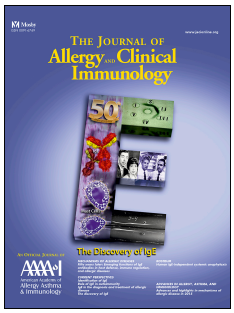
# Accepted Manuscript




Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines – 2016 Revision

Jan L. Brożek, MD, PhD, Jean Bousquet, MD, PhD, Ioana Agache, MD, PhD, Arnav Agarwal, BHSc, Claus Bachert, MD PhD, Sinthia Bosnic-Anticevich, BPharm, PhD, Romina Brignardello-Petersen, DDS, MSc, PhD, G. Walter Canonica, MD, Thomas Casale, MD, Niels H. Chavannes, MD, PhD, Jaime Correia de Sousa, MD, PhD, Alvaro A. Cruz, Carlos A. Cuello-Garcia, MD, Pascal Demoly, MD, PhD, Mark Dykewicz, MD, Itziar Etxeandia-Ikobaltzeta, PhD, Ivan D. Florez, MD, MSc, Wytske Fokkens, MD, PhD, Joao Fonseca, MD, PhD, Peter W. Hellings, MD, PhD, Ludger Klimek, MD, PhD, Sergio Kowalski, MD, Piotr Kuna, MD, PhD, Kaja-Triin Laisaar, MD, MPH, Désirée E. Larenas-Linnemann, MD, Karin C. Lødrup Carlsen, MD, PhD, Peter J. Manning, MD, Eli Meltzer, MD, Joaquim Mullol, MD, PhD, Antonella Muraro, MD, PhD, Robyn O'Hehir, PhD, Ken Ohta, MD, PhD, Petr Panzner, MD, PhD, Nikolaos Papadopoulos, MD, PhD, Hae-Sim Park, MD, PhD, Gianni Passalacqua, MD, Ruby Pawankar, MD, PhD, David Price, MD, John J. Riva, MD, Yetiani Roldán, MD, Dermot Ryan, MD, Behnam Sadeghirad, PharmD, MPH, Boleslaw Samolinski, MD, PhD, Peter Schmid-Grendelmeier, MD, Aziz Sheikh, MD, MSc, Alkis Togias, MD, Antonio Valero, MD, PhD, Arunas Valiulis, MD, PhD, Erkka Valovirta, MD, PhD, Matthew Ventresca, MSc, Dana Wallace, MD, Susan Waserman, MD, MSc, Magnus Wickman, MD, Wojtek Wiercioch, MSc, Juan José Yepes-Nuñez, MD, MSc, Luo Zhang, MD, Yuan Zhang, MPH, Mihaela Zidarn, MD, MSc, Torsten Zuberbier, MD, Holger J. Schünemann, MD, PhD, MSc

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## Table 1. Recommendations

| Recommendation | Assumed values and preferences | Explanations and other considerations |
|---|---|---|
| **Question 1: Should a combination of oral H1-antihistamine and intranasal corticosteroid vs. intranasal corticosteroid alone be used for treatment of allergic rhinitis?** | | |
| Recommendation 1A<br>In patients with seasonal allergic rhinitis, we suggest either a combination of an intranasal corticosteroid with an oral H1-antihistamine or an intranasal corticosteroid alone (conditional recommendation \| low certainty of evidence) | ARIA guideline panel acknowledged that the choice of treatment would mostly depend on patient preferences and local availability and cost of treatment. Panel members assumed that in majority of situations, potential net benefit would not justify spending additional resources. | This is a conditional recommendation, thus different choices will be appropriate for different patients – in settings where additional cost of OAH is not large and/or patient values and preferences differ from those assumed by guideline panel members a combination therapy may be a reasonable choice, especially in patients not well controlled with INCS alone, those with pronounced ocular symptoms or those commencing treatment because of likely faster onset of treatment effects.<br>This recommendation concerns regular use of newer, less sedative OAH and INCS in seasonal AR. For older OAHs with more sedative effects the balance of desirable and undesirable effects may be different. |
| Recommendation 1B<br>In patients with perennial allergic rhinitis, we suggest an intranasal corticosteroid alone rather than a combination of an intranasal corticosteroid with an oral H1-antihistamine (conditional recommendation \| very low certainty of evidence) | – | Currently available evidence suggests that there is no additional benefit from a combination therapy compared to INCS alone and there may be additional undesirable effects. This recommendation is conditional because of sparse information, thus, very low certainty of the estimated effects. |
| **Question 2: Should a combination of intranasal H1-antihistamine (INAH) and intranasal corticosteroid vs. intranasal corticosteroid alone be used for treatment of allergic rhinitis?** | | |
| Recommendation 2A<br>In patients with seasonal AR, we suggest either a combination of an intranasal corticosteroid with an intranasal H1-antihistamine or an intranasal corticosteroid alone (conditional recommendation \| moderate certainty of evidence). | The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment. At the initiation of treatment (~ first 2 weeks) a combination of INCS with INAH may act faster than INCS alone and, thus, may be preferred by some patients. | This is a conditional recommendation, thus different choices will be appropriate for different patients – in settings where additional cost of combination therapy is not large and/or patients value potential benefits more than any increased risk of adverse effects, a combination therapy may be a reasonable choice. |
| Recommendation 2B<br>In patients with perennial AR, we suggest either a combination of an intranasal corticosteroid with an intranasal H1-antihistamine or an intranasal corticosteroid alone (conditional recommendation \| very low certainty of evidence). | The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment. | This is a conditional recommendation because of the very low certainty of the evidence. At the initiation of treatment (~ first 2 weeks) a combination of INCS with INAH may act faster than INCS alone, thus, may be preferred by some patients. |
| **Question 3: Should a combination of an intranasal H1-antihistamine and an intranasal corticosteroid vs. intranasal H1-antihistamine alone be used for treatment of allergic rhinitis?** | | |
| Recommendation 3A<br>In patients with seasonal AR, we suggest a combination of an intranasal corticosteroid with an intranasal H1-antihistamine rather than an intranasal H1-antihistamine alone (conditional recommendation \| low certainty of evidence) | This recommendation places higher value on additional reduction of symptoms and improved quality of life with a combination therapy, compared to INAH alone. It places a lower value on avoiding additional cost (expenditure of resources). | This is a conditional recommendation, thus different choices will be appropriate for different patients – in settings where additional cost of a combination therapy is large, an alternative choice, i.e. INAH alone, may be equally reasonable. One panel member thought that the recommendation should be conditional for either the intervention or the comparison. |
| **Question 4: Should a leukotriene receptor antagonist (LTRA) vs. an oral H1-antihistamine be used for treatment of allergic rhinitis?** | | |
| Recommendation 4A<br>In patients with seasonal AR, we suggest either a leukotriene receptor antagonist or an oral H1-antihistamine (conditional recommendation \| moderate certainty of evidence) | Panel members acknowledged that the choice of LTRA or OAH will mostly depend on patient preferences and local availability and cost of specific medications. In many settings OAH may still be more cost-effective but this will largely depend on availability of generic LTRA and the local cost of various newer-generation OAH and LTRA. | Some patients with AR who have concomitant asthma, especially exercise-induced and/or aspirin exacerbated respiratory disease, may benefit from LTRA more than from OAH. However, this recommendation applies to treatment of AR not to treatment of asthma. Patients with asthma who have concomitant AR should receive an appropriate treatment according to the guidelines for the treatment of asthma. |
| Recommendation 4B<br>In patients with perennial AR, we suggest an oral H1-antihistamine rather than a leukotriene receptor antagonist (conditional recommendation \| low certainty of | This recommendation places a higher value on possibly larger improvement of symptoms and quality of life with OAH, compared to LTRA. It places a lower value on possible increased risk of somnolence. | This is a conditional recommendation, thus different choices will be appropriate for different patients based on their preferences for reduction of symptoms versus avoiding the risk of adverse effects – this may be more important for patients with PAR than with SAR as they might use those medications for longer periods of |

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|---|---|---|
| evidence) | | time.<br>Some patients with AR and concomitant asthma, especially exercise-induced and/or aspirin exacerbated respiratory disease, may benefit from LTRA more than from OAH. However, this recommendation applies to treatment of AR not to treatment of asthma. Patients with asthma who have concomitant AR should receive an appropriate treatment according to the guidelines for the treatment of asthma. |
| **Question 5: Should an intranasal H1-antihistamine vs. an intranasal corticosteroid be used for treatment of allergic rhinitis?** | | |
| Recommendation 5A<br>In patients with seasonal AR, we suggest an intranasal corticosteroid rather than an intranasal H1-antihistamine (conditional recommendation \| moderate certainty of evidence). | This recommendation places a higher value on likely small but greater reduction of symptoms and improvement of quality of life with INCS, compared to INAH, and a lower value on avoiding larger cost of treatment with INCS in many jurisdictions. | This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his values and preferences considering local availability and costs. |
| Recommendation 5B<br>In patients with perennial AR, we suggest an intranasal corticosteroid rather than intranasal H1-antihistamine (conditional recommendation \| low certainty of evidence). | This recommendation places a higher value on probably greater reduction of nasal symptoms with INCS, compared to INAH, although the overall difference is likely small. It places a lower value on avoiding larger cost of treatment with INCS in many jurisdictions. | This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his values and preferences considering local availability and costs. |
| **Question 6: Should an intranasal H1-antihistamine vs. an oral H1-antihistamine be used for treatment of allergic rhinitis?** | | |
| Recommendation 6A<br>In patients with SAR, we suggest either intranasal or oral H1-antihistamine (conditional recommendation \| low certainty of evidence). | The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment. | This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his preferences, considering local availability, coverage, and costs. |
| Recommendation 6B<br>In patients with perennial AR, we suggest either intranasal or oral H1-antihistamine (conditional recommendation \| very low certainty of evidence). | The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment. | This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his preferences, considering local availability, coverage, and costs. |

**Table e1: Interpretation of strong and conditional (weak) recommendations**

| Implications | Strong recommendation | Conditional (weak) recommendation |
|---|---|---|
| **For patients** | Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences. | The majority of individuals in this situation would want the suggested course of action, but many would not. |
| **For clinicians** | Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. | Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences. |
| **For policy makers** | The recommendation can be adapted as policy or performance measure in most situations | Policy making will require substantial debate and involvement of various stakeholders. Documentation of appropriate (e.g. shared) decision-making processes can serve as performance measure. |

## Table e2. Recommendations

| Recommendation | Assumed values and preferences | Explanations and other considerations |
|---|---|---|
| **Question 1: Should a combination of oral H1-antihistamine and intranasal corticosteroid vs. intranasal corticosteroid alone be used for treatment of allergic rhinitis?** | | |
| Recommendation 1A<br>In patients with seasonal allergic rhinitis, we suggest either a combination of an intranasal corticosteroid with an oral H1-antihistamine or an intranasal corticosteroid alone (conditional recommendation \| low certainty of evidence) | ARIA guideline panel acknowledged that the choice of treatment would mostly depend on patient preferences and local availability and cost of treatment. Panel members assumed that in majority of situations, potential net benefit would not justify spending additional resources. | This is a conditional recommendation, thus different choices will be appropriate for different patients – in settings where additional cost of OAH is not large and/or patient values and preferences differ from those assumed by guideline panel members a combination therapy may be a reasonable choice, especially in patients not well controlled with INCS alone, those with pronounced ocular symptoms or those commencing treatment because of likely faster onset of treatment effects.<br>This recommendation concerns regular use of newer, less sedative OAH and INCS in seasonal AR. For older OAHs with more sedative effects the balance of desirable and undesirable effects may be different. |
| Recommendation 1B<br>In patients with perennial allergic rhinitis, we suggest an intranasal corticosteroid alone rather than a combination of an intranasal corticosteroid with an oral H1-antihistamine (conditional recommendation \| very low certainty of evidence) | – | Currently available evidence suggests that there is no additional benefit from a combination therapy compared to INCS alone and there may be additional undesirable effects. This recommendation is conditional because of sparse information, thus, very low certainty of the estimated effects. |
| **Question 2: Should a combination of intranasal H1-antihistamine (INAH) and intranasal corticosteroid vs. intranasal corticosteroid alone be used for treatment of allergic rhinitis?** | | |
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| **Question 6: Should an intranasal H1-antihistamine vs. an oral H1-antihistamine be used for treatment of allergic rhinitis?** | | |
| Recommendation 6A<br>In patients with SAR, we suggest either intranasal or oral H1-antihistamine (conditional recommendation \| low certainty of evidence). | The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment. | This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his preferences, considering local availability, coverage, and costs. |
| Recommendation 6B<br>In patients with perennial AR, we suggest either intranasal or oral H1-antihistamine (conditional recommendation \| very low certainty of evidence). | The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment. | This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his preferences, considering local availability, coverage, and costs. |

**Box 1: Strength of recommendation**

***Strong recommendation***

**For patients:** most individuals in this situation would want the recommended course of action, and only a small proportion would not.

**For clinicians:** most individuals should receive the intervention. Adherence to a strong recommendation could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.

**For health care policy makers:** the recommendation can be adopted as policy or performance measure in most situations.

***Conditional recommendation***

**For patients:** the majority of individuals in this situation would want the suggested course of action, but many would not.

**For clinicians:** recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.

**For health care policy makers:** policy-making will require substantial debate and involvement of various stakeholders. Documentation of appropriate (e.g. shared) decision-making processes can serve as performance measure.

# Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines – 2016 Revision

**Authors**

Jan L. Brożek MD, PhD[1,2], Jean Bousquet MD, PhD[3], Ioana Agache MD, PhD[4], Arnav Agarwal BHSc[1,5], Claus Bachert MD PhD[6], Sinthia Bosnic-Anticevich BPharm, PhD[7], Romina Brignardello-Petersen DDS, MSc, PhD[1], G. Walter Canonica MD[8], Thomas Casale MD[9], Niels H. Chavannes MD, PhD[10], Jaime Correia de Sousa MD, PhD[11], Alvaro A. Cruz[12], Carlos A. Cuello-Garcia MD[1], Pascal Demoly MD, PhD[13], Mark Dykewicz MD[14], Itziar Etxeandia-Ikobaltzeta PhD[1,15], Ivan D. Florez MD, MSc[1,16], Wytske Fokkens MD, PhD[17], Joao Fonseca MD, PhD[18], Peter W. Hellings MD, PhD[19], Ludger Klimek MD, PhD[20], Sergio Kowalski MD[1], Piotr Kuna MD, PhD[21], Kaja-Triin Laisaar MD, MPH[22], Désirée E. Larenas-Linnemann MD[23], Karin C. Lødrup Carlsen MD, PhD[24], Peter J. Manning MD[25], Eli Meltzer MD[26], Joaquim Mullol MD, PhD[27], Antonella Muraro MD, PhD[28], Robyn O'Hehir PhD[29], Ken Ohta MD, PhD[30], Petr Panzner MD, PhD[31], Nikolaos Papadopoulos MD, PhD[32,33], Hae-Sim Park MD, PhD[34], Gianni Passalacqua MD[35], Ruby Pawankar MD, PhD[36], David Price MD[37], John J. Riva MD[1,38], Yetiani Roldán MD[1], Dermot Ryan MD[39], Behnam Sadeghirad PharmD, MPH[40], Boleslaw Samolinski MD, PhD[41], Peter Schmid-Grendelmeier MD[42], Aziz Sheikh MD, MSc[43], Alkis Togias MD[44], Antonio Valero MD, PhD[45], Arunas Valiulis MD, PhD[46], Erkka Valovirta MD, PhD[47], Matthew Ventresca MSc[1], Dana Wallace MD[48], Susan Waserman MD, MSc[2], Magnus Wickman MD[49], Wojtek Wiercioch MSc[1], Juan José Yepes-Nuñez MD, MSc[1,50], Luo Zhang MD[51], Yuan Zhang MPH[1], Mihaela Zidarn MD, MSc[52], Torsten Zuberbier MD[53], Holger J. Schünemann MD, PhD, MSc[1,54]

1 Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada
2 Division of Clinical Immunology and Allergy, Department of Medicine, McMaster University, Hamilton, ON, Canada
3 University Hospital, Montpellier, France
4 Transylvania University, Faculty of Medicine, Brasov, Romania
5 School of Medicine, University of Toronto, Toronto, Ontario, Canada

6 Ghent University Hospital, Upper Airways Research Laboratory, Ghent, Belgium
7 Woolcock Institute, University of Sydney, Sydney, Australia
8 Asthma & Allergy Clinic, Humanitas University, Rozzano, 20089 Milano, Italy
9 Division of Allergy and Immunology, University of South Florida, Tampa, Florida, USA
10 Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, The Netherlands
11 Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Braga, Portugal, ICVS/3B's - PT Government Associate Laboratory, Braga/Guimarães, Portugal
12 ProAR – Center of Excellence for Asthma, Federal University of Bahia, Brazil
13 University Hospital of Montpellier, Montpellier, and Sorbonne Universités, UPMC Paris 06, UMR-S 1136, IPLESP, Equipe EPAR, 75013, Paris, France
14 Section of Allergy and Immunology, Department of Internal Medicine, Saint Louis University School of Medicine, St. Louis, Missouri, USA
15 Dirección de Investigación e Innovación Sanitaria, Departamento de Salud, Gobierno Vasco-Eusko Jaurlaritza, Vitoria-Gasteiz, Álava-Araba, España
16 Department of Pediatrics, University of Antioquia, Medellin, Colombia
17 Department of Otorhinolaryngology, Academic Medical Centre, Amsterdam, The Netherlands
18 CINTESIS- Center for Health Technology and Services Research, Faculdade de Medicina, Universidade do Porto & Allergy, CUF Porto Hospital and Instituto, Porto, Portugal
19 Department of Otorhinolaryngology, University Hospitals Leuven, Leuven, Belgium ; Department of Otorhinolaryngology, Academic Medical Center (AMC), Amsterdam, The Netherlands
20 Center of Rhinology and Allergology, Wiesbaden, Germany
21 Division of Internal Medicine Asthma and Allergy, Faculty of Medicine, Medical University of Lodz, Poland
22 Institute of Family Medicine and Public Health, University of Tartu, Tartu, Estonia
23 Hospital Médica Sur, Mexico City, Mexico
24 Department of Paediatrics, Oslo University Hospital, University of Oslo, Oslo, Norway

25 Department of Medicine, Royal College of Surgeons in Ireland Medical School, Dublin, Ireland
26 Department of Pediatrics, Division of Allergy & Immunology, University of California, San Diego, California, USA
27 Unitat de Rinologia i Clínica de l'Olfacte, Servei d'ORL, Hospital Clínic, Clinical & Experimental Respiratory Immunoallergy, IDIBAPS, Barcelona, Spain
28 Department of Women and Child Health & Food Allergy Referral Centre Veneto Region, University of Padua, Italy
29 Alfred Hospital and Monash University, Melbourne, Victoria, Australia
30 National Hospital Organization Tokyo National Hospital, Kiyose-city, Tokyo, Japan
31 Department of Immunology and Allergology, Faculty of Medicine in Pilsen, Charles University in Prague, Czech Republic
32 Allergy Department, 2nd Pediatric Clinic, University of Athens, Greece
33 Division of Infection, Immunity & Respiratory Medicine, University of Manchester, UK
34 Department of Allergy and Rheumatology, Ajou University School of Medicine, Suwon, Korea
35 Allergy and Respiratory Diseases, IRCCS San Martino - IST - University of Genoa, Genoa, Italy
36 Department of Pediatrics, Nippon Medical School, Tokyo, Japan
37 University of Aberdeen, Aberdeen, UK
38 Department of Family Medicine, McMaster University, Hamilton, ON, Canada
39 Allergy and Respiratory Research Group, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, UK
40 HIV/STI Surveillance Research Center, and WHO Collaborating Center for HIV Surveillance, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran
41 Department of Prevention of Environmental Hazards and Allergology, Medical University of Warsaw, Poland
42 Allergy Unit, Dept. of Dermatology, University Hospital of Zürich and Christine Kühne Center for Allergy Research and Education CK-CARE, Davos, Switzerland

43 Asthma UK Centre for Applied Research, Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, UK
44 Asthma and Inflammation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA
45 Department of Pneumology and Allergy, Immunoallèrgia Respiratòria Clínica I Experimental (IDIBAPS), Centro de Investigaciones Biomédicas en Red de Enfermedades Respiratorias (CIBERES), Barcelona, Spain
46 Vilnius University Clinic of Children's Diseases and Public Health Institute, Vilnius, Lithuania; European Academy of Paediatrics (EAP/UEMS-SP), Brussels, Belgium
47 Department of Lung Diseases and Clinical Immunology, University of Turku and Allergy Clinic Terveystalo Turku, Finland
48 Nova Southeastern University, Fort Lauderdale, Florida, USA
49 Department of Pediatrics, Sachs' Children's Hospital, South General Hospital and Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
50 School of Medicine, University of Antioquia, Medellín, Colombia
51 Department of Otolaryngology Head and Neck Surgery, Beijing TongRen Hospital and Beijing Institute of Otolaryngology, Beijing, China
52 University Clinic of Pulmonary and Allergic Diseases Golnik, Slovenia
53 Department of Dermatology and Allergy, Charité - Universitätsmedizin Berlin, Germany
54 Division of General Internal Medicine, Department of Medicine, McMaster University, Hamilton, ON, Canada

**Corresponding author**
Holger J Schünemann, MD, PhD, MSc, FRCP(C)
McMaster University
Health Sciences Centre 2C16
1280 Main Street West
Hamilton, ON L8S 4K1, Canada

**Clinical Implications:** The 2016 revision of the ARIA guidelines offers updated advice for clinicians and patients about the most commonly used treatments for allergic rhinitis.

**Capsule summary:** The 2016 revision of ARIA offers updated recommendations about the use of oral H1-antihistamines, leukotriene receptor antagonists, intranasal H1-antihistamines in combination with intranasal corticosteroids, and new recommendations about the use of combinations of oral and intranasal medications.

**Key words:** allergic rhinitis, practice guideline

**Abbreviations:** AR – allergic rhinitis, ARIA – Allergic Rhinitis and its Impact on Asthma, COPD – chronic obstructive pulmonary disease, EIP on AHA – European Innovation Partnership on Active and Healthy Ageing, EtD – evidence-to-decision framework, GRADE – Grades of Recommendation, Assessment, Development and Evaluation, ICER – incremental cost-effectiveness ratio, ICP – integrated care pathway, INAH – intranasal $H_1$-antihistamine, INCS – intranasal corticosteroid, LTRA – leukotriene receptor antagonist, MID – minimal important difference, OAH – oral $H_1$-antihistamine, PAR – perennial allergic rhinitis, RCT – randomized controlled trial, SAR – seasonal allergic rhinitis, SoF – summary of findings table, TNSS – total nasal symptom score

**Word count:**
2,900 – executive summary

## Abstract

**Background:** Allergic rhinitis affects 10 to 40% of the population. It reduces quality of life, school and work performance, and is a frequent reason for office visits in general practice. Medical costs are large but avoidable costs associated with lost work productivity are even larger than those incurred by asthma. New evidence has accumulated since the last revision of the Allergic Rhinitis and its Impact on Asthma – ARIA guidelines in 2010 prompting its update.
**Objective:** To provide a targeted update of the ARIA guidelines.
**Methods:** The ARIA guideline panel identified new clinical questions and selected questions requiring an update. We performed systematic reviews of health effects and the evidence about patient values and preferences, and resource requirements (up to June 2016). We followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence-to-decision frameworks to develop recommendations.
**Results:** The 2016 revision of the ARIA guidelines provides updated and new recommendations about the pharmacological treatment of allergic rhinitis. It specifically addresses the relative merits of using oral H1-antihistamines, intranasal H1-antihistamines, intranasal corticosteroids, and leukotriene receptor antagonists either alone or their combination. The ARIA guideline panel provides specific recommendations for the choice of treatment, the rationale for the choice, and discusses specific considerations that clinicians and patients may want to review in order to choose the management most appropriate for an individual patient.
**Conclusions:** Appropriate treatment of allergic rhinitis may improve patients' quality of life, school and work productivity. ARIA recommendations support patients, their caregivers, and health care providers in choosing the optimal treatment.


## Introduction

Allergic rhinitis (AR) is among the most common diseases globally and usually persists throughout life [1]. The prevalence of self-reported AR has been estimated to be approximately 2 to 25% in children[2] and 1 to over 40% in adults[1, 3]. The prevalence of confirmed AR in adults in Europe ranged from 17% to 28.5%. Recent studies show that the prevalence of AR has increased, in particular in countries with initial low prevalence

(for a discussion of prevalence of AR see section 5.1.–5.2. in ARIA 2008 Update[1]). Classical symptoms of AR are nasal itching, sneezing, rhinorrhea, and nasal congestion. Ocular symptoms are also frequent; allergic rhino-conjunctivitis is associated with itching and redness of the eyes and tearing. Other symptoms include itching of the palate, postnasal drip and cough.

AR is also frequently associated with asthma which is found in 15% to 38% of patients with allergic rhinitis[4, 5] and that nasal symptoms are present in 6% to 85% patients with asthma[6-9]. In addition AR is a risk factor for asthma[4, 9] and uncontrolled moderate-severe AR impacts asthma control[10, 11].

Compared to other medical conditions, AR may appear not to be serious because it is not associated with a severe morbidity and mortality. However, the burden and costs are substantial[12]. AR reduces quality of life of many patients impairing sleep quality and cognitive function, and causing irritability and fatigue. Allergic rhinitis is associated with decreased school and work performance, especially during the peak pollen season[1]. AR is a frequent reason for general practice office visits. Annual direct medical costs of AR are substantial but indirect costs associated with lost work productivity are greater than those incurred by asthma[13-15]. Appropriate treatment of AR improves symptoms, quality of life and work and school performance.

Clinical practice guidelines for AR management were developed over the past 20 years [16] and have improved the care of patients with AR [17]. Transparent reporting of guidelines to facilitate understanding and acceptance are however needed. The ARIA (Allergic Rhinitis and its Impact on Asthma) initiative was initiated during a WHO workshop in 1999 [18]. It was updated in 2008 [1]. The ARIA 2010 Revision was the first evidence-based guideline in allergy to follow the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach [19] with no influence of for-profit organizations and an explicit declaration and management of potential competing interests of panel members[20]. It summarized the potential benefits and harms underlying the recommendations as well as assumptions around values and preferences that influenced the strength and direction of the recommendations. In 2014, the ARIA revision was found to rank first in the rigor of development and quality of reporting of guidelines about the management of AR [16] although recent guidelines published later were not considered[21].

## Clinical questions

Since the last revision of the ARIA guidelines in 2010[20] new treatments became available and new evidence accumulated about selected other treatments. Using a modified Delphi process, the ARIA guideline panel selected new questions that required answering with recommendations or the existing recommendations that required an updated review of the evidence and potentially updating the recommendations themselves. This revision of the

ARIA guidelines is, therefore, limited in scope and addresses 6 questions about the treatment of AR:

1. Should a combination of oral H1-antihistamine (OAH) and intranasal corticosteroid (INCS) vs. intranasal corticosteroid alone be used for treatment of allergic rhinitis?
2. Should a combination of intranasal H1-antihistamine (INAH) and intranasal corticosteroid vs. intranasal corticosteroid alone be used for treatment of allergic rhinitis?
3. Should a combination of an intranasal H1-antihistamine and an intranasal corticosteroid vs. intranasal H1-antihistamine alone be used for treatment of allergic rhinitis?
4. Should a leukotriene receptor antagonist (LTRA) vs. an oral H1-antihistamine be used for treatment of allergic rhinitis?
5. Should an intranasal H1-antihistamine vs. an intranasal corticosteroid be used for treatment of allergic rhinitis?
6. Should an intranasal H1-antihistamine vs. an oral H1-antihistamine be used for treatment of allergic rhinitis?

The target audience of these guidelines is primary care clinicians, school nurses, pharmacists, specialists in allergy and clinical immunology, general internists managing patients with allergic rhinitis, and pediatricians. Ear-nose-throat specialists, other health care professionals, and health care policy makers may also benefit from these guidelines.

### Classification of allergic rhinitis

The classification of AR was revised by ARIA in 2001. A major change was the introduction of the terms "intermittent" and "persistent" [18]. Before then, AR was classified, based on the time and type of exposure and symptoms, into seasonal (most often caused by outdoor allergens such as pollens or molds), perennial (most frequently, although not necessarily, caused by indoor allergens such as house dust mites, molds, cockroaches, and animal dander ) and occupational [22, 23]. With very few exceptions published studies refer to *seasonal* and *perennial* allergic rhinitis and enroll patients based on the offending allergen (pollen and/or house dust mites) and **we retained the terms *seasonal* and *perennial* allergic rhinitis to enable the interpretation of published evidence**.

The recommendations in the ARIA 2016 update apply directly to patients with moderate-severe AR. They may be less applicable to treatment of patients with mild AR who frequently do not seek medical help and manage their symptoms themselves with medications available other-the-counter.

### Recommendations for children

Almost all studies used to answer the questions in this update of the ARIA guidelines exclusively included adult patients. However, careful extrapolation to

pediatric population may be attempted. One may assume that the relative effects of treatment of AR are likely similar among adults and children but adverse effects may be more or less frequent and their perception and importance may be different, e.g. that of a bitter taste. Values and preferences for specific outcomes and treatments may also vary between adults and children.

## Methodology

The full description of methods used to develop recommendations in these guidelines is described in the Methods section of the full version of the guideline document (Online Repository 1). Here, we briefly describe the methodology to facilitate the interpretation of the guidelines.

### Questions and outcomes of interest

The scope and questions for this update of the ARIA guidelines were identified by the ARIA guideline panel members. The guideline panel deemed the following outcomes to be important to patients: nasal and ocular symptoms, quality of life, work/school performance, and adverse effects. As for the previous revision of the ARIA guidelines we did not formally assess the relative importance of each outcome of interest (i.e. which outcomes are more and which are less important) but rather adopted the rating agreed upon by the guideline panel following the structured discussion[24]. In general, combined nasal symptoms, ocular symptoms, quality of life, work/school performance, and serious adverse effects were considered to be critical to the decision, and individual symptoms, a composite outcome of any adverse effects, adverse effects that were not serious or did not lead to discontinuation of treatment were considered important but not critical (see evidence profiles in Online Repository 2).

### Evidence review and development of clinical recommendations

For each question the methodology group performed a full systematic review of the literature to identify and summarize the evidence about the effects of interventions on the outcomes of interest. We also systematically searched for the information about patients' values and preferences, and resource use (cost). We systematically searched Medline, Embase and Cochrane CENTRAL electronic databases. Titles and abstracts, and subsequently full-text articles were screened in duplicate to assess eligibility according to pre-specified criteria. Panel members were contacted to confirm completeness of the body of evidence and suggest additional articles that might have been missed in electronic searches.

To obtain the estimates of effects on each outcome of interest we performed meta-analyses using the Cochrane Collaboration Review Manager Software, version 5.3.5. [25]. We prepared evidence summaries (Online Repository 2) for each question following the GRADE approach [19] using the GRADEpro Guideline Development Tool online application (www.gradepro.org).

When continuous outcomes (e.g. symptoms scores or quality of life) are measured using different scales, the results may only be combined in meta-analysis using standardized mean difference (SMD) which is expressed in standard deviation (SD) units[26]. Results expressed as a SMD are challenging to interpret. To facilitate understanding we used interpretation of the effect size following Cohen's conventional criteria [27]: an SMD of around 0.2 is considered a small effect, around 0.5 – a moderate effect, and around 0.8 or higher – a large effect. We used this interpretation throughout this document whenever we referred to effects of interventions as small, moderate or large.

We assessed the risk of bias at the outcome level using the Cochrane Collaboration's risk of bias tool[28]. Subsequently, we assessed the certainty of the body of evidence (i.e. confidence in the estimated effects, also known as "quality of the evidence") for each of the outcomes of interest following the GRADE approach[29] based on the following criteria: risk of bias, precision, consistency and magnitude of the estimates of effects, directness of the evidence, risk of publications bias, presence of dose–effect relationship, and an assessment of the effect of residual, opposing confounding. Certainty of the evidence was categorized into 4 levels: high, moderate, low and very low.
For each question we summarized all information in Evidence-to-Decision (EtD) frameworks (Online Repository 2) that included concise description of desirable and undesirable health effects, certainty of the evidence about those effects, evidence and assumptions about patients' values and preferences, required resources and cost-effectiveness, potential influence on health equity, acceptability of the intervention to various stakeholders, and feasibility of implementation [30]. Judgments about all these factors and suggested recommendation in EtD frameworks were drafted by JLB who was also a clinical expert. EtDs for all questions were reviewed by the ARIA guideline panel members who provided feedback by electronic communication and during a face-to-face meeting of Integrated Care Pathways for Airway Diseases (AIRWAYS ICPs) [31, 32] and Frailty EIP on AHA Reference Sites in Lisbon, Portugal on July 1st, 2015 [33]. All comments were addressed and the frameworks were modified accordingly. Modified EtD frameworks that included judgments about the research evidence, additional considerations of ARIA panel members and draft recommendations were sent to all ARIA panel members for review and approval or disapproval and comments using the online SurveyMonkey software (www.surveymonkey.com). We recorded and addressed

all agreements/disagreements, comments and suggestions for changes. We present the final EtD frameworks in Online Repository 2.
Recommendations and their strength were decided by consensus. The ARIA guideline panel agreed on the final wording of recommendations and remarks with further qualifications for each recommendation. The final document including the recommendations was reviewed and approved by all members of the guideline panel.

According to the GRADE approach the recommendations can be either "strong" or "conditional" depending on guideline panel's confidence that following the recommendation would bring more good than harm to patients. The wording of recommendations reflects their strength and one may use the words "we recommend" for strong recommendations and "we suggest" for conditional recommendations. Box 1 provides suggested interpretation of strong and conditional recommendations.

**Recommendations**

We present all recommendations in Table 1. We provide the rationale for the recommendations and the consideration of all factors that influenced the recommendations: effects on all important health outcomes, certainty of the available evidence, values and preferences, acceptability by stakeholders, requirements for resources, feasibility, and any issues of health equity in the unabridged guideline document in the Online Repository 1. Detailed summaries of the evidence supporting each recommendation and the guideline panel judgements are in the Online Repository 2.

**How to use these guidelines**

The ARIA guidelines about treatment of allergic rhinitis are not intended to impose a standard of care for individual countries. They provide the basis for rational, informed decisions for patients, parents, clinicians, and other health care professional. Clinicians, patients, third-party payers, institutional review committees, other stakeholders, or the courts should not view these recommendations as dictates. Recommendations provide guidance for typical patients – no recommendation can take into account all of the often-compelling unique individual circumstances. Thus, no one charged with evaluating health care professionals' actions should apply the recommendations from these guidelines by rote or in a blanket fashion.
Statements regarding the underlying values and preferences as well as qualifying remarks accompanying each recommendation should never be omitted when quoting or translating recommendations from these guidelines.

**Conclusions**

Evidence-based guidelines are at the cornerstone of integrated care pathways (ICPs) [31, 32], structured multidisciplinary care plans that promote translation of guideline recommendations into local protocols and their subsequent application in clinical practice. Usually several guidelines are available providing advice about the management of the same condition [16]. It is important to wisely choose appropriate guidelines for local adaptation and creation of ICPs, because most of them have limitations owing to either the development of the guideline itself or the available research evidence and its interpretation. The most common limitations of guidelines in AR are narrow scope (addressing only a small selection of important questions about the management of a given condition), suboptimal rigor of development and reporting, and inadequate representation of the views of patients and their caregivers [16]. We acknowledge, that for the ARIA 2016 update we have not reviewed all recommendations from the ARIA 2010 but we updated only 3 recommendations suggested by the ARIA panel members as requiring the update and we addressed 3 new questions. We also acknowledge that the ARIA guideline panel included allergists, ENT specialists, pulmonologists, general practitioners and pediatricians but did not include other health care professionals, pharmacists and patients themselves. However, for the ARIA 2016 update we systematically searched and reviewed the published evidence about the patient values and preferences regarding the outcomes and treatments for AR that to certain degree helped to overcome this limitation. We summarized the results in the section about the assumed values and preferences in the full text of the ARIA 2016 update (Online Repository 1) and in the relevant sections of evidence-to-decision tables (Online Repository 2).

The available evidence has important limitations: 1) selective measurement and reporting of outcomes (e.g. few studies properly measure and report quality of life which is the most important outcome in AR), 2) selection of patients for clinical trials that may not represent appropriately the patients seen in primary care [34] as well as 3) not distinguishing between patients with different age or severity of symptoms (lack of proper stratification) [35], thus, limiting the applicability and generalizability of the research findings. Given these limitations, clinical practice guidelines – especially those with international audience – should emphasize rigorous systematic review of the health effects and explicit and detailed description of the assumed values and preferences and considerations of cost, feasibility, acceptability and health equity issues, as it is currently following the GRADE evidence-to-decision frameworks [36-38]. Such detailed, explicit and transparent reporting of guidelines facilitates local adaptation of recommendations and their translation into ICPs. Systematic and transparent summaries of the evidence clearly identifying gaps in available research evidence are needed to direct research agenda and to avoid unnecessary expenditure of resources for further clinical research when it is not necessary [39].

Implementation of guidelines in different settings and countries depends on the availability of health interventions (e.g. medical tests, medications, equipment, etc.), availability of resources, and cultural differences, among others. Thus, local adaptation of recommendations may be required and ICPs need to be developed at national, regional or local level. However, they always should be based on systematically reviewed evidence of desirable and undesirable consequences. The ARIA 2016 revision will be used to develop the ICPs proposed by the European Innovation Partnership on Active and Healthy Ageing [31, 32, 40] using MASK (MACVIA-ARIA Sentinel Network). ARIA is developing a novel implementation strategy using mobile technology [41, 42] and a clinical decision support system (CDSS) [41] and deployed in 21 countries [43]. The ARIA 2016 revision will be embedded in the CDSS for real-time patient stratification using mobile technology.

Most of the recommendations are based on low or very low certainty evidence mainly because the imprecision of the estimated effects owing to few patients being studied. For those questions there is a need for more well designed and executed randomized controlled trials that would measure and properly report all important outcomes.

**Disclosure of potential conflict of interest**

All ARIA panel members declared their actual, potential or perceived competing interests within the past 4 years related to the subject matter of these guidelines following the standard procedure of the World Health Organization.

Claus Bachert received honoraria for speaking and/or serving on advisory board from Meda, ALK, and Stallergenes; he is a member of guideline committee of the German Allergy Society (DGAKI).

Sinthia Bosnic-Anticevich is leading the update of the Pharmacy ARIA guidelines.

Jean Bousquet received honoraria for speaking and/or serving on scientific or advisory board from Almirall, AstraZeneca, Chiesi, GSK, Meda, Menarini, Merck, MSD, Novartis, Sanofi-Aventis, Takeda, Teva, and Uriach.

Jan Brozek received support from the ARIA Initiative for the development of systematic reviews supporting the recommendations in these guidelines that has been deposited to McMaster University research account; he has no other competing interests.

Giorgio Walter Canonica received honoraria for speaking and/or serving on scientific or advisory board, and research support from Alk-Abello', Almirall,

Allergy Therapeutics, Anallergo, AstraZeneca, Boeringher Ingelheim, Boston Scientific, Bruschettini, Chiesi Farmaceutici, Circassia, Danone, Faes, Glaxo Smith Kline, Lab.Guidotti, Lallemand, Lofarma, Malesci, Meda Pharmaceuticals, Menarini, Mundifarma, Novartis, Pfizer, Roche, Sanofi, Stallergenes, Thermo Fisher, Uriach, Teva and Valeas.

Thomas Casale received honoraria for consultation from Sanofi Regeneron, Ora, Circassia and Capnia.

Alvaro Cruz received honoraria for serving on advisory board from AstraZeneca, Boehringer Ingelheim, GSK, Meda Pharmaceuticals, and Roche; he also received research grants and travel support from GSK, AstraZeneca, and MSD.

Pascal Demoly received honoraria for consultation and/or speaking for Allergopharma, AllergyTherapeutics, ALK-Abello, AstraZeneca, Chiesi, Circassia, GlaxoSmithKline, Meda Pharmaceuticals, Merck, Menarini, Stallergenes-Greer, and ThermoFisherScientific.

Mark Dykewicz received honoraria for consultation from Merck; he also served as consultant for U.S. FDA about allergen immunotherapy and is a co-author of the American Academy of Otolaryngology-Head Neck Surgery Clinical Practice Guideline on Allergic Rhinitis and currently being updated U.S. Joint Task Force (AAAAI/ACAAI) Rhinitis Practice Parameter.

Wytske Fokkens reported receiving support from Allergopharma, GSK, Meda Pharmaceuticals and Stallergens, paid to her institution.

Joao Fonseca received honoraria for consultation from Novartis and for speaking from Menarini, Lab Vitoria, and Novartis and research support from MSD; he is a secretary general of the Portuguese Society of Allergy and Clinical Immunology (SPAIC).

Ludger Klimek received honoraria for consultation and/or speaking for ALK-Abelló, Allergopharma, HAL, Allergy Therapeutics/Bencard, Meda Pharmaceuticals, and Leti; he also received research support from ALK-Abelló, Allergopharma, Stallergenes, HAL, Allergy Therapeutics/Bencard, Lofarma, MEDA, Novartis, Leti, ROXALL, and Cytos.

Piotr Kuna received honoraria for speaking from Adamed, Allergopharma, AstraZeneca, Berlin Chemie, Meda, Boehringer Ingelheim, Chiesi, FAES, GSK, MSD, Novartis, Pfizer, Stallergenes, and Teva.

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Eli Meltzer received honoraria for consultation and/or speaking from AstraZeneca, Boehringer Ingelheim, Church & Dwight, Circassia, Meda, Merck, Regeneron-Sanofi and Teva; he is a co-author of the currently being updated U.S. Joint Task Force (AAAAI/ACAAI) Rhinitis Practice Parameter.

Joaquim Mullol received honoraria for speaking from UCB Pharma, Uriach Group, GSK, Hartington Pharmaceuticals, Menarini, Hyphens, Novartis, MSD, MEDA Pharma, and Sanofi-Aventis and research support from Uriach Group, Meda Pharmaceuticals, GSK, MSD, and FAES.

Petr Panzner received honoraria for speaking from Stallergenes, AstraZeneca, MEDA, and MSD.

Nikos Papadopoulos received research support from Menarini and Merck and for speaking for several undisclosed companies; he is the past president of EAACI and a member of the board of the Global Allergy and Asthma European Network (GA²LEN).

David Price received honoraria for speaking, research and travel support from Meda Pharmaceuticals.

Dermot Ryan received honoraria for speaking and/or serving on advisory board from Uriach, Stallergenes, and MEDA; he is chairing the Primary Care Interest Group in EAACI.

Boleslaw Samolinski received honoraria for speaking from Nexter-Allergopharma, Meda, Adamed, Polpharma and Teva.

Peter Schmid-Grendelmeier received honoraria for consulting from ALK ABello, Novartis and Thermo Fisher.

Holger Schünemann received support from the ARIA Initiative for the development of systematic reviews supporting the recommendations in these guidelines that has been deposited to McMaster University research account; he has no other competing interests.

Aziz Sheikh declared that his institution received research support from Asthma UK (charitable funder), the Scottish Government, EAACI and unrestricted industry funding from a multiple companies to run the Scottish Allergy and Respiratory Academy (SARA); he is involved in guideline initiatives of EAACI, BTS/SIGN, WAO and the Resuscitation Council (UK).
Antonio Valero received honoraria from Novartis, Sanofi, GSK, Chiesi, Boehringer, FAES, Meda, Orion Pharma, Stallergenes, and Leti and research support from Novartis, Uriach, FAES, and Leti.
Dana Wallace received honoraria for consultation, speaking and serving on advisory board from MEDA Pharmaceuticals; she is a co-author of the American Academy of Otolaryngology-Head Neck Surgery Clinical Practice Guideline on Allergic Rhinitis and currently being updated U.S. Joint Task Force (AAAAI/ACAAI) Rhinitis Practice Parameter.
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Torsten Zuberbier received honoraria from Ansell, Bayer Schering, DST, FAES, Fujisawa, HAL, Henkel, Kryolan, Leti, Menarini, Merck, MSD, Novartis, Procter and Gamble, Ranbaxy, Sanofi‐Aventis, Schering Plough, Stallergenes, Takeda, and UCB; he is a member of the German Society for Allergy and Clinical Immunology (DGAKI), the European Centre for Allergy Research Foundation (ECARF), the Global Allergy and Asthma European Network (GA²LEN), and the World Allergy Organization (WAO).

Other authors: Ioana Agache, Niels Chavannes, Jaime Correia de Sousa, Peter Hellings, Pat Manning, Robyn O'Hehir, Ken Ohta, Giovanni Passalacqua, Arunas Valiulis, Erkka Valovirta, Luo Zhang, and Mihaela Zidarn declared that they had no competing interests related to these guidelines.
Members of the methodology team who participated in systematic review of the literature (Romina Brignardello-Petersen, Carlos A. Cuello-Garcia, Itziar Etxeandia Ikobaltzeta, Iván Florez, Sergio Kowalski, Kaja-Triin Laisaar, John Riva, Yetiani Roldán, Behnam Sadeghirad, Matthew Ventresca, Wojtek Wiercioch, Juan José Yepes-Nuñez, Yuan Zhang) also declared that they had no competing interests related to these guidelines.
All ARIA panel members and methodology team members declared no relationship with any entity directly or indirectly involved in the production, distribution or sale of tobacco or tobacco products.

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Online Repository 1: Unabridged full text of the guideline document

# Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines – 2016 Revision (unabridged full text)

## Authors

Jan L. Brożek[1,2], Jean Bousquet[3], Ioana Agache[4], Arnav Agarwal[1,5], Claus Bachert[6], Sinthia Bosnic-Anticevich[7], Romina Brignardello-Petersen[1], G. Walter Canonica[8], Thomas Casale[9], Niels Chavannes[10], Jaime Correira de Sousa[11] Alvaro Cruz[12], Carlos A. Cuello-Garcia[1], Pascal Demoly[13], Mark Dykewicz[14], Itziar Etxeandia-Ikobaltzeta[1,15], Ivan D. Florez[1,16], Wytske Fokkens[17], Joao Fonseca[18], Peter W. Hellings[19], Ludger Klimek[20], Sergio Kowalski[1], Piotr Kuna[21], Kaja-Triin Laisaar[22], Désirée E. Larenas-Linnemann[23], Karin C. Lødrup Carlsen[24], PJ Manning[25], Eli Meltzer[26], Joaquim Mullol[27], Antonella Muraro[28], Robyn O'Hehir[29], Ken Ohta[30], Petr Panzner[31], Nikolaos Papadopoulos[32,33], Hae-Sim Park[34], Gianni Passalacqua[35], Ruby Pawankar[36], David Price[37], John J. Riva[1,38], Yetiani Roldán[1], Dermot Ryan[39], Behnam Sadeghirad[40], Boleslaw Samolinski[41], Peter Schmid-Grendelmeier[42], Aziz Sheikh[43], Alkis Togias[44], Antonio Valero[45], Arunas Valiulis[46], Erkka Valovirta[47], Matthew Ventresca[1], Dana Wallace[48], Suzan Waserman[2], Magnus Wickman[49], Wojtek Wiercioch[1], Juan José Yepes-Nuñez[1,50], Luo Zhang[51], Yuan Zhang[1], Mihaela Zidarn[52], Torsten Zuberbier[53], Holger J. Schünemann[1,54]

1 Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada
2 Division of Clinical Immunology and Allergy, Department of Medicine, McMaster University, Hamilton, ON, Canada
3 University Hospital, Montpellier, France
4 Transylvania University, Faculty of Medicine, Brasov, Romania
5 School of Medicine, University of Toronto, Toronto, Ontario, Canada
6 Ghent University Hospital, Upper Airways Research Laboratory, Ghent, Belgium
7 Woolcock Institute, University of Sydney, Sydney, Australia
8 Asthma & Allergy Clinic, Humanitas University, Rozzano, 20089 Milano, Italy
9 Division of Allergy and Immunology, University of South Florida, Tampa, Florida, USA
10 Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, The Netherlands
11 Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Braga, Portugal, ICVS/3B's - PT Government Associate Laboratory, Braga/Guimarães, Portugal
12 ProAR – Center of Excellence for Asthma, Federal University of Bahia, Brazil
13 University Hospital of Montpellier, Montpellier, and Sorbonne Universités, UPMC Paris 06, UMR-S 1136, IPLESP, Equipe EPAR, 75013, Paris, France
14 Section of Allergy and Immunology, Department of Internal Medicine, Saint Louis University School of Medicine, St. Louis, Missouri, USA
15 Dirección de Investigación e Innovación Sanitaria, Departamento de Salud, Gobierno Vasco-Eusko Jaurlaritza, Vitoria-Gasteiz, Álava-Araba, España
16 Department of Pediatrics, University of Antioquia, Medellin, Colombia
17 Department of Otorhinolaryngology, Academic Medical Centre, Amsterdam, The Netherlands
18 CINTESIS- Center for Health Technology and Services Research, Faculdade de Medicina, Universidade do Porto & Allergy, CUF Porto Hospital and Instituto, Porto, Portugal
19 Department of Otorhinolaryngology, University Hospitals Leuven, Leuven, Belgium ; Department of Otorhinolaryngology, Academic Medical Center (AMC), Amsterdam, The Netherlands
20 Center of Rhinology and Allergology, Wiesbaden, Germany

21 Division of Internal Medicine Asthma and Allergy, Faculty of Medicine, Medical University of Lodz, Poland
22 Institute of Family Medicine and Public Health, University of Tartu, Tartu, Estonia
23 Hospital Médica Sur, Mexico City, Mexico
24 Department of Paediatrics, Oslo University Hospital, University of Oslo, Oslo, Norway
25 Department of Medicine, Royal College of Surgeons in Ireland Medical School, Dublin, Ireland
26 Department of Pediatrics, Division of Allergy & Immunology, University of California, San Diego, California, USA
27 Unitat de Rinologia i Clínica de l'Olfacte, Servei d'ORL, Hospital Clínic, Clinical & Experimental Respiratory Immunoallergy, IDIBAPS, Barcelona, Spain
28 Department of Women and Child Health & Food Allergy Referral Centre Veneto Region, University of Padua, Italy
29 Alfred Hospital and Monash University, Melbourne, Victoria, Australia
30 National Hospital Organization Tokyo National Hospital, Kiyose-city, Tokyo, Japan
31 Department of Immunology and Allergology, Faculty of Medicine in Pilsen, Charles University in Prague, Czech Republic
32 Allergy Department, 2nd Pediatric Clinic, University of Athens, Greece
33 Division of Infection, Immunity & Respiratory Medicine, University of Manchester, UK
34 Department of Allergy and Rheumatology, Ajou University School of Medicine, Suwon, Korea
35 Allergy and Respiratory Diseases, IRCCS San Martino - IST - University of Genoa, Genoa, Italy
36 Department of Pediatrics, Nippon Medical School, Tokyo, Japan
37 University of Aberdeen, Aberdeen, UK
38 Department of Family Medicine, McMaster University, Hamilton, ON, Canada
39 Allergy and Respiratory Research Group, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, UK
40 HIV/STI Surveillance Research Center, and WHO Collaborating Center for HIV Surveillance, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran
41 Department of Prevention of Environmental Hazards and Allergology, Medical University of Warsaw, Poland
42 Allergy Unit, Dept. of Dermatology, University Hospital of Zürich and Christine Kühne Center for Allergy Research and Education CK-CARE, Davos, Switzerland
43 Asthma UK Centre for Applied Research, Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, UK
44 Asthma and Inflammation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA
45 Department of Pneumology and Allergy, Immunoallèrgia Respiratòria Clínica I Experimental (IDIBAPS), Centro de Investigaciones Biomédicas en Red de Enfermedades Respiratorias (CIBERES), Barcelona, Spain
46 Vilnius University Clinic of Children's Diseases and Public Health Institute, Vilnius, Lithuania; European Academy of Paediatrics (EAP/UEMS-SP), Brussels, Belgium
47 Department of Lung Diseases and Clinical Immunology, University of Turku and Allergy Clinic Terveystalo Turku, Finland
48 Nova Southeastern University, Fort Lauderdale, Florida, USA
49 Department of Pediatrics, Sachs' Children's Hospital, South General Hospital and Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
50 School of Medicine, University of Antioquia, Medellín, Colombia
51 Department of Otolaryngology Head and Neck Surgery, Beijing TongRen Hospital and Beijing Institute of Otolaryngology, Beijing, China
52 University Clinic of Pulmonary and Allergic Diseases Golnik, Slovenia
53 Department of Dermatology and Allergy, Charité - Universitätsmedizin Berlin, Germany
54 Division of General Internal Medicine, Department of Medicine, McMaster University, Hamilton, ON, Canada

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## Introduction

Since the last revision of the ARIA guidelines in 2010 [E1] new treatments became available and new evidence accumulated about selected other treatments. The ARIA guideline panel determined new questions that required answering with recommendations or the existing recommendations that required updated review of the evidence and potentially updating the recommendations themselves.

Clinical practice guidelines for AR management were developed over the past 20 years [E2] and have improved the care of patients with AR [E3]. Transparent reporting of guidelines to facilitate understanding and acceptance are however needed. The ARIA (Allergic Rhinitis and its Impact on Asthma) initiative was initiated during a WHO workshop in 1999 [E4]. It was updated in 2008 [E5]. The ARIA 2010 Revision was the first chronic respiratory disease evidence-based guideline to follow the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach [E6] with no influence of for-profit organizations and an explicit declaration and management of potential competing interests of panel members [E1]. It summarized the potential benefits and harms underlying the recommendations as well as assumptions around values and preferences that influenced the strength and direction of the recommendations. In 2014, the ARIA 2010 Revision was found to rank first in the rigor of development and quality of reporting of guidelines about the management of AR [2] although recent guidelines published later were not considered [E7].

### Allergic rhinitis

Allergic rhinitis (AR) is defined clinically by nasal hypersensitivity symptoms induced by an immunologically mediated (most often IgE-dependent) inflammation after the exposure of the nasal mucous membranes to an offending allergen. Symptoms of rhinitis include rhinorrhea, nasal obstruction or blockage, nasal itching, sneezing, and postnasal drip that are reversible spontaneously or with treatment. Allergic rhino-conjunctivitis often accompanies AR.

Allergic rhinitis (AR) is among the most common diseases globally and usually persists throughout life [E5]. The prevalence of AR has been estimated to be approximately 2 to 25% in children [E8] and 1 to over 40% in adults [E5, E9]. The prevalence of confirmed AR in adults in Europe ranged from 17% to 28.5%. Recent studies show that the prevalence of AR has increased, in particular in countries with initial low prevalence (for a discussion of prevalence of AR see section 5.1.–5.2. in ARIA 2008 Update [E5]). Classical symptoms of AR are nasal itching, sneezing, rhinorrhea, and nasal congestion. Ocular symptoms are also frequent; allergic rhino-conjunctivitis is associated with itching and redness of the eyes and tearing. Other symptoms include itching of the palate, postnasal drip and cough. AR is also frequently associated with asthma which is found in 15% to 38% of patients with allergic rhinitis [E10, E11] and that nasal symptoms are present in 6% to 85% patients with asthma [E12-E15]. In

addition AR is a risk factor for asthma [E10, E15] and uncontrolled moderate/severe AR impacts asthma control [E16, E17].

Compared to other medical conditions, AR may appear not to be serious because it is not associated with a high morbidity and mortality. However, the burden and costs are still substantial [E18]. AR symptoms are associated with decreased quality of life, sleep quality, energy levels, and ability to focus (see sections 5.3 to 5.7 in the ARIA 2008 Update) [E5]. The prevalence of AR has been estimated to be approximately 10 to 20% in the population (see sections 5.1 and 5.2 in the ARIA 2008 Update). AR is one of the main reasons for general practice office visits. Annual direct medical costs of AR in the United States alone have been estimated at from $0.8 billion in 1987 to $4.5 billion in 1997 [E19-E22]. Indirect costs associated with AR, including days missed from work or school and decreased productivity at work, were estimated to range from $2.4 billion to $4.6 billion in 1995 [E23]. Annual indirect costs associated with lost work productivity may be greater than those incurred by asthma [E24-E26]. An appropriate treatment of AR improves symptoms, quality of life, and work and school performance.

***Classification of allergic rhinitis***

The classification of AR was revised by ARIA in 2001 [E4]. A major change was the introduction of the terms "intermittent" and "persistent". Currently ARIA classifies allergic rhinitis according to:

**1. Duration** of symptoms:

*Intermittent* – symptoms are present less than 4 days a week or for less than 4 weeks.

*Persistent* – symptoms are present at least 4 days a week and for at least 4 weeks.

**2. Severity** of symptoms (sleep disturbance, impairment of daily activities, leisure and/or sport, impairment of school or work, and troublesome symptoms):

*Mild* – none of the above is present.

*Moderate-severe* – at least one of the above is present.

A modification of the ARIA severity classification has been proposed. [E27]

The recommendations in the ARIA 2016 update apply directly to patients with moderate-severe AR. They may be less applicable to treatment of patients with mild AR who frequently do not seek medical help and manage their symptoms themselves with medications available other-the-counter.

Allergic rhinitis has been traditionally subdivided into *seasonal*, *perennial*, and *occupational* rhinitis [E28, E29]. *Seasonal allergic rhinitis* (SAR) is most often caused by outdoor allergens such as pollens or molds. *Perennial allergic rhinitis* (PAR) is most frequently, although not necessarily, caused by indoor allergens such as house dust mites, molds, cockroaches, and animal dander.

With very few exceptions published studies refer to *seasonal* and *perennial* allergic rhinitis and enroll patients based on the offending allergen rather than based on the severity of symptoms. In this

document, as in the previous editions of ARIA guidelines [E1, E4, E5], **we retained the terms *seasonal* and *perennial* allergic rhinitis to enable the interpretation of published evidence**.

### Approval of medications for specific indications

The ARIA guidelines represent international effort and are meant to help patients and health care professionals worldwide. Thus, we explicitly decided not to take into consideration the approval status of individual medications in specific countries. We encourage heath care professionals and local organizations to consider those issues and, when needed, perform explicit adaptation of the ARIA guidelines to country-specific circumstances, local costs and community values and preferences (see section on Adaptation at the end of this document).

## Scope and purpose

The purpose of this document is to provide guidance about the management of adults and children with allergic rhinitis. The recommendations in this document do not apply to treatment of other types of rhinitis (i.e. non-allergic) or complications of allergic rhinitis (e.g. sinusitis).

This targeted revision of the ARIA guidelines is an update of the ARIA Revision 2010 [E1] and is limited in scope. It addresses only 6 questions related to treatment of AR that were identified by the ARIA guideline panel. These questions either have not been asked in ARIA 2010 or the panel determined that they required updating owing to new evidence being available:

1. Should a combination of oral H1-antihistamine (OAH) and intranasal corticosteroid (INCS) vs. intranasal corticosteroid alone be used for treatment of allergic rhinitis?
2. Should a combination of intranasal H1-antihistamine (INAH) and intranasal corticosteroid vs. intranasal corticosteroid alone be used for treatment of allergic rhinitis?
3. Should a combination of an intranasal H1-antihistamine and an intranasal corticosteroid vs. intranasal H1-antihistamine alone be used for treatment of allergic rhinitis?
4. Should a leukotriene receptor antagonist (LTRA) vs. an oral H1-antihistamine be used for treatment of allergic rhinitis?
5. Should an intranasal H1-antihistamine vs. an intranasal corticosteroid be used for treatment of allergic rhinitis?
6. Should an intranasal H1-antihistamine vs. an oral H1-antihistamine be used for treatment of allergic rhinitis?

### Target audience

The target audience of these guidelines is primary care clinicians, school nurses, pharmacists, and specialists in allergy and clinical immunology. General internists managing patients with allergic rhinitis, pediatricians, ear-nose-throat specialists, other health care professionals, and health care

policy makers may also benefit from these guidelines. This document may also serve as the basis for local adaptation and implementation (see Adaptation section at the end of this document).

## Methods

### Panel composition

This guideline was developed by a multidisciplinary panel that consisted of 44 members including allergists, ENT specialists, pulmonologists, general practitioners and pediatricians. The committee worked with the methodology group with experience in evidence synthesis and guideline development from McMaster University in Hamilton, Ontario, Canada.

The ARIA guideline panel members were: Ioana Agache, Claus Bachert, Sinthia Bosnic-Anticevich, Jean Bousquet (Chair), Jan Brożek (non-voting member), Giorgio Walter Canonica, Thomas Casale, Niels Chavannes, Jaime Correira da Sousa, Alvaro Cruz, Pascal Demoly, Mark Dykewicz, Wytske Fokkens, Joao Fonseca, Peter Hellings, Ludger Klimek, Piotr Kuna, Désirée Larenas Linnemann, Karin Lødrup Carlsen, PJ Manning, Eli Meltzer, Joaquim Mullol, Antonella Muraro, Robyn O'Hehir, Ken Ohta, Petr Panzner, Nikolaos Papadopoulos, Hae-Sim Park, Gianni Passalacqua, Ruby Pawankar, David Price, Dermot Ryan, Boleslaw Samolinski, Peter Schmid-Grendelmeier, Holger Schünemann (non-voting member), Aziz Sheikh, Alkis Togias, Antonio Valero, Arunas Valiulis, Erkka Valovirta, Dana Wallace, Suzan Waserman, Magnus Wickman, Luo Zhang, Mihaela Zidarn, and Torsten Zuberbier.

### Conflict of interest declaration and management

Committee members disclosed all potential conflicts of interest according to the World Health Organization policies. The declarations were reviewed and classified as no potential conflict or the interest is irrelevant or insignificant, manageable conflicts of interest, or disqualifying conflict of interest. One guideline panel member was excused from participation in the process owing to disqualifying conflict. Summary of the declarations of actual, potential or perceived conflicts of interest are provided at the end of this document. Members of the methodology group did not participate in the decision-making process and JLB and HJS were non-voting members of the panel, but they suggested the initial direction of the recommendation based on established criteria. The ARIA initiative provided US$40,000 of financial support to McMaster University to perform all systematic reviews. The views and interests of any commercial entity that might have provided external funding for ARIA initiative had no influence on the final recommendations and their names have not been revealed to the methodologists.

### Clinical questions and outcomes of interest

The scope and questions for this targeted update of the ARIA guidelines were identified by the ARIA guideline panel members. The guideline panel deemed the following outcomes to be

important to patients: nasal and ocular symptoms, quality of life, work/school performance, and adverse effects. As for the previous revision of the ARIA guidelines we did not formally assess the relative importance of each outcome of interest (i.e. which outcomes are more and which are less important) but rather adopted the rating agreed upon by the guideline panel following the structured discussion [E30]. In general, combined nasal symptoms, ocular symptoms, quality of life, work/school performance, and serious adverse effects were considered to be critical to the decision, and individual symptoms, a composite outcome of any adverse effects, adverse effects that were not serious or did not lead to discontinuation of treatment were considered important but not critical (see evidence profiles in Online Repository 2).

### Evidence review and development of clinical recommendations

For each question the methodology group performed a full systematic review of the literature to identify and summarize the evidence about the effects of interventions on the outcomes of interest. We also systematically searched for the information about patients' values and preferences, and resource use (cost). We systematically searched Medline, Embase and Cochrane CENTRAL electronic databases. Titles and abstracts, and subsequently full-text articles were screened in duplicate to assess eligibility according to pre-specified criteria. Panel members were contacted to confirm completeness of the body of evidence and suggest additional articles that might have been missed in electronic searches.

To obtain the estimates of effects on each outcome of interest we performed meta-analyses using the Cochrane Collaboration Review Manager Software, version 5.3.5. [E31]. We prepared evidence summaries (Online Repository 2) for each question following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach [E6] using GRADEpro Guideline Development Tool online application (www.gradepro.org).

When continuous outcomes (e.g. symptoms scores or quality of life) are measured using different scales, the results may only be combined in meta-analysis using standardized mean difference (SMD) which is expressed in standard deviation (SD) units. Results expressed as a SMD are challenging to interpret. To facilitate understanding we used interpretation of the effect size following Cohen's conventional criteria [E32]: an SMD of around 0.2 is considered a small effect, around 0.5 – a moderate effect, and around 0.8 or higher – a large effect. We used this interpretation throughout this document whenever we referred to effects of interventions as small, moderate or large.

We assessed the risk of bias at the outcome level using the Cochrane Collaboration's risk of bias tool [E33]. Subsequently, we assessed the certainty of the body of evidence (i.e. confidence in the estimated effects, also knoEwn as "quality of the evidence") for each of the outcomes of interest following the GRADE approach [E34] based on the following criteria: risk of bias in primary studies, precision,

consistency, and magnitude of the estimates of effects, directness of the evidence, risk of publications bias, presence of dose–effect relationship, and an assessment of the effect of residual, opposing confounding. Certainty of the evidence was categorized into 4 levels: high, moderate, low and very low.

For each question we summarized all information in Evidence-to-Decision (EtD) frameworks (Online Repository 2) that included concise description of desirable and undesirable health effects, certainty of the evidence about those effects, evidence and assumptions about patients' values and preferences, required resources and cost-effectiveness, potential influence on health equity, acceptability of the intervention to various stakeholders, and feasibility of implementation [E35]. Judgments about all these factors and suggested recommendation in EtD frameworks were drafted by JLB who was also a clinical expert. EtDs for all questions were reviewed by ARIA guideline panel members who provided feedback by electronic communication and during a face-to-face meeting of Integrated Care Pathways for Airway Diseases (AIRWAYS ICPs) and Frailty European Innovation Partnership on Active and Healthy Ageing (EIP on AHA) Reference Sites in Lisbon, Portugal on July 1st, 2015. All comments were addressed and the frameworks were modified accordingly. Modified EtD frameworks that included judgments about the research evidence, additional considerations of ARIA panel members and draft recommendations were sent to all ARIA panel members for review and approval or disapproval and comments using the online SurveyMonkey software (www.surveymonkey.com). We recorded and addressed all agreements/disagreements, comments and suggestions for changes. We present the final EtD frameworks in Online Repository 2. Following draft proposals by the methodologists, the final recommendations and their strength were decided by consensus. The ARIA guideline panel agreed on the final wording of recommendations and remarks with further qualifications for each recommendation. The final document including recommendations was reviewed and approved by all members of the guideline panel.

We labeled the recommendations as either "strong" or "conditional" according to the GRADE approach. We used the words "we recommend" for strong recommendations and "we suggest" for conditional recommendations. Table e1 provides suggested interpretation of strong and conditional recommendations.

### Document review

Each member of the ARIA guideline panel reviewed the final draft and approved the document, which was then submitted for peer review with a condition that no recommendation may be changed at this stage, unless an error of fact or missing evidence is identified. The document was revised to incorporate the pertinent comments suggested by the external reviewers.

### Use of indirect evidence

Pathophysiology of SAR and PAR is similar. When data for some outcomes were available only for SAR, we assumed that the evidence about the treatment effects in SAR would provide an indirect evidence about corresponding effects in PAR. The main difference is the usually long-term use of medications in PAR compared to mostly short-term or as needed use in SAR. Specifically, the adverse effects of treatments in PAR are likely to be similar to those in SAR, but there would be more concern about the long-term safety. In this document we explicitly stated whenever indirect evidence form SAR was used to inform recommendations for PAR.
Most patients recruited into randomized controlled trials have moderate-severe AR, thus, it is uncertain whether or not the available evidence directly applies to patients with mild AR.

(TABLE E1)

## How to use these guidelines

The ARIA guidelines about treatment of allergic rhinitis are not intended to impose a standard of care for individual countries. They provide the basis for rational, informed decisions for patients, parents, clinicians, and other health care professionals. Clinicians, patients, third-party payers, institutional review committees, other stakeholders, or the courts should not view these recommendations as dictates. Recommendations provide guidance for typical patients – no recommendation can take into account all of the often-compelling unique individual circumstances. Thus, no one charged with evaluating health care professionals' actions should apply the recommendations from these guidelines by rote or in a blanket fashion.

Statements regarding the underlying values and preferences as well as qualifying remarks accompanying each recommendation should never be omitted when quoting or translating recommendations from these guidelines. They are integral to the recommendations and serve to facilitate more accurate interpretation.

## General issues necessary for correct interpretation and implementation of recommendations

### Assumed values and preferences of patients with SAR and PAR

#### Outcomes

Our systematic search for studies of values and preferences revealed 2 studies that reported utilities associated with different severity of AR (i.e. measures of the desirability of various outcomes to a patient; the value or utility of the present health state is placed on a continuum between 0 that typically corresponds to death and 1 that typically corresponds to a perfect health). A study using

time trade-off technique [E36] found utilities 0.96 associated with mild AR, 0.94 for moderate, 0.89 for severe and 0.83 for severest AR [E37]. The same study used visual analog scale (VAS) to estimate health status (values between 0 – worst and 1 – best) and found it to be 0.82 for mild, 0.71 for moderate, 0.56 for severe, and 0.43 for severest AR. Another study used standard gamble technique [E38] and found utilities ranging 0.61 to 0.69 for severe individual symptoms, and 0.44 to 0.64 for multiple coexisting moderate to severe symptoms [E39].

Several studies assessed the relative importance of individual symptoms. One study used VAS to assess impairment associated with individual symptoms and found largest impairment associated with nasal congestion (0.70), followed by nasal itching (0.79), sneezing (0.80), and ocular itching (0.88) [E40]. A survey of 1001 patients with AR in Canada showed the following symptoms were considered extremely bothersome: stuffed nose (26%), itchy eyes (21%), runny nose (17%), headache (17%), watering eyes (16%) and sneezing (14%) [E41]. In a sample of 83 Japanese patients nasal obstruction and limitation in outdoor activities were identified as the most important factors influencing patient satisfaction from treatment [E42].
There is some uncertainty about how generalizable are the results from these studies because there are differences in preference rating with the same instrument among populations in different countries and cultures [E43].

**Treatments**
A cross-sectional study of 170 patients with AR examined the preferences in view of treatment and fear of side effects of the most common treatment options; 30% preferred a nasal spray, 25% preferred oral treatment and 16% preferred combination treatment, whereas 15% preferred injection therapy. Additionally, 48% expressed concern regarding the side effects of INCS compared to other treatments, 33% feared side effects of oral antihistamines, and 20% were concerned about adverse effects for LTRAs [E44]. A study in Turkey found similar results with 36% of 100 patients with AR perceiving INCS as being dangerous and 47% would use them if prescribed [E45]. Two studies found that patients prefer treatment options with no smell or taste [E46, E47].

## Recommendations for children

Almost all studies used to answer the questions in this update of the ARIA guidelines exclusively included adult patients. However, careful extrapolation to pediatric population may be attempted. One may assume that the relative effects of treatment of AR are likely similar among adults and children but adverse effects may be more or less frequent and their perception and importance may be different, e.g. that of a bitter taste. Values and preferences for specific outcomes and treatments may also vary between adults and children.

### Coexisting conditions

A recent systematic review of the prevalence of allergic rhinitis, asthma and eczema found 31 studies among over 1.4 million children in 102 countries. The calculated worldwide prevalence was 12.7% for allergic rhinitis, 12.00% for asthma, and 7.88% for eczema. All 3 conditions coexisted in 1.17% of children but the risk of having all three diseases was 9.8 times higher than could be expected by chance. For children with allergic rhinitis the calculated risk ratio of having the other two disorders was 6.20 (95% CI: 5.30-7.27) [E48].

Allergic rhinitis and asthma frequently coexist – epidemiological studies suggest that asthma is found in as many as 15% to 38% of patients with allergic rhinitis [E10, E49-E51]. Some studies estimate that nasal symptoms are present in at least 75% of patients with asthma, but these estimates vary widely from 6% to 85% depending on the study [E13-E15, E50, E52]. Asthma is also common in the older patients and strongly associated with rhinitis. The risk of asthma is especially high in persistent and severe ARIA classification rhinitis types [E49].

## Recommendations for specific treatment questions

We present all recommendations in Table e2. Below, we provide the complete rationale for each recommendation and the consideration of all factors that influenced the recommendations (effects on all important health outcomes, certainty of the available evidence, values and preferences, acceptability by stakeholders, requirements for resources, feasibility, and any issues of health equity). Detailed summaries of the evidence supporting each recommendation and the actual guideline panel judgments are in the Online Repository 2.

**(Table E2)**

### Question 1. Should a combination of oral H1-antihistamine and intranasal corticosteroid vs. intranasal corticosteroid alone be used for treatment of allergic rhinitis?

Intranasal corticosteroids (INCS) and oral H1-antihistamines (OAH) are the classes of medications most often used by patients with AR. A combination of INCS with OAH may have an advantage over monotherapy as their mechanisms of action are different. Their effects may be additive and each has specific advantages and disadvantages.

Summary of the evidence

We found 8 randomized controlled trials (RCTs) that compared a combined use of INCS and OAH with INCS alone in patients with SAR [E53-E60] and 2 RCTs in patients with PAR [E61, E62].

All studies in SAR included adults (1 quasi-RCT included 78 teenagers [E57]). Studies used a variety of INCS (mometasone, fluticasone and beclomethasone) and newer H1-antihistamines (loratadine, cetirizine and levocetirizine). Treatment duration in all studies was 2 weeks or longer.
One study in PAR used mometasone and levocetirizine in adults for 1 month [E62]. The other study used ciclesonide and levocetirizine in adults for 3–5 weeks [E61]. However, only 70% patients had PAR and the remaining patients had SAR.

Evidence profiles for question 1A (seasonal AR) and 1B (perennial AR) are in the Online Repository 2.

Benefits

In patients with SAR the additional reduction in nasal (SMD 0.13 SD lower, 95% CI: 0.25 lower to 0) and ocular symptoms (SMD 0.19 lower, 95% CI: 0.33 to 0.05 lower) with OAH + INCS, compared to INCS alone, is small and most likely would not be noticed by most patients (assuming that an SMD of 0.2 is a small effect and 0.5 a moderate effect). The improvement in quality of life may be large but available evidence does not allow to estimate it precisely enough to exclude a possibility of no effect or even small harm (SMD 0.61 lower, 95% CI: 1.44 lower to 0.23 higher; lower score indicates better quality of life). There was no evidence of that combination therapy might affect one the nasal symptoms more than the others (see exploratory analysis in evidence profile for question 1A in Online Repository 2).

In patients with PAR there was no observed benefit from adding OAH to INCS, compared to INCS alone, in nasal symptoms (mean difference 0.2 points on a 12-point scale favoring INCS alone) and in ocular symptoms (mean difference 0.1 points on a 9-point scale favoring INCS alone).

Harms and burden

There were no serious adverse effects reported in any of the studies in SAR and PAR. There was also no evidence of a difference in the risk of adverse effects leading to discontinuation of therapy (relative risk: 0.65, but the low total number of events did not allow to estimate it precisely and the confidence interval does not exclude harm with either treatment option – 95% CI: 0.13 to 3.23). Similarly there were too few events of sedation or epistaxis to precisely estimate the difference between the treatments (see evidence profile for question 1A in Online Repository 2).

In patients with PAR there was no difference in quality of life scores between the groups but the results did not exclude a possibility of importantly reduced quality of life with combination therapy, compared to INCS alone (mean RQLQ score was 0.2 points lower with combination therapy; 95% CI: 0.53 lower to 0.13 higher). There was no evidence of more adverse effects with any of the treatments.

All studies in SAR and PAR investigated new generation OAH. Older generation OAH, that are usually more sedating, will have more adverse effects than observed in these studies. [E63]

Decision criteria and additional considerations

ARIA panel members noted that some patients beginning treatment may prefer the combination therapy because of faster onset of action of OAH compared to INCS alone. This, however, may be less important in patients with PAR than with SAR. Adherence to treatment may be lower with an increase in the number of medications.

We found two studies that compared the cost of INCS alone to their combination with OAH –a retrospective database analysis using pharmacy and medical claims data from a US health plan that compared medical and pharmacy cost of different treatments for rhinitis [E64] and a Swedish population-based questionnaire study that estimated an annual cost of treatment with OAH and INCS [E65]. The cost per patient varied with the ARIA classification of the severity of symptoms and was higher for persons with moderate to severe persistent allergic rhinitis compared to mild persistent disease. Panel members thought that unit costs assumed in both analyses do not reflect current costs in most settings and, thus, relying on those analyses could be misleading. Panel members agreed that additional resources required for combination therapy might be a concern in settings where OAH are currently more expensive but not in settings where their relative cost is not high. From the patient perspective, increased cost of treatment with OAH + INCS, compared to INCS alone, may be particularly important in settings where OAH are available other-the-counter and not covered by drug plans. The cost of adding OAH might therefore be relatively high, particularly to those individuals with limited resources.

Conclusions and research needs

We found little additional benefit from a combination of OAH+INCS, compared to INCS alone in patients with SAR. However, there may be some patients, particularly at the beginning of treatment that might benefit from likely faster relief of symptoms.
ARIA guideline panel acknowledged that the choice of treatment would mostly depend on patient preferences and local availability and cost of treatment. Panel members felt that in majority of situations, where a combination therapy is considerably more expensive than INCS alone, any potential net benefit would not justify spending additional resources.
There is no currently available direct evidence from experimental studies about the effects in subgroups based on severity of individual symptoms. However, based on indirect evidence it is possible that selected patients may benefit more from a combination therapy (e.g. those not well

controlled with INCS alone, those with pronounced ocular symptoms or those at the beginning of treatment because of likely faster onset of treatment effect).
All evidence is available only for new generation OAHs; for older OAHs with more sedative effects the balance of desirable and undesirable effects may be different.

We found no additional benefit of a combination of OAH and INCS, compared to INCS alone, in patients with PAR.

Further research of a combination of OAH with INCS as a step-up therapy in patients with not well controlled with INCS alone is warranted. Additional information about the effects of INCS + OAH, compared to INCS alone, in subpopulation of patients with pronounced ocular symptoms or those in whom rhinorrhea rather than congestion is the main symptom may be beneficial. Studies of real life effects of the combination therapy used as needed, rather than regularly, may also be warranted. If done, studies should measure not only nasal symptoms but also quality of life and properly report adverse effects. Further research to identify subgroups of patient with PAR more likely to benefit from H1-antihistamine added to INCS may be warranted.

What others are saying

The American Academy of Otolaryngology—Head and Neck Surgery guidelines offer an option: "clinicians may offer combination pharmacologic therapy in patients with AR who have inadequate response to pharmacologic monotherapy" but state that "when patients have no response to INCS or incomplete control of nasal symptoms with an INCS, OAH should not be routinely used as additive therapy" [E7].
The American Academy of Family Physicians suggests a combination of "INCS plus OAH for severe, persistent symptoms" but "INCS alone for the initial treatment for AR with symptoms affecting quality of life". It also states that "although most patients should be treated with just one medication at a time, combination therapy is an option for patients with severe or persistent symptoms" [E66].
The Diagnosis and Management of Rhinitis: An Updated Practice Parameter developed by the Joint Task Force on Practice Parameters representing the American Academy of Allergy, Asthma & Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI) and the Joint Council of Allergy, Asthma and Immunology does not make explicit recommendations for practice but provides statements about specific treatments. It states that a "combination of OAH and INCS may be considered, although supporting studies are limited and many studies unsupportive of additive benefit of adding OAH to INCS" [E67]. Note that this Practice Parameter was developed in 2008 when much less information was available.
University of Michigan guidelines do not mention combination therapy with OAH and INCS [E68].

**Recommendation 1A**

In patients with seasonal allergic rhinitis, we suggest either a combination of an intranasal corticosteroid with an oral H1-antihistamine or an intranasal corticosteroid alone (conditional recommendation | low certainty of evidence)

Values and preferences

The ARIA guideline panel acknowledged that the choice of treatment would mostly depend on patient preferences and local availability and cost of treatment. Panel members assumed that in the majority of situations, potential net benefit would not justify spending additional resources.

Explanations and other considerations

This is a conditional recommendation, thus different choices will be appropriate for different patients – in settings where additional cost of OAH is not large and/or patient values and preferences differ from those assumed by guideline panel members a combination therapy may be a reasonable choice, especially in patients not well controlled with INCS alone, those with pronounced ocular symptoms or those commencing treatment because of likely faster onset of treatment effects. This recommendation concerns *regular* use of newer, less sedative OAH and INCS in seasonal AR. For older OAHs with more sedative effects the balance of desirable and undesirable effects may be different.

**Recommendation 1B**

In patients with perennial allergic rhinitis, we suggest an intranasal corticosteroid alone rather than a combination of an intranasal corticosteroid with an oral H1-antihistamine (conditional recommendation | very low certainty of evidence)

Explanations and other considerations

Currently available evidence suggests that there is no additional benefit from combination therapy compared to INCS alone and there may be additional undesirable effects. This recommendation is conditional because of sparse information, thus, very low certainty of the estimated effects.

## Question 2. Should a combination of intranasal H1-antihistamine and intranasal corticosteroid vs. intranasal corticosteroid alone be used for treatment of allergic rhinitis?

A combination of INCS with INAH may have an advantage over INCS alone as their mechanisms of action are different. The antihistaminic effect of INAH could be additive to anti-inflammatory effects of INCS.

Summary of the evidence

We found 5 RCTs that compared a combination of INAH with INCS with INCS alone in patients with SAR. Three studies were reported together in one journal article [E69]. Some results from one of these 3 studies were published in an additional separate article [E70]. Of the remaining 2 studies one was published in 2 separate articles [E71, E72] and the last one was published in 1 article [E73].
Four out of 5 studies used a combination drug in one container and one study used INCS and INAH as separate sprays [E73]. There is some uncertainty whether the desirable and undesirable effects of these different formulations would be the same owing to no available evidence about possible interactions of the two separate solutions. All 5 studies included adult patients and used fluticasone and azelastine nasal sprays for 2 weeks.

We found 1 RCT (results published in 2 separate articles) that investigated a combination of fluticasone and azelastine, compared to fluticasone alone, for 52 weeks in adults with PAR [E74, E75].

All 6 studies in SAR and in PAR were funded by a single manufacturer of the combination drug in one container. Evidence profiles for question 2A (seasonal AR) and 2B (perennial AR) are in the Online Repository 2.

We also found 6 studies that examined the time to onset of action in patients with SAR. Two studies presented the results only as graphs with no reported variability in results and showed that the difference between a combination of INAH+INCS vs. INCS alone was achieved already by day 2-3 of treatment [E71, E73]. Three studies assessed nasal symptoms 4 hours after drug administration and found total nasal symptom score (TNSS) being reduced by 0.5 point more (95% CI: 0.07 to 0.93; scale 0 to 24) with combination therapy compared to INCS alone [E69]. In the best case scenario a difference of 0.93 point on a 24-point scale would be unlikely to be noticed by majority of patients (we assumed that a difference of around 1.1 to 1.3 points on a 24-point TNSS scale would be the minimal important difference [MID] based on a study in SAR [E76] and on an empirical observation that a difference of around 0.5 point on a 7-point scale is frequently an MID in respiratory diseases including AR [E77], asthma [E78-E81] and COPD[82]). However, in these studies patients reached 50% reduction of symptoms up to 3 days earlier with combination therapy compared to INCS alone. One study using an allergen challenge found better improvement of symptoms with INAH+INCS compared to INCS alone over 2-4 hours after drug administration (mean difference 1.36 point on a 12-point scale; 95% CI: 0.87 to 1.85) [E83].
In studies that used combination therapy in one spray, one showed benefit with combination therapy [E71] and the other did not show the difference [E69]. Indirect evidence from bioavailability study suggests that a combination of azelastine and fluticasone acts faster than fluticasone alone [E84]. This observation is consistent with clinical observations of some ARIA panel members.

Benefits

In patients with SAR, a combination of INAH with INCS, compared to INCS alone improved nasal symptoms (mean difference 0.77 point lower on a 24-point scale; 95% CI: 0.3 to 1.24 lower), ocular symptoms (SMD 0.2 SD lower, 95% CI: 0.07 to 0.33 lower), and most likely also quality of life (mean difference 0.13 points in RQLQ higher, 95% CI: 0.01 to 0.24 higher). However, all effects were small and confidence intervals did not exclude almost no difference. A combination of azelastine and fluticasone acts faster than fluticasone alone.

In patients with PAR, use of combination of INAH with INCS may improve nasal symptoms (mean score 0.27 points lower on a 24-point scale, 95% CI: 0.56 lower to 0.02 higher) although any difference would be small, compared to INCS alone. Combination therapy most likely increased number of symptom-free days by an average of 24 days during 52 weeks of treatment (95% CI: 48 more to 0.24 fewer). Although there is no direct evidence about ocular symptoms and quality of life from studies in patients with PAR, indirect evidence from studies in patients with SAR suggest that the effect might be trivial, if any.

Harms and burden

There were no serious adverse effects among 1801 in 4 studies of patients with SAR. There is no evidence that combined therapy led to more discontinuation of treatment but confidence interval does not exclude an important increase of this risk (from 2 fewer to 25 more per 1000 patients). There were more "any adverse effects" in the combined treatment group (risk difference: 41 more per 1000 patients, 95% CI: 12 to 81 more). All studies used azelastine as INAH and bitter taste was reported by some patients in combination therapy group (risk difference 26 more per 1000 patients, 95% CI: 8 to 72 more).

There were 4 serious adverse effects in the study of patients with PAR but all were very unlikely related to treatment (Dengue fever, pyrexia, appendicitis, and gastroenteritis). There was no evidence that combination treatment would lead to more discontinuation of treatment owing to adverse effects. Azelastine was used as INAH and bitter taste was reported by some patients in combination therapy group (risk difference: 20 more per 1000 patients, 95% CI: from 2 fewer to 187 more).

Decision criteria and additional considerations

Panel members noted that some patients beginning treatment may prefer the combination therapy because of quicker onset of action of a combination of INCS with INAH, compared to INCS alone.

We found one retrospective cohort study of adult patients with AR in the United States that examined the cost of INCS monotherapy, INAH monotherapy, or their combination [E85]. Panel members thought that unit costs assumed in this study do not reflect the current costs in most settings and relying on those estimates could be misleading. Some panel members thought that a combination is not cost effective compared to INCS alone, because of little – if any – additional benefit from a combination therapy. This may be particularly important in settings where the combination therapy is more expensive that INCS alone. Some panel members thought that the combination therapy may not be acceptable to third party payers because of cost-effectiveness.

Conclusions and research needs

In SAR, the additional reduction in symptoms with combination therapy is small and unlikely to be noticed by majority of patients. There is currently no available direct evidence from experimental studies about subgroups based on severity of individual symptoms of SAR. However, based on indirect evidence it is possible that selected patients with SAR may benefit more from a combination therapy (e.g. those not well controlled with INCS alone or those in whom rhinorrhea rather than congestion is the main complaint).

Based on limited evidence in treatment of PAR, any additional reduction in symptoms with combination therapy, if existing, would likely be small and unlikely to be noticed by majority of patients.

Panel members thought that in the majority of situations, both in SAR and in PAR, where a combination therapy is more expensive than INCS alone, any possible net benefit would not justify spending additional resources.

Further research of a combination of INAH with INCS as a step-up therapy in patients with SAR not well controlled with INCS alone is warranted. A pragmatic trial in real-life setting measuring cost-effectiveness may also be warranted. The only INAH used in these studies was azelastine and the only INCS was fluticasone – studies of other INAH and INCS may provide important insight. Further research of a combination of INAH with INCS in patients with PAR may also be justified. However, indirect evidence from SAR suggests that any potential benefit from combination therapy is likely to be trivial. Thus, further research specifically in PAR may not be cost-effective.

What others are saying

The American Academy of Otolaryngology—Head and Neck Surgery guidelines offer an option: "clinicians may offer combination pharmacologic therapy in patients with AR who have inadequate response to pharmacologic monotherapy" and state that "in patients who tolerate INCS or INAH

spray and have inadequate control of AR symptoms with a single agent, combined INCS + INAH is an effective option" [E7].

The American Academy of Family Physicians suggests a combination of "INCS plus INAH for severe, persistent symptoms" but "INCS alone for the initial treatment for AR with symptoms affecting quality of life". It also states that "although most patients should be treated with just one medication at a time, combination therapy is an option for patients with severe or persistent symptoms" [E66].

The most recent AAAAI/ACAAI Practice Parameter from 2008 does not make explicit recommendations for practice but states that a "combination may be considered based on limited data" particularly "for mixed rhinitis, there may be significant added benefit to the combination of INAH with INCS" [E67]. Note, that this Practice Parameter was developed in 2008 when less information was available.

University of Michigan guidelines make no specific recommendations but state that "more recent evidence suggests that combination of intranasal antihistamines and intranasal corticosteroids are synergistic and provide greater benefit than monotherapy in the treatment of seasonal allergic rhinitis" [E68].

**Recommendation 2A**

In patients with seasonal AR, we suggest either a combination of an intranasal corticosteroid with an intranasal H1-antihistamine or an intranasal corticosteroid alone (conditional recommendation | moderate certainty of evidence).

Values and preferences

The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment. At the initiation of treatment (~ first 2 weeks) a combination of INCS with INAH may act faster than INCS alone and, thus, may be preferred by some patients.

Explanations and other considerations

This is a conditional recommendation, thus different choices will be appropriate for different patients – in settings where additional cost of combination therapy is not large and/or patients value potential benefits more than any increased risk of adverse effects, a combination therapy may be a reasonable choice.

**Recommendation 2B**

In patients with perennial AR, we suggest either a combination of an intranasal corticosteroid with an intranasal H1-antihistamine or an intranasal corticosteroid alone (conditional recommendation | very low certainty of evidence).

Values and preferences
The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment.

Explanations and other considerations
This is a conditional recommendation because of the very low certainty of the evidence. At the initiation of treatment (~ first 2 weeks) a combination of INCS with INAH may act faster than INCS alone, thus, may be preferred by some patients.

## Question 3. Should a combination of an intranasal H1-antihistamine and an intranasal corticosteroid vs. intranasal H1-antihistamine alone be used for treatment of allergic rhinitis?

A combination of INCS with INAH may have an advantage over INAH alone as their mechanisms of action are different. Their effects may be additive and each has specific advantages and disadvantages.

Summary of the evidence

The same 5 RCTs in patients with SAR that compared a combination of INAH with INCS with INCS alone, described in question 2, used INAH alone as a second comparison group [E69, E71, E73]. Four out of 5 studies used a combination drug in one container and one study used INCS and INAH as separate sprays [E73]. There also is uncertainty whether the desirable and undesirable effects of one solution compared to 2 separate containers would be the same owing to no available evidence about possible interactions of the two separate solutions. All 5 studies included adult patients and used fluticasone and azelastine nasal sprays for 2 weeks. All were funded by a single manufacturer of the combination drug in one container. Evidence profile for question 3 is in the Online Repository 2.

We did not find any study that investigated a combination of INCS with INAH, compared to INAH alone, in patients with PAR.

Benefits

There are small to moderate benefits from combined therapy. A combination of INAH with INCS, compared to INAH alone, reduced nasal symptoms (mean difference: 1.4 points on a 24-point scale lower, 95% CI: 0.98 to 1.82 lower), ocular symptoms (SMD: 0.33 SD lower, 95% CI: 0.02 to 0.65 lower), and improved quality of life (mean difference: 0.53 points in RQLQ lower, 95% CI: 0.06 to 1.01 lower, scale 1 to 7 and lower values indicate improvement). However, the effects could not be estimated precisely enough to exclude at least a moderate benefit or no difference.

Harms and burden

There were no serious adverse effects in those studies. There was no evidence of an increased risk of any adverse effect with the combination therapy, compared to INAH alone. All studies used azelastine and bitter taste was reported by some patients in both groups.

Decision criteria and additional considerations

We found one retrospective cohort study of adult patients with AR in the United States that examined the cost of INAH monotherapy and a combination of INAH and INCS [E85]. Panel members thought that unit costs assumed in this study do not reflect the current costs in most settings and relying on the estimates from this study could be misleading. Panel members noted that the choice of therapy will highly depend on the local health system owing to large variability in cost and coverage: public or private insurance plans, co-payment models and patient out of the pocket expenses. Some panel members thought that, a combination therapy may not be cost effective compared to INAH alone.

Conclusions and research needs

There is a small improvement in symptoms and quality of life with a combination of INAH with INCS, compared to INAH alone. Mean estimates of improvement of symptoms are close to minimal important difference (MID) and an estimate of mean improvement in QoL is larger than MID – it is therefore likely that the difference would be noticed by many patients.

Further research may be warranted to better estimate the effect of a combination of INAH with INCS on quality of life. The only INAH used in these studies was azelastine and the only INCS was fluticasone – studies of other INAH and INCS may be warranted.

What others are saying

The American Academy of Otolaryngology—Head and Neck Surgery guidelines offer an option: "clinicians may offer combination pharmacologic therapy in patients with AR who have inadequate response to pharmacologic monotherapy" and state that "in patients who tolerate INCS or INAH spray and have inadequate control of AR symptoms with a single agent, combined INCS + INAH is an effective option" [E7].

The American Academy of Family Physicians suggests a combination of "INCS plus INAH for severe, persistent symptoms" but "INAH as needed for mild intermittent symptoms" and adds that "because INAH are more expensive, less effective, and have more adverse effects than INCS, they are not recommended as first-line therapy for AR" [E66]. It also states that "although most patients

should be treated with just one medication at a time, combination therapy is an option for patients with severe or persistent symptoms".
The AAAAI/ACAAI Practice Parameter does not make explicit recommendations for practice but states that a "combination may be considered based on limited data" particularly "for mixed rhinitis, there may be significant added benefit to the combination of INAH with INCS" [E67]. Note that this Practice Parameter was developed in 2008 when much less information was available.
University of Michigan guidelines make no specific recommendations but state that "more recent evidence suggests that combination of intranasal antihistamines and intranasal corticosteroids are synergistic and provide greater benefit than monotherapy in the treatment of seasonal allergic rhinitis" [E68].

### Recommendation 3

In patients with seasonal AR, we suggest a combination of an intranasal corticosteroid with an intranasal H1-antihistamine rather than an intranasal H1-antihistamine alone (conditional recommendation | low certainty of evidence)

Values and preferences
This recommendation places higher value on additional reduction of symptoms and improved quality of life with a combination therapy, compared to INAH alone. It places a lower value on avoiding additional cost (expenditure of resources).

Explanations and other considerations
This is a conditional recommendation, thus different choices will be appropriate for different patients – in settings where additional cost of a combination therapy is large, an alternative choice, i.e. INAH alone, may be equally reasonable.
One panel member thought that the recommendation should be conditional for either the intervention or the comparison.

## Question 4. Should a leukotriene receptor antagonist (LTRA) vs. an oral H1-antihistamine (OAH) be used for treatment of allergic rhinitis?

Oral H1-antihistamines and leukotriene receptor antagonists (LTRA) are used for the treatment of AR. LTRA may have an advantage over OAH as they may cause less somnolence attributed to OAH. Both medications have different mechanisms of action and each may have specific advantages. In the 2010 revision of the ARIA guidelines we recommended OAH rather than LTRA based on lower cost of OAH. With the generic LTRA available since late 2012 the ARIA guideline panel decided that this recommendation should be revisited.

Summary of the evidence

We found 11 RCTs described in 10 articles that compared LTRA to OAH in adult patients with SAR [E86-E95]. No study included children. In 7 studies some or all patients had concomitant asthma. Montelukast was used in all studies except for one that used pranlukast [E92]. Studies used loratadine in the control group except for one that used cetirizine [E86], another that used levocetirizine [E87], and one that used fexofenadine [E92]. Follow-up was between 2 and 6 weeks. All studies were funded by Merck, manufacturer of montelukast, except for one that was independently funded by an academic institution and possibly also 2 that failed to report the source of funding.

We identified one additional RCT of LTRA vs. OAH in patients with SAR but the LTRA used was ibudilast which is not commonly used for treatment of AR [E96]. We did not include this study in further analyses.

We also found 7 RCTs of LTRA compared to OAH in patients with PAR. Five included adults [E97-E101] and 2 included children [E102, E103]. Five studies used montelukast and 3 used zafirlukast. Cetirizine was used as the control medication in 5 studies and levocetirizine, loratadine and desloratadine were used in one study each. All studies followed patients for 4 to 12 weeks, except for one that followed patients only for 2 weeks [E100]. However, its results were consistent with those of other studies, thus, we included it in the analyses.

Evidence profiles for question 4A (seasonal AR) and 4B (perennial AR) are in the Online Repository 2.

Benefits

There is high certainty evidence showing that the health effects of LTRA in patients with SAR are similar to those of newer generation OAH: nasal symptoms (SMD: 0.06 higher, 95% CI: 0.01 lower to 0.13 higher), ocular symptoms (SMD: 0.06 higher, 95% CI: 0.04 lower to 0.16 higher), and quality of life (mean difference in RQLQ score: 0.04 higher, 95% CI: 0.04 lower to 0.13 higher).

In patients with PAR, the effects could not be precisely estimated owing to small number of patients and the evidence is of low certainty. OAH possibly reduce nasal symptoms more than LTRA (SMD: 0.26 higher with LTRA, 95% CI: 0.45 lower to 0.97 higher) but the confidence interval does not exclude a moderate benefit from LTRA or a large benefit from OAH. The effect on ocular symptoms seemed to differ between adults (mean difference: 0.19 point lower on a 4-point scale, 95% CI: 1.03 lower to 0.65 higher) and children (mean difference: 0.29 point higher on a 3-point scale, 95% CI: 0.04 lower to 0.62 higher). Similarly, quality of life seemed to improve more in adults (mean difference: 0.17 point lower RQLQ score, 95% CI: 0.98 lower to 0.58 higher) than in children (mean difference: 12

points higher in a 138-point PRQLQ score, 95% CI: 1.66 lower to 25.66 higher). However, studies were very small and the differences were not large, thus, any dissimilarities in the effects between children and adults may be spurious.

Harms and burden

There were no serious adverse effects in any of the studies of SAR and PAR. There is also no evidence that more patients might discontinue treatment owing to adverse effects with either medication. There was no difference in any adverse effects observed in patients with SAR and somnolence was not reported in any of the studies of SAR.

In patients with PAR, fewer any adverse effects were observed (14 events fewer per 100 patients over 6 weeks, 95% CI: 5 to 23 fewer) and less somnolence (5 fewer per 100 patients, 95% CI: 3 to 5 fewer) with LTRA compared to OAH. However, there is low confidence that the observed results reflect true effects owing to limitations in study designs (see evidence profile for question 4B in Online Repository 2).

Decision criteria and additional considerations

We found one retrospective analysis of an insurance claim database in the United States that analyzed costs of treatment with montelukast compared with oral, branded second-generation antihistamines [E104]. We also found descriptions of two economic models that compared various OAH and montelukast [E105, E106]. However, all analyses were based on historical prices from 2000s and panel members thought they were not applicable today. The ARIA panel members noted that the cost of LTRA will frequently be higher compared to OAH but the cost of various OAH is also highly variable across countries and health care systems. Cost may be a more important factor for patients with PAR since they might use medications for longer periods of time. In settings where generic LTRA are available, cost of treatment may be lower compared to branded LTRA. When choosing the optimal treatment option clinicians need to consider the local availability and costs of LTRA and various OAH. Panel members also noted that many clinicians currently start therapy of AR from OAH rather than LTRA, most likely based on actual or perceived cost effectiveness.

Panel members also noted that in some countries LTRA are currently available only for treatment of asthma which may be a barrier to implementation for treatment of AR.

Conclusions and research needs

There seems to be no clear difference in health outcomes between LTRA and OAH in patients with SAR, thus, the panel members concluded that the choice of treatment will largely depend on patient preferences and local availability and cost of medications.

In patients with PAR, there is low certainty about the differences in health outcomes between LTRA and OAH – OAH may reduce symptoms and improve quality of life more but the risk of somnolence is possibly higher. Any true differences are likely to be small.

Studies investigating the comparative effects of LTRA and OAH in patients with AR and specific subgroups defined by type of concomitant asthma may be warranted.

What others are saying

The American Academy of Otolaryngology—Head and Neck Surgery guidelines not make a specific recommendation for the choice of OAH or LTRA but make a separate strong recommendation to use "second generation/less sedating OAH for patients with AR and primary complaints of sneezing and itching" and a recommendation against the use of LTRA: "clinicians should not offer oral LTRA as primary therapy for patients with AR" [E7]. The rationale provided was "to reduce the use of a more expensive, less effective agent as first-line treatment of AR".
The American Academy of Family Physicians makes no specific recommendation for the use of LTRA versus OAH but states that "montelukast is comparable to OAH but is less effective than INCS" and that "it may be particularly useful in patients with coexistent asthma" [E66].
The AAAAI/ACAAI Practice Parameter does not make explicit recommendations for practice but states that there is "no significant difference in efficacy between LTRA and OAH" and that LTRA may be considered in patients who have both AR and asthma and has minimal side effects [E67]. Note that this Practice Parameter was developed in 2008 when less information was available.
University of Michigan guidelines make no specific recommendations but state that OAH are the first or second and LTRA are a second or third option to add in the treatment of allergic rhinitis" [E68].

**Recommendation 4A**

In patients with seasonal AR, we suggest either a leukotriene receptor antagonist or an oral H1-antihistamine (conditional recommendation | moderate certainty of evidence)

Values and preferences

Panel members acknowledged that the choice of LTRA or OAH will mostly depend on patient preferences for the affected outcomes and local availability and cost of specific medications. In many settings OAH may still be more cost-effective but this will largely depend on availability of generic LTRA and the local cost of various newer-generation OAH and LTRA.

Explanations and other considerations
Some patients with AR who have concomitant asthma, especially exercise-induced and/or aspirin exacerbated respiratory disease, may benefit from LTRA more than from OAH. However, *this recommendation applies to treatment of AR not to treatment of asthma*. Patients with asthma who have concomitant AR should receive an appropriate treatment according to the guidelines for the treatment of asthma.

**Recommendation 4B**

In patients with perennial AR, we suggest an oral H1-antihistamine rather than a leukotriene receptor antagonist (conditional recommendation | low certainty of evidence)

Values and preferences
This recommendation places a higher value on possibly greater improvement of symptoms and quality of life with OAH, compared to LTRA. It places a lower value on possible increased risk of somnolence.

Explanations and other considerations
This is a conditional recommendation, thus different choices will be appropriate for different patients based on their preferences for reduction of symptoms versus avoiding the risk of adverse effects – this may be more important for patients with PAR than with SAR as they might use those medications for longer periods of time.

Some patients with AR and concomitant asthma, especially exercise-induced and/or aspirin exacerbated respiratory disease, may benefit from LTRA more than from OAH. However, *this recommendation applies to treatment of AR not to treatment of asthma*. Patients with asthma who have concomitant AR should receive an appropriate treatment according to the guidelines for the treatment of asthma.

## Question 5. Should an intranasal H1-antihistamine vs. an intranasal corticosteroid be used for treatment of allergic rhinitis?

INAH and INCS are two most effective intranasal therapies for AR. INAH may have an advantage over INCS in their faster onset of symptom relief as their mechanisms of action are different. In the 2010 revision of the ARIA guidelines we recommended INCS rather than INAH. However, no well done systematic review was available at that time and new studies have been performed and published that might change the recommendation. The ARIA guideline panel decided that this recommendation should be reviewed.

Summary of the evidence

We identified 15 RCTs that compared INAH to INCS in patients with SAR [E69, E71-E73, E107-E116] and 4 RCTs in patients with PAR [E117-E120]. All studies included adult patients and none included children. Studies in patients with SAR used various INCS (beclomethasone, budesonide, flunisolide, fluticasone, and mometasone) and various INAH (azelastine, levocabastine and olopatadine) for 2 to 6 weeks. For those studies that have not reported numerical results and/or variability in the results we used numbers provided in two previous systematic reviews [E121, E122]. We performed sensitivity analyses and the combined results were similar with and without those studies.
We found some differences among different INAH and daily doses of INAH but they were not consistent across outcomes and there is not enough information to allow any conclusions about specific INAH or INCS.

Evidence profiles for question 5A (seasonal AR) and 5B (perennial AR) are in the Online Repository 2.

Benefits

There seem be no desirable effects of INAH when compared to INCS in SAR and in PAR.

There was no evidence of a difference in ocular symptoms in patients with SAR (SMD: 0.08 SD higher, 95% CI: 0.11 lower to 0.26 higher) and with PAR (mean difference: 0.29 point higher on a 5-point scale, 95% CI: 0.39 lower to 0.97 higher).

Eight studies examined the time to onset of action in patients with SAR. Results were most often reported as graphs with no variability and showed inconsistent results: 2 studies [E110, E112] showed that INAH may relieve symptoms faster over the first 2-4 days with INCS being more effective from day 4 onwards, two additional studies showed no difference [E71, E73] and 4 studies showed quicker relief of symptoms in the INCS group [E69, E111]. One study using an allergen challenge found better improvement of symptoms with INAH compared to INCS over the first 2-4 hours after drug administration [E83].

Harms and burden

In patients with SAR, effects of INAH were smaller compared to INCS on nasal symptoms (SMD: 0.17 SD higher, 95% CI: 0.07 to 0.28 higher) and quality of life (mean difference in RQLQ score: 0.26 points higher, 95% CI: 0.09 to 0.43 higher). However, confidence intervals around the estimated effects do not exclude the possibility that this difference may not be large enough to be perceived by a substantial proportion of patients.

In patients with PAR, there is some evidence, albeit of low certainty, that INAH do not relieve nasal symptoms as well as INCS (mean difference: 1.08 points higher on a 10-point scale, 95% CI: 0.36 to 1.8 higher). There is no information about quality-of-life in patients with PAR. However, assuming that symptoms are a good surrogate for quality of life, it is very likely that it would also be improved more with INCS.

There were no serious adverse effects in any of the studies in SAR and in PAR. There was no evidence of higher risk of discontinuation of treatment owing to adverse effects with either medication. There were more any adverse effects with INAH compared to INCS in studies of SAR (risk difference: 35 more per 1000 patients, 95% CI: 4 to 77 more). As expected, bitter taste was more frequent with INAH than with INCS. Increased risk of somnolence was higher in patients with PAR (risk difference: 170 more per 1000 patients, 95% CI: 1 fewer to 330 more) than in SAR (risk difference: 3 more per 1000 patients, 95% CI: 0 to 17 more), but the confidence intervals did not exclude the possibility of no difference between the groups. There was no evidence of a difference in the risk of epistaxis.

Decision criteria and additional considerations

Panel members noted that relative effects of INAH and INCS may be different when used continuously (as in these studies) vs. as need (not investigated in clinical trials).

We found one retrospective cohort study of adult patients with AR in the United States that examined the cost of INAH and INCS [E85]. Panel members thought that unit costs assumed in this study do not reflect the current costs in most settings and relying on the estimates from this study could be misleading. Panel members noted that the choice of therapy will likely highly depend on the local health system owing to large variability in cost and coverage among countries, healthcare systems, public and private insurance plans, co-payment models, and patient out of the pocket expenses.

Conclusions and research needs

There seem be no desirable effects of INAH when compared to INCS in SAR and PAR. There is some evidence that INCS relieve nasal symptoms better and have fewer adverse effects. However, the differences in the effects are small and adverse effects mild, thus, the choice may primarily depend on availability and cost of particular medications, and patient's values and preferences.

Further research of an effect of INAH compared with INCS on quality of life in patients with PAR may be warranted. The only INAH used in these 3 studies was azelastine – studies of other INAH may also be beneficial.

What others are saying

The American Academy of Otolaryngology—Head and Neck Surgery guidelines do not make a specific recommendation for the choice of INAH or INCS but make a separate strong recommendation to use INCS "for patients with a clinical diagnosis of AR whose symptoms affect their quality of life" and give an option to use of INAH: "clinicians may offer INAH for patients with seasonal, perennial, or episodic AR" [E7].
The American Academy of Family Physicians suggests "INCS alone for the initial treatment for AR with symptoms affecting quality of life" and "INAH as needed for mild intermittent symptoms" and adds that "because INAH are more expensive, less effective, and have more adverse effects than INCS, they are not recommended as first-line therapy for AR" [E66].
The AAAAI/ACAAI Practice Parameter does not make explicit recommendations for practice but states that INAH is "effective for SAR and PAR" but "less effective than INS" [E67]. Note that this Practice Parameter was developed in 2008 when less information was available.
University of Michigan guidelines make no specific recommendations but state that INCS are the first and INAH are the fourth option to add in the treatment of seasonal allergic rhinitis" [E68].

**Recommendation 5A**

In patients with seasonal AR, we suggest an intranasal corticosteroid rather than an intranasal H1-antihistamine (conditional recommendation | moderate certainty of evidence).

Values and preferences

This recommendation places a higher value on greater reduction of symptoms and improvement of quality of life with INCS, compared to INAH, but and a lower value on avoiding larger cost of treatment with INCS in many jurisdictions.

Explanations and other considerations

This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his values and preferences considering local availability and costs.

**Recommendation 5B**

In patients with perennial AR, we suggest an intranasal corticosteroid rather than intranasal H1-antihistamine (conditional recommendation | low certainty of evidence).

Values and preferences

This recommendation places a higher value on probably greater reduction of nasal symptoms with INCS, compared to INAH, although the overall difference is likely small. It places a lower value on avoiding larger cost of treatment with INCS in many jurisdictions.

Explanations and other considerations

This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his values and preferences considering local availability and costs.

## Question 6. Should a intranasal H1-antihistamine (INAH) vs. an oral H1-antihistamine (OAH) be used for treatment of allergic rhinitis?

Theoretically the major advantage of INAH is the delivery directly into the nose and possible avoidance or reduction in severity of systemic side effects of OAH. In 2010 revision of the ARIA guidelines we suggested that for majority of patients OAH would be a better choice, but the recommendation was mainly based on indirect evidence of the likely higher patient preference for an oral versus intranasal route of administration.

Summary of the evidence

We found 9 RCTs that investigated the effects of INAH compared to OAH in patients with SAR [123-134] and 4 studies in patients with PAR [E135-E138]. All studies in SAR and 3 studies in PAR included only adult patients; only one study in PAR included older children and teenagers [E135]. All studies in SAR and PAR used newer OAH except for 2 studies in SAR that used chlopheniramine [E131, E134]. Most studies used azelastine as INAH but one study in SAR and 2 studies in PAR used levocabastine. Studies in SAR followed patients for 2 to 6 weeks whereas only one study in PAR followed patient for at least 4 weeks [138] that is recommended for studies in PAR [E139, E140].

Evidence profiles for questions 6A (seasonal AR) and 6B (perennial AR) are in the Online Repository 2.

Benefits

There seem to be differences in the effects among different INAH and OAH on nasal symptoms. There is moderate certainty evidence that azelastine has a smaller effect on nasal symptoms compared to cetirizine (SMD 0.21 SD higher, 95% CI: 0.06 to 0.36 higher). There is low certainty evidence that azelastine (in either dose) improves nasal symptoms more than chlorpheniramine

(SMD 0.48 SD lower, 95% CI: 0.08 to 0.87 lower). However, in both cases confidence intervals do not exclude almost no effect. For all other comparisons there is no evidence that either INAH or OAH better relieve nasal symptoms (SMD 0 SD, 95% CI: 0.19 lower to 0.19 higher). In one study that measured this outcome, azelastine improved quality of life more than cetirizine (mean difference 0.3 point in RQLQ lower, 95% CI: 0.03 to 0.57 lower).

Panel members commented that there is a belief among researchers that INAH have a larger effect on nasal congestion, compared to OAH. We were not able to prove this effect in the 5 studies in SAR that reported congestion. Two studies reported end-of-study values (SMD: 0.01; 95% CI: 0.21 lower to 0.23 higher) and 3 studies reported changes from baseline (SMD: 0.08; 95% CI: 0.10 lower to 0.26 higher). This observation remained almost unchanged when we included only 2 studies that used larger doses of INAH (SMD: 0.13; 95% CI: 0.07 lower to 0.33 higher).

In patients with PAR, there was no evidence of a difference between INAH and OAH in nasal symptoms (SMD 0.13 higher, 95% CI: 0.12 lower to 0.39 higher) and in ocular symptoms (SMD 0.03 higher, 95% CI: 0.23 lower to 0.28 higher). No study in PAR measured quality of life.

Panel members noted that nasal congestion is an important persistent symptom of PAR. However, none of the studies in PAR reported the symptoms separately.

Harms and burden

There were no serious adverse effects in any of the trials in SAR or PAR. There was also no evidence of a difference in all adverse effects taken together.

Patients receiving INAH, compared to OAH, were more likely to discontinue treatment owing to adverse effect in studies of SAR (12 more per 1000 patients , 95% CI: from 1 fewer to 41 more) but not PAR (2 fewer per 1000 patients, 95% CI: from 20 fewer to 248 more). Patients receiving INAH, compared to OAH, were less likely to experience somnolence in studies of SAR (37 fewer per 1000 patients, 95% CI: 16 to 51 fewer) and PAR (24 fewer per 1000 patients, 95% CI: from 39 fewer to 67 more). We have not seen any inconsistency in comparative sedating effects in 8 studies of SAR irrespective of the newer or older OAH being used). Bitter taste was the most common adverse effect of INAH (120 more per 1000 patients, 95% CI: 60 to 190 more).

Decision criteria and additional considerations

We found no studies comparing cost of treatment with INAH and OAH. However, as with other treatment of AR, cost of treatment will very much depend on local availability and cost of branded and generic OAH and INAH. Generic OAH or INAH, if available, may be more cost-effective.

Panel members noted that the availability of OAH and/or INAH other-the-counter in many countries may have an impact on the choice of treatment because patients' access to one or the other medication may be different based on their ability to cover out of the pocket expenses.

Conclusions and research needs

There is no consistent evidence showing better health outcomes with INAH or OAH in SAR and in PAR. However the evidence is of low or very low certainty. Choice of treatment will likely depend on patient's preferences for relief of specific symptoms and aversion to adverse effects – increased somnolence with OAH and increased bitter or perverted taste with INAH.

Additional RCTs of individual INAH vs. individual OAH that properly measure and report symptoms and quality of life may be warranted in SAR and in PAR. Specifically, the studies that measure real life effects of continuous or as-needed use of INAH and OAH that also measure patient preference for the route of administration may be beneficial.

What others are saying

The American Academy of Otolaryngology—Head and Neck Surgery guidelines do not make a specific recommendation for the choice of INAH or OAH but make a separate strong recommendation to use "second generation/less sedating OAH for patients with AR and primary complaints of sneezing and itching" and give an option to use of INAH: "clinicians may offer INAH for patients with seasonal, perennial, or episodic AR" [E7].
The American Academy of Family Physicians suggests either "OAH or INAH as needed for mild intermittent symptoms" and adds that "although INAH are an option if symptoms do not improve with nonsedating OAH, their use as first- or second-line therapy is limited by adverse effects, twice daily dosing, cost, and decreased effectiveness compared with INCS" [E66].
The AAAAI/ACAAI Practice Parameter does not make explicit recommendations for practice but states that the effectiveness of INAH for AR is equal or superior to second-generation OAH [E67]. Note that this Practice Parameter was developed in 2008 when less information was available.
University of Michigan guidelines make no specific recommendations but state that OAH are the first and INAH are the fourth option to add in the treatment of allergic rhinitis" [E68].

### Recommendation 6A

In patients with SAR, we suggest either intranasal or oral H1-antihistamine (conditional recommendation | low certainty of evidence).

Values and preferences

The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment.

Explanations and other considerations
This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his preferences, considering local availability, coverage, and costs.

**Recommendation 6B**
In patients with perennial AR, we suggest either intranasal or oral H1-antihistamine (conditional recommendation | very low certainty of evidence).

Values and preferences
The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment.

Explanations and other considerations
This is a conditional recommendation, thus different choices will be appropriate for different patients – clinicians must help each patient to arrive at a decision consistent with her or his preferences, considering local availability, coverage, and costs.

## Plans for updating these guidelines

Guidelines are living products. To remain useful, they need to be updated regularly as new information accumulates. A revision of this document will be needed, because there was limited evidence for many clinical questions. This document will be updated when major new research is published. The need for update will be determined not later than in 2020.

## Updating or adapting recommendations locally

The methods used to develop these guidelines are transparent. The recommendations have been developed to be as specific and detailed as possible without losing sight of the simplicity of the document. Since ARIA are meant as international guidelines, the guideline panel encourages feedback on all its aspects including applicability of recommendations in individual countries.[E141] This feedback will be considered with the next revision of ARIA guidelines.
Adaptation of ARIA guidelines will be necessary in many circumstances and we suggest that responsible parties use the GRADE-Adolopment process, a combination of adoption, adaptation of

de novo creation of recommendations, with collaboration of the authors of this document. Depending on when such a process takes place, the following steps are part of that process:

- Appointing a guideline committee comprising clinicians and methodologists
- Determining the scope of the local guidelines
- Defining the relevant clinical questions to be addressed in local guidelines
- Updating the evidence profiles and Evidence-to-Decision tables, if necessary
- Reviewing the recommendations in the ARIA guidelines (the recommendations may need to be modified at a local level, depending on the local values and preferences, availability of medications, costs, etc.)

## Conclusions

Evidence-based guidelines are at the cornerstone of integrated care pathways (ICPs) [E142, E143], structured multidisciplinary care plans that promote translation of guideline recommendations into local protocols and their subsequent application in clinical practice. Usually several guidelines are available providing advice about the management of the same condition [E2]. It is important to wisely choose appropriate guidelines for local adaptation and creation of ICPs, because most of them have limitations owing to either the development of the guideline itself or the available research evidence and its interpretation. The most common limitations of guidelines in AR are narrow scope (addressing only a small selection of important questions about the management of a given condition), suboptimal rigor of development and reporting, and inadequate representation of the views of patients and their caregivers [E2]. We acknowledge, that for the ARIA 2016 update we have not reviewed all recommendations from the ARIA 2010 but we updated only 3 recommendations suggested by the ARIA panel members as requiring the update and we addressed 3 new questions. We also acknowledge that the ARIA guideline panel included allergists, ENT specialists, pulmonologists, general practitioners and pediatricians but did not include other health care professionals, pharmacists and patients themselves. However, for the ARIA 2016 update we systematically searched and reviewed the published evidence about the patient values and preferences regarding the outcomes and treatments for AR that to certain degree helped to overcome this limitation. We summarized the results in the section about the assumed values and preferences above and in the relevant sections of evidence-to-decision tables (Online Repository 2).

The available evidence has important limitations: 1) selective measurement and reporting of outcomes (e.g. few studies properly measure and report quality of life which is the most important outcome in AR), 2) selection of patients for clinical trials that may not represent appropriately the patients seen in primary care [E144] as well as 3) not distinguishing between patients with different age or severity of symptoms (lack of proper stratification) [E145], thus, limiting the applicability and generalizability of the research findings. Given these limitations, clinical practice guidelines – especially those with international audience – should emphasize rigorous systematic review of the

health effects and explicit and detailed description of the assumed values and preferences and considerations of cost, feasibility, acceptability and health equity issues, as it is currently following the GRADE evidence-to-decision frameworks [E146-E148]. Such detailed, explicit and transparent reporting of guidelines facilitates local adaptation of recommendations and their translation into ICPs. Systematic and transparent summaries of the evidence clearly identifying gaps in available research evidence are needed to direct research agenda and to avoid unnecessary expenditure of resources for further clinical research when it is not necessary [E149].

Implementation of guidelines in different settings and countries depends on the availability of health interventions (e.g. medical tests, medications, equipment, etc.), availability of resources, and cultural differences, among others. Thus, local adaptation of recommendations may be required and ICPs need to be developed at national, regional or local level. However, they always should be based on systematically reviewed evidence of desirable and undesirable consequences. The ARIA 2016 revision will be used to develop the ICPs proposed by the European Innovation Partnership on Active and Healthy Ageing [E142, E143, E150] using MASK (MACVIA-ARIA Sentinel Network). ARIA is developing a novel implementation strategy using mobile technology [E151, E152] and a clinical decision support system (CDSS) [E151] and deployed in 21 countries [E153]. The ARIA 2016 revision will be embedded in the CDSS for real-time patient stratification using mobile technology.
Most of the recommendations are based on low or very low certainty evidence mainly because the imprecision of the estimated effects owing to few patients being studied. For those questions there is a need for more well designed and executed randomized controlled trials that would measure and properly report all important outcomes.

## Disclosure of potential conflict of interest

All ARIA panel members declared their actual, potential or perceived competing interests within the past 4 years related to the subject matter of these guidelines following the standard procedure of the World Health Organization.
Claus Bachert received honoraria for speaking and/or serving on advisory board from Meda, ALK, and Stallergenes; he is a member of guideline committee of the German Allergy Society (DGAKI).
Sinthia Bosnic-Anticevich is leading the update of the Pharmacy ARIA guidelines.
Jean Bousquet received honoraria for speaking and/or serving on scientific or advisory board from Almirall, AstraZeneca, Chiesi, GSK, Meda, Menarini, Merck, MSD, Novartis, Sanofi-Aventis, Takeda, Teva, and Uriach.
Jan Brozek together with Holger Schünemann received US$40,000 from the ARIA Initiative to support performing systematic reviews for these guidelines that have been deposited to McMaster University research account (it was used to support research assistants involved in this work; the majority of funding for the systematic reviews was contributed by McMaster University internal research funds); he has no other competing interests.

Giorgio Walter Canonica received honoraria for speaking and/or serving on scientific or advisory board, and research support from Alk-Abello', Almirall, Allergy Therapeutics, Anallergo, AstraZeneca, Boeringher Ingelheim, Boston Scientific, Bruschettini, Chiesi Farmaceutici, Circassia, Danone, Faes, Glaxo Smith Kline, Lab.Guidotti, Lallemand, Lofarma, Malesci, Meda Pharmaceuticals, Menarini, Mundifarma, Novartis, Pfizer, Roche, Sanofi, Stallergenes, Thermo Fisher, Uriach, Teva and Valeas.

Thomas Casale received honoraria for consultation from Sanofi Regeneron, Ora, Circassia and Capnia.

Alvaro Cruz received honoraria for serving on advisory board from AstraZeneca, Boehringer Ingelheim, GSK, Meda Pharmaceuticals, and Roche; he also received research grants and travel support from GSK, AstraZeneca, and MSD.

Pascal Demoly received honoraria for consultation and/or speaking for Allergopharma, AllergyTherapeutics, ALK-Abello, AstraZeneca, Chiesi, Circassia, GlaxoSmithKline, Meda Pharmaceuticals, Merck, Menarini, Stallergenes-Greer, and ThermoFisherScientific.

Mark Dykewicz received honoraria for consultation from Merck; he also served as consultant for U.S. FDA about allergen immunotherapy and is a co-author of the American Academy of Otolaryngology-Head Neck Surgery Clinical Practice Guideline on Allergic Rhinitis and currently being updated U.S. Joint Task Force (AAAAI/ACAAI) Rhinitis Practice Parameter.

Wytske Fokkens reported receiving support from Allergopharma, GSK, Meda Pharmaceuticals and Stallergens, paid to her institution.

Joao Fonseca received honoraria for consultation from Novartis and for speaking from Menarini, Lab Vitoria, and Novartis and research support from MSD; he is a secretary general of the Portuguese Society of Allergy and Clinical Immunology (SPAIC).

Ludger Klimek received honoraria for consultation and/or speaking for ALK-Abelló, Allergopharma, HAL, Allergy Therapeutics/Bencard, Meda Pharmaceuticals, and Leti; he also received research support from ALK-Abelló, Allergopharma, Stallergenes, HAL, Allergy Therapeutics/Bencard, Lofarma, MEDA, Novartis, Leti, ROXALL, and Cytos.

Piotr Kuna received honoraria for speaking from Adamed, Allergopharma, AstraZeneca, Berlin Chemie, Meda, Boehringer Ingelheim, Chiesi, FAES, GSK, MSD, Novartis, Pfizer, Stallergenes, and Teva.

Désirée Larenas Linnemann received honoraria for consultation and/or speaking from AstraZeneca, Glenmark, MEDA, Mit-pharma, MSD, Novartis, Pfizer, Sanofi, and TEVA; she also received research support from MEDA, MSD, AstraZeneca, Novartis, GSK, TEVA, Senosiain, Carnot, Sanofi, Pfizer and travel support from MEDA, MSD, Sanofi, Novartis, Stallergenes, UCB, Pfizer, ALK-Abelló.

Eli Meltzer received honoraria for consultation and/or speaking from AstraZeneca, Boehringer Ingelheim, Church & Dwight, Circassia, Meda, Merck, Regeneron-Sanofi and Teva; he is a co-author of the currently being updated U.S. Joint Task Force (AAAAI/ACAAI) Rhinitis Practice Parameter.

Joaquim Mullol received honoraria for speaking from UCB Pharma, Uriach Group, GSK, Hartington Pharmaceuticals, Menarini, Hyphens, Novartis, MSD, MEDA Pharma, and Sanofi-Aventis and research support from Uriach Group, Meda Pharmaceuticals, GSK, MSD, and FAES.
Petr Panzner received honoraria for speaking from Stallergenes, AstraZeneca, MEDA, and MSD.
Nikos Papadopoulos received research support from Menarini and Merck and for speaking for several undisclosed companies; he is the past president of EAACI and a member of the board of the Global Allergy and Asthma European Network (GA²LEN).
David Price received honoraria for speaking, research and travel support from Meda Pharmaceuticals.
Dermot Ryan received honoraria for speaking and/or serving on advisory board from Uriach, Stallergenes, and MEDA; he is chairing the Primary Care Interest Group in EAACI.
Boleslaw Samolinski received honoraria for speaking from Nexter-Allergopharma, Meda, Adamed, Polpharma and Teva.
Peter Schmid-Grendelmeier received honoraria for consulting from ALK ABello, Novartis and Thermo Fisher.
Holger Schünemann together with Jan Brozek received US$40,000 from the ARIA Initiative to support performing systematic reviews for these guidelines that have been deposited to McMaster University research account (it was used to support research assistants involved in this work; the majority of funding for the systematic reviews was contributed by McMaster University internal research funds); he has no other competing interests.
Aziz Sheikh declared that his institution received research support from Asthma UK (charitable funder), the Scottish Government, EAACI and unrestricted industry funding from a multiple companies to run the Scottish Allergy and Respiratory Academy (SARA); he is involved in guideline initiatives of EAACI, BTS/SIGN, WAO and the Resuscitation Council (UK).
Antonio Valero received honoraria from Novartis, Sanofi, GSK, Chiesi, Boehringer, FAES, Meda, Orion Pharma, Stallergenes, and Leti and research support from Novartis, Uriach, FAES, and Leti.
Dana Wallace received honoraria for consultation, speaking and serving on advisory board from MEDA Pharmaceuticals; she is a co-author of the American Academy of Otolaryngology-Head Neck Surgery Clinical Practice Guideline on Allergic Rhinitis and currently being updated U.S. Joint Task Force (AAAAI/ACAAI) Rhinitis Practice Parameter.
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