



**HAL**  
open science

## The Role of Mobile Health Technologies in Stratifying Patients for AIT and Its Cessation: The ARIA-EAACI Perspective

Jean Bousquet, Marek Jutel, Oliver Pfaar, Joao Fonseca, Ioana Agache, Wienczyslawa Czarlewski, Claus Bachert, Karl Christian Bergmann, Alvaro Cruz, Ludger Klimek, et al.

### ► To cite this version:

Jean Bousquet, Marek Jutel, Oliver Pfaar, Joao Fonseca, Ioana Agache, et al.. The Role of Mobile Health Technologies in Stratifying Patients for AIT and Its Cessation: The ARIA-EAACI Perspective. *The Journal of Allergy and Clinical Immunology: In Practice*, 2021, 9 (5), pp.1805-1812. 10.1016/j.jaip.2021.02.035 . hal-03672676

**HAL Id: hal-03672676**

**<https://hal.science/hal-03672676>**

Submitted on 9 May 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

# 1 The role of mobile health technologies in stratifying patients for AIT and its 2 cessation. The ARIA-EAACI perspective

3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54

Jean Bousquet, MD <sup>1-3\*</sup>, Marek Jutel, MD <sup>4\*</sup>, Oliver Pfaar, MD <sup>5\*</sup>, Joao A Fonseca, MD <sup>6</sup>, Ioana Agache, MD <sup>7</sup>, Wienczyslawa Czarlewski, MD <sup>8,9</sup>, Claus Bachert, MD <sup>10</sup>, Karl Christian Bergmann, MD <sup>1</sup>, Alvaro A Cruz, MD,<sup>11</sup> Ludger Klimek, MD <sup>12</sup>, Violeta Kvedariene, MD,<sup>13</sup> Désirée E Larenas-Linnemann, MD,<sup>14</sup> Nikolaos G Papadopoulos, MD <sup>15</sup>, Vincenzo Patella, MD,<sup>16</sup> Frederico S Regateiro, MD <sup>17</sup>, Nicola Scichilone, MD,<sup>18</sup> Mohamed H Shamji, MD <sup>19</sup>, Aziz Sheikh, MD <sup>20</sup>, Erkka Valovirta, MD <sup>21</sup>, Maria-Teresa Ventura, MD,<sup>22</sup> Torsten Zuberbier, MD <sup>1</sup>

1. Charité, Universitätsmedizin Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Comprehensive Allergy Center, Department of Dermatology and Allergy, Berlin, Germany.
2. University Hospital Montpellier, France.
3. MACVIA-France, Montpellier, France.
4. Department of Clinical Immunology, Wrocław Medical University, Poland.
5. Department of Otorhinolaryngology, Head and Neck Surgery, Section of Rhinology and Allergy, University Hospital Marburg, Philipps-Universität Marburg, Germany.
6. CINTESIS, Center for Research in Health Technology and Information Systems, Faculdade de Medicina da Universidade do Porto; and Medida, Lda Porto, Portugal
7. Faculty of Medicine, Transylvania University, Brasov, Romania.
8. Medical Consulting Czarlewski, Levallois, France.
9. MASK-air, Montpellier, France.
10. Upper Airways Research Laboratory, ENT Dept, Ghent University Hospital, Ghent, Belgium, and Sun Yat-sen University, International Airway Research Center, First Affiliated Hospital Guangzhou, China, and Division of ENT Diseases, CLINTEC, Karolinska Institutet, Stockholm and Department of ENT Diseases, Karolinska University Hospital, Stockholm, Sweden.
11. ProAR – Nucleo de Excelencia em Asma, Federal University of Bahia, Brasil and GARD/WHO Executive Committee, Bahia, Brazil.
12. Center for Rhinology and Allergology, Wiesbaden, Germany.
13. 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
14. Center of Excellence in Asthma and Allergy, Médica Sur Clinical Foundation and Hospital, México City, Mexico
15. Allergy Department, 2nd Pediatric Clinic, Athens General Children's Hospital "P&A Kyriakou," University of Athens, Athens, Greece
16. Division of Allergy and Clinical Immunology, Department of Medicine, Agency of Health ASL Salerno, "Santa Maria della Speranza" Hospital, Battipaglia, Salerno, Italy
17. Allergy and Clinical Immunology Unit, Centro Hospitalar e Universitário de Coimbra, Faculty of Medicine, Institute of Immunology, University of Coimbra, Faculty of Medicine, ICBR - Coimbra Institute for Clinical and Biomedical Research, CIBB, University of Coimbra, Coimbra, Portugal.
18. PROMISE Department, University of Palermo, Palermo, Italy.
19. Usher Institute, The University of Edinburgh, Edinburgh, UK
20. Immunomodulation and Tolerance Group, Imperial College London, and Allergy and Clinical Immunology, Imperial College London, London, UK.
21. Department of Lung Diseases and Clinical Immunology, University of Turku and Terveystalo allergy clinic, Turku, Finland.
22. University of Bari Medical School, Unit of Geriatric Immunoallergology, Bari, Italy.

\*: The three first authors have equally contributed to the paper

55 **Address for correspondence**

56 Professor Jean Bousquet  
57 273 avenue d'Occitanie, 34090 Montpellier, France

58 Tel +33 611 42 88 47, Fax +33 467 41 67 01

59 jean.bousquet@orange.fr

60

61 **Disclosure**

62 J. Bousquet is a member of the advisory boards of, provided consultations for, and received  
63 honoraria for meeting lectures from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan,  
64 Novartis, Sanofi-Aventis, Takeda, Teva, and Uriach; has shares in KYomed-Innov; and has  
65 received personal fees from Purina.

66 M. Jutel has received lecture fees from ALK-Abello; has received lecture fees, advisory board,  
67 and clinical investigator fees from Allergopharma; has received lecture fees and clinical  
68 investigator fees from Stallergenes; has received advisory board and clinical investigator fees  
69 from Anergis; has received clinical investigator fees from Allergy Therapeutics, Circassia,  
70 Leta, and HAL; has received advisory board fees from Biomay; has received clinical  
71 investigator fees outside the submitted work from AstraZeneca, GlaxoSmithKline, Novartis,  
72 Teva, Vectura, Takeda, Roche, Janssen, MedImmune, and Chiesi; has received advisory  
73 board fees outside the submitted work from UCB.

74 O. Pfaar has received research support and personal fees from ALK-Abello, Allergopharma,  
75 Stallergenes Greer, HAL Allergy Holding BV/HAL Allergie GmbH, Bencard Allergie  
76 GmbH/Allergy Therapeutics, Lofarma, ASIT Biotech Tools SA, Laboratorios LETI/LETI Pharma,  
77 Anergis SA, and GlaxoSmithKline; has received research support from Biomay, Circassia, Phl-  
78 Boskamp, and Immunotek SL; has received personal fees from MEDA Pharma/MYLAN,  
79 Mobile Chamber Experts (a GA2LEN Partner), Indoor Biotechnologies, Astellas Pharma  
80 Global, EUFOREA, ROXALL Medizin, Novartis, Sanofi Aventis and Sanofi Genzyme, Med  
81 Update Europe GmbH, streamedup! GmbH, and John Wiley and Sons, as.

82 J. Fonseca has received personal fees from AstraZeneca, GlaxoSmithKline, and  
83 Mundipharma; has received research support and personal fees from Novartis.

84 I. Agache is Associate Editor of Allergy and CTA.

85 W. Czarlewski no COI

86 C. Bachert no COI

87 K. Bergmann no COI

88 A. A. Cruz has received an investigator initiated grant, and honoraria for advisory board and  
89 lectures from GlaxoSmithKline; has received honoraria for advisory board and lectures and a  
90 contract for clinical trial from Sanofi and Novartis; has received honoraria for advisory board  
91 and lectures from Chiesi, Boehringer Ingelheim, Glenmark, Mylan, and Eurofarma; and has  
92 received honoraria for consultancy and lecture from Mantecorp.

93 L. Klimek has received research support from personal fees from Allergopharma,  
94 MEDA/MyLAN, LETI Pharma, and Sanofi; has received research support from ALK Abello,  
95 Stallergenes, Quintiles, ASIT Biotech, Lofarma, AstraZeneca, GlaxoSmithKline, and Immunotk;  
96 has received personal fees from HAL Allergie, Allergy Therapeut, and Cassella Med; and is a  
97 member of AeDA, DGHNO, Deutsche Akademie für Allergologie und klinische Immunologie,  
98 HNO-BV, GPA, and EAACI.

99 V. Kvedariene has received consultancy fees from GlaxoSmithKline; has received non  
100 financial sponsorship for professional education from AstraZeneca and DIMUNA.  
101 D. Larenas Linnemann has received speakers fees from and is on the advisory board and  
102 safety boards of Allakos, Amstrong, Astrazeneca, DBV Technologies, Grunenthal, GSK, Mylan,  
103 Menarini, MSD, Novartis, Pfizer, Novartis, Sanofi, UCB, Alakos, and Gossamer; has received  
104 travel grants from Sanofi, Astrazeneca, Novartis, UCB, GSK, TEVA, and Purina institute.  
105 N. G. Papadopoulos has received advisory and speaker fees from Novartis, Nutricia, HAL,  
106 Menarini/Faes Farma, and Mylan/MEDA; has received speaker fees from Sanofi, Biomay,  
107 MSD, ASIT Biotech, and Boehringer Ingelheim; has received advisory fees from AstraZeneca;  
108 and has received research support from Gerolymatos International SA and Capricare.  
109 V. Patella no COI  
110 F. S. Regateiro no COI  
111 N. Scichilone no COI  
112 M. Shamji no COI  
113 A. Sheikh no COI  
114 E. Valovirta no COI  
115 M. T. Ventura no COI  
116 T. Zuberbier has received consultancy fees from Bayer Health Care, FAES, Novartis, and  
117 Henkel; has received research support paid to his institution from Novartis, and Henkel; has  
118 received speaker fees from AstraZeneca, Abbvie, ALK, Almirall, Astellas, Bayer Health Care,  
119 Bencard, Berlin Chemie, FAES, HAL, Leti, Meda, Menarini, Merck, MSD, Novartis, Pfizer,  
120 Sanofi, Stallergenes, Takeda, Teva, UCB, Henkel, Kryolan, and L'Oreal; and is a committee  
121 member for WHO-Initiative "Allergic Rhinitis and Its Impact on Asthma" (ARIA); is a member  
122 of the Board of the German Society for Allergy and Clinical Immunology (DGAKI); is Head of  
123 the European Centre for Allergy Research Foundation (ECARF); is President of Global Allergy  
124 and Asthma European Network (GA2LEN); and is a member of the Committee on Allergy  
125 Diagnosis and Molecular Allergology, World Allergy Organization (WAO).

126 **Abstract**

127 Allergen immunotherapy (AIT) is a proven therapeutic option for the treatment of allergic rhinitis  
128 and/or asthma. Many international or national practice guidelines have been produced, but the  
129 evidence-based method varies and they do not usually propose care pathways. The present paper  
130 considers the possible role of mHealth in AIT for allergic rhinitis/asthma. There are no currently  
131 available validated biologic biomarkers that can predict AIT success, and mHealth biomarkers have  
132 some relevance. In the current paper, the following aspects will be discussed: patient stratification for  
133 AIT, symptom medication scores for the follow-up of patients, clinical trials as well as the approach of  
134 the European Academy of Allergy and Clinical Immunology.

135

136 **Key words:** mHealth, ARIA, EAACI, allergic rhinitis, immunotherapy

137

138 **Abbreviations**

139

140 AIT: Allergen immunotherapy

141 AR: Allergic rhinitis

142 CDSS: Clinical decision support system

143 CSMS: Combined symptom-medication score

144 EAACI: European Academy of Allergy and Clinical Immunology

145 MASK: Mobile Airways Sentinel network

146 SMS: Symptom-medication score

147 RCT: Randomised controlled trial

148 RWD: Real world data

149 RWE: Real world evidence

150 VAS: Visual analogue scale

## 151 **Introduction**

152 Allergen immunotherapy (AIT) is a proven therapeutic option for the treatment of respiratory  
153 allergies. Many guidelines or national practice parameters or care pathways for AIT have been  
154 proposed (1-3). The decision to prescribe AIT for the patient should be individualized and based on  
155 the relevance of the allergens, the persistence of symptoms despite use of appropriate medications  
156 prescribed according to guidelines, as well as on the availability of good-quality and efficacious  
157 extracts (4). AIT should be reserved for patients with moderate/severe rhinitis or mild to moderate  
158 asthma who, despite appropriate pharmacotherapy and adherence, continue to exhibit exacerbations  
159 that appear to be related to allergen exposure, except in some specific cases (5, 6).

160 The digital transformation of health and healthcare (including mHealth and artificial intelligence)  
161 places the patient at the centre of the health system and is revolutionizing the practice of medicine (7,  
162 8). Biomarkers associated with mHealth and clinical decision support systems (CDSS) (9) may change  
163 the scope of AIT as they will help monitor a patient's disease control (10, 11) to enable: (i) patient  
164 stratification; (ii) clinical trials and real-world evidence; (iii) monitoring the efficacy and safety of  
165 targeted therapies (a critical process for identifying appropriate reimbursement); and (iv)  
166 implementation of stopping rules (Figure 1). Clinical stopping rules should be developed for AIT -  
167 similarly to those currently considered for biologics in severe asthma - as a guidance for the  
168 continuation or cessation of treatment after a short (early stopping rule) or long (late stopping rule)  
169 period. As an example, a global treatment evaluation after 16 weeks is used as an early stopping rule  
170 for omalizumab treatment (12, 13).

171 There are however two pre-requisites before any mHealth tool should be used. The tool should comply  
172 with privacy regulations and should be validated. To date, very few tools are available for rhinitis (14).  
173 Evidence-based development was found for four apps: MASK-air (24 papers reviewed in (15-19)),  
174 AllergyMonitor (20, 21), Pollen (Polleninfo.org) (22) and Air Rater (23).

## 175 **Concept of patient stratification for AIT**

176 The stratification of patients into subpopulations is the basis of clinical decision-making for  
177 increased diagnostic and treatment efficacy (24, 25). Patient stratification also integrates costs and  
178 social determinant risk models to propose the right care management for the individual patient (26).

179 In diseases with a very high prevalence, such as allergic diseases, patient stratification is required to:  
180 (i) identify the best candidates for intervention through complex care management; (ii) reduce the  
181 amount of time and resources needed to match the right patient to a care management programme; and  
182 (iii) optimize costs as some therapeutic interventions cannot be administered to all patients. Patient  
183 stratification may also help to improve the patient's engagement (27).

184 There are currently no genetic or blood biomarkers validated for predicting or monitoring the efficacy  
185 of AIT at an individual patient level, although several candidates have been investigated (28). mHealth  
186 biomarkers are likely to represent the future, before genetic or blood biomarkers are available.

### 187 **Symptom-medication scores using mHealth**

188 Symptom-medication scores (SMSs) are needed to investigate the efficacy of AIT, particularly in  
189 clinical practice or for randomized controlled trials (RCTs) (29, 30) and observational studies. The  
190 European Academy of Allergy and Clinical Immunology (EAACI) proposed a combined symptom  
191 and medication score (CSMS) for allergen immunotherapy (AIT) trials (31). However, it had not  
192 been fully evaluated until recently.

193 A study using MASK (Mobile Airways Sentinel NetworK) (32, 33) (Table 1) attempted to validate  
194 CSMS using work productivity as a surrogate marker in over 6,800 users. There was a highly  
195 significant correlation between the visual analogue scales (VASs) “allergy” and “work” ( $r=0.73$ ,  
196  $p<0.0001$ ). The CSMS showed a lower correlation with VAS work ( $r=0.56$ ,  $P<0.0001$ ). This can be  
197 explained by many reasons, but one appears to be relevant: adding the same coefficient to all values of  
198 a symptom score or to a VAS level may not be optimal.

199 Since the CSMS was not highly correlated with VAS work, a new score was based on (i) the results  
200 obtained in MASK (32, 33), and (ii) the algorithm for AR treatment developed by the MACVIA  
201 expert group (34) revised by the MASK expert group after a modified Delphi exercise (9). Real-world  
202 data from MASK (32, 35) showed that (i) medications are likely to have a different effectiveness  
203 depending on rhinitis control level: higher impact for a lower VAS level and lower impact for a higher  
204 VAS level and (ii) co-medication should be considered. A new CSMS was therefore constructed and a  
205 higher correlation was found ( $r=0.82$ ) (Bousquet, in preparation). However, this score needs to be  
206 refined and should be regularly updated using new data and machine learning.

207 When available, this CSMS will be combined with the pollen and air pollution data of the geolocalized  
208 patient, making it possible to correlate daily allergen and pollution exposure to CSMS (36) (ARIA-  
209 EAACI-CMS).

210 The ARIA-EAACI-CSMS can be used to stratify patients for AIT and to follow the patient during AIT  
211 (and beyond when AIT is stopped) in RCTs and real-life observational studies.

212

## 213 **mHealth for patient stratification and follow up in AIT**

214 In MAKS-air, we have devised a very simple tool for shared-decision making that shows the symptom  
215 control, medications and adherence to treatment on the screen of the physician (37). Moreover, we  
216 have developed an electronic clinical decision support system that can be used for this purpose. It is  
217 currently in English only and should be translated soon (38). Finally, we plan to use machine learning  
218 to help the physician to refine the stratification.

### 219 **Indication of AIT**

220 AIT is not required for all allergic patients. As proposed in the ARIA care pathways for AIT <sup>1</sup>, it  
221 should be indicated in patients with poor control of the disease (Table 2) and in some patients  
222 controlled by pharmacotherapy who may develop asthma exacerbations (such as pollen-induced  
223 asthma or thunderstorm-induced asthma) (39, 40).

224 A stratification is therefore needed to propose a patient-centred approach using several steps for  
225 personalized medicine. These include an optimal allergy diagnosis, the assessment of adherence to  
226 medications as well as the demonstration of uncontrolled disease associated with allergen exposure  
227 despite optimal medications.

228 It is very important to stratify the patient as rapidly as possible, and mHealth has a relevant  
229 importance. Using the ARIA-EAACI-CSMS, the physician can, after the first pollen season, daily  
230 assess the adherence to treatment, the level of pharmacotherapy, the control of AR and asthma as well  
231 as the impact on work or school. Only stratified patients who require AIT will be selected. This should  
232 improve the efficacy of AIT and may have a relevant impact on health economics and reimbursement  
233 strategies.

### 234 **Follow-up and early stopping rule**

235 AIT is a long-term treatment. It is important to identify patients who are not well controlled and who  
236 should stop AIT from those who are benefitting from the treatment. Using the ARIA-EAACI-CSMS,  
237 the physician will recognize the exact symptoms and medications during pollen exposure by  
238 comparison to the previous year for each individual patient. This will allow an improved shared  
239 decision making (SDM) with the patient in order to determine whether to continue or stop AIT. It is  
240 likely that the patient will be prone to continuing AIT, thereby improving adherence to the treatment.

### 241 **Follow-up and late stopping rule**



242 AIT is proposed for a duration of 3 years and it is stopped without objective assessment of its efficacy.  
243 A late stopping rule is therefore needed to help physicians to stop or continue AIT. The same approach  
244 will be used for each year of AIT, and the physician will be able to assess the benefits of the treatment,  
245 thereby potentially improving SDM. After 3 years, the physician may be in a better position to  
246 propose the continuation or cessation of AIT.

#### 247 **Follow-up after AIT is stopped**

248 Using the same ARIA-EAACI-CSMS, the patient will be followed after AIT is stopped, and the  
249 physician will know whether AIT should eventually be re-initiated. Once again, SDM and the link  
250 between the different health professionals will potentially be improved.

#### 251 **Stratification in house dust mite allergy**

252 In allergic diseases for house dust mites, the seasonality is not clear and symptoms cannot be  
253 associated to allergen exposure. However, the stratification of patients is required as the indication of  
254 acarizax<sup>®</sup> (house dust mite sublingual immunotherapy) in Europe proposes AIT in “persistent  
255 moderate to severe house dust mite allergic rhinitis despite use of symptom-relieving medication”  
256 ([https://mri.cts-mrp.eu/Human/Downloads/DE\\_H\\_1947\\_001\\_FinalPI.pdf](https://mri.cts-mrp.eu/Human/Downloads/DE_H_1947_001_FinalPI.pdf)) (6). The early and late  
257 stopping rules using objective data are also of great importance.

#### 258 **The global allergy solution: mHealth transformation of care**

259 The delivery of cost-effective modern health care is challenging for the management of chronic  
260 diseases - and in particular for allergic diseases (41) - as management, which is often dependent on  
261 specialist and supporting services, is becoming unaffordable. Accordingly, innovative solutions, often  
262 based on mobile health, are required(42, 43). Authorities should be supported for the transformation of  
263 health and care towards integrated care with organizational health literacy for allergic diseases (16, 44,  
264 45). A Global Allergy Simple Solution should provide the framework to digitally transform the  
265 prevention and control of allergic diseases in a cost-effective manner (46). Mobile health could be  
266 used to achieve optimal guaranty for an accessible and affordable treatment in stratified and  
267 participatory patients with allergic diseases and to provide change management (8).

#### 268 **Clinical trials**

##### 269 **The problems**

270 Major problems of the double blind, placebo controlled (DBPC) RCTs of AIT include the relatively  
271 low mean symptom intensity in the active treatment group since many days of the survey may be

272 without allergen exposure and the small active vs. placebo difference. Although there are many  
273 possible causes, some appear to have more weight than others:

- 274 • Patients receiving AIT are scattered over a large area that may not be covered by clinically relevant  
275 pollen counts of the area.
- 276 • In a given area, the level of exposure to airborne allergen varies from one day to the next during the  
277 pollen season.
- 278 • The duration of the pollen season is approximated for a given area and does not take account of  
279 variations in allergen exposure, although attempts have been made to resolve this problem (47, 48).
- 280 • Patients often move between sites (work and home, for example), and the level of allergen  
281 exposure varies from one site to the next. However, technical issues prevent this important issue  
282 from being considered in DBPC RCTs.
- 283 • The assessment of environmental exposure requires more than pollen counts. Weather parameters  
284 and pollutants can modulate allergen exposure.
- 285 • Pollen counts do not completely reflect symptoms during the whole season (49, 50).
- 286 • Personal exposure data are needed, but individual pollen samplers cannot be used daily in large-  
287 scale trials, and these methods have not been validated.
- 288 • Next-generation real-time pollen monitoring (51) cannot be used throughout Europe and does not  
289 account for individual exposure.

#### 290 **Potential mHealth solutions**

291 The evaluation of the allergic risk requires:

- 292 • Assessment of allergen exposure in individual patients;
- 293 • Evaluation of pollen counts across Europe, using a standardized method;
- 294 • The embedding pollution and climate data (52);
- 295 • The evaluation of symptoms in the local area (15).

296 As part of the POLLAR project, the Finnish Meteorological Institute is using artificial intelligence  
297 techniques to finalize a predictive model of daily pollen exposure by using climatologic data and air  
298 pollution. The model will be refined at the end of 2020 and embedded in MASK-Air.

#### 299 **Embedding pollen exposure data and patients' symptom severity in an app**

300 As an example, the MASK-air app (including daily geolocation) - in line with the European Union's  
301 General Data Protection Regulation (53-55) - can feature:

- 302 1. A model of pollen, pollution and symptoms, with a grid of around 10 x 10 km across Europe  
303 (already embedded in the app).
- 304 2. The daily symptoms and medications (over-the-counter and prescription medications customized  
305 for each individual country) that will be scored and used to construct the ARIA-EAACI-CSMS.

306 Other tools with the desired features can also be used.

### 307 **Assessing the placebo effect using mHealth**

308 The placebo effect commonly occurs in clinical trials. The psychological and physiological factors  
309 associated with patients' expectations about a treatment's positive and negative effects have yet to be  
310 well characterized. mHealth may provide some help in reducing the placebo effect (Table 3). (56)

### 311 **Real-world data (RWD) in observational studies**

312 Real-world evidence (derived from observational studies) combines the results of DBPC RCTs and  
313 RWD. This provides clinically relevant information that usefully complements DBPC RCTs (33, 57-  
314 59). The real-life approach can be extended to a variety of allergens and AIT methods.

315 Since all patients use the same app and system, the application of machine learning is likely to  
316 enhance the efficacy of AIT at the individual level. It may also automatically provide advice to the  
317 physician (e.g. on early stopping) in clinical practice.

### 318 **Evaluating the role of mHealth technologies in AIT – the EAACI Task force**

319 As millions of patients suffering from allergic diseases may benefit from mHealth innovations, the  
320 EAACI created a Task Force to assess the state of the art as well as the future potential of (Information  
321 and communication technology) ICT in the field of allergy. The evaluation of 136 mobile apps in 2016  
322 depicted a broad heterogeneity in terms of content and quality. As the mobile health environment is a  
323 very dynamic field, some of these may no longer exist or comply with regulatory requirements. Very  
324 few apps had been clinically validated and many were not based on guidelines or clinical evidence  
325 (14). The Task Force assessed the design, user engagement, content, potential of inducing behavioural  
326 change, credibility/accountability, and privacy policies of mHealth products. The perspectives of  
327 healthcare professionals and allergic patients were provided. This underlined the need of thorough  
328 investigation for an effective design of mHealth technologies as auxiliary tools to improve quality of  
329 care. mHealth technology, including telemonitoring, integrated care pathways (ICPs), and CDSS are  
330 suggested as potential tools to aid decision-making for AIT, improve adherence, monitor efficacy and  
331 safety as well as identify clinical responders to treatment. This approach was acknowledged as a  
332 facilitator for the change in AIT perspective from clinician- to patient-centred care.

333 **EAACI Research and Outreach Committee**

334 The newly formed EAACI Research and Outreach Committee (EAACI ROC) aims to (i) provide new  
335 forms of translation of key research findings, (ii) better meet the needs of clinicians and (ii) more  
336 rapidly develop precision approaches that will facilitate the development of EAACI Guidelines to  
337 improve and cure allergic disease and asthma. Telemedicine and e-Health, novel clinical trial designs  
338 and a special focus on high-quality real-world evidence are amongst the top priorities of the EAACI  
339 2021-2022 Research Agenda (60).

340 **Conclusion**

341  
342 mHealth has the potential to change the management of allergic diseases using validated tools in order  
343 to better stratify patients. (8) However, these tools may be non-beneficial if improperly used or if they  
344 have not been fully validated.

345 **Table 1: Features of MASK (Mobile Airways Sentinel Network)**

- 346
- 347
- 348
- 349
- 350
- 351
- 352
- 353
- 354
- 355
- 356
- 357
- 358
- 359
- MASK has been recognized as an example of good practice in the field of digitally-enabled, integrated, person-centred care by the European Commission’s Directorate General for Health and Food Safety (16). It includes a smartphone application (MASK-air) tested in 27 countries and 17 languages by 40,000 users (technology readiness level, TRL 9) (15) and the POLLAR project (interaction between air pollution, asthma and rhinitis) funded by the European Institute of Innovation & Technology to monitor the patient’s day-to-day allergen and pollution exposure (52). MASK is fully GDPR compliant (61).
  - In MASK, geolocalized users self-assessed their daily symptom control using the touchscreen functionality on their smart phone to click on VAS scores (ranging from 0 to 100) for overall symptoms (global), nose, eyes, asthma and work asked in this order with several other screens in between.
  - Users input their daily medications using a scroll list which contains all country-specific OTC and prescribed medications available for each country.
  - The MASK-air results have changed the concept of allergy phenotypes (62) and the management of allergic diseases (8, 57).
  - MASK is freely available in 27 countries and 18 languages for patients or research purposes.

360

361

362

363 **Table 2: Global applicability of MASK (from (15) (61))**

Applicability	MASK
<b>Clinical practice</b>	<p>Physicians will be able to read the files of the patients in order to:</p> <ul style="list-style-type: none"> <li>• Optimize treatment for the patient and, in particular, the current or the next pollen season.</li> <li>• Assess and increase the adherence to treatment.</li> <li>• Better stratify the patient</li> <li>• Help for shared decision making</li> <li>• Prescribe allergen immunotherapy (AIT) more rapidly when the patient is not controlled despite optimal pharmacologic treatment.</li> <li>• Determine the efficacy of AIT in patients</li> <li>• Essential tool to provide personalized medicine in AR and asthma</li> </ul> <p>In the future , clinical decision support system and machine learning will be used</p>
<b>Change management</b>	<ul style="list-style-type: none"> <li>• Many patients are uncontrolled and non -adherent to treatment.</li> <li>• Moreover, patients use their medications as needed and not as a regular basis as prescribed</li> <li>• These features are found in all countries</li> <li>• Change management is needed for value added medicine</li> </ul>
<b>Patient empowerment</b>	<ul style="list-style-type: none"> <li>• Better understanding of the symptoms</li> <li>• Sentinel network linking aerobiology data and control</li> <li>• Improved adherence</li> <li>• Self-management</li> <li>• Patient empowerment</li> <li>• Messages sent by the App.</li> </ul>
<b>Clinical trials</b>	<ul style="list-style-type: none"> <li>• For RCTs, it is essential to have clarity on definitions, and relevant tools. <ul style="list-style-type: none"> <li>• To better stratify the patients needing AIT</li> <li>• To assess the efficacy of AIT during the trial</li> <li>• To assess the efficacy when AIT is stopped</li> </ul> </li> <li>• Observational studies are of key importance to confirm RCTs and bring new hypotheses for the treatment of AR and asthma</li> </ul>
<b>Registration and reimbursement of medicines</b>	<ul style="list-style-type: none"> <li>• Controlled trials designed with a uniform approach will be more easily evaluated by the Health Technology Assessment agencies for reimbursement. The Allergy Diary uses EQ-5D, a validated measure of utility</li> <li>• Better understanding of direct and indirect costs</li> <li>• Controlled trials designed with a uniform approach will help to synchronize data from real-life world regarding clinical effects and safety/tolerability of new drugs (post-marketing pharmacovigilance)</li> </ul>

365 **Table 3: Precision Medicine in the indication of AIT in allergy to inhalants (1)**

- |     |  |
|-----|--|
| 366 | 1. Precise diagnosis with disease history, skin prick tests and/or specific IgE and, if needed, component- |
| 367 | resolved <i>in vitro</i> diagnosis (CRD) (63). In some rare instances, provocation tests may be needed.    |
| 368 | 2. Proven indications: Allergic rhinitis, conjunctivitis and/or asthma.                                    |
| 369 | 3. Allergic symptoms predominantly induced by the relevant allergen exposure.                              |
| 370 | 4. Patient stratification: Poor control of symptoms despite appropriate pharmacotherapy according to       |
| 371 | guidelines with adherence to treatment during the allergy season and/or the alteration of the natural      |
| 372 | history of allergy (64). Mobile technology may become of relevant importance in the stratification of      |
| 373 | patients (mHealth biomarker).  |
| 374 | 5. Demonstration of efficacy and safety for the product with relevant trials.                              |
| 375 | 6. The patient (and caregiver)'s views represent an essential component for shared decision making.        |

376

377

378

379 **Table 4: Digital health and machine learning to assess the placebo effect in pollen DBPC RCTs (56)**

Problem		Solution	Strengths	Weaknesses
Allergen exposure varies from one patient location to another	Daily environment assessment	App with daily geolocation	The patient will be assessed with ONE geolocation per day (1 for privacy reasons)	If the patient moves during the day, one geolocation will be insufficient
Allergen exposure needs to be assessed daily		Model of the pollen season embedded in the app with a resolution of 10 x 10 km (usually)	Precise determination of the pollen exposure	10 x 10 km may be insufficient for some patients
Pollution is a confounding factor for allergy		Inclusion of pollution data in the model	More than simply pollen exposure	To be tested
Symptoms may not be correlated with pollen exposure	App	Inclusion of symptoms in the area in the model with machine learning	Symptoms of the area will inform of the overall allergic risk	To be tested
Symptom-medication score	Novel symptom-medication score	Symptoms and all medications of the different European countries	Validated for pharmacotherapy (32, 35)	Low adherence

380

381



382 **References**

383

- 384 1. Bousquet J, Pfaar O, Togias A, Schunemann HJ, Ansotegui I, Papadopoulos NG, et al. 2019  
385 ARIA Care pathways for allergen immunotherapy. *Allergy*. 2019;74(11):2087-102.
- 386 2. Agache I, Lau S, Akdis CA, Smolinska S, Bonini M, Cavkaytar O, et al. EAACI Guidelines on  
387 Allergen Immunotherapy: House dust mite-driven allergic asthma. *Allergy*. 2019;74(5):855-73.
- 388 3. Muraro A, Roberts G, Halken S, Agache I, Angier E, Fernandez-Rivas M, et al. EAACI  
389 guidelines on allergen immunotherapy: Executive statement. *Allergy*. 2018;73(4):739-43.
- 390 4. Pfaar O, Angier E, Muraro A, Halken S, Roberts G. Algorithms in allergen immunotherapy in  
391 allergic rhinoconjunctivitis. *Allergy*. 2020;75(9):2411-4.
- 392 5. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic  
393 Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol*.  
394 2010;126(3):466-76.
- 395 6. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and  
396 its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization,  
397 GA(2)LEN and AllerGen). *Allergy*. 2008;63 Suppl 86:8-160.
- 398 7. Bousquet J, Ansotegui IJ, Anto JM, Arnavielhe S, Bachert C, Basagana X, et al. Mobile  
399 Technology in Allergic Rhinitis: Evolution in Management or Revolution in Health and Care? *J*  
400 *Allergy Clin Immunol Pract*. 2019;7(8):2511-23.
- 401 8. Bousquet J, Hellings PW, Agache I, Amat F, Annesi-Maesano I, Ansotegui IJ, et al. Allergic  
402 Rhinitis and its Impact on Asthma (ARIA) Phase 4 (2018): Change management in allergic  
403 rhinitis and asthma multimorbidity using mobile technology. *J Allergy Clin Immunol*.  
404 2019;143(3):864-79.
- 405 9. Courbis AL, Murray RB, Arnavielhe S, Caimmi D, Bedbrook A, Van Eerd M, et al. Electronic  
406 Clinical Decision Support System for allergic rhinitis management: MASK e-CDSS. *Clin Exp*  
407 *Allergy*. 2018.
- 408 10. Bousquet J, Arnavielhe S, Bedbrook A, Alexis-Alexandre G, Eerd Mv, Murray R, et al.  
409 Treatment of allergic rhinitis using mobile technology with real world data: The MASK  
410 observational pilot study. *Allergy*. 2018:sous presse.
- 411 11. Bousquet J, Hellings PW, Agache I, Bedbrook A, Bachert C, Bergmann KC, et al. ARIA 2016:  
412 Care pathways implementing emerging technologies for predictive medicine in rhinitis and  
413 asthma across the life cycle. *Clin Transl Allergy*. 2016;6:47.
- 414 12. Bousquet J, Rabe K, Humbert M, Chung KF, Berger W, Fox H, et al. Predicting and evaluating  
415 response to omalizumab in patients with severe allergic asthma. *Respir Med*. 2007.
- 416 13. Diaz RA, Charles Z, George E, Adler AI. NICE guidance on omalizumab for severe asthma.  
417 *Lancet Respir Med*. 2013;1(3):189-90.
- 418 14. Matricardi PM, Dramburg S, Alvarez-Perea A, Antolin-Amerigo D, Apfelbacher C, Atanaskovic-  
419 Markovic M, et al. The role of mobile health technologies in allergy care: An EAACI position  
420 paper. *Allergy*. 2020;75(2):259-72.
- 421 15. Bousquet J, Arnavielhe S, Bedbrook A, Bewick M, Laune D, Mathieu-Dupas E, et al. MASK  
422 2017: ARIA digitally-enabled, integrated, person-centred care for rhinitis and asthma  
423 multimorbidity using real-world-evidence. *Clin Transl Allergy*. 2018;8:45.
- 424 16. Bousquet J, Bedbrook A, Czarlewski W, Onorato GL, Arnavielhe S, Laune D, et al. Guidance to  
425 2018 good practice: ARIA digitally-enabled, integrated, person-centred care for rhinitis and  
426 asthma. *Clin Transl Allergy*. 2019;9:16.
- 427 17. Bousquet JJ, Schunemann HJ, Togias A, Erhola M, Hellings PW, Zuberbier T, et al. Next-  
428 generation ARIA care pathways for rhinitis and asthma: a model for multimorbid chronic  
429 diseases. *Clin Transl Allergy*. 2019;9:44.
- 430 18. Bedard A, Basagana X, Anto JM, Garcia-Aymerich J, Devillier P, Arnavielhe S, et al. Treatment  
431 of allergic rhinitis during and outside the pollen season using mobile technology. A MASK study.  
432 *Clin Transl Allergy*. 2020;10(1):62.
- 433 19. Bousquet J, Anto JM, Haahtela T, Jousilahti P, Erhola M, Basagana X, et al. Digital  
434 transformation of health and care to sustain Planetary Health: The MASK proof-of-concept for  
435 airway diseases-POLLAR symposium under the auspices of Finland's Presidency of the EU, 2019

- 436 and MACVIA-France, Global Alliance against Chronic Respiratory Diseases (GARD, WHO)  
437 demonstration project, Reference Site Collaborative Network of the European Innovation  
438 Partnership on Active and Healthy Ageing. *Clin Transl Allergy*. 2020;10:24.
- 439 20. Di Fraia M, Tripodi S, Arasi S, Dramburg S, Castelli S, Villalta D, et al. Adherence to Prescribed  
440 E-Diary Recording by Patients With Seasonal Allergic Rhinitis: Observational Study. *J Med*  
441 *Internet Res*. 2020;22(3):e16642.
- 442 21. Pizzulli A, Perna S, Florack J, Pizzulli A, Giordani P, Tripodi S, et al. The impact of  
443 telemonitoring on adherence to nasal corticosteroid treatment in children with seasonal allergic  
444 rhinoconjunctivitis. *Clin Exp Allergy*. 2014;44(10):1246-54.
- 445 22. Bastl K, Bastl M, Bergmann KC, Berger M, Berger U. Translating the Burden of Pollen Allergy  
446 Into Numbers Using Electronically Generated Symptom Data From the Patient's Hayfever Diary  
447 in Austria and Germany: 10-Year Observational Study. *J Med Internet Res*. 2020;22(2):e16767.
- 448 23. Jones PJ, Koolhof IS, Wheeler AJ, Williamson GJ, Lucani C, Campbell SL, et al. Can  
449 smartphone data identify the local environmental drivers of respiratory disease? *Environ Res*.  
450 2020;182:109118.
- 451 24. Hellings PW, Fokkens WJ, Bachert C, Akdis CA, Bieber T, Agache I, et al. Positioning the  
452 principles of precision medicine in care pathways for allergic rhinitis and chronic rhinosinusitis -  
453 A EUFOREA-ARIA-EPOS-AIRWAYS ICP statement. *Allergy*. 2017;72(9):1297-305.
- 454 25. Muraro A, Fokkens WJ, Pietikainen S, Borrelli D, Agache I, Bousquet J, et al. European  
455 symposium on precision medicine in allergy and airways diseases: report of the European Union  
456 parliament symposium (October 14, 2015). *Rhinology*. 2015.
- 457 26. Canonica GW, Bachert C, Hellings P, Ryan D, Valovirta E, Wickman M, et al. Allergen  
458 Immunotherapy (AIT): a prototype of Precision Medicine. *World Allergy Organ J*. 2015;8(1):31.
- 459 27. Pfaar O, Bonini S, Cardona V, Demoly P, Jakob T, Jutel M, et al. Perspectives in allergen  
460 immunotherapy: 2017 and beyond. *Allergy*. 2018;73 Suppl 104:5-23.
- 461 28. Shamji MH, Kappen JH, Akdis M, Jensen-Jarolim E, Knol EF, Kleine-Tebbe J, et al. Biomarkers  
462 for monitoring clinical efficacy of allergen immunotherapy for allergic rhinoconjunctivitis and  
463 allergic asthma: an EAACI Position Paper. *Allergy*. 2017;72(8):1156-73.
- 464 29. Godicke V, Hundt F. Registration trials for specific immunotherapy in Europe: advanced  
465 guidance from the new European Medical Agency guideline. *Allergy*. 2010;65(12):1499-505.
- 466 30. Pfaar O, Alvaro M, Cardona V, Hamelmann E, Mosges R, Kleine-Tebbe J. Clinical trials in  
467 allergen immunotherapy: current concepts and future needs. *Allergy*. 2018;73(9):1775-83.
- 468 31. Pfaar O, Demoly P, Gerth van Wijk R, Bonini S, Bousquet J, Canonica GW, et al.  
469 Recommendations for the standardization of clinical outcomes used in allergen immunotherapy  
470 trials for allergic rhinoconjunctivitis: an EAACI Position Paper. *Allergy*. 2014;69(7):854-67.
- 471 32. Bousquet J, Devillier P, Arnavielhe S, Bedbrook A, Alexis-Alexandre G, van Eerd M, et al.  
472 Treatment of allergic rhinitis using mobile technology with real-world data: The MASK  
473 observational pilot study. *Allergy*. 2018;73(9):1763-74.
- 474 33. Menditto E, Costa E, Midao L, Bosnic-Anticevich S, Novellino E, Bialek S, et al. Adherence to  
475 treatment in allergic rhinitis using mobile technology. The MASK Study. *Clin Exp Allergy*.  
476 2019;49(4):442-60.
- 477 34. Bousquet J, Schunemann HJ, Hellings PW, Arnavielhe S, Bachert C, Bedbrook A, et al.  
478 MACVIA clinical decision algorithm in adolescents and adults with allergic rhinitis. *J Allergy*  
479 *Clin Immunol*. 2016;138(2):367-74 e2.
- 480 35. Bedard A, Basagana X, Anto JM, Garcia-Aymerich J, Devillier P, Arnavielhe S, et al. Mobile  
481 technology offers novel insights on control and treatment of allergic rhinitis. The MASK study. *J*  
482 *Allergy Clin Immunol*. 2019.
- 483 36. Sofiev M, Palamarchuk Y, Bedard A, Basagana X, Anto JM, Kouznetsov R, et al. A  
484 demonstration project of Global Alliance against Chronic Respiratory Diseases: Prediction of  
485 interactions between air pollution and allergen exposure-the Mobile Airways Sentinel Network-  
486 Impact of air POLLution on Asthma and Rhinitis approach. *Chin Med J (Engl)*. 2020.
- 487 37. Bousquet J, Agache I, Aliberti MR, Angles R, Annesi-Maesano I, Anto JM, et al. Transfer of  
488 innovation on allergic rhinitis and asthma multimorbidity in the elderly (MACVIA-ARIA) - EIP  
489 on AHA Twinning Reference Site (GARD research demonstration project). *Allergy*.  
490 2018;73(1):77-92.

- 491 38. Courbis AL, Murray RB, Arnavielhe S, Caimmi D, Bedbrook A, Van Eerd M, et al. Electronic  
492 Clinical Decision Support System for allergic rhinitis management: MASK e-CDSS. *Clin Exp*  
493 *Allergy*. 2018;48(12):1640-53.
- 494 39. Lee J, Kronborg C, O'Hehir RE, Hew M. Who's at risk of thunderstorm asthma? The ryegrass  
495 pollen trifecta and lessons learnt from the Melbourne thunderstorm epidemic. *Respir Med*.  
496 2017;132:146-8.
- 497 40. O'Hehir RE, Varese NP, Deckert K, Zubrinich CM, van Zelm MC, Rolland JM, et al. Epidemic  
498 Thunderstorm Asthma Protection with Five-Grass Pollen Tablet Sublingual Immunotherapy: A  
499 Clinical Trial. *Am J Respir Crit Care Med*. 2018;198(1):126-8.
- 500 41. Stenberg K, Lauer JA, Gkountouras G, Fitzpatrick C, Stanciole A. Econometric estimation of  
501 WHO-CHOICE country-specific costs for inpatient and outpatient health service delivery. *Cost*  
502 *Eff Resour Alloc*. 2018;16:11.
- 503 42. Russell J, Greenhalgh T. Affordability as a discursive accomplishment in a changing National  
504 Health Service. *Soc Sci Med*. 2012;75(12):2463-71.
- 505 43. Hunter DJ, Erskine J, Small A, McGovern T, Hicks C, Whitty P, et al. Doing transformational  
506 change in the English NHS in the context of "big bang" reorganisation. *J Health Organ Manag*.  
507 2015;29(1):10-24.
- 508 44. Farmanova E, Bonneville L, Bouchard L. Organizational Health Literacy: Review of Theories,  
509 Frameworks, Guides, and Implementation Issues. *Inquiry*. 2018;55:46958018757848.
- 510 45. Bousquet J, Anotegui IJ, Anto JM, Arnavielhe S, Bachert C, Basagana X, et al. Mobile  
511 technology in allergic rhinitis: evolution in management or revolution in health and care? *J*  
512 *Allergy Clin Immunol Pract*. 2019.
- 513 46. Bousquet J, Anto JM, Bachert C, Baiardini I, Bosnic-Anticevich S, Walter Canonica G, et al.  
514 Allergic rhinitis. *Nat Rev Dis Primers*. 2020;6(1):95.
- 515 47. Karatzas K, Katsifarakis N, Riga M, Werchan B, Werchan M, Berger U, et al. New European  
516 Academy of Allergy and Clinical Immunology definition on pollen season mirrors symptom load  
517 for grass and birch pollen-induced allergic rhinitis. *Allergy*. 2018;73(9):1851-9.
- 518 48. Pfaar O, Bastl K, Berger U, Buters J, Calderon MA, Clot B, et al. Defining pollen exposure times  
519 for clinical trials of allergen immunotherapy for pollen-induced rhinoconjunctivitis - an EAACI  
520 position paper. *Allergy*. 2017;72(5):713-22.
- 521 49. Karatzas K, Papamanolis L, Katsifarakis N, Riga M, Werchan B, Werchan M, et al. Google  
522 Trends reflect allergic rhinitis symptoms related to birch and grass pollen seasons. *Aerobiologia*.  
523 2018;34(4):437-44.
- 524 50. Karatzas K, Riga M, Berger U, Werchan M, Pfaar O, Bergmann KC. Computational validation of  
525 the recently proposed pollen season definition criteria. *Allergy*. 2018;73(1):5-7.
- 526 51. Buters J, Schmidt-Weber C, Oteros J. Next-generation pollen monitoring and dissemination.  
527 *Allergy*. 2018;73(10):1944-5.
- 528 52. Bousquet J, Anto JM, Annesi-Maesano I, Dedeu T, Dupas E, Pepin JL, et al. POLLAR: Impact of  
529 air POLLution on Asthma and Rhinitis; a European Institute of Innovation and Technology  
530 Health (EIT Health) project. *Clin Transl Allergy*. 2018;8:36.
- 531 53. Recital 26-EU GDPR. EU general data protection regulation 2016/679. [http://www.privacy-](http://www.privacy-regulation.eu/en/recital-26-GDPR.htm)  
532 [regulation.eu/en/recital-26-GDPR.htm](http://www.privacy-regulation.eu/en/recital-26-GDPR.htm).
- 533 54. Article 4 EU GDPR. « Definitions ». EU general data protection regulation 2016/679 (GDPR).  
534 <http://www.privacy-regulation.eu/en/article-4-definitions-GDPR.htm>.
- 535 55. Article 28 EU General Data Protection Regulation (EU-GDPR). <https://www.eugdpr.org>. 2018.
- 536 56. Pfaar O, Agache I, Bergmann KC, Bindslev-Jensen C, Bousquet J, Creticos PS, et al. Placebo  
537 effects in allergen immunotherapy - an EAACI Task Force Position Paper. *Allergy*. 2020.
- 538 57. Bedard A, Basagana X, Anto JM, Garcia-Aymerich J, Devillier P, Arnavielhe S, et al. Mobile  
539 technology offers novel insights into the control and treatment of allergic rhinitis: The MASK  
540 study. *J Allergy Clin Immunol*. 2019;144(1):135-43 e6.
- 541 58. Bousquet J, Schunemann HJ, Togias A, Bachert C, Erhola M, Hellings PW, et al. Next-  
542 generation Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for allergic rhinitis  
543 based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and  
544 real-world evidence. *J Allergy Clin Immunol*. 2019.

- 545 59. Roche N, Anzueto A, Bosnic Anticevich S, Kaplan A, Miravittles M, Ryan D, et al. The  
546 importance of real-life research in respiratory medicine: manifesto of the Respiratory  
547 Effectiveness Group: Endorsed by the International Primary Care Respiratory Group and the  
548 World Allergy Organization. *Eur Respir J*. 2019;54(3).
- 549 60. Shamji MH, Akdis CA, Barber D, Canonica W, Chivato T, Del Giacco S, et al. EAACI Research  
550 and Outreach Committee: Improving standards and facilitating global collaboration through a  
551 Research Excellence Network. *Allergy*. 2020;75(8):1899-901.
- 552 61. Bousquet J, Anto JM, Bachert C, Haahtela T, Zuberbier T, Czarlewski W, et al. ARIA digital  
553 anamorphosis: Digital transformation of health and care in airway diseases from research to  
554 practice. *Allergy*. 2020.
- 555 62. Bousquet J, Devillier P, Anto JM, Bewick M, Haahtela T, Arnavielhe S, et al. Daily allergic  
556 multimorbidity in rhinitis using mobile technology: A novel concept of the MASK study.  
557 *Allergy*. 2018;73(8):1622-31.
- 558 63. Canonica GW, Ansotegui IJ, Pawankar R, Schmid-Grendelmeier P, van Hage M, Baena-Cagnani  
559 CE, et al. A WAO - ARIA - GA(2)LEN consensus document on molecular-based allergy  
560 diagnostics. *World Allergy Organ J*. 2013;6(1):17.
- 561 64. Halken S, Larenas-Linnemann D, Roberts G, Calderon MA, Angier E, Pfaar O, et al. EAACI  
562 guidelines on allergen immunotherapy: Prevention of allergy. *Pediatr Allergy Immunol*.  
563 2017;28(8):728-45.  
564