³², M. L. Kowalski^{33*}, D. Larenas-Linnemann³⁴, J. Li³⁵, Y. Mohammad³⁶, J. Mullol^{37*}, R. Naclerio³⁸, R. E. O'Hehir³⁹, N. Papadopoulos^{40*}, G. Passalacqua^{7*}, K. F. Rabe^{41*}, R. Pawankar⁴², D. Ryan⁴³, B. Samolinski⁴⁴, F. E. R. Simons⁴⁵, E. Valovirta^{46*}, A. Yorgancioglu⁴⁷, O. M. Yusuf⁴⁸, I. Agache⁴⁹, N. Ait-Khaled⁵⁰, I. Annesi-Maesano⁵¹, B. Beghe⁵², A. Ben Kheder⁵³, M. S. Blaiss⁵⁴, D. A. Boakye⁵⁵, J. Bouchard⁵⁶, P. G. Burney⁵⁷, W. W. Busse⁵⁸, M. Chan-Yeung⁵⁹, Y. Chen⁶⁰, A. G. Chuchalin⁶¹, D. J. Costa⁶², A. Custovic⁶³, R. Dahl⁶⁴, J. Denburg⁶⁵, H. Douagui⁶⁶, R. Emuzyte⁶⁷, L. Grouse⁶⁸, M. Humbert⁶⁹, C. Jackson⁷⁰, S. L. Johnston⁷¹, M. A. Kaliner⁷², P. K. Keith⁷³, Y. Y. Kim⁷⁴, J. M. Klossek⁷⁵, P. Kuna⁷⁶, L. T. Le⁷⁷, C. Lemiere⁷⁸, B. Lipworth⁷⁹, B. Mahboub⁸⁰, J. L. Malo⁸¹, G. D. Marshall⁸², S. Mavale-Manuel⁸³, E. O. Meltzer⁸⁴, M. Morais-Almeida⁸⁵, C. Motala⁸⁶, C. Naspitz⁸⁷, K. Nekam⁸⁸, B. Niggemann⁸⁹, E. Nizankowska-Mogilnicka^{90*}, Y. Okamoto⁹¹, M. P. Orru⁹², S. Ouedraogo⁹³, S. Palkonen⁹⁴, T. A. Popov⁹⁵, D. Price⁹⁶, J. Rosado-Pinto⁹⁷, G. K. Scadding⁹⁸, T. M. Sooronbaev⁹⁹, S. W. Stoloff¹⁰⁰, E. Toskala¹⁰¹, P. van Cauwenberge¹⁰², O. Vandenplas¹⁰³, C. van Weel¹⁰⁴, G. Viegi¹⁰⁵, J. C. Virchow¹⁰⁶, D. Y. Wang¹⁰⁷, M. Wickman¹⁰⁸, D. Williams¹⁰⁹, B. P. Yawn¹¹⁰, H. J. Zar¹¹¹, M. Zernotti¹¹² & N. Zhong¹¹³, In collaboration with the WHO Collaborating Center of Asthma and Rhinitis (Montpellier)

¹University Hospital, Hôpital Arnaud de Villeneuve, Montpellier, and INSERM, CESP Centre for Research in Epidemiology and Population Health, U1018, Villejuif, France; ²Department of Clinical Epidemiology and Biostatistics, and Department of Medicine, McMaster University, Hamilton, ON, Canada; ³Allergy Centre Charité, Charité – Universitätsmedizin Berlin, Berlin, Germany; ⁴Ghent University, Ghent, Belgium; ⁵Faculty of Medicine, Catholic University of Cordoba, Cordoba, Argentina and Faculty of Specialization – Respiratory Medicine, University of Genoa, Genoa, Italy; ⁶University Hospital, Nîmes, France; ⁷Allergy & Respiratory Diseases Clinic, University of Genova, Genova, Italy; ⁸Creighton University, Omaha, NE, USA; ⁹University Hospital of Montpellier – Inserm U657, Hôpital Arnaud de Villeneuve, Montpellier, France; ¹⁰Section of Allergology, Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands; ¹¹Teikyo University School of Medicine, Tokyo, Japan; ¹²Health Sciences Faculty, University of Cape Town, Cape Town, South Africa; ¹³Allergy Unit, Imperial College, London, UK; ¹⁴Faculdade de Medicina da Bahia, UFBA, and CNPq, Bahia, Brazil; ¹⁵Medical College of Georgia, Augusta, GA, USA; ¹⁶University of Aberdeen, Aberdeen, UK; ¹⁷Division of Allergy and Immunology, University of South Florida College of Medicine, Tampa, FL, USA; ¹⁸University of Gothenburg, Gothenburg, Sweden; ¹⁹McMaster University, Hamilton, ON, Canada; ²⁰EFA (European Federation of Allergy and Airways Diseases Patients Associations), Brussels, Belgium; ²¹National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA; ²²Second University of Naples, INMM-CNR, Rome, Italy; ²³Institut de cardiologie et de pneumologie de l'Hôpital Laval and Université Laval, Laval, QC, Canada; ²⁴Medical School, University Hospital, Federal University of Minas Gerais, Minas Gerais, Brazil; ²⁵Department of Paediatrics, Ullevål University Hospital and The Faculty of Medicine, University of Oslo, Oslo, Norway; ²⁶Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, the Netherlands; ²⁷Faculdade de Medicina, University of Porto, Porto, Portugal; ²⁸National Heart and Lung Institute, Imperial College, London, UK; ²⁹Academic Medical Center, Amsterdam, the Netherlands; ³⁰Allergy, Hospital S. Joao & Instituto, CUF; CINTESIS, Porto University Medical School, Porto, Portugal; ³¹Skin and Allergy Hospital, Helsinki University Hospital, Helsinki, Finland; ³²Pediatric Allergy and Asthma Unit, Hacettepe, Ankara, Turkey; ³³Department of Immunology, Rheumatology and Allergy, Medical University of Lodz, Lodz, Poland; ³⁴Allergy Department, Hospital Médica Sur, Mexico city, Mexico; ³⁵Guangzhou Institute of Respiratory Diseases, The First Affiliated Hospital of Guangzhou Medical School, Guangzhou, China; ³⁶Tishreen University School of Medicine, Lattakia, Syria; ³⁷Hospital Clínic i Universitari, IDIBAPS, CIBERES, Barcelona, Catalonia, Spain; ³⁸University of Chicago, Chicago, IL, USA; ³⁹Alfred Hospital and Monash University, Melbourne, Vic., Australia; ⁴⁰Allergy Research Center, University of Athens, Athens, Greece; ⁴¹Department of Pulmonology, Leiden University Medical Center, Leiden, the Netherlands; ⁴²Nippon Medical School, Bunkyo-ku, Tokyo, Japan; ⁴³Woodbrook Medical Centre, Loughborough, England And University of Aberdeen, Aberdeen, UK; ⁴⁴Medical University of Warsaw, Warsaw, Poland; ⁴⁵University of Manitoba, Winnipeg, MB, Canada; ⁴⁶Terveyystalu Turku, Turku, Finland; ⁴⁷Celal Bayar University School of Medicine Department of Pulmonology, Manisa, Turkey; ⁴⁸The Allergy & Asthma Institute, Islamabad, Pakistan; ⁴⁹Transylvania University, Brasov, Romania; ⁵⁰The Union, Paris, France; ⁵¹EPAR U707 INSERM and EPAR UMR-S UPMC, Paris, France; ⁵²Department of Oncology, Haematology and Respiratory Diseases, University of Modena and Reggio Emilia, Modena, Italy; ⁵³Hopital a Mami Ariana, Ariana, Tunisia; ⁵⁴University of Tennessee Health Science Center, Memphis, TN, USA; ⁵⁵Noguchi Memorial Institute for Medical Research, College of Health Sciences, University of Ghana, Legon, Accra, Ghana; ⁵⁶Université Laval, Laval, QC, and Hôpital de la Malbaie, la Malbaie, QC, Canada; ⁵⁷National Heart & Lung Institute at Imperial College, London, UK; ⁵⁸Professor of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA; ⁵⁹University of British Columbia, Vancouver, BC, Canada; ⁶⁰National Cooperative Group of Pediatric Research on Asthma, Asthma Clinic and Education Center of the Capital Institute of Pediatrics, Peking, China; ⁶¹Pulmonology Research Institute and Russian Respiratory Society, Moscow, Russia; ⁶²Primary Care Department, Montpellier University, Montpellier, France; ⁶³University of Manchester, Manchester, UK; ⁶⁴Aarhus University Hospital, Aarhus, Denmark; ⁶⁵AllerGen NCE, McMaster University, Hamilton, ON, Canada; ⁶⁶Centre Hospitalo-Universitaire de Béni-Messous, Algiers, Algeria; ⁶⁷Vilnius University Faculty of Medicine, Vilnius, Lithuania;

⁶⁸University of Washington School of Medicine, Seattle, WA, USA; ⁶⁹Hôpital Antoine-Béclère, Université Paris-Sud, Clamart, France; ⁷⁰Bute Medical School, University of St Andrews, St Andrews, UK; ⁷¹National Heart and Lung Institute, Imperial College London, London, UK; ⁷²Geo Washington University School of Medicine, Washington DC – Institute for Asthma and Allergy, Chevy Chase, MD, USA; ⁷³McMaster University, Hamilton, ON, Canada; ⁷⁴Seoul National University Hospital, Seoul, Korea; ⁷⁵University of Poitiers, Poitiers, France; ⁷⁶Barlicki University Hospital, Medical University of Lodz, Lodz, Poland; ⁷⁷University of Medicine and Pharmacy, Hochiminh City, Vietnam; ⁷⁸Hôpital du Sacré-Coeur de Montréal and University of Montreal, Montreal, QC, Canada; ⁷⁹University of Dundee, Dundee, UK; ⁸⁰University of Sharjah, Sharjah, UAE; ⁸¹Hôpital du Sacré-Coeur de Montréal and University of Montreal, Montreal, QC, Canada; ⁸²University of Mississippi, Jackson, MS, USA; ⁸³Children's Hospital, Maputo, Mozambique; ⁸⁴Allergy & Asthma Medical Group & Research Center, University of California, San Diego, CA, USA; ⁸⁵Immunoallergy Department, CUF-Descobertas Hospital, Lisbon, Portugal; ⁸⁶School of Child and Adolescent Health, UCT and Red Cross War Memorial Children's Hospital, Cape Town, South Africa; ⁸⁷Federal University of São Paulo, São Paulo, Brazil; ⁸⁸Hospital of the Hospitaller Brothers in Buda, Budapest, Hungary; ⁸⁹German Red Cross Hospital Berlin, Berlin, Germany; ⁹⁰Jagiellonian University School of Medicine, Krakow, Poland; ⁹¹Chiba University, Chiba, Japan; ⁹²Pharmacist, Italy; ⁹³Centre Hospitalier Universitaire Pédiatrique Charles de Gaulle, Ouagadougou, Burkina Faso, West Africa; ⁹⁴EFA European Federation of Allergy and Airways Diseases Patients' Associations, Brussels, Belgium; ⁹⁵Clinic of Allergy and Asthma, Medical University Sofia, Sofia, Bulgaria; ⁹⁶University of Aberdeen, Aberdeen, UK; ⁹⁷Immunoallergy Department, Hospital da Luz, Lisboa, Portugal; ⁹⁸Royal National TNE Hospital, London, UK; ⁹⁹National Centre Cardiology and Internal Medicine, Bishkek, Kyrgyzstan; ¹⁰⁰University of Nevada School of Medicine, Reno, NV, USA; ¹⁰¹Finnish Institute of Occupational Health, Helsinki, Finland; ¹⁰²Ghent University, Ghent, Belgium; ¹⁰³University Hospital of Mont-Godinne, Catholic University of Louvain, Yvoir, Belgium; ¹⁰⁴Department of Primary and Community Care, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands; ¹⁰⁵CNR Institutes of Biomedicine and Molecular Immunology (IBIM), Palermo, and of Clinical Physiology (IFC), Pisa, Italy; ¹⁰⁶University of Rostock, Rostock, Germany; ¹⁰⁷Yong Loo Lin School of Medicine, National University of Singapore, Singapore; ¹⁰⁸Sachs' Children's Hospital, Stockholm, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; ¹⁰⁹School of Pharmacy, University of North Carolina, Chapel Hill, NC, USA; ¹¹⁰Olmsted Medical Center, University of Minnesota, Rochester, MN, USA; ¹¹¹Department of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa; ¹¹²Faculty of Medicine, Catholic University of Córdoba, Córdoba, Argentina; ¹¹³Guangzhou Institute of Respiratory Diseases, Guangzhou, China

To cite this article: Bousquet J, Schönemann HJ, Zuberbier T, Bachert C, Baena-Cagnani CE, Bousquet PJ, Brozek J, Canonica GW, Casale TB, Demoly P, Gerth van Wijk R, Ohta K, Bateman ED, Calderon M, Cruz AA, Dolen WK, Haughey J, Lockey RF, Lötval J, O'Byrne P, Spranger O, Togias A, Bonini S, Boulet LP, Camargos P, Carlsen KH, Chavannes NH, Delgado L, Durham SR, Fokkens WJ, Fonseca J, Haahtela T, Kalayci O, Kowalski ML, Larenas-Linnemann D, Li J, Mohammad Y, Mullol J, Naclerio R, O'Hehir RE, Papadopoulos N, Passalacqua G, Rabe KF, Pawankar R, Ryan D, Samolinski B, Simons FER, Valovirta E, Yorgancioglu A, Yusuf OM, Agache I, Ait-Khaled N, Annesi-Maesano I, Beghe B, Ben Kheder A, Blaiss MS, Boakye DA, Bouchard J, Burney PG, Busse WW, Chan-Yeung M, Chen Y, Chuchalin AG, Costa DJ, Custovic A, Dahl R, Denburg J, Douguy H, Emuzyte R, Grouse L, Humbert M, Jackson C, Johnston SL, Kaliner MA, Keith PK, Kim YY, Klossek JM, Kuna P, Le LT, Lemiere C, Lipworth B, Mahboub B, Malo JL, Marshall GD, Mavale-Manuel S, Meltzer EO, Morais-Almeida M, Motala C, Naspitz C, Nekam K, Niggemann B, Nizankowska-Mogilnicka E, Okamoto Y, Orru MP, Ouedraogo S, Palkonen S, Popov TA, Price D, Rosado-Pinto J, Scadding GK, Sooronbaev TM, Stoloff SW, Toskala E, van Cauwenberge P, Vandenplas O, van Weel C, Viegi G, Virchow JC, Wang DY, Wickman M, Williams D, Yawn BP, Zar HJ, Zernotti M, Zhong N, In collaboration with the WHO Collaborating Center of Asthma and Rhinitis (Montpellier). Development and implementation of guidelines in allergic rhinitis – an ARIA-GA²LEN paper. *Allergy* 2010; **65**: 1212–1221.

Keywords

ARIA; asthma; EAACI; EFA; GA²LEN; IPCRG; rhinitis.

Correspondence

Professor Jean Bousquet, MD, PhD, Service des Maladies Respiratoires, Hôpital Arnaud de Villeneuve, 371, avenue Doyen Gaston Giraud, F-34295 Montpellier Cedex 5, France. Tel.: +33-467-33-61-05 Fax: +33-467-41-67-01 E-mail: jean.bousquet@inserm.fr

*Members of GA²LEN (Global Allergy and Asthma European Network), supported by the Sixth EU Framework program for research, contract n° FOOD-CT-2004-506378.

Accepted for publication 1 May 2010

DOI:10.1111/j.1398-9995.2010.02439.x

Edited by: Thomas Bieber

Abbreviations

ARIA, Allergic Rhinitis and its Impact on Asthma; CARAT, Control of Rhinitis and Asthma Test; EAACI, European Academy of Allergology and Clinical Immunology; EFA, European Federation of Allergy and Airways Diseases Patients Associations; GA²LEN, Global Allergy and Asthma European Network; GRADE, Grading of Recommendation, Assessment, Development, and Evaluation; IPCRG, International Primary Care Respiratory Group.

Abstract

The links between asthma and rhinitis are well characterized. The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines stress the importance of these links and provide guidance for their prevention and treatment. Despite effective treatments being available, too few patients receive appropriate medical care for both diseases. Most patients with rhinitis and asthma consult primary care physicians and therefore these physicians are encouraged to understand and use ARIA guidelines. Patients should also be informed about these guidelines to raise their awareness of optimal care and increase control of the two related diseases. To apply these guidelines, clinicians and patients need to understand how and why the recommendations were made. The goal of the ARIA guidelines is to provide recommendations about the best management options for most patients in most situations. These recommendations should be based on the best available evidence. Making recommendations requires the assessment of the quality of available evidence, deciding on the balance between benefits and downsides, consideration of patients' values and preferences, and, if applicable, resource implications. Guidelines must be updated as new management options become available or important new evidence emerges. Transparent reporting of guidelines facilitates understanding and acceptance, but implementation strategies need to be improved.

Allergic rhinitis and asthma represent a global health problem in both children and adults. Allergic diseases are common worldwide. In some countries, they affect over 40% of the young adult population, and their prevalence is increasing. Allergic rhinitis adversely affects social life, school performance, and work productivity (1), particularly in patients with severe disease (2). Rhinitis symptoms have a detrimental effect on academic performance (3). Some medications to treat these diseases can increase functional impairment (4). Moreover, the costs incurred by subjects with rhinitis are substantial. Nonallergic rhinitis, another common problem, is a heterogeneous group of diseases less well understood and controlled than allergic rhinitis (5).

Epidemiologic studies consistently show that asthma and rhinitis frequently co-exist in the same subjects throughout the world (1, 6). Rhinitis, often self-reported, is also a significant problem for patients with asthma (7). The prevalence of asthma in subjects without rhinitis is usually <2%, whereas the prevalence of asthma in patients with rhinitis varies from 10% to over 40%. Asthma appears more prevalent in patients with persistent and more severe rhinitis (8–12). Most patients with allergic or nonallergic asthma have rhinitis (6, 13). There is a probable association between the severity of asthma and rhinitis or rhinosinusitis (14–18).

Clinicians are confronted with various treatment choices to manage allergic rhinitis. This contributes to considerable variation in clinical practice, and patients, clinicians, and other health care professionals worldwide are faced with uncertainty about the relative merits and downsides of the various treatment options (1, 19). Clinical practice guidelines for the management of allergic rhinitis have been developed over the past 15 years and have improved the care of patients with allergic rhinitis (20). Allergic Rhinitis and its Impact on Asthma (ARIA) was the first in the field of these evidence-based guidelines (21). ARIA was developed in collaboration with specialists in allergy, primary care physicians, and patient representatives from the European Federation of Allergy and Airways Diseases Patients Associations (EFA). Several guidelines have recently been published, including those from the International Primary Care Respiratory Group (22), the British Society of Allergy and Clinical Immunology (BSACI) (23), the American Academy of Allergy, Asthma and Clinical Immunology, the American College of Allergy, Asthma and Immunology (24) and the ARIA 2008 Update (1). ARIA and its update as well as the Spanish Asthma Management Guide (25) are the only guidelines, which assess the management of patients with both allergic rhinitis and asthma in the same document. These guidelines were based on various evidence-based models, but none except the latest ARIA Revision used the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) approach – a systematic and transparent way of developing health care recommendations (26, 27).

The methodology for the development of guidelines is essential for their validity and acceptance in the clinical community. Methodologists without important conflicts of

interest should be involved (28, 29, 30) with input from all stakeholders, including physician experts, and patients. The majority of patients with allergic rhinitis and asthma are treated by primary care physicians (31, 32) and therefore it is important that these physicians should be involved in the development and implementation of such guidelines (33). However, in primary care, there is an inadequate implementation of guidelines for allergic and chronic respiratory diseases. One of the reasons for this lack of implementation is the lack of involvement of primary care practitioners in the guideline development process in respiratory medicine and their potential lack of understanding the true intent of a clinical practice guideline. In regard to rhinitis and allergy, there is indeed a need for more awareness of the links between rhinitis and asthma as well as an improved global management readily applicable to primary care and patients. Patient organizations have a key role in contributing and objectively interpreting available evidence, such as evidence on patient values and preferences.

Similarly to the development of guidelines, the management of patients should be undertaken using a comprehensive approach. Physicians, in particular primary care providers, need to understand that asthma and rhinitis are similar disease processes and may be different manifestations of the same disease. To satisfy patient expectations, both asthma and rhinitis should be appropriately diagnosed and controlled, and attempts should be made to prevent their occurrence. Thus, rigorous, unbiased guidelines are needed and should be developed for easy understanding and application by all physicians, health professionals, and patients. An example of such a guideline adapted from ARIA is proposed for the management and control of allergic rhinitis and its major comorbidity, asthma.

Guideline development using GRADE in allergic rhinitis

GRADE

The 'Guidelines for WHO Guidelines' recommend using a specific, uniform grading system (34). The GRADE approach is recommended by the WHO (26) and is being used increasingly by a number of prominent organizations throughout the world (35–40). It grades recommendations on two levels – strong and weak (an alternative term is conditional) and quantifies evidence into four categories – high (in symbolic language: four plus), moderate (three plus), low (two plus), and very low (one plus) (26, 41). While the quality of evidence is one of the factors influencing the strength of a recommendation, these strengths are also influenced by a balance between the benefits and downsides, values and preferences, and considerations around resource utilization (42) (Table 1).

Development of ARIA Revision using GRADE

The ARIA 2010 Revision was developed following the GRADE approach (43) by the ARIA guideline panel (Fig. 1).

Table 1 Grading the strength of recommendations and quality of evidence in the ARIA guidelines according to the GRADE system

Strength of recommendation and quality of evidence	Clarity of balance between desirable and undesirable consequences	Implications (for patients, clinicians, and policy makers) and interpretation of the quality of evidence
<i>Strong recommendation</i>		
High-quality (four plus: ⊕⊕⊕⊕) evidence	Desirable consequences clearly outweigh undesirable consequences, or vice versa	<p>Patients: Most people in your situation would want the recommended course of action and only a small proportion would not</p> <p>Clinicians: Most patients should receive the recommended course of action</p> <p>Policy makers: The recommendation can be adapted as a policy in most situations</p> <p>There is confidence that the true effect lies close to that of the estimate of the effect. Further research is unlikely to change the confidence in the estimate of effect</p>
Moderate-quality (three plus: ⊕⊕⊕○) evidence	Desirable consequences clearly outweigh undesirable consequences, or vice versa	<p>Patients: Most people in your situation would want the recommended course of action and only a small proportion would not</p> <p>Clinicians: Most patients should receive the recommended course of action</p> <p>Policy makers: The recommendation can be adapted as a policy in most situations</p> <p>There is moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Further research (if performed) is likely to have an important impact on the confidence in the estimate of effect and may change the estimate</p>
Low-quality (two plus: ⊕⊕○○) evidence	Desirable consequences clearly outweigh undesirable consequences, or vice versa	<p>Patients: Most people in your situation would want the recommended course of action and only a small proportion would not</p> <p>Clinicians: Most patients should receive the recommended course of action</p> <p>Policy makers: The recommendation can be adapted as a policy in most situations</p> <p>The confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate</p>
Very low-quality (one plus: ⊕○○○) evidence (these recommendations are very rarely issued)	Desirable consequences clearly outweigh undesirable consequences, or vice versa	<p>Patients: Most people in your situation would want the recommended course of action and only a small proportion would not</p> <p>Clinicians: Most patients should receive the recommended course of action</p> <p>Policy makers: The recommendation can be adapted as a policy in most situations</p> <p>The confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect</p>
<i>Weak recommendation</i>		
High-quality (four plus: ⊕⊕⊕⊕) evidence	Desirable consequences closely balanced with undesirable consequences	<p>Patients: The majority of people in your situation would want the recommended course of action, but many would not</p> <p>Clinicians: Be prepared to help patients to make a decision that is consistent with their own values</p> <p>Policy makers: The recommendation can be adapted as a policy in most situations</p> <p>There is confidence that the true effect lies close to that of the estimate of the effect. Further research is unlikely to change the confidence in the estimate of effect</p>
Moderate-quality (three plus: ⊕⊕⊕○) evidence	Desirable consequences closely balanced with undesirable consequences	<p>Patients: The majority of people in your situation would want the recommended course of action, but many would not</p> <p>Clinicians: Be prepared to help patients to make a decision that is consistent with their own values</p>

Table 1 (Continued)

Strength of recommendation and quality of evidence	Clarity of balance between desirable and undesirable consequences	Implications (for patients, clinicians, and policy makers) and interpretation of the quality of evidence
Low-quality (two plus: ⊕⊕○○) evidence	Uncertainty in the estimates of desirable and undesirable consequences; desirable consequences may be closely balanced with undesirable consequences	<p>Policy makers: The recommendation can be adapted as a policy in most situations</p> <p>There is moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Further research (if performed) is likely to have an important impact on the confidence in the estimate of effect and may change the estimate</p> <p>Patients: The majority of people in your situation would want the recommended course of action, but many would not</p> <p>Clinicians: Be prepared to help patients to make a decision that is consistent with their own values</p> <p>Policy makers: The recommendation can be adapted as a policy in most situations</p> <p>The confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate</p>
Very low-quality (one plus: ⊕○○○) evidence (this recommendation is very rarely issued)	Major uncertainty in the estimates of desirable and undesirable consequences; desirable consequences may be closely balanced with undesirable consequences	<p>Patients: The majority of people in your situation would want the recommended course of action, but many would not</p> <p>Clinicians: Be prepared to help patients to make a decision that is consistent with their own values</p> <p>Policy makers: The recommendation can be adapted as a policy in most situations</p> <p>The confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect</p>

Adapted from Schünemann et al. (26) and Brozek et al. (27).

GRADE, Grading of Recommendation, Assessment, Development, and Evaluation; ARIA, Allergic Rhinitis and its Impact on Asthma.

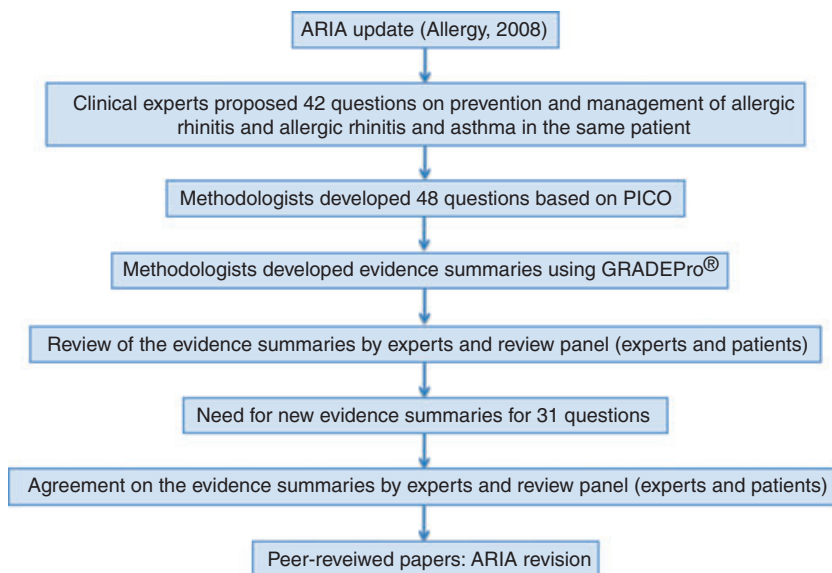


Figure 1 Development of Allergic Rhinitis and its Impact on Asthma revision.

Group composition

The guideline panel included two methodologists who developed evidence summaries with the help of an information scientist with experience in GRADE and two biostatisticians. Eight clinicians with experience in treating allergic rhinitis and asthma in adults and children were also members of the panel.

Formulation of questions and rating the importance of outcomes

The ARIA guideline panel identified 42 clinical problems requiring guidance. These general disease-oriented problems led to 48 specific, structured clinical questions based on the Population, Intervention, Comparison, and Outcome (PICO) approach (44) (Table 2). Only the ARIA guidelines approached the management of comorbid allergic rhinitis and asthma in the same patient.

An evidence summary (evidence profile and narrative summary) was prepared for each question using the GRADE approach. The following patient-important outcomes were identified: development of any allergy, allergic rhinitis, and/or asthma; presence and severity of nasal, ocular, and bronchial symptoms; exacerbations of asthma; hospitalization for asthma; quality of life; work/school performance; adverse effects; and resource utilization. For this revision of the ARIA guidelines, the authors did not formally assess the relative importance of each outcome, but used an informal assessment by the guideline panel for agreeing on which outcomes were critical, which were important and which were not important to patients (45).

Preparation of evidence summaries

One or more evidence profiles were prepared for most questions following the GRADE approach (27, 46) and using the GRADEPRO[®] software version 3.1 (47).

The evidence summaries were based on existing up-to-date, well-prepared systematic reviews identified by search-

ing MEDLINE, the Cochrane Library, reference lists of the most recent narrative reviews, related systematic reviews, or studies on this subject. Systematic reviews were supplemented, as necessary, with additional randomized trials (until August 2007 and for selected clinical questions until January 2009). When recent valid systematic reviews were unavailable, rigorous systematic reviews were not performed, but MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL) were systematically searched for relevant studies. Where possible, the results of identified studies using meta-analysis were used. The identified original studies were evaluated to inform judgements about the underlying evidence as long as they addressed the relevant PICO question. The reporting of most trials did not employ the approach recommended by the CONSORT statement (48).

Panel meetings

Two meetings were held to discuss the clinical questions and the results of the evidence reviews, as well as to agree on recommendations. The panel agreed that recommendations would be based on a formal consensus of the panel and that voting would be used solely if agreement could not be reached through discussion. Agreement on the type and wording of the recommendations that reflect their strength was also reached during the panel meeting by consensus. No recommendation required voting. There was no disagreement after discussion.

Balancing desirable and undesirable consequences of management options and developing recommendations

Evidence profiles were made available before, during and after the meetings. Formulating the recommendations included consideration of the quality of evidence, desirable and undesirable consequences of following the recommended course of action, and values and preferences of those for whom the recommendations are intended. For most of the recommendations, resource utilization (cost) was also taken into account (37). Statements about the underlying values and preferences as well as the remarks are integral parts of the recommendations and serve to facilitate accurate interpretation. They should not be omitted when citing or translating recommendations in the ARIA GRADE guidelines. The expression 'values and preferences' refers to the relative worth or importance of a healthy state of mind or the consequences of a decision to follow a particular course of action (i.e., the relative weight one attributes to particular benefits, risks, burdens and costs to determine their balance).

Consultation

A consultation process for the ARIA GRADE guidelines included 80 clinicians: allergists, pediatricians, primary care physicians, otolaryngologists, and pulmonary specialists from a variety of countries as well as three members of patient organizations to review the guidelines. As a result, additional searches were performed for more recent studies for 31 questions.

Table 2 Key questions of Allergic Rhinitis and its Impact on Asthma Revision

Should allergen avoidance methods or strategies be used by parents to avoid the development of allergic disease in children?
Should occupational allergen avoidance methods or strategies be used to avoid the development of allergic disease?
Should patients with allergic rhinitis and/or conjunctivitis use H1-antihistamines, glucocorticosteroids, antileukotrienes, chromones, decongestants, or ipratropium bromide? What is the relative effect of each of these medications?
Should allergen-specific immunotherapy be used in patients with allergic rhinitis? What is the effect of subcutaneous, intranasal, and sublingual-specific immunotherapy?
Should complementary and alternative treatments be used to treat allergic rhinitis?
Should medications for the treatment of allergic rhinitis be used in patients to treat concomitant asthma?

Update and adaptation of guidelines

Guidelines are living documents. As for any guideline document, the ARIA guidelines will have to be revised, primarily because:

- The science and evidence concerning rhinitis is evolving, and guidelines are based on published evidence up to a fixed point in time.
- For many clinical questions, there were no systematic reviews of current evidence available. This document will be updated when such reviews are available and if any major new research is published or new medications become available.
- These guidelines cover only some of the many possible clinical questions; the authors believe that the most important ones are currently addressed.

Many other questions relevant to the management of allergic rhinitis and its impact on asthma have been identified as potentially important. ARIA will develop a process to register and prioritize additional questions to be included in subsequent revisions. Topics that were identified during the consultation as potential priorities for update and additional evidence reviews include:

- Recommendations on using special formulas containing hydrolyzed protein for the prevention of allergic diseases in infants.
- Relative effectiveness and safety of different homeopathic methods and herbal medicines.
- Recommendations on using intranasal saline to treat allergic rhinitis.
- Recommendations on the prevention and treatment of the complications of allergic rhinitis.
- Refinement of the recommendations on the use of particular medications to treat intermittent/seasonal or persistent/perennial allergic rhinitis.

The guidelines should be applicable to all countries, all settings and, in particular, to low and middle-income countries. In the first set of ARIA guidelines, the management of allergic rhinitis was carefully considered in developing countries, taking into account affordability and availability of medications as well as the WHO essential lists of medicines (21). In the GRADE Revision, 16 experts from developing countries have drafted or reviewed the recommendations. As an example, a very careful approach was used, in particular for oral H₁-antihistamines. In the former WHO list, only chlorpheniramine was accepted, but in the latest revisions, alternative medications were listed (49). Experts and reviewers discussed in great length the relative risk/benefit ratio of these drugs (19).

Adaptation of these guidelines by an expert panel will be necessary in some circumstances. Moreover, guidelines may require adaptation for local circumstances and must be culturally appropriate and acceptable. Depending on when such a process occurs, a publication co-authored by WHO suggests that the following steps should be taken (50):

- Appoint a guideline committee comprising clinicians and methodologists.
- Determine the scope of the guidelines.

- Define the clinical questions to be addressed.
- Update the evidence-based tables, as necessary.
- Review the recommendations in the guidelines (the recommendations may need to be modified at a national level, depending on the local values, availability of medications, and costs).
- Disseminate the guidelines, with a 'use by' date.
- Develop a method to obtain feedback and plans for review and update.

The update of these ARIA GRADE guidelines is planned for December 2011.

Applicability of guidelines to the general patient population and research needs

There is a clear need to perform real-life studies to provide concrete evidence that the applicability of evidence obtained in mechanistic randomized controlled trials appropriately reported (48, 51) translates into daily practice settings (52). Such studies should be well designed, appropriately carried out, and answer clinical questions that are highly relevant for clinical practice. Moreover, they should be reported using appropriate methodology (53, 54). Finally, studies need to be conducted in special populations, including young children, elderly patients, patients with occupational allergic rhinitis and asthma, and patients in low-resource countries.

Implementing guidelines

In allergic rhinitis, two cluster, randomized trials have been performed comparing free treatment choice by physicians with guideline-based treatment. The first study was carried out on patients with seasonal allergic rhinitis consulting primary care physicians of three countries (Belgium, France, UK). The guideline-based strategy used the International Consensus of Rhinitis (55) and a visual analog scale to assess the severity of nasal or conjunctival symptoms (56). The second study was carried out with specialists in France. This guideline-based strategy used ARIA and a visual analog scale to assess the severity of combined nasal or conjunctival symptoms (20). Both studies showed that guideline-based management of allergic rhinitis is more effective than free treatment choice.

Implementation and dissemination of guidelines

Guidelines are sometimes difficult to apply (57), especially by users who need a rapid answer to a question about a patient without reading the entire document. A first step for a better understanding of the ARIA revision using GRADE is available (43) and summarizes 48 questions. For maximum transparency, the evidence profiles are available in an online supplementary document to inform those who require more complete information.

The appropriate dissemination of guidelines is essential as a start to implementation. Derivatives of guidelines (such as pocket guides, web-based activities, questionnaires, web-based documents) should follow the guideline recommendations

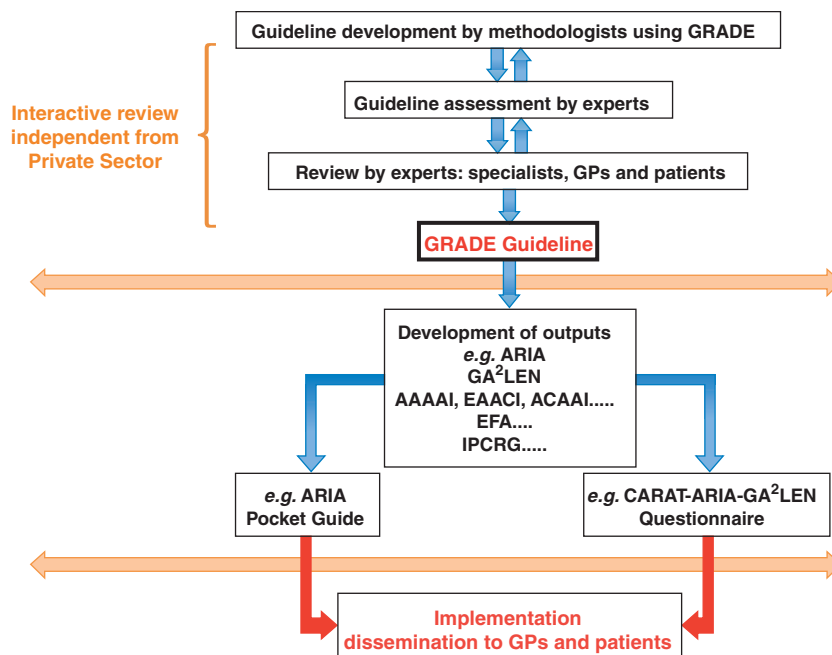


Figure 2 From guideline development to implementation.

exactly. As with the 2008 ARIA Pocket Guide, translated into more than 50 languages, we plan to disseminate the 2010 update internationally. Specialists and primary care physicians should be encouraged to use the guidelines and should be involved in the production of guideline summaries and educational materials derived from that guideline. There is an important need to disseminate the outputs to all involved in patient care. Pharmacists should also be aware as they are often the first portal approached by the patient. Patients likewise should be informed about these guidelines to create awareness of available treatments and to raise expectations. Simple fact sheets for patients should also be available (Fig. 2).

A question to be addressed in evaluating the efficacy of implementation is to obtain a validated and simple combined questionnaire to assess asthma and rhinitis in the same patient and to inform patients and physicians about the impact of the combined disease on quality of life, and school and work performance. This could be used as a tool for physician consultation or to give to patients before the consultation. As an example, in Portugal, a simple questionnaire (CARAT) includes 10 questions on the diagnosis of rhinitis and asthma in the same patient and the impact of these diseases on quality of life (58). This tool was developed using

a comprehensive set of methodological steps ensuring its design quality and validity. Additional validation studies to assess the psychometric properties of the questionnaire have been completed for patients with asthma who also suffer from rhinitis (59). The GA²LEN network (60) covers all countries and regions of Europe and offers all the advantages needed to rapidly test the CARAT in different languages and to provide a first tool to implement ARIA guidelines by primary care physicians and their patients. In addition, the ARIA online, interactive rhinitis and asthma questionnaires (<http://www.whiar.org>) can be used to identify comorbidities, to diagnose rhinitis and asthma as well as rhinitis severity and asthma control, and to compose letters to patients' physicians about the findings of the questionnaires. These questionnaires have been validated in large studies (SACRA).

The development of guidelines and educational outputs, their translation and validation are a prerequisite for successful guideline implementation. Implementation involves changing the behavior of physicians, health care professionals, and patients. Specifically targeted tools, special networks, and complementary strategies are needed. Evidence should be applied (and further obtained) for the effectiveness of various methods of guideline dissemination.

References

1. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008;**63**(Suppl 86): 8–160.
2. Bousquet J, Neukirch F, Bousquet PJ, Gehano P, Klossek JM, Le Gal M et al. Severity and impairment of allergic rhinitis in patients consulting in primary care. *J Allergy Clin Immunol* 2006;**117**:158–162.
3. Walker S, Khan-Wasti S, Fletcher M, Cullinan P, Harris J, Sheikh A. Seasonal allergic rhinitis is associated with a detrimental effect on examination performance in United Kingdom teenagers: case-control study. *J Allergy Clin Immunol* 2007;**120**: 381–387.
4. Weiler JM, Bloomfield JR, Woodworth GG, Grant AR, Layton TA, Brown TL et al.

- Effects of fexofenadine, diphenhydramine, and alcohol on driving performance. A randomized, placebo-controlled trial in the Iowa driving simulator. *Ann Intern Med* 2000;**132**:354–363.
5. Bousquet J, Fokkens W, Burney P, Durham SR, Bachert C, Akdis CA et al. Important research questions in allergy and related diseases: nonallergic rhinitis: a GA2LEN paper. *Allergy* 2008;**63**:842–853.
 6. Ait-Khaled N, Pearce N, Anderson HR, Ellwood P, Montefort S, Shah J. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. *Allergy* 2009;**64**:123–148.
 7. Walker S, Sheikh A. Self reported rhinitis is a significant problem for patients with asthma. *Prim Care Respir J* 2005;**14**:83–87.
 8. Ciprandi G, Cirillo I, Vizzaccaro A, Tosca M, Passalacqua G, Pallestrini E et al. Seasonal and perennial allergic rhinitis: is this classification adherent to real life? *Allergy* 2005;**60**:882–887.
 9. Bachert C, van Cauwenberge P, Olbrecht J, van Schoor J. Prevalence, classification and perception of allergic and nonallergic rhinitis in Belgium. *Allergy* 2006;**61**:693–698.
 10. Antonicelli L, Micucci C, Voltolini S, Senna GE, Di Blasi P, Visona G et al. Relationship between ARIA classification and drug treatment in allergic rhinitis and asthma. *Allergy* 2007;**62**:1064–1070.
 11. Castillo J, Molina J, Valero A, Mullol J. Prevalence and characteristics of rhinitis in asthmatic patients attending primary care in Spain. *Rhinology* 2010;**48**:35–40.
 12. Clatworthy J, Price D, Ryan D, Haughney J, Horne R. The value of self-report assessment of adherence, rhinitis and smoking in relation to asthma control. *Prim Care Respir J* 2009;**18**:300–305.
 13. Terreehorst I, Oosting AJ, Tempels-Pavlica Z, de Monchy JG, Bruijnzeel-Koomen CA, Hak E et al. Prevalence and severity of allergic rhinitis in house dust mite-allergic patients with bronchial asthma or atopic dermatitis. *Clin Exp Allergy* 2002;**32**:1160–1165.
 14. Bresciani M, Paradis L, Des Roches A, Vernhet H, Vachier I, Godard P et al. Rhinosinusitis in severe asthma. *J Allergy Clin Immunol* 2001;**107**:73–80.
 15. ten Brinke A, Grootendorst DC, Schmidt JT, De Bruine FT, van Buchem MA, Sterk PJ et al. Chronic sinusitis in severe asthma is related to sputum eosinophilia. *J Allergy Clin Immunol* 2002;**109**:621–626.
 16. Bousquet J, Gaugris S, Kocevar VS, Zhang Q, Yin DD, Polos PG et al. Increased risk of asthma attacks and emergency visits among asthma patients with allergic rhinitis: a subgroup analysis of the improving asthma control trial. *Clin Exp Allergy* 2005;**35**:723–727.
 17. Price D, Zhang Q, Kocevar VS, Yin DD, Thomas M. Effect of a concomitant diagnosis of allergic rhinitis on asthma-related health care use by adults. *Clin Exp Allergy* 2005;**35**:282–287.
 18. Sole D, Camelo-Nunes IC, Wandalsen GF, Melo KC, Naspitz CK. Is rhinitis alone or associated with atopic eczema a risk factor for severe asthma in children? *Pediatr Allergy Immunol* 2005;**16**:121–125.
 19. Church MK, Maurer M, Simons FE, Bindlev-Jensen C, van Cauwenberge P, Bousquet J et al. Risk of first-generation H(1)-antihistamines: a GA(2)LEN position paper. *Allergy* 2010;**65**:459–466.
 20. Bousquet J, Bodez T, Gehano P, Klossek JM, Liard F, Neukirch F et al. Implementation of Guidelines for Allergic Rhinitis in Specialist Practices. A Randomized Pragmatic Controlled Trial. *Int Arch Allergy Immunol* 2009;**150**:75–82.
 21. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;**108**(5 Suppl):S147–S334.
 22. Price D, Bond C, Bouchard J, Costa R, Keenan J, Levy ML et al. International Primary Care Respiratory Group (IPCRG) Guidelines: management of allergic rhinitis. *Prim Care Respir J* 2006;**15**:58–70.
 23. Scadding GK, Durham SR, Mirakian R, Jones NS, Leech SC, Farooque S et al. BSACI guidelines for the management of allergic and non-allergic rhinitis. *Clin Exp Allergy* 2008;**38**:19–42.
 24. Wallace DV, Dykewicz MS, Bernstein DI, Blessing-Moore J, Cox L, Khan DA et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol* 2008;**122**(2 Suppl): S1–S84.
 25. GEMA. Spanish Asthma Management Guide. *Arch Bronconeumol* 2009;**45**(Suppl 7):2–35.
 26. Schünemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A et al. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. *Am J Respir Crit Care Med* 2006;**174**:605–614.
 27. Brozek JL, Baena-Cagnani CE, Bonini S, Canonica GW, Rasi G, van Wijk RG et al. Methodology for development of the Allergic Rhinitis and its Impact on Asthma guideline 2008 update. *Allergy* 2008;**63**:38–46.
 28. Guyatt G, Alk A, Hirsh J, Kearon C, Grouther M, Gutterman D et al. The vexing problem of guidelines and conflict of interest: a potential solution. *Ann Intern Med* 2010;**152**:738–741.
 29. Schunemann HJ, Osborne M, Moss J, Manthous C, Wagner G, Sicilian L et al. An official American Thoracic Society Policy statement: managing conflict of interest in professional societies. *Am J Respir Crit Care Med* 2009;**180**:564–580.
 30. Hirsh J, Guyatt G. Clinical experts or methodologists to write clinical guidelines? *Lancet* 2009;**374**:273–275.
 31. van Weel C. General practitioners' central role in management of asthma and allergic rhinitis. *Allergy* 2008;**63**:1005–1007.
 32. Ryan D, van Weel C, Bousquet J, Toskala E, Ahlstedt S, Palkonen S et al. Primary care: the cornerstone of diagnosis of allergic rhinitis. *Allergy* 2008;**63**:981–989.
 33. Costa DJ, Bousquet PJ, Ryan D, Price D, Demoly P, Brozek J et al. Guidelines for allergic rhinitis need to be used in primary care. *Prim Care Respir J* 2009;**18**:250–257.
 34. World Health Organization. Global Programme on Evidence for Health Policy. Guidelines for WHO Guidelines. EIP/GPE/EQC/2003.1. Geneva, 2003.
 35. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**:1490.
 36. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A et al. Going from evidence to recommendations. *BMJ* 2008;**336**:1049–1051.
 37. Guyatt GH, Oxman AD, Kunz R, Jaeschke R, Helfand M, Liberati A et al. Incorporating considerations of resources use into grading recommendations. *BMJ* 2008;**336**:1170–1173.
 38. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians? *BMJ* 2008;**336**: 995–998.
 39. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**:924–926.
 40. Schunemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ* 2008;**336**:1106–1110.
 41. Guyatt G, Vist G, Falck-Ytter Y, Kunz R, Magrini N, Schunemann H. An emerging consensus on grading recommendations. <http://www.evidence-basedmedicine.com> 2005; Module 37. Topic 2011:189.
 42. Green RJ, Davis G, Price D. Concerns of patients with allergic rhinitis: the Allergic Rhinitis Care Programme in South Africa. *Prim Care Respir J* 2007;**16**:299–303.
 43. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB et al.

- Allergic rhinitis and its impact on asthma (ARIA) guidelines – 2010 revision. *J Allergy Clin Immunol* 2010; (in press).
44. Oxman AD, Guyatt GH. Guidelines for reading literature reviews. *CMAJ* 1988;**138**: 697–703.
 45. Schünemann HJ, Oxman AD, Fretheim A. Improving the use of research evidence in guideline development: 6. Determining which outcomes are important. *Health Res Policy Syst* 2006;**4**:18.
 46. Oxman AD, Schunemann HJ, Fretheim A. Improving the use of research evidence in guideline development: 8. Synthesis and presentation of evidence. *Health Res Policy Syst* 2006;**4**:20.
 47. Schünemann H, Brozek J, Oxman A. GRADEpro profiler. (<http://www.cc-ims.net/revman/gradepr>). 2008 [cited; Available from: <http://www.cc-ims.net/revman/gradepr> 2009.
 48. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001;**357**:1191–1194.
 49. Essential Medicines. WHO Model List, (revised March 2008). <http://www.who.int/medicines/publications/essentialmedicines/en/> 2008.
 50. Schünemann HJ, Fretheim A, Oxman AD. Improving the use of research evidence in guideline development: 13. Applicability, transferability and adaptation. *Health Res Policy Syst* 2006;**4**:25.
 51. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;**340**:c332.
 52. Holgate S, Bisgaard H, Bjermer L, Haahtela T, Haughney J, Horne R et al. The Brussels Declaration: the need for change in asthma management. *Eur Respir J* 2008;**32**:1433–1442.
 53. Campbell MK, Elbourne DR, Altman DG. CONSORT statement: extension to cluster randomised trials. *BMJ* 2004;**328**:702–708.
 54. Zwarenstein M, Treweek S, Gagnier JJ, Altman DG, Tunis S, Haynes B et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ* 2008;**337**:a2390.
 55. International Rhinitis Management Working Group. International Consensus Report on Diagnosis and Management of Rhinitis. *Allergy* 1994;**49**(19 Suppl):1–34.
 56. Bousquet J, Lund VJ, Van Cauwenberge P, Bremard-Oury C, Mounedji N, Stevens MT et al. Implementation of guidelines for seasonal allergic rhinitis: a randomized controlled trial. *Allergy* 2003;**58**:733–741.
 57. Hussain T, Michel G, Shiffman RN. The Yale Guideline Recommendation Corpus: a representative sample of the knowledge content of guidelines. *Int J Med Inform* 2009;**78**: 354–363.
 58. Nogueira-Silva L, Martins SV, Cruz-Correira R, Azevedo LF, Morais-Almeida M, Bugalho-Almeida A et al. Control of allergic rhinitis and asthma test—a formal approach to the development of a measuring tool. *Respir Res* 2009;**10**:52.
 59. Fonseca J, Nogueira-Silva L, Morais-Almeida M, Azevedo L, Sa-Sousa A, Branco-Ferreira M et al. Validation of a questionnaire (CARAT 10) to assess rhinitis and asthma in asthmatic patients. *Allergy* 2010; **65**:1042–1048.
 60. Bousquet J, Burney PG, Zuberbier T, Cauwenberge PV, Akdis CA, Bindslev-Jensen C et al. GA2LEN (Global Allergy and Asthma European Network) addresses the allergy and asthma ‘epidemic’. *Allergy* 2009; **64**:969–977.