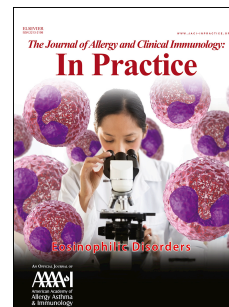


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Mobile technology in allergic rhinitis: evolution in management or revolution in health and care?

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Mobile technology in allergic rhinitis: evolution in management or revolution in health and care?

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112 Conflict of interest

113

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162 **Abstract**

163 Smart devices and internet-based applications are largely used in allergic rhinitis and may help to
 164 address some unmet needs. However, these new tools need to first of all be tested for privacy rules,
 165 acceptability, usability and cost-effectiveness. Secondly, they should be evaluated in the frame of the
 166 digital transformation of health, their impact on healthcare delivery and health outcomes. This review
 167 (i) summarizes some existing mHealth apps for allergic rhinitis and reviews those in which testing has
 168 been published, (ii) discusses apps that include risk factors of allergic rhinitis, (iii) examines the impact
 169 of mHealth apps in phenotype discovery, (iv) provides real-world evidence for care pathways, and
 170 finally (v) discusses mHealth tools enabling the digital transformation of health and care, empowering
 171 citizens and building a healthier society.

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174 **Key words**

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176 Apps, digital transformation of health, MASK, mHealth, Mobile technology, rhinitis

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179 **Abbreviations**

180

181 AHA: Active and healthy ageing

182 AIRWAYS ICPs: Integrated care pathways for airway diseases

183 AR: Allergic rhinitis

184 ARIA: Allergic Rhinitis and Its Impact on Asthma

185 CARAT: Control of Allergic Rhinitis and Asthma Test

186 CDS: clinical decision support

187 CDSS: Clinical decision support system

188 DG CONNECT: Directorate General for Communications Networks, Content & Technology

189 DG Santé: Directorate General for Health and Food Safety

190 DG: Directorate General

191 EIP on AHA: European Innovation Partnership on AHA

192 EU: European Union

193 EQ-5D: Euroquol

194 FDA : US Food and Drug Administration

195 GARD: WHO Global Alliance against Chronic Respiratory Diseases

196 GDPR: General Data Protection Regulation

197 GIS: Geographic Information System

198 GP: Good Practice

199 GRADE: Grading of Recommendations Assessment, Development and Evaluation

200 GT: Google Trends

201 ICP: Integrated care pathway

202 ICT: Information and Communication Technology

203 JA-CHRODIS: Joint Action on Chronic Diseases and Promoting Healthy Ageing across the Life Cycle

204 MACVIA-LR: contre les MALadies Chroniques pour un Vieillissement Actif (Fighting chronic diseases for AHA)

205 MASK: Mobile Airways Sentinel Network

206 MeDALL: Mechanisms of the Development of ALLergy (FP7)

207 mHealth: mobile health

208 POLLAR: Impact of air POLLution on Asthma and Rhinitis

209 RCT: Randomized control trial

210 RWD: Real-world data

211 RWE: Real-world evidence

212 TRL: Technology Readiness level
213 VAS: Visual analogue scale
214 WHO: World Health Organization

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216 **Text:** 4839 words

217

218 **Abstract:** 125 words

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219 Introduction

220 Mobile technology has spread rapidly around the globe. Today, it is estimated that over 5 billion people
221 have mobile devices, over half of which are smartphones
222 ([https://www.pewglobal.org/2019/02/05/smartphone-ownership-is-growing-rapidly-around-the-world-but-](https://www.pewglobal.org/2019/02/05/smartphone-ownership-is-growing-rapidly-around-the-world-but-not-always-equally/)
223 [not-always-equally/](https://www.pewglobal.org/2019/02/05/smartphone-ownership-is-growing-rapidly-around-the-world-but-not-always-equally/)).

224 mHealth (mobile health) is the use of information and communication technology (ICT) for health services
225 and information transfer (1). mHealth, including apps running on consumer smart devices (i.e.,
226 smartphones and tablets), is becoming increasingly popular and has the potential to profoundly impact
227 healthcare (2, 3). The rapid advances in mobile technologies have given rise to new opportunities for the
228 digital transformation of health and the continued growth in coverage of mobile cellular networks. The
229 potential applications and benefits of mHealth are extensive and expanding (4). Implementing mHealth
230 innovations may also have disruptive consequences (5), so it is important to test applicability in each
231 individual situation (6). Appropriately identifying and representing stakeholders' interests and viewpoints in
232 evaluations of mHealth is a critical part of ensuring continued progress and innovation (7). Patient,
233 caregiver and clinician evaluations and recommendations play an important role in the development of
234 asthma / AR mHealth tools in supporting the provision of disease management (8).

235 Smart devices and internet-based applications are already used in allergic rhinitis (AR) and may help to
236 address some of the unmet needs (2). According to recent position papers from EAACI (9) and from the
237 American College of Allergy and Immunology (10), mHealth apps can support the provision of high-
238 quality care to allergic patients, in particular those with AR and/or asthma. This is satisfying for patients
239 and health care professionals, and has led to a reduction in health care utilization and costs. However, these
240 new tools need to first of all be tested for privacy rules, acceptability, usability and cost-effectiveness.
241 Secondly, they should be evaluated in the frame of the digital transformation of health, their impact on
242 healthcare delivery and health outcomes.

243 1- Strengths and weaknesses of mHealth

244 Smartphones have radically changed people's lives. However, despite the global advent of mHealth over
245 the past two decades, their use and benefits in disease management are unclear.

246 The benefits of mHealth include paperless information, the potential increase in medication adherence and
247 improved monitoring (Table 1). mHealth technology has great potential to increase healthcare quality,
248 expand access to services, reduce costs, and improve personal wellness and public health (11). However,
249 mHealth may be harmful. Technically, the development of an app is an easy task, which incurs very low
250 initial investments and does not require in-depth knowledge of the subject itself. The low entry barrier,

251 dramatically democratizing the app development environment, also results in a large number of ad-hoc
252 apps targetting various health concerns of the public. The majority of mHealth apps have neither been
253 tested on patients nor approved by regulatory organizations such as the US Food and Drug Administration
254 (FDA) or the European Medicines Agency (EMA). However, many patients rely on these apps in their
255 everyday lives.

256 A few weaknesses emerge from the use of mHealth apps that are used in observational studies to assess
257 real-world evidence for the evaluation of allergy phenotypes or treatments. As for all studies using
258 participatory data, potential biases include (i) the likelihood of sampling bias, (ii) the difficulty to assess
259 generalizability of the study, as app users are usually not representative of all patients with AR. In MASK,
260 it was found that most users report bothersome symptoms (Bedard, submitted) (iii) outcome
261 misclassification that cannot be assessed, (iv) very little information on patient characteristics, (v) lack of
262 physicians' support in the diagnosis of AR, (vi) potential measurement biases due to the so-called
263 "informatics illiteracy" of many patients (12), and (vii) poor adherence to e-Diary compilation, which
264 makes proving poor adherence to treatment impossible.

265 One of the major problems with apps is the low adherence to their use. Achieving sufficient mHealth app
266 engagement and user retention rates is a difficult task. In MASK-air (Mobile Airways Sentinel NetworK),
267 around half of the patients use the app only once (13).

268 The benefits of mHealth apps are presented in Table 1.

269 **2- Regulatory framework**

270 mHealth raises significant privacy and security challenges in terms of IT privacy, data sharing and consent
271 management, access control and authentication, confidentiality and anonymity, policies and compliance,
272 accuracy and data provenance, and security technology (11).

273 In May 2018, the EU General Data Protection Regulation (GDPR) brought major changes in data privacy
274 regulation in the EU. The aim of the GDPR is to protect all EU citizens from privacy and data breaches in
275 today's data-driven world. It harmonizes data privacy laws across Europe, protects and empowers all EU
276 citizens' data privacy and reshapes the way organizations across the region approach data privacy. Thus, all
277 mHealth apps used in the EU should follow the GDPR. The law applies to personal data (Art. 4 para. 1 no.
278 1, GDPR) (14). Anonymous or anonymized data should lack identifiability. Anonymization principally
279 enables the sharing of data in a way that preserves privacy with minimal data loss. Geolocation information
280 is not only personal data but also has to be considered as an identifier itself (15, 16). Thus, mHealth apps
281 should follow a geolocation de-anonymization that is rarely found in apps. The k-anonymity method is
282 acceptable and was found to fulfill the GDPR regulations in AR (17). The GDPR fixes general rules

283 applying to any kind of personal data processing as well as specific rules applying to the processing of
284 special categories of personal data such as health data (18). In May 2020, a new EU law will regulate
285 mobile technology (Medical Device Regulation, MDR) (19) making its use tightly regulated.

286 The US regulations were recently reviewed in detail (20). The FDA and the Federal Trade Commission
287 (FTC) both guide the development and regulation of mHealth devices. Since the recently enacted
288 amendment to the Twenty-First Century Cures Act - the Food, Drug and Cosmetic Act - certain software
289 functions are no longer considered to be medical devices (21). Thus, the FDA is now using enforcement
290 discretion for mHealth apps that do not present risks to patients and consumers.

291 **3- mHealth apps for allergic rhinitis**

292 **a. Apps informing on risk factors for allergic rhinitis**

293 Risk factors for exacerbations of AR and asthma include allergen exposure (22), climatic factors (23, 24)
294 and air pollutants (25). It is therefore of great importance to identify levels of risk factors that can induce
295 symptoms in allergic patients. Among these, pollen exposure is the most important for pollen allergic
296 patients. Therefore, forecasting symptoms of pollen-related AR for the individual patient should improve
297 disease control and plan pharmacological intervention and/or prevention of exposure. Besides pollen
298 diaries, mHealth apps allow an easy and fast documentation of pollen allergy counts (26-28). A study that
299 analyzed 9 mobile apps delivering pollen information and pollen forecasts found that the quality of pollen
300 forecasts needs to be improved. It recommended quality control for pollen forecasts to avoid potential harm
301 to patients (29). AR patients could consider the need to avoid the more polluted routes when walking,
302 biking, or exercising. In many cities, traffic air pollution concentrations decline rapidly at a few hundred
303 metres from roadways, and web-based applications can assist individuals in finding alternative routes
304 (30).

305 There are, however, drawbacks that need to be understood in order to provide better information: (i) The
306 pollen season does not necessarily correspond to an individual patient's symptoms (31) and sub-micronic
307 particles from pollens can induce severe symptoms such as thunderstorm-induced asthma (32); (ii) The
308 definition of the pollen season is still unclear (33) although some clarification efforts have been made for
309 clinical trials (34); (iii) There is a weak correlation between pollen counts and symptoms (35); (iv)
310 Pollutants and weather conditions can interact with pollens to induce symptoms; (v) Only predictive
311 models are to be used, not only for forecasting but also for near-real-time analysis (now-casting) since it
312 takes a few days to count pollens (36). However, these models may need more testing in order to be fully
313 accepted; (vi) Next-generation pollen monitoring is very promising but its cost prevents a large use (37);
314 (vii) The onset of individual symptoms (AR, asthma, conjunctivitis) may be associated with different levels
315 of allergen exposure in patients with different intensities of sensitization and target organ reactivity.

316 Google Trends are interesting for complementing pollen counts (38) but they cannot be readily used as a
317 predictor of the pollen season. However, Google Trends, when used retrospectively, are better correlated
318 with symptoms than pollen counts (35, 39, 40).

319 A large number of apps provide information to allergy sufferers regarding pollen counts and/or pollution
320 data (41). Some examples are given below and in Table 2.

321 BreezoMeter uses the CAMS pollen predictions and big data analysis to provide a continuous current
322 condition pollen index (<https://breezometer.com/products/pollen-api>). However, its validation is not yet available.

323 Air Matters broadcasts pollen and air quality data in most countries of the world (<https://air-matters.com>).

324 The Copernicus Atmosphere Monitoring Service (CAMS), implemented by the European Centre for
325 Medium-Range Weather Forecasts (ECMWF) on behalf of the European Union, provides forecasts for
326 birch, olive and grass pollen to allow allergy sufferers in the EU to take preventive measures days before
327 exposure. (<https://atmosphere.copernicus.eu/news-and-media/news/cams-helping-allergy-sufferers>). CAMS
328 supports a range of smartphone applications designed to limit exposure to such allergens. One of these is
329 MetéoPollen for France (<https://meteopollen.com>).

330 AccuPollen (<http://www.nynjpollen.com>) and My Pollen Forecast (<https://www.jrustonapps.com/apps/my-pollen-forecast>)
331 track pollen counts in the US using forecasts for pollen and climatic data.

332 The POLLEN app of the European Aeroallergen Network (EAN), maintained by the Medical University of
333 Vienna (<https://www.polleninfo.org>), evaluates the pollen situation in European countries using the pollen
334 counts of EAN and predictions of the SILAM pollen forecasting model (<http://silam.fmi.fi>).

335 **b. Apps including health data**

336 Many mHealth apps support patients with AR via self-monitoring through an electronic diary (e-Diary),
337 personalized feedback and/or patient education (42). They aim to improve patient education and self-
338 management on a daily basis but require an evidence-based evaluation given that the information provided
339 on the app stores is limited, in particular for the apps' validity (43-45). This can be done by evaluating the
340 effectiveness of the app with the patients' clinical outcomes (13, 28, 46). For example, children with
341 moderate-severe seasonal allergic rhinitis, treated with daily mometasone, improved their disease
342 knowledge thanks to daily informative messages sent by their e-Diary app (42). If patients are seeking an
343 approach involving the minimal interaction with health care professionals in AR management (47), it is
344 then crucial that the mHealth app is in line with evidence-based essential self-management principles. A
345 Mobile app Rating Scale (MARS) instrument (48) - available in Australia - has been used to assess the
346 mHealth apps for AR (Tan et al, in revision). A 'patient empowerment index through mobile technology'

347 was recently designed and used to evaluate AR in order to support patients choosing an mHealth app and
 348 physicians recommending it (42).

349 Most but not all mHealth apps which include clinical data are available in English and some are available
 350 in over 15 languages (Table 2). The majority of mHealth apps are freely available on iOS and Android.
 351 However, very few have provided clinical data supporting their validity. mHealth apps for AR include:

- 352 • Self-monitoring
- 353 • Patient's feedback
- 354 • Patient's education
- 355 • Patient's empowerment
- 356 • Pollen and/or air pollution data

357 At present (May 2019), some mHealth apps are in non-English languages such as ALK-Allergik
 358 (<https://maviedallergik.fr/nos-services>), Allergy Track, (<https://www.android-logiciels.fr/allergy-track/>),
 359 AllyScience (<https://allyscience.ch/>), e-symptoms (<https://www.aha.ch/centre-allergie-suisse>), i-pollen
 360 (<http://www.gammehumex.fr/lapplication-i-pollen/>), Plume Air Report (<https://air.plumelabs.com/fr/>) and Pollen
 361 App (<http://www.pollenstiftung.de/ak>). Others in English may be restricted to a limited geographic area such
 362 as Air Rater in Australia (<https://airrater.org>) or are not available from app stores.

363 Besides those with a commercial interest (e.g. Sensio Air <https://www.wlab.io> and Zyrtec AllergyCast
 364 <https://www.zyrtec.com/allergy-forecast-tools-apps>), there are few mHealth apps with health data on AR (e.g.
 365 AllergyMonitor[®], MASK-air[®], WebMD Allergy[®] <https://www.webmd.com/allergy-app> and the Austrian
 366 Pollen Information Service www.pollenwarndienst.at) (Table 2).

367 **c. Apps connected with sensors**

368 In asthma, many mHealth apps are connected with sensors for inhalers (20). Such devices do not yet exist
 369 in AR but there are attempts to connect pollution sensors to mHealth apps. Unfortunately, those existing for
 370 asthma appear to be in an exploratory phase and need validation. In addition to external sensors,
 371 smartphones and tablets have embedded sensors such as camera, microphone, atmospheric pressure sensor,
 372 accelerometer and GPS. These sensors can be used to provide contextual information for the collected
 373 clinical data. Moreover, using signal processing, data from on board sensors, already available in off-the-
 374 shelf devices and used by millions of patients, are being tested as ubiquitous technologies to provide
 375 verified information on cough (49), lung function (50), adherence to inhaled treatment (51), physical
 376 activity parameters and other human behaviours of clinical interest (52).

377 **d- Examples of apps**

- 378 • AllergyMonitor[®] (<http://www.tpsproduction.com/>)

379 AllergyMonitor[®] is an app that has been translated into 10 languages. Its target is to improve allergy
380 diagnosis by matching trajectories of symptom-medication scores and pollen counts (26, 28, 46, 53, 54).
381 Furthermore, it enhances shared decision-making by fostering the exchange of information between users
382 and their health care professionals. The latter can access and view their patients' recorded data in a back-
383 office, which allows the management of patients' clinical data and gives a structured overview on the
384 individual disease management. The data recorded by the user then complete the set of information being
385 integrated in the back-office in real-time. As users also register the intake of their prescribed medication,
386 this feature allows the monitoring of compliance which has been shown to effectively increase the
387 adherence to treatment with nasal corticosteroids and sublingual allergen-specific immunotherapy. To this
388 end, the app includes customized lists of over-the-counter and prescribed medications for many countries,
389 patient-doctor communication via SMS and e-mail, patient alerts for a better knowledge of the disease as
390 well as reminders for a better adherence to treatment. The potential of data sets generated through
391 AllergyMonitor[®] has also been investigated for the short-term prediction of patients' symptoms with
392 several symptom and medication scores for rhinitis and asthma.

393 • **MASK** (<http://www.mask-air.com>)

394 MASK (Mobile Airways Sentinel network), the Phase 3 ARIA initiative, was instigated to reduce the
395 global burden of AR and asthma multimorbidity, giving the patient and the health care professional simple
396 tools to better prevent and manage respiratory allergic diseases. The MASK app (MASK-air[®], formerly *the*
397 *Allergy Diary*, freely available for Android and iOS) (55) is the most extensively published mHealth app
398 for AR. It is an ICT system centred around the patient (13, 55-57) and is operational in 23 countries and 17
399 languages. It uses a treatment scroll list which includes all medications customized for each country as well
400 as visual analogue scales (VASs) to assess rhinitis control and work productivity (58, 59). MASK-air[®] is
401 being combined with data on allergen and pollution exposure (POLLAR) (25). MASK-air[®] results are
402 given in Table 3.

403 MASK is scaled up using the EU European Innovation Partnership on Active and Healthy Ageing (EIP on
404 AHA) strategy (60). MASK is supported by several EU grants and is a GARD (Global Alliance against
405 Chronic Respiratory Diseases, WHO (61)) research demonstration project. It is a Good Practice of DG
406 Santé (62).

407

408 • **European Aeroallergen Network Pollen Information Service**

409 The EAN Pollen Information Service (www.polleninfo.org), developed and maintained at the Medical
410 University of Vienna, provides a pollen assessment and a three-day forecast in co-operation with local and
411 international institutions. It is available for European countries in over 10 languages. The app includes

412 symptoms and treatments. The components and functionality of the app vary between the countries
413 depending on the requests of the national pollen observing groups.

414 The service also takes the user's pollen diary entries into account and calculates personal burden level.
415 Allergic symptoms can be documented and compared with the pollen count in the pollen diary. Personal
416 load, Pollen News, Pollen-Countdown notifications and a reminder for a doctor's visit are all available. The
417 pollen diary was restructured in 2018 and provides information on preventing impaired performance in
418 everyday life, the time of the highest burden and the time(s) of being outdoors. The encyclopedia of
419 allergenic plants is also available to answer questions on allergy.

420 • **e-allergy**

421 The under-recognition of AR is common due to a low level of public awareness as well as limitations in
422 access to allergologists (63). AR sufferers often use OTC drugs and self-medicate. mHealth tools
423 supporting the pre-medical early diagnosis of allergic diseases are important. They use algorithms able to
424 classify respondents into certain risk groups of AR and asthma. An algorithm was created - with the use of
425 advanced statistical methods (neural networks) - on ECAP (Epidemiology of the Allergic Diseases in
426 Poland) data containing both questionnaire answers and medical diagnosis (64). This tool is constantly
427 being updated. The latest results show a sensitivity for AR in children and adolescents of 0.852 and a
428 specificity of 0.840 (65).

429 **4- Clinical decision support systems (CDSSs)**

430 A CDSS is a health information technology (IT) system designed to assist clinicians and other health care
431 professionals in clinical decision-making. In medicine, CDSSs have become a major topic in artificial
432 intelligence. According to the National Academy of Medicine (Washington DC) (66), "facilitative clinical
433 decision support (CDS) is a practical necessity for every clinician in our rapidly-evolving health and
434 healthcare landscape." A CDSS can reduce the burden that exponentially-expanding clinical knowledge
435 and care complexity places on clinicians, other health care professionals or patients. CDSs provide
436 clinicians and other health care professionals with knowledge and person-specific information -
437 intelligently filtered or presented at appropriate times - to enhance health and health care (67). CDSs can
438 enhance decision-making through the use of the following tools: (i) computerized alerts and reminders to
439 health care providers and patients, (ii) clinical guidelines, (iii) focused patient data reports and (iv)
440 diagnostic support (68). Many apps used in AR provide patients with some help for AR control. However,
441 for this, they should be labelled as CE2A in the EU. Apps that do not provide help can be registered as
442 CE1. An electronic CDSS (eCDSS) based on MASK now exists in AR and is in the process of validation
443 (69). It is not clear whether other tools have been validated as they have not been published. CDSSs may

444 also be very useful in stratification strategies and in reporting outcomes in clinical trials such as in Allergen
445 Immunotherapy (<https://www.ncbi.nlm.nih.gov/pubmed/30955224>).

446 **5- Potential of mHealth apps for allergy phenotype discovery**

447 Conventionally, phenotypic studies have relied on traditional observational designs. Apps provide a new
448 source of information on daily symptoms and the opportunity to discover new phenotypes. Few studies
449 have been published concerning allergy phenotypes assessed with an app.

450 A prospective analysis has compared six disease severity scores for AR against pollen counts (53). Many
451 different and incomparable symptom (medication) scores are used to assess AR control. Disease severity
452 scores for seasonal AR evaluated by an internet-based platform provide similar results at population level
453 but are heterogeneous in individual patients.

454 Multimorbidity in allergic airway diseases is well known (70), but no data has ever existed regarding how
455 multimorbidity impacts the daily dynamics of specific symptoms, including severity and work. MASK-
456 air[®] has enabled this investigation in a novel approach of the intra-individual variability of allergic
457 multimorbidity from day to day (71). AR and rhinoconjunctivitis did not appear to be the same disease.
458 Moreover, MASK-air[®] identified a previously unrecognized extreme pattern of uncontrolled
459 multimorbidity (uncontrolled rhinitis, conjunctivitis and asthma on the same day) (71). However, mHealth
460 apps are only tools generating hypotheses and need to be confirmed in classical epidemiologic studies.
461 Differences between AR alone or associated with conjunctivitis were already known (72) but new studies
462 carried out following MASK-air[®] data showed that (i) ocular symptoms are more common in
463 polysensitized patients whether or not they have asthma (73), (ii) ocular symptoms are associated with the
464 severity of nasal symptoms (74), (iii) ocular symptoms are important to consider in severe asthma (74) and
465 (iv) the severity of allergic diseases increases with the number of allergic multimorbidities (75). This is the
466 first time that novel allergic phenotypes have been discovered using an mHealth app and then confirmed
467 by classical epidemiologic studies.

468 **5- Real world evidence using mHealth in next-generation care** 469 **pathways**

470 mHealth apps for a better AR management are growing in number. However, their usefulness for doctors
471 and patients is still being debated. Most studies have also highlighted certain shortcomings and limitations,
472 mainly concerning security and cost-effectiveness (76).

473

474

475 **a. Adherence to treatment**

476 mHealth may help to better understand adherence to treatment and its determinants as well as how to
477 improve it. In medicine, many mHealth apps are available to support people in taking their medications and
478 thus to improve medication adherence (77, 78). However, a meta-analysis found that the majority did not
479 have many of the desirable features and/or were of low quality (77). A systematic review including 16
480 RCTs found that mobile phone text messaging approximately doubles the odds of medication adherence,
481 resulting in a net increase in adherence of 17.8% (78). A Cochrane systemic review of 7 trials in
482 cardiovascular disease found that, while the results are promising, there is insufficient evidence to draw
483 conclusions on the effectiveness of text message-based interventions for adherence to medications. The
484 authors suggested that sufficiently powered, high-quality randomised trials are needed, particularly in low-
485 and middle-income countries (79).

486 Adherence in randomized control trials (RCTs) is high but does not reflect the real-life situation (29,30)
487 and alternative measurements of adherence in a real-life setting are needed. The best studies would be
488 using electronic devices that count and record the drugs taken. However, these devices are still exploratory
489 and expensive and, as such, they are not currently a viable solution for large studies in AR patients (80) or
490 individual patients. A potential palliative solution can be to use the smartphone's camera to register the
491 drug uptake. The photo of the drug is then processed by image recognition algorithms to provide verified
492 data on adherence to AR treatment during the patient's daily life. However, there are technical challenges
493 and limitations to some types of vials and packaging. The automatic detection of progression of use of the
494 liquid in the vial using computer vision may be of special relevance for sublingual allergen immunotherapy
495 for which adherence can be a major issue (81). Other approaches already being tested for asthma but not
496 for AR are mobile direct observation of therapy (82) and multicomponent interventions based on mobile
497 technologies (83). Although there are already some mHealth apps for AR, there are few studies evaluating
498 their benefits and impact (76). One study suggested that a short message service (SMS) helps to improve
499 AR treatment (84). Internet-based telemonitoring using the AllergyMonitor[®] improved adherence to intra-
500 nasal corticosteroid treatment and disease knowledge among children and adolescents with seasonal AR as
501 well as adherence to sub-lingual immunotherapy (46). In MASK-air[®], a major lack of adherence to
502 treatment was observed for all medications (85). Auto-medication was very common (12) suggesting that
503 patients, like allergists when they are allergic (86), do not follow physicians' prescriptions or guidelines.

504 **b. mHealth in observational studies allowing novel assessment of patients'**
505 **behaviour**

506 The treatment of AR is complex as many drugs are available in oral and/or topical formulations, and
507 allergen immunotherapy and avoidance increase the complexity of the management. Many AR guidelines
508 are evidence-based and have led to a better understanding and management of AR (87-89). However,
509 guidelines are mostly based on RCTs, typically undertaken on highly-selected populations and often with
510 limited/unclear generalizability to routine care contexts. Large observational implementation studies are
511 needed to triangulate RCTs as they reflect “real world” every-day use and practice more closely than RCTs
512 in terms of the heterogeneous patient populations included and the variety of medical interventions
513 assessed. In RCTs, each subject is randomly assigned to a treatment or control group, whereas
514 observational studies examine the possible effect of a treatment on subjects where the investigator has no
515 control over the experiment and cannot randomize subject allocation (94). However, observational studies
516 provide clinically relevant information in addition to RCTs. Real-world evidence (RWE) using RCTs and
517 real-world data (RWD) is becoming increasingly important in supporting regulatory decisions using
518 mobile technology (95).

519 A pilot study in over 2,900 users allowed differentiation between treatments (12) showing that the
520 assessment of series of consecutive days was useful in understanding treatment patterns. The study showed
521 that patients did not necessarily use treatment on a daily basis and in a regular way; rather, they appeared to
522 increase treatment use when their symptom control worsened. Differences in efficacy between medications
523 were observed. This pilot study was confirmed in almost 9,000 users (96). The studies confirm the
524 usefulness of mHealth in accessing and assessing everyday use and practice in AR (12). It is hoped that
525 mHealth apps will increase patient empowerment and improve adherence.

526 **c. Next generation guidelines**

527 The selection of pharmacotherapy for patients with allergic rhinitis aims to control the disease and depends
528 on many factors. GRADE (Grading of Recommendations Assessment, Development and Evaluation)
529 guidelines have considerably improved AR management. However, there is an increasing trend to use
530 RWD to inform clinical practice, especially as RCTs are often limited with regards to the applicability of
531 results. The MACVIA algorithm proposed an AR treatment by a consensus group (97). This simple
532 algorithm can be used to step-up or step-down AR treatment. Next-generation guidelines for the
533 pharmacologic treatment of allergic rhinitis (98) were developed using existing GRADE-based guidelines
534 (87-89), RWD provided by mHealth apps (12, 85, 96) and additive studies (allergen chamber studies (99))
535 to refine the MACVIA algorithm (97).

536 **6- mHealth tools enabling the digital transformation of health and** 537 **care, empowering citizens and building a healthier society**

538 The recent report on the State of Health in the EU (State of Health in the EU "Companion Report 2017",
539 <https://ec.europa.eu/health/state>) concluded that rethinking our health and care systems can ensure its
540 sustainability aiming to continue health promotion, disease prevention and to provide patient-centred care
541 that meets citizens' needs ([https://ec.europa.eu/transparency/regdoc/rep/1/2018/FR/COM-2018-233-F1-FR-](https://ec.europa.eu/transparency/regdoc/rep/1/2018/FR/COM-2018-233-F1-FR-MAIN-PART-1.PDF)
542 [MAIN-PART-1.PDF](https://ec.europa.eu/transparency/regdoc/rep/1/2018/FR/COM-2018-233-F1-FR-MAIN-PART-1.PDF)).

543 Digital solutions for health and care can increase the well-being of millions of citizens and radically change
544 health and care services. In its mid-term review on the implementation of the digital single market strategy
545 (<https://ec.europa.eu/transparency/regdoc/rep/1/2017/EN/COM-2017-228-F1-EN-MAIN-PART-1.PDF>),
546 the EU Commission took further action in three areas:

- 547 • Citizens' secure access to and sharing of health data across borders.
- 548 • Better data to advance research, disease prevention and personalized health and care.
- 549 • Digital tools for citizen empowerment and person-centred care to allow citizens to assume responsibility
550 for their health, improve their well-being and quality of care and contribute to sustainable health
551 systems. By using digital solutions, such as wearables and mHealth apps, citizens can actively engage in
552 the health promotion and self-management of chronic diseases. Digital tools can potentially disseminate
553 scientific knowledge in an easily accessible form, so as to help people stay in good health – thus
554 preventing them from turning into patients. Building on scientific information on risk factors, digital
555 solutions can be used across all sectors, including education, transport, and urban policies to promote
556 information and awareness campaigns on healthy lifestyles. Digital tools also enable citizens to provide
557 feedback and data about their health to their doctors. This can improve the quality of health services and
558 ultimately people's health and well-being.

559 Digital tools can also empower patients in the context of the UN sustainable development goals and in
560 particular regarding those related to sustainability and natural resources (100). Future apps in AR could
561 consider providing information to promote behavioural changes that could reduce the planetary impacts of
562 human activity.

563 In the context of implementing communication on the digital transformation of health and care, DG
564 SANTE, in collaboration with the newly-established EU Commission Expert Group "Steering Group on
565 Health Promotion, Disease Prevention and Management of Non-Communicable Diseases"
566 (https://ec.europa.eu/health/non_communicable_diseases/steeringgroup_promotionprevention_en),
567 supported the scaling-up and wider implementation of good practices in the field of digitally-enabled,
568 integrated, person-centred care. MASK was one of the nine Good Practices selected along with chronic
569 disease and Parkinson's disease (62).

570 8. Global implementation

571 When mobile technology was initiated, it was thought that it would be used mainly in developed countries.
572 However, smartphone ownership is growing rapidly around the world. According to ITU (International
573 Telecommunication Union, Geneva), in 2015, there were more than 7 billion mobile telephone
574 subscriptions across the world, over 70% of which were in low- or middle-income countries (101).
575 However, in these countries, smartphone use is still much more among the young and educated
576 ([https://www.pewglobal.org/2019/02/05/smartphone-ownership-is-growing-rapidly-around-the-world-but-](https://www.pewglobal.org/2019/02/05/smartphone-ownership-is-growing-rapidly-around-the-world-but-not-always-equally/)
577 [not-always-equally/](https://www.pewglobal.org/2019/02/05/smartphone-ownership-is-growing-rapidly-around-the-world-but-not-always-equally/)).

578 WHO recognizes the significant role that digital technologies can play in strengthening the health systems
579 in countries to achieve universal health coverage, the health-related Sustainable Development Goals and
580 other health objectives. In 2018, 121 countries had national eHealth strategies, representing the beginning
581 of a shift from an unsustainable project-based approach towards a systematic, integrated approach designed
582 for cost-effective investment and alignment of partners (102). The joint WHO-ITU initiative “Be He@lthy,
583 Be Mobile” for the prevention and management of noncommunicable diseases, their comorbidities and
584 their risk factors, including improving disease diagnosis and tracking, is of great importance. MASK is one
585 of the examples of the “Be He@lthy, Be Mobile” handbook on how to implement mBreatheFreely for
586 asthma and COPD (103).

587 Conclusion

588 mHealth has the potential to profoundly impact healthcare (3). mHealth apps now represent an important
589 evolution of health and care for AR since RWE has identified patients’ behaviours and practices and this
590 will have a profound impact on current guidelines and care pathways. Rhinitis is not a severe disease but it
591 does have a major impact on social life, school and work productivity (104). Asthma-rhinitis
592 multimorbidity plays a key role in understanding asthma and can be used as a model of multimorbidity.
593 Moreover, asthma and rhinitis have a life course approach whereas most chronic diseases start early in life
594 but are only clinically evident in adulthood. The revolution is underway for AR and asthma, and the lessons
595 learnt are transposable to other chronic diseases and will design innovative health strategies and services as
596 well as change management (105).

597

598

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Journal Pre-proof

Table 1: Global applicability of mHealth Apps in allergic rhinitis (adapted from (13))

Applicability	mHealth Apps
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, for the current or the next pollen season. • Assess and increase adherence to treatment. • Help in shared decision making. • Prescribe allergen immunotherapy (AIT) more rapidly when the patient is not controlled despite optimal pharmacologic treatment. • Determine the efficacy of any treatment including AIT . • Apps are an essential tool for providing personalized medicine in AR and asthma.
Change management	<ul style="list-style-type: none"> • 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
Patient empowerment	<ul style="list-style-type: none"> • Better understanding of the symptoms • Sentinel network linking aerobiology data and control • Improved adherence • Self-management • Alert systems • Messages sent by the app.
Clinical trials	<ul style="list-style-type: none"> • To assess environmental control measures • To assess pharmacotherapy • For RCTs, it is essential to have clarity on definitions, and relevant tools. Apps allow <ul style="list-style-type: none"> • To better stratify the patients, in particular for AIT • To assess the efficacy of treatments during the trial • To assess the efficacy when the treatment is stopped • Feasibility of real-life studies <ul style="list-style-type: none"> • 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 (such as NICE) for reimbursement. • Better understanding of direct and indirect costs • Controlled trials designed with a uniform approach will help to synchronize the data from real-life world regarding clinical effects and safety/tolerability of new drugs (post-marketing pharmacovigilance for some apps)
Research on mechanisms and genetics	<ul style="list-style-type: none"> • A uniform definition and a collaborative approach to epidemiological, genetic and mechanistic research are important and will be enhanced by the stratification of patients using apps. • Different levels of phenotype characterization (granularity) can be applied to assess phenotypic characterization in old age subjects.
Epidemiology	<ul style="list-style-type: none"> • In epidemiologic population studies, standardized definitions and tools are fundamental. • Apps may allow novel approaches combining classical cross-sectional and longitudinal studies with real life studies in large populations.

Employers

- AR and asthma represent a major burden for the employers, and the estimated annual costs in the EU range from 30 to 60 B€. Better control of the disease was 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.

Journal Pre-proof

Table 2: Examples of mHealth apps for allergic rhinitis

		Pollen	Other risk factors	Health data					
Multicountry									
	Air Matters	X	X		https://air-matters.com				
	AllergyMonitor	X		X					
	Austria Pollen Information Service	X		X	www.pollenwarndienst.at				
	Breezometer	X	X		https://breezometer.com/products/pollen-api				
	The Weather Channel	X			https://play.google.com/store/apps/details?id=com.weather.Weather				
	POLLEN & PHD	X		X	https://www.polleninfo.org , two separate but interlinked apps				
	MASK-air			X	https://www.mask-air.com				
	Pollen alert Europe	X			https://play.google.com/store/apps/details?id=com.bluesula.allergyalarmeurop&hl=en	MASK-air		X	https://www.mask-air.com
Argentina	Alerta Polen Argentina	X			https://play.google.com/store/apps/details?id=com.mobillers.alertapolen&hl=es				
Australia	Air Rater				https://airrater.org				
Denmark	Dagens Pollental	X			https://www.astma-allergi.dk/dagenspollental				
France	ALK-Allergik				https://maviedallergik.fr/nos-services				
	Allergy Track				https://www.android-logiciels.fr/allergy-track/				
	i-pollen				http://www.gammehumex.fr/lapplication-i-pollen/				
	Plume Air Report				https://air.plumelabs.com/fr/				
Germany	Pollen App	X		X	http://www.pollenstiftung.de/ak				
Italy	Pollen App	X	X		https://itunes.apple.com/it/app/polliniitalia/id621302844?mt=8				
		X	X		https://www.ilpolline.it/i-calendari-pollinici				
	Allergy Control	X	X	X	https://itunes.apple.com/it/app/allergy-control/id973452501?mt=8				
	Allergy Monitor	X		X	https://play.google.com/store/apps/details?id=com.tpsproduction.allergymonitor&hl=it				
	MeteoAllergie	X			https://play.google.com/store/apps/details?id=com.dlsolutions.meteoallergie&hl=it				
	Bollettino meteo Pollini e allergie in Italia	X			https://www.3bmeteo.com/meteo/italia/pollini				

	RAPP (Rhinitis and Asthma Patient Perspective)			X	https://play.google.com/store/apps/details?id=com.wellnessandwireless.rapp
NL		X			https://pollennieuws.nl/
		X			https://hooikoortsradar.nl/
Poland	e-allergy			X	
Portugal	INSPIRERSMUNDI			X	https://www.facebook.com/Projeto-Inspirers-218849795347948
Spain	INSPIRERSMUNDI			X	https://www.facebook.com/Projeto-Inspirers-218849795347948
	R-Alergo	X			http://alergialafe.org/noticias/172-r-alergo
	Polen Control	X			https://www.seaic.org/inicio/polen-control
	Niveles de Polen	X			https://play.google.com/store/apps/details?id=es.diox.android.alergia&hl=es
	Intolerapp	X			https://socialmediatica.com/intolerapp-la-aplicacion-ideal-para-alergicos-e-intolerantes-alimentarios/
	ALK Polen	X			http://www.ticsalut.cat/observatori/es_apps/265/al-k-polen
	Planttes	X			http://www.planttes.com/
Switzerland	AllyScience				https://allyscience.ch/
UK	My Pollen forecast UK	X			https://itunes.apple.com/gb/app/my-pollen-forecast-uk/id1244428929?mt=8
	Piri	X			http://www.piriallergy.com/pollen-count.html
USA	AcuPollen				http://www.nynjpollen.com
	My Pollen Forecast	X		X	https://www.jrustonapps.com/apps/my-pollen-forecast
	Plume Air Report	X		X	https://plumelabs.com/en/air/
	Poncho: wake up weather	X			https://www.crunchbase.com/apptopia_app/39a4271c-7286-4523-bed3-7cecdf55e0bf
	WeathterBug				https://www.weatherbug.com

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Table 3: The global MASK Good Practice and IT solution (modified from (62))

App (MASK-air) deployed in 23 countries: TRL9 (Technology Readiness level), Electronic clinical decision support system (ARIA e-CDSS): TRL 7, e-physician questionnaire deployed in 16 countries: TRL9.

- App: 29,000 users, 23 countries, 17 languages
- Tested with patients
- GDPR including geolocation (17)
- Good Practice of the EIP on AHA, follows CHRODIS (106)
- Good Practice on digitally-enabled, integrated, patient-centred care endorsed by DG Santé (62)
- Based on 11 EU grants (MeDALL (107), GA²LEN (108)) including - in 2018 - POLLAR (25), VIGOUR, DigitalHealthEurope, Euriphi (Digital transformation of health) and -in 2019- Gatekeeper
- From a validated “research” tool (2004-2018) to large scale deployment (2019-)
 - Validation with COSMIN guidelines (109).
 - Baseline characteristics (110)
 - Work productivity (111, 112)
 - EQ-5D and WPAI-AS (113)
 - Novel phenotypes of allergic diseases (71)
 - Adherence to treatment (12, 85)
 - Novel approaches to inform the efficacy of treatment (12, 96)
- Patient’s organizations and scientific societies involved
- GARD (WHO alliance)
- Presented during WHO and EU ministerial meetings (114, 115)
- Next-generation care pathways meeting (Dec 3, 2018) with the EIP on AHA, POLLAR (EIT Health) and GARD
- 51 MASK papers in 12 languages (116-119)
- Dissemination according to the EIP on AHA (60)

Transfer of innovation (TWINNING (120))

- Interoperable platform with MASK
- 25 Reference Sites of the European Innovation Partnership on Active and Healthy Ageing plus Argentina, Australia, Brazil, Canada, Mexico (116-119)
- 900 patients enrolled
- GDPR solutions solved

ARIA e-CDSS

- Interoperable platform with MASK
- Based on an expert meeting (97), and validation by Delphi questionnaire (69) and real-world evidence using MASK-air (12, 96)
- Electronic version available (69)