

THE UNIVERSITY of EDINBURGH

Edinburgh Research Explorer

The ARIA approach of Value-Added Medicines

Citation for published version:
Bousquet, J, Toumi, M, Sousa-Pinto, B, Anto, JM, Bedbrook, A, Czarlewski, W, Valiulis, A, Ansotegui, IJ, Bosnic-Anticevich, S, Brussino, L, Canonica, GW, Cecchi, L, Cherrez-Ojeda, I, Chivato, T, Costa, EM, Cruz, AA, Del Giacco, S, Fonseca, JA, Gemicioglu, B, Haahtela, T, Ivancevich, JC, Jutel, M, Kaidashev, I, Klimek, L, Kvedariene, V, Kuna, P, Larenas-Linnemann, DE, Lipworth, B, Morais-Almeida, M, Mullol, J, Papadopoulos, NG, Patella, V, Pham-Thi, N, Regateiro, FS, Rouadi, PW, Samolinski, B, Sheikh, A, Taborda-Barata, L, Ventura, MT, Yorgancioglu, A, Zidarn, M & Zuberbier, T 2022, 'The ARIA approach of Value-Added Medicines: as-needed treatment in allergic rhinitis', *The journal of allergy and clinical immunology. In practice*, vol. 10, no. 11, pp. 2878-2888. https://doi.org/10.1016/j.jaip.2022.07.020

Digital Object Identifier (DOI):
10.1016/j.jaip.2022.07.020

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Peer reviewed version

Published In:
The journal of allergy and clinical immunology. In practice

General rights
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

OPEN ACCESS

Download date: 15. Jul. 2023

Journal Pre-proof

Rostrum

The ARIA approach of Value-Added Medicines: as-needed treatment in allergic rhinitis

Short title: Drug repurposing in allergic rhinitis

Jean Bousquet (1-3), Mondher Toumi, (4) Bernardo Sousa-Pinto [5-7], Josep M Anto (8-11), Anna Bedbrook [12], Wienczyslawa Czarlewski (13), Arunas Valiulis (14), Ignacio J Ansotegui (15), Sinthia Bosnic-Anticevich (16), Luisa Brussino (17), G Walter Canonica (18), Lorenzo Cecchi [19], Ivan Cherrez-Ojeda (20), Tomas Chivato (21), Elísio M Costa [22], Alvaro A Cruz (23), Stefano Del Giacco (24), Joao A. Fonseca [5-7], Bilun Gemicioglu (25), Tari Haahtela (26), Juan Carlos Ivancevich (27), Marek Jutel (28), Igor Kaidashev [29], Ludger Klimek (30), Violeta Kvedariene (31), Piotr Kuna (32), Désirée E. Larenas-Linnemann (33), Brian Lipworth [34], Mario Morais-Almeida (35), Joaquim Mullol (36), Nikolaos G Papadopoulos (37), Vincenzo Patella (38), Nhân Pham-Thi (39), Frederico S Regateiro [40], Philip W. Rouadi [41], Boleslaw Samolinski (42), Aziz Sheikh (43), Luis Taborda-Barata [44], Maria Teresa Ventura (45), Arzu Yorgancioglu (46), Mihaela Zidarn [47],[48], Torsten Zuberbier[1,3]

1. Institute of Allergology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany
2. University Hospital Montpellier, France.
3. Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany
4. Public Health, Aix-Marseille University, Marseille, France.
5. MEDCIDS - Department of Community Medicine, Information and Health Decision Sciences; Faculty of Medicine, University of Porto, Porto, Portugal.
6. CINTESIS – Center for Health Technology and Services Research; University of Porto, Porto, Portugal.
7. RISE – Health Research Network; University of Porto, Porto, Portugal.
8. ISGlobaL, Barcelona Institute for Global Health, Barcelona, Spain.
9. IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain.
10. Universitat Pompeu Fabra (UPF), Barcelona, Spain.
11. CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain.
12. ARIA, Montpellier, France.
13. Medical Consulting Czarlewski, Levallois, France.
14. Institute of Clinical Medicine and Institute of Health Sciences, Medical Faculty of Vilnius University, Vilnius, Lithuania.
15. Department of Allergy and Immunology, Hospital Quironsalud Bizkaia, Bilbao, Spain.
16. Quality Use of Respiratory Medicine Group, Woolcock Institute of Medical Research, The University of Sydney, and Sydney Local Health District, Sydney, NSW, Australia.
17. Department of Medical Sciences, Allergy and Clinical Immunology Unit, University of Torino & Mauriziano Hospital, Torino, Italy.
18. Department of Biomedical Sciences, Humanitas University, Pieve Emanuele & Personalized Medicine, Asthma and Allergy, Humanitas Clinical and Research Center IRCCS, Rozzano, Italy.
19. SOS Allergology and Clinical Immunology, USL Toscana Centro, Prato, Italy.

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

20. Espiritu Santo University. Samborondon- Ecuador.
21. School of Medicine, University CEU San Pablo, Madrid, Spain.
22. UCIBIO, REQUINTE, Faculty of Pharmacy and Competence Center on Active and Healthy Ageing of University of Porto (Porto4Ageing), Porto, Portugal.
23. Fundaçao ProAR, Federal University of Bahia and GARD/WHO Planning Group, Salvador, Bahia, Brazil.
24. Department of Medical Sciences and Public Health and Unit of Allergy and Clinical Immunology, University Hospital 'Duilio Casula', University of Cagliari, Cagliari, Italy
25. Department of Pulmonary Diseases, Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Istanbul, Turkey.
26. Skin and Allergy Hospital, Helsinki University Hospital, University of Helsinki, Finland.
27. Servicio de Alergia e Immunologia, Clinica Santa Isabel, Buenos Aires, Argentina.
28. Department of Clinical Immunology, Wrocław Medical University, and ALL-MED Medical Research Institute, Wroclaw, Poland.
29. Poltava State Medical University, Ukraine.
30. Department of Otolaryngology, Head and Neck Surgery, Universitätsmedizin Mainz, Mainz, and Center for Rhinology and Allergology, Wiesbaden, Germany.
31. Institute of Biomedical Sciences, Department of Pathology, Faculty of Medicine, Vilnius University and Institute of Clinical medicine, Clinic of Chest diseases and Allergology, Faculty of Medicine, Vilnius University, Vilnius, Lithuania.
32. Division of Internal Medicine, Asthma and Allergy, Barlicki University Hospital, Medical University of Lodz, Poland.
33. Center of Excellence in Asthma and Allergy, Médica Sur Clinical Foundation and Hospital, México City, Mexico.
34. Scottish Centre for Respiratory Research, Cardiovascular & Diabetes Medicine, Medical Research Institute, Ninewells Hospital, University of Dundee, UK.
35. Allergy Center, CUF Descobertas Hospital, Lisbon, Portugal
36. Rhinology Unit & Smell Clinic, ENT Department, Hospital Clínic; Clinical & Experimental Respiratory Immunoallergy, IDIBAPS, CIBERES, University of Barcelona, Spain.
37. Allergy Department, 2nd Pediatric Clinic, University of Athens, Athens, Greece.
38. Division of Allergy and Clinical Immunology, Department of Medicine, Agency of Health ASL Salerno, "Santa Maria della Speranza" Hospital, Battipaglia, Salerno, Italy.
39. Ecole Polytechnique Palaiseau, IRBA (Institut de Recherche bio-Médicale des Armées), Bretigny, France.
40. Allergy and Clinical Immunology Unit, Centro Hospitalar e Universitário de Coimbra, Coimbra and Institute of Immunology, Faculty of Medicine, University of Coimbra, and Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, University of Coimbra, Coimbra, Portugal.
41. Department of Otolaryngology-Head and Neck Surgery, Eye and Ear University Hospital, Beirut, Lebanon and ENT Department, Dar Al Shifa Hospital- Salmiya, Kuwait.
42. Department of Prevention of Environmental Hazards, Allergology and Immunology, Medical University of Warsaw, Poland.
43. Usher Institute, The University of Edinburgh, Edinburgh, UK.
44. UBIAir - Clinical & Experimental Lung Centre, University of Beira Interior, Covilhã and CICS-Health Sciences Research Centre, University of Beira Interior, Covilhã and Department of Immunoallergology, Cova da Beira University Hospital Centre, Covilhã, Portugal.
45. Unit of Geriatric Immunoallergology, University of Bari Medical School, Bari, Italy.
46. Department of Pulmonology, Celal Bayar University, Manisa, Turkey.
47. University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia.
48. University of Ljubljana, Faculty of Medicine, Ljubljana, Slovenia

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

Address for correspondence

Professor Jean Bousquet, Institute of Allergology, Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany ;

Telephone: +33 611 42 88 47; Mail: jean.bousquet@orange.fr

Word count: 2990

Funding: none

Conflict of Interests

Dr. Bousquet reports personal fees from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Purina, Sanofi-Aventis, Takeda, Teva, Uriach, other from KYomed-Innov, outside the submitted work.
Dr. Toumi has nothing to disclose.
Dr. Sousa-Pinto has nothing to disclose.
Dr. ANTÓ has nothing to disclose.
Dr. Bedbrook has nothing to disclose.
Dr. Czarlewski has nothing to disclose.
Dr. Valiulis has nothing to disclose.
Dr. Ansotegui reports personal fees from Roxall, personal fees from UCB, personal fees from Faes Farma, personal fees from Sanofi, personal fees from Bial, personal fees from Abbott, personal fees from Bayer, personal fees from Organon, outside the submitted work; .
Dr. Bosnic-Anticevich reports grants from TEVA, personal fees from TEVA, personal fees from TEVA, personal fees from AstraZeneca, personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, personal fees from Boehringer Ingelheim, personal fees from GSK, personal fees from Sanofi, personal fees from Mylan, outside the submitted work; .
Dr. Brussino has nothing to disclose.
Dr. Canonica has nothing to disclose.
Dr. Cecchi reports personal fees from Thermofisher, personal fees from Sanofi, personal fees from Astra Zeneca, personal fees from Novartis, outside the submitted work; .
Dr. Cherrez-Ojeda has nothing to disclose.
Dr. Chivato has nothing to disclose.
Dr. Costa has nothing to disclose.
Dr. Cruz reports personal fees from AstraZeneca, personal fees from Boehringer-Ingelheim, personal fees from CHIESI, personal fees from GSK, personal fees from SANOFI, personal fees from Novartis, personal fees from EUROFARMA, personal fees from Abdi-Ibrahim , outside the submitted work; .
Dr. Del Giacco reports grants and personal fees from AstraZeneca, grants and personal fees from GSK, grants and personal fees from Novartis, personal fees from Sanofi, personal fees from Chiesi, outside the submitted work; .
Dr. Fonseca reports and is co-founder of a company that develops mHealth technologies.
Dr. Gemicioglu has nothing to disclose.
Dr. Haahtela reports other from GSK, Orion Pharma, and Sanofi, outside the submitted work; .
Dr. Ivancevich reports personal fees from Laboratorios Casasco, personal fees from Faes Farma, personal fees from Abbott Ecuador, personal fees from Bago Bolivia, outside the submitted work; .
Dr. Jutel reports personal fees from ALK-Abello, personal fees from Allergopharma , personal fees from Stallergenes, personal fees from Anergis, personal fees from Allergy Therapeutics , personal fees from Leti , personal fees from HAL, during the conduct of the study; personal fees from GSK, personal fees from Novartis, personal fees from Teva, personal fees from Takeda, personal fees from Chiesi, outside the submitted work.

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

Dr. Kaidashev has nothing to disclose.
Dr. Klimek has nothing to disclose.
Dr. Kvedariene reports other from Norameda, other from BerlinCHemie Menarini, outside the submitted work; .
Dr. Kuna reports personal fees from Adamed, personal fees from Berlin Chemie Menarini, personal fees from Boehringer Ingelheim, personal fees from AstraZeneca, personal fees from Glenmark, personal fees from Krka, personal fees from Novartis, personal fees from Polpharma, personal fees from GSK, personal fees from Sanofi, outside the submitted work; .
Dr. Larenas Linnemann reports personal fees from ALK, Allakos, Amstrong, Astrazeneca, Chiesi, DBV Technologies, Grunenthal, GSK, Mylan/Viatris, Menarini, MSD, Novartis, Pfizer, Sanofi, Siegfried, UCB, Alakos, Gossamer, Carnot, grants from Sanofi, Astrazeneca, Lilly, Pfizer, Novartis, Circassia, UCB, GSK, Purina institute., outside the submitted work; .
Dr. Lipworth reports personal fees from Glenmark , grants and personal fees from Mylan , grants from Sanofi , from AstraZeneca , from null, from null, during the conduct of the study; and Son of BJL employee of AstraZeneca.
Dr. Morais-Almeida has nothing to disclose.
Dr. MULLOL reports personal fees and other from SANOFI-GENZYME & REGENERON, personal fees and other from NOVARTIS, personal fees and other from ALLAKOS, grants and personal fees from MYLAN Pharma, grants and personal fees from URIACH Group, personal fees from Mitsubishi-Tanabe, personal fees from Menarini, personal fees from UCB, personal fees from AstraZeneca, personal fees from GSK, personal fees from MSD, outside the submitted work.
Dr. Papdopoulos reports other from Gerolymatos Int., other from Capricare, other from Nutricia, from ALK, Asit Biotech, AstraZeneca, Biomay, Boehringer Ingelheim, GSK, HAL, Faes Farma, Medscape, Menarini, MSD, Mylan/Meda, Novartis, Nutricia, OM Pharma, Regeneron, Sanofi, Takeda, outside the submitted work; .
Dr. Patella has nothing to disclose.
Dr. Pham-Thi has nothing to disclose.
Dr. Regateiro has nothing to disclose.
Dr. ROUADI has nothing to disclose.
Dr. Samoliński reports personal fees from Polpharma, personal fees from Viatris, grants and personal fees from AstraZeneca, personal fees from TEVA, personal fees from patient ombudsman, personal fees from Polish Allergology Society, grants from GSK, outside the submitted work; .
Dr. Sheikh has nothing to disclose.
Dr. Taborda-Barata has nothing to disclose.
Dr. Ventura has nothing to disclose.
Dr. Yorgancioglu has nothing to disclose.
Dr. Zidarn has nothing to disclose.
Dr. Zuberbier reports personal fees from AstraZeneca, personal fees from AbbVie, personal fees from ALK, personal fees from Almirall, personal fees from Astellas, personal fees from Bayer Health Care, personal fees from Bencard, personal fees from Berlin Chemie, personal fees from FAES, personal fees from HAL, personal fees from Leti, personal fees from Meda, personal fees from Menarini, personal fees from Merck, personal fees from MSD, grants and personal fees from Novartis, personal fees from Pfizer, personal fees from Sanofi, personal fees from Stallergenes, personal fees from Takeda, personal fees from Teva, personal fees from UCB, grants from Henkel, personal fees from Kryolan, personal fees from L´Oréal, outside the submitted work; and Organizational affiliations:Üommitee member: WHO-Initiative "Allergic Rhinitis and Its Impact on Asthma" (ARIA)Đember of the Board: German Society for Allergy and Clinical Immunology (DGAKI)Ûoard Chairman: European Centre for Allergy Research Foundation (ECARF)Đresident: Global Allergy and Asthma European Network (GA2LEN)Đember: Committee on Allergy Diagnosis and Molecular Allergology, World Allergy Organization (WAO).

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

Abstract

Drug repurposing is one of the major fields of Value-Added Medicines. It involves the investigation and evaluation of existing drugs for new therapeutic purposes that address unmet healthcare needs. There are several unmet needs in allergic rhinitis that could be improved by drug repurposing. This could be game-changing for disease management. The current medications for allergic rhinitis are centered around a continuous long-term treatment, and medication registration is based on randomized controlled trials carried out for a minimum of 14 days with adherence ≥70%. A new way of treating allergic rhinitis is to propose an as-needed treatment depending on symptoms, rather than the classical continuous treatment. This rostrum will discuss the existing clinical trials on as-needed treatment for allergic rhinitis and real-world data obtained by the mobile health app MASK-air that has a focus on digitally-enabled, patient-centered care pathways.

Key words: value-added medicines, repurposing, allergic rhinitis, MASK-air, treatment

Abbreviations

AI: Artificial intelligence
AIT: Allergen immunotherapy
AR : allergic rhinitis
ARIA : Allergic Rhinitis and its Impact on Asthma
FF: Fluticasone furoate
FP: Fluticasone propionate
GINA: Global Initiative for Asthma
GRADE: Grading of Recommendations, Assessment, Development and Evaluation
INCS: Intra-nasal corticosteroid
LABA: Long-acting ß agonist
MASK: Mobile Airways Sentinel networK
mHealth: Mobile health
OTC: Over-the-counter
QoL: Quality-of-life
PRN: on-demand/as needed
RCT: Randomized controlled trial
RWD: Real-world data
RWE: Real-world evidence
SABA: Short-acting ß agonist
SCUAD: Severe Chronic Upper Airway Disease
SMART: Single Maintenance and Reliever Therapy
TNSS: Total nasal symptom score
VAM: Value-added medicine
VAS: Visual Analog Scale

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

Introduction

Allergic rhinitis (AR) is one of the most common chronic conditions in high-income settings, with a lifetime prevalence of up to 50% in some countries.(48) It is a global health problem that causes major illness and disability worldwide.(49) It affects social life, school, and work.(50) Patients may also suffer from sleep disorders and emotional problems. The economic effect of AR is often underestimated, as indirect costs are substantial. The effects of AR on work productivity are estimated to cost €30–50 billion per year in the European Union alone.(50-52)

AR treatment is complex as many treatments are available including allergen avoidance, pharmacotherapy, and allergen immunotherapy (AIT).(48, 53-55) Medications are dispensed in oral and/or topical formulations. Many guidelines for AR are evidence-based(55-58) and have led to an improved understanding and management of AR. They all propose long-term continuous treatment. However, guidelines are mostly based on randomized controlled trials (RCTs), typically undertaken on highly selected populations, often with limited/unclear generalizability to routine care contexts.(59-61) Many patients are however dissatisfied with their treatment as their symptoms remain poorly controlled. Moreover, adherence to treatment is usually poor in AR, even when using mobile health (mHealth).(62) Patients treat themselves according to their symptoms (irrespective of how they understand AR), and co-medication use is driven by symptom severity.(63) Many patients are on-demand (PRN) users although there is no guideline that approaches this issue.

Large observational implementation studies are needed to triangulate RCTs. The former reflect "real-world" everyday use and practice more closely than RCTs in terms of the heterogeneous patient populations included, as well as the variety of medical interventions assessed.(64) Observational studies with real-world data (RWD) examine the possible effect of a treatment on subjects where the investigator has no control over the experiment and cannot randomize subject allocation.(65) However, they provide clinically relevant information that is complementary to the insights gained from RCTs, as they assess implementation considerations in routine care.

In AR, there is an urgent need for change management.(66) Novel treatment options are required and should consider unmet medical needs, demonstrating a faster and more complete symptom control in direct comparison studies versus the currently available first-line AR therapy. They should also show superior efficacy in patients, regardless of disease severity, and in those who present with a particularly bothersome or predominant symptom. The importance of mHealth needs to be stressed. (67)

Repurposing current medical options is another complementary strategy.(68) The definition of repurposing is complex. Given the disparity and inconsistency of terminologies and classifications in the literature, a systematic review was carried out in 2013 in order to obtain a harmonized nomenclature

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

for drug repositioning, reformulation, and combination cases.(69) It was proposed that "The term repurposing includes all the re-development strategies based on the same chemical structure of the therapeutically active ingredient as in the original product." Drug repurposing involves exploring new medical uses for existing drugs.(70) Drug repurposing should be based on RCTs or RWD and provide the patient with an effective and acceptable treatment. The model of AR has been used in this paper. It includes results obtained using real-world evidence (RWE), and combines RCTs, RWD, and chamber studies.(71-74) The Food and Drug Administration (FDA) as well as the European Medicine Agency (EMA) have approved drug repurposing based on RWD (e.g., palbocilib, https://www.ema.europa.eu/en/documents/product-information/ibrance-epar-product-information_en.pdf,). However, RWD is better accepted by regulators in the UK and Canada than in certain other countries.

The purpose of this article is to argue that Value-Added Medicines (VAMs), such as the PRN use of nasal sprays, may address the unmet needs in rhinitis management.

Value-added medicines

Value-added medicines (VAMs) address different healthcare needs,(75) including (i) innovation on existing molecules in the form of repurposing,(76-78) reformulation, and combination of therapies, (ii) improving patient adherence, (iii) addressing problems related to polypharmacy, and (iv) enhancing personalized healthcare services. VAMs deliver relevant benefits for patients, healthcare professionals, and/or payers. Although most VAM solutions are based on generic medications, they can also develop patented ones. VAMs can empower patients by putting their needs at the center of therapy design, improving overall therapy outcomes (Table 1).

Drug repurposing, also known as drug repositioning or drug reprofiling, involves the investigation of existing drugs for new therapeutic purposes. Repurposing can start serendipitously (unintentional fortunate observations) or through systematic approaches, including artificial intelligence (AI),(79) with RCTs also having a key role in establishing drug repurposing. It provides a novel way of exploring old drugs for new uses. As the new indication is built on already-available safety, as well as pharmacokinetic and manufacturing data, drug repurposing represents an expedited way of developing innovative medications.(76-78) A well-known example of a repurposed drug is that of sildenafil. Originally developed as an anti-hypertensive, sildenafil was later repositioned for the treatment of erectile dysfunction and benign prostatic hyperplasia, pulmonary arterial hypertension, and cancer.(80-82) Repurposing has been widely used, particularly in cancer(83) or COVID-19.(84) One example in COVID-19 is the successful use of dexamethasone in hospitalized patients.(85) It is estimated that about one-third of recent approvals correspond to repurposing examples, and different public and private

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

initiatives (such as Medicines for Europe (https://www.medicinesforeurope.com/value-added-medicines/) have been launched to foster the exploration of repurposing opportunities. The issues surrounding the challenges of repurposing established medicines have been discussed in meetings of the European Commission's Safe and Timely Access to Medicines for Patients (STAMP) Expert Group.(86)

However, several barriers prevent maximizing the benefits of VAM innovation.(75) Despite the wide interest surrounding drug repurposing, no common terminology has been agreed upon for VAMs, and their full potential value is not always understood.(68) Drug repurposing definitions are based on outcomes, processes, or a mixture of both. Generic manufacturers have limited budget and experience in demonstrating the value of new VAMs. Current market exclusivity options do not guarantee a return on investment for VAM innovators. Although there is an increasing regulatory authority interest in capturing VAM benefits, it is associated with the resistance of Health Technology Assessment (HTA) bodies/payers.(68) A core framework for VAMs has been proposed.(87) However, the current European environment does not allow this approach to be fully exploited. Three key enablers are needed in the EU to promote continuous and sustainable innovation: (i) a fit-for-purpose regulatory framework ensuring predictability in early development, (ii) the recognition of innovation with proportionate incentives, and (iii) the definition and recognition of added value. Finally, in addition to regulatory barriers, there are also limitations inherent to repurposing strategies. If not assessed by adequate studies on their effectiveness and safety, drugs used for purposes other than the ones for which they were developed may be ineffective and even dangerous. An illustrative example concerns the attempt of using hydroxychloroquine or ivermectin in patients with COVID-19. Not only were they shown to be ineffective,(88, 89) but also associated with relevant adverse events (e.g., hydroxychloroquine may increase the risk of cardiac toxicity and cognitive dysfunction).(90)

Unmet needs in allergic rhinitis

Many patients are dissatisfied with their treatment as their symptoms are inadequately controlled, they do not want a long-time treatment for a condition they perceive as non-threatening, and/or they experience unacceptable side-effects. Several unmet needs have been identified in AR.(91, 92) RWD offer new insights into the phenotypes and management of AR, which may help to better understand and mitigate these unmet needs.(93)

Control and severity need to be better delineated. SCUAD (Severe Chronic Upper Airway Disease) has defined uncontrolled AR patients pharmacologically,(94-96) but more information is needed to fully understand extreme allergy phenotypes that do not respond to treatment.(97) A common language of AR control does not exist. Measures of AR control include symptom scores, visual analog scale (VAS) scores, quality-of-life (QoL) instruments, or scores with several items.(98-108) The VAS represents a

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

common control 'language' for AR, and enables effective communication between healthcare providers and patients in order to better manage this disease. Moreover, VAS has been validated and digitalized in the mHealth apps for AR, AllergyMonitor(109, 110) and MASK-air®.(111) Approximately 20% of patients with severe persistent rhinitis are not controlled, with some having severe symptoms, particularly due to associated eye symptoms.(112, 113) Poorly-controlled symptoms of AR are associated with an impairment of social functioning, school, and work productivity, and may contribute to sleep loss or disturbance.(53) Moreover, oral H_1-antihistamines with sedative properties can increase functional disturbances in AR patients.(114)

Complexity of the AR landscape manifests in many ways (Table 2).

Real-world evidence proposing change management in allergic rhinitis

Randomized controlled trials

Although there are no large RCTs available, some studies have assessed the benefits of the PRN use of intranasal corticosteroids (INCSs) in AR.(115) The first study was carried out in the 1990s. In 60 ragweed pollen allergic patients with seasonal AR, the regular use of INCSs resulted in fewer symptoms and better quality of life than when the spray was taken only PRN.(116) In the 2000s, PRN fluticasone propionate (FP) was found to be more effective than oral loratadine for the control of AR symptoms.(117) In a randomized placebo-controlled study, the as-needed use of FP improved the nasal symptoms of seasonal AR.(118) In the US, the indication for FP is as needed (PRN) for AR treatment. In an RCT including 150 children with pollen-related AR, patients received FP daily, or FP PRN, or oral antihistamine PRN (levocetirizine) for three months during the grass pollen season.(119) The percentage of symptom-free days was in favor of INCS PRN (30%), compared with INCS daily (22%). In a 6-week RCT, patients with perennial AR were assigned to either fluticasone furoate (FF) nasal spray, (27.5 µg) as-needed, or 2 sprays once daily for 6 weeks (FF-regular). In 108 patients, the total nasal symptom score (TNSS) and quality-of-life between the 2 groups were not significantly different at week 6. The FF-regular group had a higher mean change in nasal peak inspiratory flow than the FF-as-needed group at week 6 (-19.21 L/min; 95% CI, -33.54 to -4.89; P = .009). The as-needed use had half of the INCS exposure of the regular use.(120) In patients with persistent AR, the efficacy of the continuous administration of oral levocetirizine is higher than the on-demand use only in the long term (after 4 months of treatment).(121) Although these studies alone cannot lead to any firm conclusions, and larger studies are needed, they suggest that the PRN use of INCSs may be of interest.

Adherence to treatment

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

Globally, non-adherence to medications is a major obstacle in the effective delivery of health care. Medication adherence is defined as an active, cooperative, and voluntary participation of the patient on following recommendations from a healthcare provider. This is a multifactorial behavior that involves three critical steps: initiation, implementation, and discontinuation. Few studies have reported the prevalence of adherence in AR adults in the real-life context, but some data suggest that 35% of patients were non-adherent for some time during the treatment, and that 38% discontinued treatment when they felt better.(122) Using an app for AR (MASK-air), it was found that adherence to treatment was below 10% in patients reporting data for 7 to 30 days.(123) Many patients do not seek advice from physicians, do not follow the physician's prescriptions, and self-medicate to control their symptoms, often using OTC medications.(124)

Real-world data

The 2017 report on the State of Health in the EU (State of Health in the EU "Companion Report 2017") proposes to rethink health and care systems in order to ensure their sustainability and their ability to enhance health promotion as well as to provide patient-centered care meeting citizens' needs.(125) In this context, as-needed AR treatment should be studied using more RTCs and, more importantly, in real-world settings.

Patients consulting primary care physicians usually have uncontrolled symptoms despite using multiple medications. Real-life observational studies using mHealth have found that most patients with AR self-medicate or use OTC medications, placing the pharmacist at the forefront of treatment.(124) mHealth can be used to generate innovative insights into optimizing treatment to improve AR control.

Without confounding by indication, the use of multiple medications is associated with poor rhinitis control.(126) Patients increase the number of medications during the pollen season, hoping to gain better control.(127) Interestingly, a MASK-air study performed in Europe found that patients increased their medications to control symptoms during the pollen season, and that most treatments included oral H1-antihistamine monotherapy, or were combined with INCS. This is not in line with the recommendations. Two cross-sectional real-world observational studies were undertaken in 22 countries to complement a pilot study(128) and to provide novel information on medication use, disease control, and work productivity in the everyday life of patients with AR.(126, 129) MASK-air® was used to collect the data of daily VAS scores for (i) overall allergic symptoms, (ii) nasal, ocular, and asthma symptoms, and (iii) work. A scroll list is used for all allergy medications (prescribed and over-the-counter) customized for 22 countries. The four most common intranasal medications containing INCS and eight oral H1-antihistamines were studied. 9,122 users filled in 112,054 days of VAS in 2016 and 2017. The assessment of days was informative. The daily control of rhinitis differed between no (best control), single (good control for intranasal corticosteroid-treated days), or multiple (worst control)

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

treatments. Users with the worst control increased the range of treatments being used. The same trend was found for asthma, eye symptoms, and work productivity. Differences between oral H1-antihistamine molecules were found.(126) The second study showed that the overall efficacy of treatments is similar during and outside the pollen season, and indicates that medications are similarly effective during the year. These studies confirm the usefulness of MASK-air® in accessing and assessing the behavior of patients with AR. This observational study using a very simple assessment tool (VAS) on a mobile phone answered questions previously thought infeasible.

mHealth-based RWD studies can therefore be a key tool in the assessment of AR and their treatments, as they allow for the collection of large volumes of data (potentially with an international scope), reflecting patients' real behaviour. However, these studies also have some inherent limitations and should, therefore, be complemented by other study designs. Firstly, there is the possibility of selection biases, as patients using mHealth apps may be younger, more affluent and more concerned about their health than the remainder.(130) Among mHealth app users, reported days may not be necessarily representative of all AR days, with the possibility of an overrepresentation of more severe days.(130) Finally, there is the possibility of information biases, particularly in the reporting of medication use.

Chamber studies

Chamber studies are widely used to assess the onset of action of medications.(74, 131) INCSs are not usually very effective within the first few hours, as shown in chamber studies. Combined INCSs and intranasal antihistamines act faster,(132, 133) and may represent an alternative for PRN use.(74)

Next-generation guidelines

Some recommendations for AR treatment are based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guidelines.(134-137) Next-generation guidelines(74) were subsequently developed using existing GRADE-based guidelines and real-world evidence, including data from RCTs, real-world data provided by mobile technology,(123, 126) and additive studies, such as allergen chamber studies assessing the speed of onset of medications(132, 133) (Table 2). Real-life data clearly indicate that patients prefer as-needed treatment to continuous treatments.(115) This should be reflected in future guidelines.

Value-added medicines in airway diseases

Repurposing asthma treatment

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

For the past 40 years,(138) asthma management guidelines have recommended a stepwise approach, based on the daily administration of controller medications (especially inhaled corticosteroids (ICSs) with or without long-acting ß-agonists, LABA), with the use of PRN rescue medication when needed (mostly short-acting β-agonists, SABA). In the 2000s, Single Maintenance and Reliever Therapy (SMART) with a daily inhalation of ICS+LABA, and the same medication for rescue, showed its efficacy and safety.(139) However, SMART was still based on a daily use of ICS+LABA. It is clear that this treatment was not patient centered since adherence to asthma treatment is low. A debate was initiated to discuss the benefits of the PRN use of controller medications in asthma. This debate has been resolved by four trials (two randomized placebo control trials of the SYGMA project and two real-life studies, Novel START, and the PRACTICAL trial) (for review see (140)) that have shown the benefits of substituting SABA with budesonide-formoterol as a rescue medication in mild asthma patients. It is now clear that the patient-centered approach is favored for mild asthma, and GINA 2019 recommended as-needed ICS-LABA as an option for step 2 patients.(141, 142)

Repurposing allergic rhinitis treatment

The same debate is now ongoing for allergic rhinitis.(115) There is a large body of evidence suggesting the need for a patient-centered approach. Real-life observational studies such as MASK showed that a large number of AR sufferers self-medicate using OTC drugs,(143) are poorly adherent,(123) and use a PRN approach for their treatment.

Despite the availability of efficacious molecules to treat AR, low adherence to treatments contributes to poor patient outcomes. mHealth apps may help to improve shared-decision making. This would (i) provide the patient with a personalized treatment approach for a better understanding of the disease control, both by the patient and the physician, and (ii) allow a better PRN use of medications based on symptoms and pollen alerts.(66)

All patients differ, and what works for one may not work as well for another. In a society where patients want to take responsibility for their own health, value-added medicines can help to empower patients in feeling better with their treatment. With this in mind, the VAMs Group is developing a framework to provide new opportunities to help patients, offering more adapted medicines to those who are in need (Tables 3 and 4).

Conclusions

VAMs address the following needs: (i) innovation on existing molecules in the form of repurposing therapies, (ii) poor patient adherence, and (iii) possible problems related to polypharmacy that are relevant with the proposal.

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

As already proposed,(49) patients consulting primary care physicians usually have uncontrolled symptoms, despite using multiple medications. Real-life observational studies using mobile health have confirmed that adherence to treatment is a major issue,(123) as many patients do not seek advice from physicians, do not follow the physician's prescription, and self-medicate to control their symptoms, often using over-the-counter medications.(124) The use of multiple medications is associated with poor rhinitis control.(126) PRN therapy should be the goal: 90% of patients with rhinitis use their medications when they are symptomatic, as recently found using real-world data in over 10,000 patients in European countries.(63) Real-life data clearly indicate that patients prefer as-needed treatment to continuous treatment, and this should be reflected in future guidelines. AR treatment should be individualized according to the symptom profile, severity and duration, the patient's preference of oral versus intranasal administration, and the availability and affordability of medications.

However, since the vast majority of patients already use as-need treatment, first-line therapy should consider the speed of onset of the treatment. Current guidelines for AR are centered around a continuous long-term treatment, and medication registration is based on RCTs carried out for 14 days (at least) with adherence ≥70%.

Due to a lack of agreed phenotype, few studies have been carried out in non-allergic rhinitis. However, the concept of PRN therapy in AR may be expanded to non-allergic rhinitis. Many patients suffer from AR and non-allergic rhinitis and it is of great importance to understand the PRN use of rhinitis medications in patients with mixed rhinitis.

A new way of treating AR is to propose as-needed treatment depending on symptoms, rather than the classical continuous treatment.(115) However, to fully endorse this repurposing, well designed, adequate powered clinical trials need to be carried out.

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

Journal Pre-proof

Table 1: Benefits of value-added medicines (from Medicines for Europe)

Relevant improvements include:

- Better efficacy, safety, and/or tolerability profile
- Better way of administration and/or ease of use
- New therapeutic usages (indication/population)

These improvements may contribute to:

- Better adherence, health outcomes or quality of life
- Improved safety and efficiency of healthcare professional resources
- Increased treatment options & prevention of therapeutic escalation
- Improved cost-effectiveness and, ultimately, access to health care

The added value may be achieved through:

- Drug repositioning
- Drug reformulation
- Drug combination (drug/drug or drug/device or drug/service).

Impact on healthcare systems: Value-added medicines benefits are expected to impact healthcare systems through increasing treatment options, preventing therapeutic escalation, or increasing rational use of medicines. As a consequence, they are likely to reduce the use of healthcare resources and improve cost-effectiveness, therefore contributing to the efficiencies of the healthcare system and better patient health and access.

Journal Pre-proof

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

Journal Pre-proof

Table 2: Complexity of the AR landscape

(i)	Management does not take the patient's needs into consideration, and shared decision making is insufficiently used. mHealth apps may help to improve patient-physician interactions. (144) A disparity exists in perspectives between physicians and AR patients, to the effect that AR is under-diagnosed, under-estimated, and under-treated. In MASK-air, adherence to treatment is below 10%. (123)
(ii)	AR patient behavior pertains to AR management and is disorganized and inconsistent. The vast majority of AR patients use two or more AR medications in an effort to achieve faster and more effective relief from their nasal and ocular symptoms,(127) even though this does not accord with guidelines. (145) Many patients are calling for more efficacious OTC AR medications to better manage their AR symptoms. There is an urgent need to encourage patient empowerment. (95, 146)
(iii)	Reticence to seek professional medical advice, and a tendency to do so only when symptoms become intolerable or if symptoms persist after trying several OTC options.
(iv)	AR patients glean a great deal of information about their disease from the internet, and there is a high degree of self-management, a consequence of the large choice of available OTC AR medications.
(v)	Lack of communication between healthcare professionals. (147, 148) It is therefore crucial that AR care pathways should consider pharmacists. (124, 149)
(vi)	Potential lack of healthcare access to specialist physicians (e.g., lack of specialists in several countries, barriers to healthcare access).
(vii)	Most patients suffer from several episodes of short-term AR symptoms, and therefore rarely take their medication continuously for 14 days, as envisaged in the vast majority of seasonal AR RCTs.

AR=Allergic rhinitis; OTC=over-the-counter; RCT=randomized controlled trial

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

Journal Pre-proof

533 **Table 3: Value-added medicines of the MASK approach**

534

Value-added medicines	MASK approach	Refs
VAMs are medicines based on known molecules that address healthcare needs	• Current medications for AR are based on a continuous long-term treatment, and medication registration is based on RCTs carried out for 14 days (at least) with adherence ≥70%. • **A new way of treating AR is to propose as-needed treatment** depending on symptoms, rather than the classical continuous treatment. • **RWD has confirmed the value of this novel approach in over 17,000 patients (MASK).**	(150-152)
Deliver relevant improvement for patients	MASK has shown that • A PRN combination of intra-nasal antihistamine and INCS treatment was more effective than INCS alone. • Onset of action is extremely important	(92, 97, 128, 153)
Deliver relevant improvement for healthcare professionals	• Optimize treatment for the patient and, in particular, for the current or next pollen season. • Assess and increase adherence to treatment. • Help in shared decision making. • Prescribe AIT more rapidly when the patient is not controlled despite optimal pharmacologic treatment. • Determine the efficacy of any treatment including AIT.	(97, 128, 154)
Deliver relevant improvement for payers	• A combination of INCS and intranasal H1-antihistamine treatment needs less co-medication than INCS alone. • Work productivity is increased in days with combined intranasal antihistamine and INCS treatment more than in those using INCS alone. • AR represents a major burden for the employers, and the estimated annual costs in the EU range from 30 to 60 B€. A better control of the disease has been shown to reduce costs. • Apps have the potential to improve the control of allergic diseases and to significantly improve work productivity at the EU level.	(155-158)
Contribute to addressing unmet patient needs	MASK has shown that • Patients are not adherent to treatment • They often self-medicate • They do not follow physicians' prescriptions • They do not follow guidelines	(123, 128)

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

	• They need an effective PRN treatment • When allergists are allergic, they do not follow their prescription and adherence is close to zero.	(159)
Moving from a one-size-fits-all to a much more tailored and patient-specific approach	• Better understanding of the symptoms • Sentinel network linking aerobiology data and control. • Improved adherence. • Self-management. • Alert systems for air pollution and pollen exposure. • Messages sent by the app.	(160)
VAMs are one of the key components of the customization of health care	• Apps are an essential tool in providing personalized medicine in AR. • MASK has shown that a PRN approach is needed to optimize the treatment of AR. • Studies in asthma are ongoing.	(97, 128)
By answering patients' unmet needs, they represent a new horizon for those who are currently looking forward to a better quality of life with their treatment	• Many patients are uncontrolled and non-adherent to treatment. Apps can indirectly assess and help (e.g., reminders) adherence. • Patients appear to use their medications as needed and not on a regular basis as prescribed. • Change management is needed and may be facilitated by apps such as MASK-air®. • MASK using PRN treatment will improve patient empowerment. • Development of next-generation guidelines and care pathways.	(66, 143, 161-169)

535 AIT=Allergen immunotherapy; AR=Allergic rhinitis; EU=European Union; INCS=Intranasal corticosteroids; PRN=on-demand;
536 RCT=Randomized controlled trial; RWD=Real-world data; VAM=Value-added medicine
537
538

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

Journal Pre-proof

539 **Table 4: Evaluation framework of Value-Added Medicines for allergic rhinitis (from (87, 170))**

540

Cluster name	Domain name	Definition	Application to AR	
Unmet medical need	Extending treatment options in new indication with unmet medical need	Reduction of the unmet medical need for patients in a new indication due to additional therapeutic value	The vast majority of AR patients • Do not follow guidelines • Do not follow physicians' prescriptions • Are non-adherent to treatment (RWD show that less than 10% of patients are adherent) • Treat themselves according to symptoms	(93, 123, 126, 129, 171)
	Individual needs/special needs of patient (sub)population	Reduction of the unmet medical need in patients with special needs in the original indication (e.g., treatment-resistant patients, vulnerable patients, etc.)	Approximately 20% of AR patients have uncontrolled disease despite optimal pharmacotherapy (SCUAD)	(112)
Health gain (measured by healthcare professionals)	Efficacy Effectiveness	Improved clinical outcomes of a pharmaceutical treatment (e.g., extending survival, stabilizing disease, improving treatment response, etc.) in trial and real-world settings	• Limited amount of data suggests that the PRN use of INCS has an efficacy similar to that of long-term treatment • More data are needed	(118-120)
	Patient safety and tolerability	Improved safety and/or tolerability of the pharmaceutical treatment	• Limited amount of data suggests that the PRN use of INCS needs a lower dose than long-term treatment	(120)
Patient Reported Outcomes	Patient experience related to the therapy	Improved patient satisfaction, acceptance, convenience with the pharmaceutical therapy	Not done	
	Adherence and persistence	Improved adherence and/or persistence of patients with the prescription guidelines (including duration, timing, dosage and frequency of medication use)	Not done	

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

Cluster name	Domain name	Definition	Application to AR	
	Quality of life	Improved health-related quality of life reported by patients	• Limited amount of data suggests that the PRN use of INCS has an efficacy similar to that of long-term treatment	
Burden on households	Patient's economic burden	Improved productivity of patients and/or reduced health and non-healthcare resource use (such as travel time) covered by patients	Patients with controlled AR have an improved work productivity	(155, 172, 173)
	Economic and health burden on informal caregiver	Improved quality of life of family caregivers and/or reduced financial or non-financial burden on households	Not done	
Burden on healthcare system	Healthcare resource utilization, costs or efficiency	Reduced utilization of healthcare cost and/or resources	Not done	
	Technological improvement with logistical considerations	Improved stability and/or shelf life of pharmaceuticals through technological improvement	Not applicable	

AR=Allergic rhinitis; INCS=Intranasal corticosteroids; PRN=on-demand; RWD=Real-world data; SCUAD=Severe chronic upper airway disease

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

References

1. BOUSQUET-Charité. Institute of Allergology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

2. BOUSQUET-CHU. . University Hospital Montpellier, France.
3. BOUSQUET-Franhofer. . Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany

4. TOUMI. Public He. Public Health, Aix-marseille University, Marseille, France.
5. SOUSA-PINTO-1. MEDCIDS - Department of Community Medicine, Information and Health Decision Sciences; Faculty of Medicine, University of Porto, Porto, Portugal.
6. SOUSA-PINTO-2. CINTESIS – Center for Health Technology and Services Research; University of Porto, Porto, Portugal.
7. SOUSA-PINTO-3. RISE – Health Research Network; University of Porto, Porto, Portugal.
8. ANTO-ISGlobal. ISGlobAL, Barcelona Institute for Global Health, Barcelona, Spain.
9. ANTO-2. IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain.
10. ANTO-3. Universitat Pompeu Fabra (UPF), Barcelona, Spain.
11. ANTO-4. CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain.
12. BEDBROOK-ARIA. ARIA, Montpellier, France.
13. CZARLEWSKI. Medical Consulting Czarlewski, Levallois, France.
14. VALIULIS. Vilnius University Faculty of Medicine, Institute of Clinical Medicine & Institute of Health Sciences, Vilnius, Lithuania; European Academy of Paediatrics (EAP/UEMS-SP), Brussels, Belgium.
15. ANSOTEGUI. Department of Allergy and Immunology, Hospital Quironsalud Bizkaia, Bilbao, Spain.
16. BOSNIC. Quality Use of Respiratory Medicine Group, Woolcock Institute of Medical Research, The University of Sydney, and Sydney Local Health District, Sydney, NSW , Australia.
17. BRUSSINO. Department of Medical Sciences, Allergy and Clinical Immunology Unit, University of Torino & Mauriziano Hospital, Torino, Italy.
18. CANONICA-1. Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, 20090 Pieve Emanuele, Milan, Italy

19. CHECCI. SOS Allergology and Clinical Immunology, USL Toscana Centro, Prato, Italy.
20. CHERREZ-OJEDA. Universidad de Especialidades Espíritu Santo, Samborondón, Ecuador.
21. CHIVATO. School of Medicine, University CEU San Pablo, Madrid, Spain.
22. COSTA-E. UCIBIO, REQUINTE, Faculty of Pharmacy and Competence Center on Active and Healthy Ageing of University of Porto (Porto4Ageing), Porto, Portugal
23. CRUZ. Fundaçao ProAR, Federal University of Bahia and GARD/WHO Planning Group, Salvador, Bahia, Brazil.
24. DEL-GIACCO. Department of Medical Sciences and Public Health and Unit of Allergy and Clinical Immunology, University Hospital "Duilio Casula", University of Cagliari, Cagliari, Italy.

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

25. GEMICIOGLU. Department of Pulmonary Diseases, Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Istanbul, Turkey.
26. HAAT. Haahtela. Skin and Allergy Hospital, Helsinki University Hospital, Helsinki, Finland.
27. IVANCEVICH. Servicio de Alergia e Immunologia, Clinica Santa Isabel, Buenos Aires, Argentina.
28. JUTEL. Department of Clinical Immunology, Wrocław Medical University, and ALL-MED Medical Research Institute, Wroclaw, Poland.
29. KAIDASHEV. Poltava State Medical University, Ukraine.
30. KLIMEK. Department of Otolaryngology, Head and Neck Surgery, Universitätsmedizin Mainz, Mainz, and Center for Rhinology and Allergology, Wiesbaden, Germany.
31. KVEDARIENNE. Institute of Biomedical Sciences, Department of Pathology, Faculty of Medicine, Vilnius University and Institute of Clinical medicine, Clinic of Chest diseases and Allergology, faculty of Medicine, Vilnius University, Vilnius, Lithuania.
32. KUNA. Division of Internal Medicine, Asthma and Allergy, Barlicki University Hospital, Medical University of Lodz, Poland.
33. LARENAS. Center of Excellence in Asthma and Allergy, Médica Sur Clinical Foundation and Hospital, México City, Mexico.
34. LIPWORTH. Scottish Centre for Respiratory Research, Cardiovascular & Diabetes Medicine, Medical Research Institute, Ninewells Hospital, University of Dundee, UK.
35. MORAIS-ALMEIDA. Allergy Center, CUF Descobertas Hospital, Lisbon, Portugal
36. MULLOL. Rhinology Unit & Smell Clinic, ENT Department, Hospital Clínic; Clinical & Experimental Respiratory Immunoallergy, IDIBAPS, CIBERES, University of Barcelona, Spain.
37. PAPADOPOULOS. Division of Infection, Immunity & Respiratory Medicine, Royal Manchester Children's Hospital, University of Manchester, Manchester, UK.
38. PATELLA. Division of Allergy and Clinical Immunology, Department of Medicine, Agency of Health ASL Salerno, "Santa Maria della Speranza" Hospital, Battipaglia, Salerno, Italy.
39. PHAM-THI. Ecole Polytechnique Palaiseau, IRBA (Institut de Recherche bio-Médicale des Armées), Bretigny, France.
40. REGATEIRO. Allergy and Clinical Immunology Unit, Centro Hospitalar e Universitário de Coimbra, Coimbra and Institute of Immunology, Faculty of Medicine, University of Coimbra, and ICBR - Coimbra Institute for Clinical and Biomedical Research, CIBB, Coimbra, Portugal.
41. ROUADI. Department of Otolaryngology-Head and Neck Surgery, Eye and Ear University Hospital, Beirut, Lebanon and ENT Department, Dar Al Shifa Hospital- Salmiya, Kuwait.
42. SAMOLINSKI. Department of Prevention of Environmental Hazards, Allergology and Immunology, Medical University of Warsaw, Poland.
43. SHEIKH. Usher Institute, The University of Edinburgh, Edinburgh, UK.
44. taborda-BARRATA. CICS-Heath Sciences Research Center Faculty of Health Sciences, University of Beira Interior, Covilhã. UBIAir - Clinical & Experimental Lung Centre , University of Beira Interior, Covilhã. Department of Immunoallergology, Cova da Beira University Hospital Centre, Covilhã, Portugal.
45. VENTURA. University of Bari Medical School, Unit of Geriatric Immunoallergology, Bari, Italy.
46. YORGANCIOGLU. Celal Bayar University Department of Pulmonology, Manisa, Turkey.
47. ZIDARN. University Clinic of Respiratory and Allergic Diseases, and internal medicine, Golnick, Slovenia.

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

637 48. Bousquet PJ, Leynaert B, Neukirch F, Sunyer J, Janson CM, Anto J, et al. Geographical
638 distribution of atopic rhinitis in the European Community Respiratory Health Survey I. Allergy.
639 2008;63(10):1301-9.
640 49. Bousquet J, Anto JM, Bachert C, Baiardini I, Bosnic-Anticevich S, Walter Canonica G, et
641 al. Allergic rhinitis. Nat Rev Dis Primers. 2020;6(1):95.
642 50. Vandenplas O, Vinnikov D, Blanc PD, Agache I, Bachert C, Bewick M, et al. Impact of
643 Rhinitis on Work Productivity: A Systematic Review. J Allergy Clin Immunol Pract.
644 2018;6(4):1274-86 e9.
645 51. Zuberbier T, Lotvall J, Simoens S, Subramanian SV, Church MK. Economic burden of
646 inadequate management of allergic diseases in the European Union: a GA(2) LEN review.
647 Allergy. 2014;69(10):1275-9.
648 52. Colas C, Brosa M, Anton E, Montoro J, Navarro A, Dordal MT, et al. Estimate of the total
649 costs of allergic rhinitis in specialized care based on real-world data: the FERIN Study. Allergy.
650 2017;72(6):959-66.
651 53. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis
652 and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health
653 Organization, GA(2)LEN and AllerGen). Allergy. 2008;63 Suppl 86:8-160.
654 54. Scadding GK. Optimal management of allergic rhinitis. Arch Dis Child. 2015;100(6):576-
655 82.
656 55. Scadding GK, Kariyawasam HH, Scadding G, Mirakian R, Buckley RJ, Dixon T, et al. BSACI
657 guideline for the diagnosis and management of allergic and non-allergic rhinitis (Revised
658 Edition 2017; First edition 2007). Clin Exp Allergy. 2017;47(7):856-89.
659 56. Padjas A, Kehar R, Aleem S, Mejza F, Bousquet J, Schunemann HJ, et al. Methodological
660 rigor and reporting of clinical practice guidelines in patients with allergic rhinitis: QuGAR study.
661 J Allergy Clin Immunol. 2014;133(3):777-83 e4.
662 57. Brozek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, et al. Allergic
663 Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. J Allergy Clin Immunol.
664 2017;140(4):950-8.
665 58. Dykewicz MS, Wallace DV, Baroody F, Bernstein J, Craig T, Finegold I, et al. Treatment
666 of seasonal allergic rhinitis: An evidence-based focused 2017 guideline update. Ann Allergy
667 Asthma Immunol. 2017;119(6):489-511 e41.
668 59. Costa DJ, Amouyal M, Lambert P, Ryan D, Schunemann HJ, Daures JP, et al. How
669 representative are clinical study patients with allergic rhinitis in primary care? J Allergy Clin
670 Immunol. 2011;127(4):920-6.e1.
671 60. Price D, Smith P, Hellings P, Papadopoulos N, Fokkens W, Muraro A, et al. Current
672 controversies and challenges in allergic rhinitis management. Expert Rev Clin Immunol.
673 2015:1-13.
674 61. Travers J, Marsh S, Williams M, Weatherall M, Caldwell B, Shirtcliffe P, et al. External
675 validity of randomised controlled trials in asthma: to whom do the results of the trials apply?
676 Thorax. 2017;62(3):219-23.
677 62. Baxter MS, Tibble H, Bush A, Sheikh A, Schwarze J. Effectiveness of mobile health
678 interventions to improve nasal corticosteroid adherence in allergic rhinitis: A systematic
679 review. Clin Transl Allergy. 2021;11(9):e12075.
680 63. Sousa-Pinto B, Sa-Sousa A, Vieira RJ, Amaral R, Klimek L, Czarlewski W, et al.
681 Behavioural patterns in allergic rhinitis medication in Europe: A study using MASK-air((R)) real-
682 world data. Allergy. 2022.

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

64. Yang W, Zilov A, Soewondo P, Bech OM, Sekkal F, Home PD. Observational studies: going beyond the boundaries of randomized controlled trials. Diabetes Res Clin Pract. 2010;88 Suppl 1:S3-9.
65. DiPietro NA. Methods in epidemiology: observational study designs. Pharmacotherapy. 2010;30(10):973-84.
66. Bousquet J, Hellings PW, Agache I, Amat F, Annesi-Maesano I, Ansotegui IJ, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) Phase 4 (2018): Change management in allergic rhinitis and asthma multimorbidity using mobile technology. J Allergy Clin Immunol. 2019;143(3):864-79.
67. Alvarez-Perea A, Dimov V, Popescu FD, Zubeldia JM. The applications of eHealth technologies in the management of asthma and allergic diseases. Clin Transl Allergy. 2021;11(7):e12061.
68. Toumi M, Remuzat C. Value added medicines: what value repurposed medicines might bring to society? J Mark Access Health Policy. 2017;5(1):1264717.
69. Murteira S, Ghezaiel Z, Karray S, Lamure M. Drug reformulations and repositioning in pharmaceutical industry and its impact on market access: reassessment of nomenclature. J Mark Access Health Policy. 2013;1.
70. Talevi A, Bellera CL. Challenges and opportunities with drug repurposing: finding strategies to find alternative uses of therapeutics. Expert Opin Drug Discov. 2020;15(4):397-401.
71. Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices. Guidance for Industry and Food and Drug Administration Staff Document issued on August 31, 2017. Bethesda: US Food and Drug Adlministration, U.S. Department of Health and Human Services Food and Drug Administration, Center for Devices and Radiological Health Center for Biologics Evaluation and Research. CDRHClinicalEvidence@fda.hhs.gov.; 2017.
72. Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL, et al. Real-World Evidence - What Is It and What Can It Tell Us? N Engl J Med. 2016;375(23):2293-7.
73. Briere JB, Bowrin K, Taieb V, Millier A, Toumi M, Coleman C. Meta-analyses using real-world data to generate clinical and epidemiological evidence: a systematic literature review of existing recommendations. Curr Med Res Opin. 2018;34(12):2125-30.
74. Bousquet J, Schunemann HJ, Togias A, Bachert C, Erhola M, Hellings PW, et al. Next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for allergic rhinitis based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and real-world evidence. J Allergy Clin Immunol. 2020;145(1):70-80 e3.
75. Petyko ZI, Inotai A, Holtorf AP, Brixner D, Kalo Z. Barriers and facilitators of exploiting the potential of value-added medicines. Expert Rev Pharmacoecon Outcomes Res. 2020;20(3):229-36.
76. Pushpakom S, Iorio F, Eyers PA, Escott KJ, Hopper S, Wells A, et al. Drug repurposing: progress, challenges and recommendations. Nat Rev Drug Discov. 2019;18(1):41-58.
77. Baker NC, Ekins S, Williams AJ, Tropsha A. A bibliometric review of drug repurposing. Drug Discov Today. 2018;23(3):661-72.
78. Parvathaneni V, Kulkarni NS, Muth A, Gupta V. Drug repurposing: a promising tool to accelerate the drug discovery process. Drug Discov Today. 2019;24(10):2076-85.
79. Issa NT, Stathias V, Schurer S, Dakshanamurthy S. Machine and deep learning approaches for cancer drug repurposing. Semin Cancer Biol. 2021;68:132-42.
80. Rudrapal M, Khairnar S, AGJadhav. Drug Repurposing (DR). In: Badria F, editor. An Emerging Approach in Drug Discovery, Drug Repurposing - Hypothesis, Molecular Aspects and

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

730 Therapeutic Applications,. p. IntechOpen, DOI: 10.5772/intechopen.93193. Available from:
731 https://www.intechopen.com/chapters/72744.
732 81. Drug Repurposing and Repositioning: Workshop Summary. The National Academies
733 Collection: Reports funded by National Institutes of Health. Washington (DC)2014.
734 82. Pantziarka P, Sukhatme V, Crispino S, Bouche G, Meheus L, Sukhatme VP. Repurposing
735 drugs in oncology (ReDO)-selective PDE5 inhibitors as anti-cancer agents.
736 Ecancermedicalscience. 2018;12:824.
737 83. Sleire L, Forde HE, Netland IA, Leiss L, Skeie BS, Enger PO. Drug repurposing in cancer.
738 Pharmacol Res. 2017;124:74-91.
739 84. Yousefi H, Mashouri L, Okpechi SC, Alahari N, Alahari SK. Repurposing existing drugs
740 for the treatment of COVID-19/SARS-CoV-2 infection: A review describing drug mechanisms
741 of action. Biochem Pharmacol. 2021;183:114296.
742 85. Group RC, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in
743 Hospitalized Patients with Covid-19. N Engl J Med. 2021;384(8):693-704.
744 86. Proposal for a framework to support not-for-profit organisations and academia
745 (institutions and individuals) in drug repurposing. Prepared by a working group of the Safe and
746 Timely Access to Medicines for Patients (STAMP) expert group.
747 https://eceuropaeu/health/sites/default/files/files/committee/pharm773_repurposing_ann
748 ex_enpdf. 2019.
749 87. Kalo Z, Petyko ZI, Fricke FU, Maniadakis N, Tesar T, Podrazilova K, et al. Development
750 of a core evaluation framework of value-added medicines: report 2 on pharmaceutical policy
751 perspectives. Cost Eff Resour Alloc. 2021;19(1):42.
752 88. Kashour Z, Riaz M, Garbati MA, AlDosary O, Tlayjeh H, Gerberi D, et al. Efficacy of
753 chloroquine or hydroxychloroquine in COVID-19 patients: a systematic review and meta-
754 analysis. J Antimicrob Chemother. 2021;76(1):30-42.
755 89. Roman YM, Burela PA, Pasupuleti V, Piscoya A, Vidal JE, Hernandez AV. Ivermectin for
756 the Treatment of Coronavirus Disease 2019: A Systematic Review and Meta-analysis of
757 Randomized Controlled Trials. Clin Infect Dis. 2022;74(6):1022-9.
758 90. Izcovich A, Siemieniuk RA, Bartoszko JJ, Ge L, Zeraatkar D, Kum E, et al. Adverse effects
759 of remdesivir, hydroxychloroquine and lopinavir/ritonavir when used for COVID-19:
760 systematic review and meta-analysis of randomised trials. BMJ Open. 2022;12(3):e048502.
761 91. Baena-Cagnani CE, Canonica GW, Zaky Helal M, Gomez RM, Compalati E, Zernotti ME,
762 et al. The international survey on the management of allergic rhinitis by physicians and
763 patients (ISMAR). World Allergy Organ J. 2015;8(1):10.
764 92. Bachert C, Bousquet J, Hellings P. Rapid onset of action and reduced nasal
765 hyperreactivity: new targets in allergic rhinitis management. Clin Transl Allergy. 2018;8:25.
766 93. Bousquet J, Anto JM, Bachert C, Haahtela T, Zuberbier T, Czarlewski W, et al. ARIA
767 digital anamorphosis: Digital transformation of health and care in airway diseases from
768 research to practice. Allergy. 2021;76(1):168-90.
769 94. Bousquet J, Bachert C, Canonica GW, Casale TB, Cruz AA, Lockey RJ, et al. Unmet needs
770 in severe chronic upper airway disease (SCUAD). J Allergy Clin Immunol. 2009;124(3):428-33.
771 95. Hellings PW, Fokkens WJ, Akdis C, Bachert C, Cingi C, Dietz de Loos D, et al.
772 Uncontrolled allergic rhinitis and chronic rhinosinusitis: where do we stand today? Allergy.
773 2013;68(1):1-7.
774 96. Prokopakis EP, Vlastos IM, Ferguson BJ, Scadding G, Kawauchi H, Georgalas C, et al.
775 SCUAD and chronic rhinosinusitis. Reinforcing hypothesis driven research in difficult cases.
776 Rhinology. 2014;52(1):3-8.

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

97. Bousquet J, Devillier P, Anto JM, Bewick M, Haahtela T, Arnavielhe S, et al. Daily allergic multimorbidity in rhinitis using mobile technology: A novel concept of the MASK study. Allergy. 2018;73(8):1622-31.
98. Schatz M, Meltzer EO, Nathan R, Derebery MJ, Mintz M, Stanford RH, et al. Psychometric validation of the rhinitis control assessment test: a brief patient-completed instrument for evaluating rhinitis symptom control. Ann Allergy Asthma Immunol. 2010;104(2):118-24.
99. Demoly P, Calderon MA, Casale T, Scadding G, Annesi-Maesano I, Braun JJ, et al. Assessment of disease control in allergic rhinitis. Clin Transl Allergy. 2013;3(1):7.
100. Demoly P, Jankowski R, Chassany O, Bessah Y, Allaert FA. Validation of a self-questionnaire for assessing the control of allergic rhinitis. Clin Exp Allergy. 2011;41(6):860-8.
101. Demoly P, Bosse I, Maigret P. Perception and control of allergic rhinitis in primary care. NPJ Prim Care Respir Med. 2020;30(1):37.
102. Sousa-Pinto B, Sá-Sousa A, Amaral A, Czarlewski W, Bedbrook A, Anto J, et al. Assessment of the Control of Allergic Rhinitis and Asthma Test (CARAT) using MASK-air. J Allergy Clin Immunol Pfract. 2021;in press.
103. Linhares DV, da Fonseca JA, Borrego LM, Matos A, Pereira AM, Sa-Sousa A, et al. Validation of control of allergic rhinitis and asthma test for children (CARATKids)--a prospective multicenter study. Pediatr Allergy Immunol. 2014;25(2):173-9.
104. Azevedo P, Correia de Sousa J, Bousquet J, Bugalho-Almeida A, Del Giacco SR, Demoly P, et al. Control of Allergic Rhinitis and Asthma Test (CARAT): dissemination and applications in primary care. Prim Care Respir J. 2013;22(1):112-6.
105. Tosca MA, Del Barba P, Licari A, Ciprandi G, Asthma, Rhinitis Control Study G. The Measurement of Asthma and Allergic Rhinitis Control in Children and Adolescents. Children (Basel). 2020;7(5).
106. Bousquet PJ, Combescure C, Neukirch F, Klossek JM, Mechin H, Daures JP, et al. Visual analog scales can assess the severity of rhinitis graded according to ARIA guidelines. Allergy. 2007;62(4):367-72.
107. Demoly P, Bousquet PJ, Mesbah K, Bousquet J, Devillier P. Visual analogue scale in patients treated for allergic rhinitis: an observational prospective study in primary care: Asthma and Rhinitis. Clin Exp Allergy. 2013;43(8):881-8.
108. Baiardini I, Pasquali M, Giardini A, Specchia C, Passalacqua G, Venturi S, et al. Rhinasthma: a new specific QoL questionnaire for patients with rhinitis and asthma. Allergy. 2003;58(4):289-94.
109. Giordani P, Perna S, Bianchi A, Pizzulli A, Tripodi S, Matricardi PM. A study of longitudinal mobile health data through fuzzy clustering methods for functional data: The case of allergic rhinoconjunctivitis in childhood. PLoS One. 2020;15(11):e0242197.
110. Tripodi S, Giannone A, Sfika I, Pelosi S, Dramburg S, Bianchi A, et al. Digital technologies for an improved management of respiratory allergic diseases: 10 years of clinical studies using an online platform for patients and physicians. Ital J Pediatr. 2020;46(1):105.
111. . !!! INVALID CITATION !!! 101-103.
112. Bousquet PJ, Bachert C, Canonica GW, Casale TB, Mullol J, Klossek JM, et al. Uncontrolled allergic rhinitis during treatment and its impact on quality of life: a cluster randomized trial. J Allergy Clin Immunol. 2010;126(3):666-8 e1-5.
113. Wang Y, Zhu R, Liu G, Li W, Chen H, Daures JP, et al. Prevalence of uncontrolled allergic rhinitis in Wuhan, China: a prospective cohort study. Am J Rhinol Allergy. 2014;28(5):397-403.

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

114. Church MK, Maurer M, Simons FE, Bindslev-Jensen C, van Cauwenberge P, Bousquet J, et al. Risk of first-generation H(1)-antihistamines: a GA(2)LEN position paper. Allergy. 2010.
115. Bousquet J, Klimek L, Kuna P, Mullol J, Toppila-Salmi S. The Debate: Regular Versus As-Needed Use of Intranasal Corticosteroids for a Patient-Centered Approach. J Allergy Clin Immunol Pract. 2021;9(3):1374-5.
116. Juniper EF, Guyatt GH, O'Byrne PM, Viveiros M. Aqueous beclomethasone diproprionate nasal spray: regular versus "as required" use in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol. 1990;86(3 Pt 1):380-6.
117. Kaszuba SM, Baroody FM, deTineo M, Haney L, Blair C, Naclerio RM. Superiority of an intranasal corticosteroid compared with an oral antihistamine in the as-needed treatment of seasonal allergic rhinitis. Arch Intern Med. 2001;161(21):2581-7.
118. Dykewicz MS, Kaiser HB, Nathan RA, Goode-Sellers S, Cook CK, Witham LA, et al. Fluticasone propionate aqueous nasal spray improves nasal symptoms of seasonal allergic rhinitis when used as needed (prn). Ann Allergy Asthma Immunol. 2003;91(1):44-8.
119. Wartna JB, Bohnen AM, Elshout G, Pijnenburg MW, Pols DH, Gerth van Wijk RR, et al. Symptomatic treatment of pollen-related allergic rhinoconjunctivitis in children: randomized controlled trial. Allergy. 2017;72(4):636-44.
120. Thongngarm T, Wongsa C, Phinyo P, Assanasen P, Tantilipikorn P, Sompornrattanaphan M. As-Needed Versus Regular Use of Fluticasone Furoate Nasal Spray in Patients with Moderate to Severe, Persistent, Perennial Allergic Rhinitis: A Randomized Controlled Trial. J Allergy Clin Immunol Pract. 2021;9(3):1365-73 e6.
121. Canonica GW, Fumagalli F, Guerra L, Baiardini I, Compalati E, Rogkakou A, et al. Levocetirizine in persistent allergic rhinitis: continuous or on-demand use? A pilot study. Curr Med Res Opin. 2008;24(10):2829-39.
122. Bender BG. Motivating patient adherence to allergic rhinitis treatments. Curr Allergy Asthma Rep. 2015;15(3):10.
123. Menditto E, Costa E, Midao L, Bosnic-Anticevich S, Novellino E, Bialek S, et al. Adherence to treatment in allergic rhinitis using mobile technology. The MASK Study. Clin Exp Allergy. 2019;49(4):442-60.
124. Bosnic-Anticevich S, Costa E, Menditto E, Lourenco O, Novellino E, Bialek S, et al. ARIA pharmacy 2018 "Allergic rhinitis care pathways for community pharmacy": AIRWAYS ICPs initiative (European Innovation Partnership on Active and Healthy Ageing, DG CONNECT and DG Sante) POLLAR (Impact of Air POLLution on Asthma and Rhinitis) GARD Demonstration project. Allergy. 2019;74(7):1219-36.
125. Bousquet J, Ansotegui IJ, Anto JM, Arnavielhe S, Bachert C, Basagana X, et al. Mobile Technology in Allergic Rhinitis: Evolution in Management or Revolution in Health and Care? J Allergy Clin Immunol Pract. 2019;7(8):2511-23.
126. Bedard A, Basagana X, Anto JM, Garcia-Aymerich J, Devillier P, Arnavielhe S, et al. Mobile technology offers novel insights into the control and treatment of allergic rhinitis: The MASK study. J Allergy Clin Immunol. 2019;144(1):135-43 e6.
127. Price DB, Scadding G, Bachert C, Saleh H, Nasser S, Carter V, et al. UK prescribing practices as proxy markers of unmet need in allergic rhinitis: a retrospective observational study. NPJ Prim Care Respir Med. 2016;26:16033.
128. Bousquet J, Devillier P, Arnavielhe S, Bedbrook A, Alexis-Alexandre G, van Eerd M, et al. Treatment of allergic rhinitis using mobile technology with real-world data: The MASK observational pilot study. Allergy. 2018;73(9):1763-74.

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

129. Bedard A, Basagana X, Anto JM, Garcia-Aymerich J, Devillier P, Arnavielhe S, et al. Treatment of allergic rhinitis during and outside the pollen season using mobile technology. A MASK study. Clin Transl Allergy. 2020;10(1):62.
130. Sousa-Pinto B, Eklund P, Pfaar O, Klimek L, Zuberbier T, Czarlewski W, et al. Validity, reliability, and responsiveness of daily monitoring visual analog scales in MASK-air(R). Clin Transl Allergy. 2021;11(7):e12062.
131. Dykewicz MS, Wallace DV, Amrol DJ, Baroody FM, Bernstein JA, Craig TJ, et al. Rhinitis 2020: A practice parameter update. J Allergy Clin Immunol. 2020;146(4):721-67.
132. Bousquet J, Meltzer EO, Couroux P, Koltun A, Kopietz F, Munzel U, et al. Onset of Action of the Fixed Combination Intranasal Azelastine-Fluticasone Propionate in an Allergen Exposure Chamber. J Allergy Clin Immunol Pract. 2018;6(5):1726-32 e6.
133. Patel P, Salapatek AM, Tantry SK. Effect of olopatadine-mometasone combination nasal spray on seasonal allergic rhinitis symptoms in an environmental exposure chamber study. Ann Allergy Asthma Immunol. 2019;122(2):160-6 e1.
134. Brozek JL, Baena-Cagnani CE, Bonini S, Canonica GW, Rasi G, van Wijk RG, et al. Methodology for development of the Allergic Rhinitis and its Impact on Asthma guideline 2008 update. Allergy. 2008;63(1):38-46.
135. Brozek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines - 2016 Revision. J Allergy Clin Immunol. 2017.
136. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol. 2010;126(3):466-76.
137. Wallace DV, Dykewicz MS, Oppenheimer J, Portnoy JM, Lang DM. Pharmacologic Treatment of Seasonal Allergic Rhinitis: Synopsis of Guidance From the 2017 Joint Task Force on Practice Parameters. Ann Intern Med. 2017.
138. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, Fitzgerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J. 2008;31(1):143-78.
139. Kew KM, Karner C, Mindus SM, Ferrara G. Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children. Cochrane Database Syst Rev. 2013(12):CD009019.
140. Domingo C, Rello J, Sogo A. As-needed ICS-LABA in Mild Asthma: What Does the Evidence Say? Drugs. 2019;79(16):1729-37.
141. Reddel HK, FitzGerald JM, Bateman ED, Bacharier LB, Becker A, Brusselle G, et al. GINA 2019: a fundamental change in asthma management: Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. Eur Respir J. 2019;53(6).
142. Reddel HK, Bacharier LB, Bateman ED, Brightling CE, Brusselle GG, Buhl R, et al. Global Initiative for Asthma Strategy 2021: executive summary and rationale for key changes. Eur Respir J. 2022;59(1).
143. Bousquet J, Bedbrook A, Czarlewski W, Onorato GL, Arnavielhe S, Laune D, et al. Guidance to 2018 good practice: ARIA digitally-enabled, integrated, person-centred care for rhinitis and asthma. Clin Transl Allergy. 2019;9:16.
144. Bousquet J, Jutel M, Pfaar O, Fonseca JA, Agache I, Czarlewski W, et al. The role of mobile health technologies in stratifying patients for AIT and its cessation. The ARIA-EAACI perspective. J Allergy Clin Immunol Pract. 2021.

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

145. Wallace DV, Dykewicz MS. Comparing the evidence in allergic rhinitis guidelines. Curr Opin Allergy Clin Immunol. 2017;17:286-94.
146. Bousquet J, Schunemann HJ, Fonseca J, Samolinski B, Bachert C, Canonica GW, et al. MACVIA-ARIA Sentinel NetworK for allergic rhinitis (MASK-rhinitis): the new generation guideline implementation. Allergy. 2015;70(11):1372-92.
147. Liccardi G, Calzetta L, Berra A, Caiazzo R, Califano F, Ciccarelli A, et al. Unmet needs and relationship between general practitioners (GPs) and allergists living in Campania region (southern Italy). Eur Ann Allergy Clin Immunol. 2020;52(5):230-4.
148. Abdullah B, Kandiah R, Hassan N, Ismail AF, Mohammad ZW, Wang Y. Assessment of perception, attitude, and practice of primary care practitioners towards allergic rhinitis practice guidelines: Development and validation of a new questionnaire. World Allergy Organ J. 2020;13(12):100482.
149. Lourenco O, Bosnic-Anticevich S, Costa E, Fonseca JA, Menditto E, Cvetkovski B, et al. Managing Allergic Rhinitis in the Pharmacy: An ARIA Guide for Implementation in Practice. Pharmacy (Basel). 2020;8(2).
150. Bousquet J, Barbara C, Bateman E, Bel E, Bewick M, Chavannes NH, et al. AIRWAYS-ICPs (European Innovation Partnership on Active and Healthy Ageing) from concept to implementation. Eur Respir J. 2016;47(4):1028-33.
151. Bousquet J, Hellings PW, Agache I, Bedbrook A, Bachert C, Bergmann KC, et al. ARIA 2016: Care pathways implementing emerging technologies for predictive medicine in rhinitis and asthma across the life cycle. Clin Transl Allergy. 2016;6:47.
152. Bousquet J, Arnavielhe S, Bedbrook A, Bewick M, Laune D, Mathieu-Dupas E, et al. MASK 2017: ARIA digitally-enabled, integrated, person-centred care for rhinitis and asthma multimorbidity using real-world-evidence. Clin Transl Allergy. 2018;8:45.
153. Bousquet J, Meltzer EO, Couroux P, Koltun A, Kopietz F, Munzel U, et al. Onset of Action of the Fixed Combination Intranasal Azelastine-Fluticasone Propionate in an Allergen Exposure Chamber. J Allergy Clin Immunol Pract. 2018;6(5):1726-32.
154. Pfaar O, Sousa-Pinto B, Devillier P, Canonica GW, Klimek L, Zuberbier T, et al. Effects of allergen immunotherapy in the MASK-air study: a proof-of-concept analysis. Allergy. 2021.
155. Bousquet J, Bewick M, Arnavielhe S, Mathieu-Dupas E, Murray R, Bedbrook A, et al. Work productivity in rhinitis using cell phones: The MASK pilot study. Allergy. 2017;72(10):1475-84.
156. Bousquet J, Caimmi DP, Bedbrook A, Bewick M, Hellings PW, Devillier P, et al. Pilot study of mobile phone technology in allergic rhinitis in European countries: the MASK-rhinitis study. Allergy. 2017;72(6):857-65.
157. Bousquet J, Arnavielhe S, Bedbrook A, Fonseca J, Morais Almeida M, Todo Bom A, et al. The Allergic Rhinitis and its Impact on Asthma (ARIA) score of allergic rhinitis using mobile technology correlates with quality of life: The MASK study. Allergy. 2018;73(2):505-10.
158. Bousquet J, VandenPlas O, Bewick M, Arnavielhe S, Bedbrook A, Murray R, et al. The Work Productivity and Activity Impairment Allergic Specific (WPAI-AS) Questionnaire Using Mobile Technology: The MASK Study. J Investig Allergol Clin Immunol. 2018;28(1):42-4.
159. Bousquet J, Murray R, Price D, Somekh D, Munter L, Phillips J, et al. The allergic allergist behaves like a patient. Ann Allergy Asthma Immunol. 2018;121(6):741-2.
160. Bousquet J, Anto JM, Annesi-Maesano I, Dedeu T, Dupas E, Pepin JL, et al. POLLAR: Impact of air POLLution on Asthma and Rhinitis; a European Institute of Innovation and Technology Health (EIT Health) project. Clin Transl Allergy. 2018;8:36.

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

161. Bousquet J, Schunemann HJ, Hellings PW, Arnavielhe S, Bachert C, Bedbrook A, et al. MACVIA clinical decision algorithm in adolescents and adults with allergic rhinitis. J Allergy Clin Immunol. 2016;138(2):367-74 e2.
162. Calderon MA, Demoly P, Casale T, Akdis CA, Bachert C, Bewick M, et al. Allergy immunotherapy across the life cycle to promote active and healthy ageing: from research to policies: An AIRWAYS Integrated Care Pathways (ICPs) programme item (Action Plan B3 of the European Innovation Partnership on active and healthy ageing) and the Global Alliance against Chronic Respiratory Diseases (GARD), a World Health Organization GARD research demonstration project. Clin Transl Allergy. 2016;6:41.
163. Bousquet J, Chavannes NH, Guldemond N, Haahtela T, Hellings PW, Sheikh A. Realising the potential of mHealth to improve asthma and allergy care: how to shape the future. Eur Respir J. 2017;49(5).
164. Bosnic-Anticevich S, Costa E, Menditto E, Lourenco O, Novellino E, Bialek S, et al. ARIA pharmacy 2018 "Allergic rhinitis care pathways for community pharmacy". Allergy. 2019.
165. Bousquet J, Ansotegui IJ, Anto JM, Arnavielhe S, Bachert C, Basagana X, et al. Mobile technology in allergic rhinitis: evolution in management or revolution in health and care? J Allergy Clin Immunol Pract. 2019.
166. Bousquet J, Pfaar O, Togias A, Schunemann HJ, Ansotegui I, Papadopoulos NG, et al. 2019 ARIA Care pathways for allergen immunotherapy. Allergy. 2019.
167. Bousquet J, Pham-Thi N, Bedbrook A, Agache I, Annesi-Maesano I, Ansotegui I, et al. Next-generation care pathways for allergic rhinitis and asthma multimorbidity: a model for multimorbid non-communicable diseases-Meeting Report (Part 1). J Thorac Dis. 2019;11(8):3633-42.
168. Bousquet J, Schünemann H, Togias A, Bachert C, Erhola M, Hellings P, et al. Next-generation ARIA guidelines for allergic rhinitis based on GRADE and real-world evidence. J Allergy Clin Immunol. 2019;in press.
169. Bousquet JJ, Schunemann HJ, Togias A, Erhola M, Hellings PW, Zuberbier T, et al. Next-generation ARIA care pathways for rhinitis and asthma: a model for multimorbid chronic diseases. Clin Transl Allergy. 2019;9:44.
170. Petyko ZI, Kalo Z, Espin J, Podrazilova K, Tesar T, Maniadakis N, et al. Development of a core evaluation framework of value-added medicines: report 1 on methodology and findings. Cost Eff Resour Alloc. 2021;19(1):57.
171. Bousquet J, Murray R, Price D, Somekh D, Munter L, Phillips J, et al. The allergic allergist behaves like a patient. Ann Allergy Asthma Immunol. 2018;121(6):741-2.
172. Bedard A, Anto JM, Fonseca JA, Arnavielhe S, Bachert C, Bedbrook A, et al. Correlation between work impairment, scores of rhinitis severity and asthma using the MASK-air((R)) App. Allergy. 2020;75(7):1672-88.
173. Vandenplas O, Suarthana E, Rifflart C, Lemiere C, Le Moual N, Bousquet J. The Impact of Work-Related Rhinitis on Quality of Life and Work Productivity: A General Workforce-Based Survey. J Allergy Clin Immunol Pract. 2020.

Downloaded for Anonymous User (n/a) at The University of Edinburgh from ClinicalKey.com by Elsevier on August 11, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.