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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.

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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 ¹, 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[®] (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) (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)**

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- 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.

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

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

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

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| 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. |

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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

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