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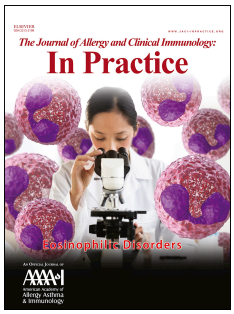

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Abstract

The traditional healthcare model is focused on diseases (medicine and natural science) and does not acknowledge patients' resources and abilities to be experts in their own life based on their lived experiences. Improving healthcare safety, quality and coordination, as well as quality of life, are important aims in the care of patients with chronic conditions. Person-centred care needs to ensure that people's values and preferences guide clinical decisions. This paper reviews current knowledge to develop (i) digital care pathways for rhinitis and asthma multimorbidity and (ii) digitally-enabled person-centred care (1). It combines all relevant research evidence, including the so-called real-world evidence, with the ultimate goal to develop digitally-enabled, patient-centred care. The paper includes (i) Allergic Rhinitis and its Impact on Asthma (ARIA), a two-decade journey, (ii) Grading of Recommendations, Assessment, Development and Evaluation (GRADE), the evidence-based model of guidelines in airway diseases, (iii) mHealth impact on airway diseases, (iv) from guidelines to digital care pathways, (v) embedding Planetary Health, (vi) novel classification of rhinitis and asthma, (vi) embedding real-life data with population-based studies, (vii) the ARIA-EAACI strategy for the management of airway diseases using digital biomarkers, (viii) Artificial Intelligence, (ix) the development of digitally-enabled ARIA Person-Centred Care and (x) the political agenda. The ultimate goal is to propose ARIA 2024 guidelines centred around the patient in order to make them more applicable and sustainable.

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Key words: ARIA, artificial intelligence, asthma, evidence-based medicine, person-centred care, rhinitis, mHealth

Abbreviations

ACQ: Asthma Control Questionnaire
ACT: Asthma Control Test
AD: Atopic dermatitis
AHA: Active and Healthy Ageing
AIRWAYS-ICPs: Integrated Care Pathways for Airway Diseases
AIT: Allergen immunotherapy
AR: Allergic rhinitis
ARIA: Allergic Rhinitis and its Impact on Asthma
CARAT: Control of Allergic Rhinitis and Asthma Test
CSMS: Combined symptom-medication score
DCP: Digital care pathway
e-DASTHMA: Electronic daily control-medication score in asthma
EACCI: European Academy of Allergy and Clinical Immunology
EIP: European Innovation Partnership
GARD: Global Alliance against chronic Respiratory Diseases
GRADE: Grading of Recommendations, Assessment, Development and Evaluation

ICP: Integrated care pathway
ICS: Inhaled Corticosteroids
INCS: Intranasal corticosteroids
LABA: Long-Acting Beta Agonists
MACVIA: Contre les Maladies Chroniques pour un Vieillissement Actif
MASK: Mobile Airways Sentinel networK
MeDALL: Mechanisms of the Development of Allergy
MPAzeFlu: Intra-nasal azelastine and fluticasone
OAH: Oral H_1-antihistamines
OECD: Organisation for Economic Co-operation and Development
OTC: Over-the-counter
PICO: Population, Interventions, Comparators and Outcomes
RCT: Randomised controlled trials
RNA: Ribonucleic acid
RT-PCR: Real-time-polymerase chain reaction
RWE: Real-world evidence
SABA: Short-Acting Beta Agonists
SCUAD: Severe Chronic Upper Airway Disease
SDM: Shared Decision Making
UHC: Universal Health Coverage
VAS: Visual Analogue Scale
WHO: World Health Organization

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Introduction

Allergic rhinitis (AR), caused by immunoglobulin E (IgE)-mediated reactions to inhaled allergens, is one of the most common chronic conditions globally. (1) AR often occurs concomitantly with asthma and conjunctivitis. AR impairs quality of life, affects social life, school and work, and is associated with substantial economic costs. (1, 2)

The Allergic Rhinitis and its Impact on Asthma (ARIA) initiative classified AR into intermittent or persistent and mild or moderate/severe, as it proposed guidelines for AR and asthma multimorbidity. (3) Over the past 20 years, ARIA has evolved, with strong policy maker commitments, from the first multimorbidity guideline in respiratory diseases (3) to GRADE (Grading of Recommendations, Assessment, Development and Evaluation) (4, 5) and next-generation guidelines enhancing the use of patient-centred data (person-centred care, real-world data) and chamber studies. (6)

Applying the GRADE methodology to appraise available evidence has considerably improved the understanding of AR treatment and guideline development. (4, 5, 7, 8) However, there is an increasing use as well as confusion regarding the role of the so-called real-world evidence (RWE) to inform the clinical practice on concerns about the applicability of results of randomised controlled trials (RCTs) with restricted inclusion criteria. (9)

Integrated Care Pathways for Airway Diseases (AIRWAYS-ICPs) (10) launched a collaboration to develop multisectoral integrated care pathways (ICPs) for chronic respiratory diseases with a strategic relevance to the European Union Health Strategy and the Digital Single Market. Initiated in 2013 under the frame of the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA, Directorate General [DG] Santé & DG Connect), (10, 11) it was a GARD (Global Alliance against chronic Respiratory Diseases, World Health Organization, WHO) Research Demonstration Project. (12, 13) MASK (Mobile Airways Sentinel networK) was developed as the information technology (IT) solution (14) to deploy AIRWAYS-ICPs. (15) Digital Care Pathways (DCPs) employ digital technologies in ICPs.

The traditional healthcare model is focused on diseases (medicine and natural science) and does not acknowledge patients' resources and abilities to be experts in their own life based on their lived experiences and expectations. (16, 17) Improving healthcare safety, quality and coordination, as well as health outcomes including quality of life, are important aims in the care of patients with chronic conditions. Person-centred care needs to ensure that people's preferences, needs and values guide clinical decisions. It provides care that is respectful of and responsive to patients and ensures that they are empowered and involved in decision making. (18) Nine themes have been identified in person-centred care: (i) empathy, (ii) respect, (iii) engagement, (iv) relationship, (v) communication, (vi) shared

decision making, (vii) holistic focus, (viii) individualised focus and (ix) coordinated care. (19) Digital tools are promoters for person-centred care practices in chronic care (20) but, alone, cannot achieve the ideals of person-centred care. (21) Politicians and policy makers have an increased interest in adopting and implementing person-centred care. (22, 23)

This global paper (Table E1) reviews the current knowledge to develop (i) DCPs for rhinitis and asthma multimorbidity and (ii) digitally-enabled person-centred care (24) using the GRADE approach to integrate both RCT and RWE. The ultimate goal is to develop guidelines centred around the patient in order to make them more applicable.

Some diseases have not been considered in this document (Table 1)

1- ARIA: A two-decade journey

ARIA was initiated during a WHO workshop in 1999. (3) It has evolved in six phases:

Phase 1 (1999-2009):

- Development and update of an evidence-based document (37) to provide a guide for the diagnosis and management of AR and asthma multimorbidity by physicians (3, 38) and pharmacists. (39) A specific focus was placed on developing countries.
- Dissemination and implementation: ARIA has been translated into over 50 languages, disseminated and implemented in over 80 countries. (40)
- Update using the same evidence-based system. (37, 38)

Phase 2 (2010-2016):

- ARIA was revised using the GRADE approach for assessing the strength of evidence underpinning recommendations. ARIA was one of the first guidelines to use GRADE Evidence-to-Decision (EtD) Frameworks. (4, 41) An update was published in 2017.(5)
- Deployment to policy makers. (42)

Phase 3 (2016-2018):

- An algorithm (MACVIA: Contre les Maladies Chroniques pour un Vieillissement Actif) was devised (43) and digitalised (44) to step-up or step-down AR treatment based on control (Figures 1A and 1B). (43) Algorithms require testing with RWE that includes RCTs and observational research with person-centred care. (45-47) A consensus refined the algorithm. (43)
- Implementation of mHealth tools for individualised and predictive medicine to develop ICPs for the management of AR and asthma by a multidisciplinary team centred on the needs of patients (MASK). (48-50)

- Initiation of MASK-air®.(48)

Phase 4 (2018-2019):

- Digital transformation of health and care. (24)
- Change management to improve population health and provide well-being for rhinitis and asthma sufferers across the life cycle, irrespective of their gender, age or socio-economic status and with the overarching aim to reduce health and social inequities. (51)
- Development of MASK-air®, the ARIA app.

Phase 5 (2019-2021):

- Next-generation guidelines for the AR pharmacologic treatment were developed using existing GRADE-based guidelines for the disease, RWE provided by mobile technology and additive studies (allergen chamber studies) to refine the MACVIA algorithm. (6)
- MASK-air®, a Good Practice of DG Health and Food Safety: Digitally-enabled, patient-centred care. (24, 52)
- Value-added medicine for the repurposing of AR medications. (53)
- High-Level Meeting (Finnish Presidency of the European Union [EU]) on Planetary Health. (54)

Phase 6 (2022-)

- Participation in initiatives on Planetary Health with climate change (EU Horizon Europe grant CATALYSE 2022-7). (55)
- Digitally-enabled, person-centred care including Next-Generation care pathways embedding RWE based on data with the GRADE evaluation of interventions.

ARIA has participated in several EU or WHO projects and grants and European Academy of Allergy and Clinical Immunology (EAACI) Task Forces (Table E1).

2- GRADE, the evidence-based model of guidelines in airway diseases

2-1- Strengths

To evaluate the confidence in the evidence underlying estimates of effects of interventions and to develop recommendations in guidelines, the GRADE (4, 5) methodology explicitly considers all types of study designs from RCTs to case reports, although guideline developers often restrict guidelines to RCTs. (56-58) For the formulation of recommendations on interventions, GRADE considers not only their benefits and harms, but also – and among others – patients' values and preferences, costs and cost-effectiveness, acceptability and feasibility. The EtD of GRADE allows the evidence to be considered on all of these criteria, based on which recommendations are formulated.

The ARIA revision 2016, (41) the US Practice Parameters 2017 (7) and three questions of the US Practice Parameters 2020 (8) used GRADE as their methodological approach. Interestingly, the same questions were considered and the results of these guidelines supported the MACVIA algorithm. (43) The ARIA revision was used as the case scenario on the review published on "How to interpret guidelines." (59)

In cluster-randomised trials, guideline-driven treatment was reported to be more effective than free treatment choice. (60, 61) Moreover, guidelines (in AR or asthma) have led to a better understanding of the treatment of the disease and have had an important teaching role which has led to a change in the management.(51) Evidence from direct patient data, however, suggests that guidelines are not sufficiently followed, possibly because they would need to be closer to patients' concerns.

2-2- Combining information from RCTs with real-world data studies

Applicability of the results of RCTs is restricted due to some serious issues (Table 2). (9)

There is an increasing trend to use person-centred care to inform the clinical practice, especially as RCTs are often limited to the generalisability and applicability of results (62). The trade-off that is made is one between risk of bias, primarily selection and confounding bias, and applicability. Ideally, both types of evidence are merged in a way to reduce bias and increase applicability. (9)

3. The mHealth impact on airway diseases

3.1. mHealth in allergic diseases and asthma

In order to select apps for rhinitis, a new approach to market research was based on the automatic screening of the Apple App and Google Play stores using a Java Script. (63) Three apps were available internationally and could be used in 2021 (Vienna Pollen, (64) AllergyMonitor (65, 66) and MASK-air®). (67)

MASK-air® was developed to implement AIRWAYS-ICPs. It is an app centred around the patient (50) and is operational in 27 countries and 19 languages (Annex 1). Around 35,000 users with AR and/or asthma have been registered. MASK-air® has been classified as a Medical Device regulation Class IIa. It is a Good Practice of DG Santé on digitally-enabled, patient-centred care. (24) It is also a Best Practice of OECD (Organisation for Economic Co-operation and Development). MASK-air® data has enabled large observational person-centred care studies, novel phenotype discovery and characterisation, (68) as well as novel insights into the management of AR. (69-71) MASK-air has also allowed for the

development and validation of the ARIA-EAACI combined symptom-medication score for allergic diseases (CSMS) and a daily electronic asthma symptom-medication score (e-DASTHMA). (72)

3.2. Messages from MASK-air® in rhinitis pertinent to guideline development

Several digital studies in up to 35,000 users (39,000 weeks with 6 or 7 days of reporting and over 5,000 months with over 26 days of reporting) in 27 countries enabled an assessment of AR treatments. (73) Their results yield important observations that should be considered in the management of AR (Table 3).

The current medications for allergic rhinitis are centred around continuous long-term treatment, and medication registration is based on RCTs carried out for a minimum of 14 days with adherence ≥70%. Similarly to the Global Initiative of Asthma (GINA) in asthma, a novel approach to treating allergic rhinitis involves suggesting an as-needed treatment regimen based on the presence and severity of symptoms, as opposed to the traditional continuous treatment approach. (53)

3.3. Digital health in shared decision making

There is a complete disconnection between the physician's prescription and the patient's behaviour for the treatment of pollen-induced AR. (69) The vast majority of allergists prescribe medications for the entire season, recommending the patient to use them regularly, even on days with few symptoms. Some allergists prescribe a pre-season treatment without clear evidence of efficacy. (74) On the other hand, the vast majority of patients use their medications on demand, when their AR is not well controlled. They do not follow the guidelines. (49, 50)

When physicians are patients themselves, they behave like patients when they treat their own AR and do not follow the prescriptions they would usually recommend to their patients (75). Health literacy is an important component of adherence to medications (76, 77), but, given the behaviour of allergists as patients, it appears that other factors are also important. Human behaviour appears to be a major driver of adherence.

The shift from a paternalistic model of health care to a doctor-patient relationship (in which the doctor and patient make shared decisions (shared decision making (SDM))) requires an actively involved patient who takes responsibilities. (78, 79) Rather than being passive, mHealth solutions provide the opportunity for the patient to be an active participant in his/her health. (80, 81) Informed self-management is a crucial aspect of patient care in AR but, as evidenced by MASK-air®, most patients do not adhere to the recommended treatment regimens. (69)

4. Use of Artificial Intelligence in guideline development

In the future, Artificial Intelligence (AI) is most likely to have an important impact on guideline development. Currently, it is already adept at expediting the evidence synthesis and translating content: between languages, but also generating plain language summaries. Used appropriately (e.g. using Retrieval Augmented Generation), it can help patients navigate contents of the guidelines.

"ARIA 2024, we will use ChatGPT in two different ways for question generation: (i) we will prompt ChatGPT to either assume the role of a patient or of a healthcare provider and provide relevant guideline questions in the PICO format; (ii) we will retrieve popular queries on allergic rhinitis using Google Trends and use ChatGPT to classify these queries into those conveying potentially relevant questions versus those not conveying questions (queries identified as potentially conveying relevant questions will then be manually transformed into guideline questions in the PICO format)." -

In the future, AI-based methods may be used to support the analysis of real-world data (including direct patient data from MASK-air®), allowing the obtention of findings that may support the development of guideline recommendations.

5. Patient values and preferences

Healthcare interventions typically result in benefits and harms. Patients' values and preferences concern the relative importance patients place on specific benefits and harms. Taking them into account is therefore essential for patient-centred guidelines. For example, in AR, antihistamines can lead to reduced allergy symptoms (benefits) and to an increased risk of side effects (risks). In order to formulate recommendations on antihistamines, we would need to consider the importance that patients attribute to the possibility of having their nasal symptoms improved over the risk of having mild side effects. Values and preferences can be quantitatively measured using different approaches, the most common of which involving utilities. Given that values and preferences are one of the criteria of the GRADE EtD framework, they will be considered in the context of the ARIA guidelines. In fact, a systematic review on patients' values and preferences for health states in AR has been conducted .(82) The results of this systematic review will be considered when judging the balance of effects when comparing different interventions – for example, in the comparison between two equally-safe treatments, we will say that a treatment that results in a greater improvement in nasal symptoms may be favored over another that results in a greater improvement in ocular symptoms (as patients tend more often to rate nasal symptoms as more important compared to ocular symptoms).

6. From guidelines to DCPs

ICPs are structured multidisciplinary care plans detailing the key steps of patient care (83). They promote the translation of guideline recommendations into local protocols and their application to the clinical practice. They may be of particular interest in patients with multimorbidities since guidelines often fail to adequately address their specific needs and concerns. (84, 85) ICPs should be carried out by a multidisciplinary team including physicians, pharmacists (86, 87) and allied healthcare professionals. (88) ICPs should integrate recommendations from clinical practice guidelines, but they usually (i) enhance recommendations by combining interventions, integrating quality assurance and (ii) describe care coordination. Self-care and SDM are at the forefront of ICPs with the aim of empowering patients and their (professional / lay) caregivers.

DCPs should incorporate all the steps of disease management in a multisectoral ICP using digital technologies. In ARIA 2019-2022, several consensus documents have been produced for ICPs (15, 89, 90): ARIA in the pharmacy, (91-93) allergen immunotherapy (AIT) (94, 95) and Next-Generation guidelines. (6) However, DCPs need to embed environmental triggers (96, 97) and extend their recommendations to non-medical treatments. (98) Indoor and outdoor pollution is important to include but it is not known whether air pollution increases the severity of AR and/or its prevalence. (99-101) Biodiversity, climate change (102) and Planetary Health should also be considered (Figure 2). (54, 103-105)

7. Embedding Planetary Health and nature deficiency in the ARIA framework

There is an urgent need to safeguard our planet and our health in line with the Helsinki declaration. (104, 106) *To protect human health in the Anthropocene epoch, human health and the health of the Planet should go together. (107, 108) In AR, as in other chronic diseases, it is important to understand both its close connection to natural systems as well as how much AR care affects the health of the Planet. Nature (biodiversity) loss* is the loss or decline of the state of nature. (109) A novel concept, *nature deficiency,* refers to nature loss in the human body influencing health. The urban-like environment and lifestyle have weakened the connection of the human body as an ecosystem to wider ecosystems.

ARIA has already been involved in these actions that now need to be deployed to citizens. *During the High-Level* meeting (Finnish Presidency of the EU *and DG Research*) on Planetary Health, (104, 106) *there was a session on MASK-air® in the frame of* Impact of air Pollution on Asthma and Rhinitis *(POLLAR)*. (54) *MASK-air® is one of the partners of a* new Horizon Europe grant, CATALYSE (Climate Action to Advance HeaLthY Societies in Europe; grant agreement number 101057131). (55) *One of the CATALYSE aims is to develop* early warning systems and predictive models to improve the effectiveness of adaptation strategies to climate change, including a specific tool for AR.

The ARIA 2024 guidelines will attempt to embed considerations of Planetary Health into guideline development, by including it in the EtD framework for the formulation of recommendations. When producing guideline recommendations, one aspects that will be taken into account will be how the interventions fare in terms of their impact on planetary health. For example, for comparisons between intranasal *versus* oral treatments, aspects such as the global warming potential and ozone depletion potential of the different packaging types will be assessed. However, whilst we begin piloting this, the methodological approaches necessary to embed Planetary Health into guidelines are under development. *(105)*

8. Novel classification of rhinitis and asthma

Allergic diseases [asthma, AR and atopic dermatitis in early life (AD)] are associated with allergen-specific IgE and non-allergic mechanisms that may coexist. These diseases tend to cluster and patients present concomitant or consecutive diseases (multimorbidity). Substantial clinical and immunological differences exist between mono- and polysensitised subjects. (110, 111) The concept of "one-airway-one-disease", coined over 20 years ago, (3) is a simplistic approach of the links between upper- and lower-airway allergic diseases. (112) Moreover:

- The clinical observations that led to ARIA clearly indicated that only 30% of rhinitis patients suffer from asthma, whereas most patients with asthma suffer from rhinitis. (113, 114)
- In birth and children's cohorts, mono- and polysensitisation to different allergens represent expressions of distinct diseases. (115, 116) Compared to monosensitisation, polysensitisation was linked to more robust global IgE response, disease phenotypes (rhinitis alone versus asthma+rhinitis), symptoms and trajectories. Multimorbidity is partly independent of IgE sensitisation, suggesting distinct causal (genomic and mechanistic) pathways. (117) There is an association between IgE polysensitisation and multimorbidity including age of onset, number of allergic multimorbidities (conjunctivitis and atopic dermatitis), severity of disease, (118) eosinophil levels and total IgE levels.
- The MASK-air® study showed that there is a multimorbid phenotype (asthma+rhinitis+conjunctivitis) associated with more severe symptoms and a higher impact of symptoms on work productivity compared to the observations with individual diseases. (68) This phenotype was confirmed using rhinitis (119) or asthma (120) to perform cluster analyses.
- These data were confirmed in canonical epidemiologic studies (121, 122). Rhinitis and rhinoconjunctivitis are separate diseases. The extreme allergy phenotype including

asthma+rhinitis+conjunctivitis has been confirmed. (123-129) For all parameters studied, multimorbidity differs from asthma or rhinitis alone. In the French general population epidemiologic study Constances, participants with asthma+rhinitis had more severe symptoms than those with rhinitis alone as well as an earlier age of onset (129). This suggests that multimorbidity behaves differently than rhinitis alone.

- Genomic findings: Two methods (transcriptomics and RNA sequencing) yielded the same results in two different cohorts (Mechanisms of the Development of Allergy [MeDALL] and Epigenetic Variation and Childhood Asthma in Puerto Ricans [EVA-PR]): Multimorbidity was associated with seven genes of T2 signalling: *IL5* (eosinophils) and *IL33* (polysensitisation and eosinophilia). (130) 27 genes were identified for rhinitis alone and included Toll-Like-Receptors (TLR) and IL-17. These studies suggest that rhinitis alone is a local IL-17-driven disease whereas T2-associated rhinitis+asthma are systemic IL-33-driven diseases. There are shared epigenetic patterns of allergic multimorbidities but, in children, these patterns were found only in rhinitis+asthma (and not in asthma alone).
- There are therapeutic differences between patients with rhinitis and patients with rhinitis+asthma. Multimorbid patients more often reported a treatment with intranasal corticosteroids (INCS) and oral antihistamines (OAH) (129) which is associated with poor control. (71) In MASK-air®, the comedication pattern was associated with a poorer rhinitis control than in monotherapy. (73, 131) In the combined symptom-medication score, the distinction between rhinitis and asthma+rhinitis was clear with large effect sizes.

These studies lead to the recognition of two distinct diseases: rhinitis alone (local, IL-17 and TLR associated) and rhinitis+asthma (systemic, IL-33 associated) with almost no overlap. (112) This new classification needs to be integrated in guideline development, namely by providing – whenever justified – recommendations for patients with rhinitis alone *versus* rhinitis with asthma.

9. Real-life data from population-based studies

Embedding MASK-air® data from general population studies allows the bridging of several fields in order to assess the relevance of RCTs, observational studies, registries, research in the general population and others. It appears to be particularly important to compare population and disease-specific epidemiologic studies as an essential step for person-centred care (Figure 3).

10. The ARIA-EAACI strategy for the management of airway diseases using digital biomarkers

Biomarkers for the diagnosis, treatment and follow-up of asthma or rhinitis patients are urgently needed. Although some biologic biomarkers exist in specialist care for asthma (e.g. sputum eosinophils or fractional exhaled nitric oxide [FeNO]), they cannot be largely used in primary care. There are no validated biomarkers in rhinitis or allergen immunotherapy (AIT) that can be used in the clinical practice. The digital transformation of health and health care (including mHealth) places the patient at the centre of the health system and is likely to optimise the practice of allergy. ARIA and EAACI developed a Task Force aimed at proposing digital biomarkers that can be easily used for different purposes in AR and asthma and that form a bridge between the clinical practice, RCTs and allergen challenges. (132) Using the MASK-air® app as a model, a daily electronic CSMS for allergic diseases (133) and asthma (e-DASTHMA) (72) was embedded in a strategy similar to the diabetes approach for disease control. The potential implications for the management of allergic respiratory diseases were proposed (Table 4).

In diabetes, two types of biomarkers are defined to monitor disease control. (134, 135) The daily control monitoring is assessed using glycemia measurement, and longer-term monitoring using glycated haemoglobin (HbA1c) measurement. It is recommended that both tests should be used to optimise diabetes management. By analogy with the diabetes approach, two types of patient-centred digital biomarkers are available for rhinitis and asthma:

- Long-term monitoring using control scores (analogous to HbA1c measurement): CARAT (Control of Allergic Rhinitis and Asthma Test) (136-138) is proposed as it combines rhinitis and asthma control. Furthermore, there is a recall period of 4 weeks, whereas many other rhinitis (e.g., Allergic Rhinitis Control Test (139), Rhinitis Control Assessment Test (140)) or asthma (e.g., Asthma Control Questionnaire - ACQ,(141)) control questionnaires are based on a one-week recall period. The Asthma Control Test (ACT) is based on a 4-week period. (142) These questionnaires, however, do not fully capture the control in patients with fluctuating symptoms (particularly those with severe asthma).
- Daily monitoring of the control (analogous to glycemia measurement): This can be measured using the ARIA-EAACI allergy CSMS (133) or the e-DASTHMA. (72)

11. Development of digitally-enabled ARIA Person-Centred Care

The development of guidelines according to the GRADE methodology involves a stepwise approach resulting in the formulation of recommendations for a set of selected questions. For ARIA, we propose the development of guidelines that are (i) digitally enabled, by formally integrating into the guideline development process real-life data obtained from mobile apps such as MASK-air® and from web searches, (ii) person-centred, by taking into account patients' values and preferences when issuing

recommendations (as recommended by GRADE) and (iii) AI-assisted, by formally integrating large language models (LLM) into the guideline development process (Figure 4).

11.1. Generation and prioritisation of PICO questions (Step 1)

11.1.1 Question generation

Questions for the ARIA guidelines will follow the Population, Interventions, Comparators and Outcomes (PICO) framework. In the first phase, questions to be considered by the panel members will be:

1- **Questions developed for ARIA 2010** (4) **and 2016**. (5)

2- **Questions suggested by panel members:** Panel members will suggest questions that have not been considered in ARIA 2010 or 2016, which may include some of the questions of the US practice parameters. (8)

3- **Real-life data-driven questions:** Studies based on MASK-air® data will be systematically assessed by two independent members of the methodology team. Additionally, AR-related popular queries will be obtained using Google Trends, as web searches may provide a glimpse into what is of most interest to internet users and, therefore, contribute to the development of patient-centred guidelines. Foreground questions will be developed based on (i) the hypotheses and conclusions in MASK-air® studies and (ii) the search queries on Google Trends.

4- **AI-assisted questions:** LLMs, namely ChatGPT (version 4.0., OpenAI, San Francisco, California), will be used for the generation of direct guideline questions (Sousa-Pinto *et al.*, draft). Additionally, ChatGPT will be used to help with processing and classifying Google Trends queries. In detail, we will use ChatGPT in two different ways for question generation: (i) we will prompt ChatGPT to either assume the role of a patient or of a healthcare provider and provide relevant guideline questions in the PICO format; (ii) we will retrieve popular queries on allergic rhinitis using Google Trends and use ChatGPT to classify these queries into those conveying potentially relevant questions *versus* those not conveying questions (queries identified as potentially conveying relevant questions will then be manually transformed into guideline questions in the PICO format).

A consensus meeting to review the set of proposed questions will be held before question prioritisation.

11.1.2. Question prioritisation

Panel members will be asked to use a Visual Analogue Scale (VAS) to rate the priority of each question on a scale of 1-9. The ratings will be reviewed by panel co-chairs and the results discussed in a panel meeting. A consensus will then be reached with regards to the questions to be approached in the guidelines.

11.1.3. Outcome generation and prioritisation

The questions described previously will also include a list of potential patient-important outcomes identified by the co-chairs, panel suggestions and a systematic review of patients' values and preferences (Brozek *et al.*, submitted). Panel members will be asked to use a VAS to rate the priority of each outcome. To ensure that panel members envision the same outcome when discussing the evidence, we will develop health-outcome descriptors to create common definitions that describe the outcomes with respect to symptoms, time horizon, testing and treatment, and consequences (Vieira *et al.*, draft).

11.2. From evidence to recommendations and digitally-enabled ARIA Person-Centred Care (Steps 2 and 3)

For each of the prioritised guideline questions, new or updated systematic reviews of RCTs will be conducted to obtain the best available evidence. In the GRADE approach, incorporation of the best available evidence for the formulation of recommendations involves the use of the EtD framework. The EtD comprises 12 criteria (including, among others, the priority of the problem, benefits and harms, patients' values and preferences, resource use and cost-effectiveness, impact on health equity, feasibility and acceptability), enabling each prioritised question to be answered by the formulation of recommendations. When relevant, evidence from RCTs will be complemented by:

- evidence obtained by observational studies, including the Constances general population cohort or national health data.
- real-life direct patient data from MASK-air®: The database (currently 600,000 days) will be used to provide complementary evidence to the guideline questions, especially for subgroup analyses (e.g. considering patients with AR+asthma and AR without asthma), resource use, feasibility and acceptability of interventions. This aims to incorporate evidence more aligned with the actual experiences of patients in the decision-making process.

Importantly, the EtD framework includes patients' values and preferences as one of the criteria for decision making. Therefore, we conducted a systematic review to synthesize and appraise all available evidence on patients' values and preferences for health outcomes associated with AR (Brozek et al., submitted), thereby allowing for panel members to issue recommendations aligned with patients' values and preferences.

11.3. Consensus to develop the final ARIA 2024 recommendation

A consensus will be made using recommendations obtained from EtDs of RCTs and real-life data (Step 3). Importantly, the EtD framework includes patients' values and preferences as one of the criteria for decision-making. Therefore, we conducted a systematic review to synthesize and appraise all available

evidence on patients' values and preferences for health outcomes associated with allergic rhinitis (82), thereby allowing for panel members to issue recommendations which are aligned with patients' values and preferences.

11.4. ARIA covers all age groups (Steps 2b and 3b)

As already done in ARIA 2010, special attention will be paid to children and old-age people, even though the number of RCTs or RWE studies is relatively low. A special subgroup will assess this important topic.

12. The political agenda

Current digital health tools such as MASK-air® were developed initially for rhinitis and asthma. However, the technology itself is generic and can be applied to other diseases (e.g. the Chronic Urticaria Self Evaluation [CRUSE] mobile app in urticaria). (143) The digital tool enables patients to be guided for an ICP to adapt the medication based on symptom load but also to allow better SDM. The success strongly depends on the patients' adherence, particularly among the elderly, to these digital tools.

Building an alliance among patients, healthcare providers and policy makers is therefore essential for saving healthcare costs and providing better care for the patients. Healthcare providers or insurers could offer a financial reward to encourage patients with chronic disease to use digital health tools. Allergic diseases are the most frequent chronic diseases in the younger population of industrialised countries. It has been shown that up to €100 billion can be saved every year in socio-economic costs, mainly due to presenteeism, if patients are correctly treated. (2) Saving socio-economic costs will not only present a short-term benefit for the healthcare system but could also result in a strong benefit for society. Therefore, an urgent need also exists for support from policy makers to optimise patient care.

Several policy-focused initiatives have been made in collaboration with ARIA. They include the Polish Presidency of the EU (2012: Prevention and control of childhood asthma and allergy in the EU from the public health point of view) (144), the Vilnius declaration (2019, Vilnius Declaration on chronic respiratory diseases: multisectoral care pathways embedding guided self-management, mHealth and air pollution in chronic respiratory diseases) (145), the Finnish Presidency of the EU (2019) Europe that protects) (54, 104, 106) and UCRAID (2023, Ukrainian Citizen and refugee electronic support in Respiratory diseases, Allergy, Immunology and Dermatology) (146). Moreover, MASK-air® is a Best Practice of OECD (Organisation for economic co-operation and Development) for Public Health on integrated care for chronic diseases (147) and it has been endorsed by the ministries of health of Ukraine (2023) (146) and Poland (2024).

MASK-air® has recently been listed as one of the 13 OECD Best Practices of an integrated care model of key strategic interest to policy makers. (148) UCRAID (Ukrainian Citizen and refugee electronic support in Respiratory diseases, Allergy, Immunology and Dermatology), developed by ARIA and UCARE (Urticaria Centers of Reference and Excellence), is under the auspices of the Ukraine Ministry of Health as well as EAACI, the European Respiratory Society (ERS), the European Society of Dermatologic Research (ESDR) and national societies. (146)

A special effort needs to be undertaken to globalise the care pathways. The first ARIA report involved low and middle-income countries. (149) A specific group of members of developing countries will be involved in ARIA 2024. Smartphone ownership is growing rapidly around the world. In 2015, there were more than 7 billion mobile telephone subscriptions across the world, of which over 70% were in low- or middle-income countries (150). The joint WHO-ITU (International Telecommunication Union) initiative "Be He@lthy, Be Mobile" for the prevention and management of noncommunicable diseases, their comorbidities and their risk factors, including improving disease diagnosis and tracking, is of significant importance. MASK-air® is one of the examples of the "Be He@lthy, Be Mobile" handbook on how to implement mBreatheFreely for asthma and chronic obstructive pulmonary disease. (151) The ultimate goal of the initiative would be to propose a "Universal Health Coverage (UHC)", although this may be beyond the scope of ARIA 2024. *(https://www.who.int/westernpacific/health-topics/detail/universal-health-coverage)*

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Figure captions

Figure 1A: Management algorithm of untreated symptomatic patients using control (VAS) (from (31))

Figure 1B: Management algorithm of treated symptomatic patients using control (VAS)

Figure 2: Digital care pathways in rhinitis and asthma and the evidence ecosystem (from (2))

Figure 3: Impact of the interaction between MASK-air and population studies

Figure 4: Stepwise approach for the development of the ARIA 2024 recommendations

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Tables

Table 1: Excluded diseases

Although **non-allergic rhinitis (NAR)** is very common and may be associated with AR, it cannot be considered in ARIA because (i) there are many distinct NAR diseases (25) and many phenotypes that may overlap and are still poorly defined (26). (ii) Although in clinical practice questionnaires (27) and treatments are proposed (28), many medications have been tested in RCTs and most were not effective, possibly because the NAR phenotypes were not characterized (29). Moreover, many trials have not been published because of lack of efficacy. In published trials, the effect of treatment is often insignificant (30), low, incomplete or found only in some types of NAR (31-34). Observational studies cannot be used in guideline development if NAR phenotypes are not considered. Well-conducted randomized controlled trials in different phenotypes of NAR are required to further advance our understanding of the effectiveness of treatments in NAR. Based on these limitations, a meta-analysis would be difficult to interpret and recommendations for NAR cannot be developed using the EtD (Evidence to Decision) GRADE method used in this document.
Local allergy is a well-characterized phenotype (35) and it was identified as a research question by the ARIA group. However, it was not prioritized since there is apparently no pharmacologic RCT in this IgE-mediated phenotype (36). Large-scale observational studies are also lacking.
Rhinosinusitis.

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Table 2: Some weaknesses of randomized controlled trials (RCTs) of rhinitis interventions

	RCT	Putative problems
Severity/control	The worst controlled patients	The recommendations may not apply to patients with mild or partly controlled symptoms which represent the largest population of patients
Patient selection criteria	Asthma usually excluded	• Treatment differences exist in patients with rhinitis alone or rhinitis and asthma • However, patients with uncontrolled disease may respond equally • Do not consider the patient's experience with previous treatments
	Other exclusion criteria	Less than 10% of patients seen in primary care can be enrolled in RCTs (152)
Adherence to treatment	In most studies ≥ 70%	Only a small subset of rhinitis patients is adherent ≥70%

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Table 3: Patient-centred lessons in rhinitis provided by MASK-air® data

- Patients are poorly adherent to treatment. (153, 154)
- Most AR patients use on-demand treatment when they are sub-optimally controlled. This is suggested by the fact that days on which patients do not take medications are usually well-controlled. (153, 155) (69, 119, 156) Switching of treatment is common. (69, 119)
- The vast majority of patients do not follow the prescriptions of their physicians, who, often, do not follow guidelines. (153-155) Medication use peaked during the pollen season in all of the investigated European countries (156) whereas cultural behaviours - assessed using Google Trends - (157) differed. Oral antihistamines (OAH) were the most common medications reported in monotherapy and combined medications (comedication). This is against guideline recommendations and does not accord with the dispensing of medications (OTC and prescribed) in the pharmacy. (157)
- On most of the days with patients reporting a worse control, an increased number of medications is used (69-71, 73, 153, 155). This accords with the concept of SCUAD (Severe Chronic Upper Airway Disease). (158)
- Days with OAH monotherapy are associated with a poorer level of control than days with intranasal corticosteroid (INCS)-containing medications. Days with INCS are associated with a poorer control than those with azelastine-fluticasone (MPAzeFlu). (153, 155) Days with co-medication use are associated with a poorer level of control than those reporting monotherapy. (69-71, 153, 155)

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Table 4: Potential implications of the allergy combined symptom-medication score (CSMS) (from Bousquet et al. (132))

1- Clinical practice

- Indication of a treatment in stratified patients.
- Follow-up of a treatment and early stopping rule.
- Follow-up of a treatment and regular review of efficacy.
- Follow-up of the patient when the treatment is stopped.
- Re-introduction and follow-up of the treatment in patients who relapsed.

2- **Randomised Controlled Trials (RCTs):** mHealth biomarkers are currently exploratory endpoints but may become primary end points mimicking real life after validation.

3- **Observational studies** can triangulate RCTs and make a link with the clinical practice.

4- **Direct-patient data (Real-world data)** are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources including apps. This data can be obtained by performing large simple trials and pragmatic clinical trials.

5- **Epidemiologic studies** will use the same approach to better relate RCTs and the clinical practice.

6- **Allergen challenge** can triangulate RCTs and make a link with the clinical practice.

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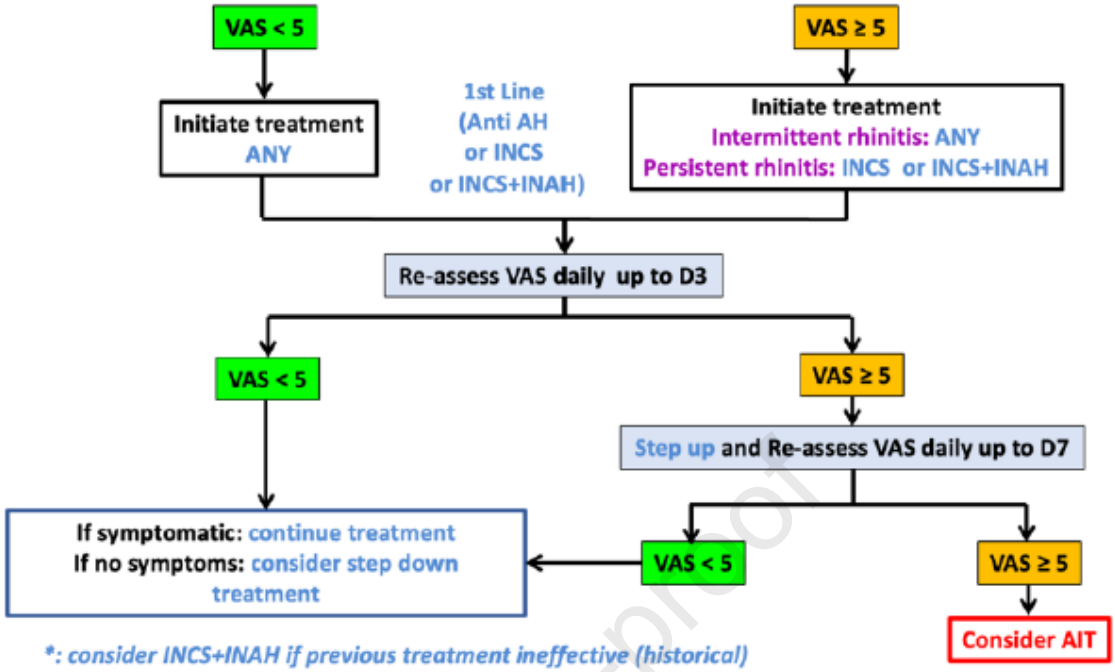

AH: H1-anti-histamine
INAH: Intra-nasal H1-anti-histamine
INCS: Intra-nasal corticosteroid
AIT: Allergen immunotherapy
VAS: Visual analogue scale

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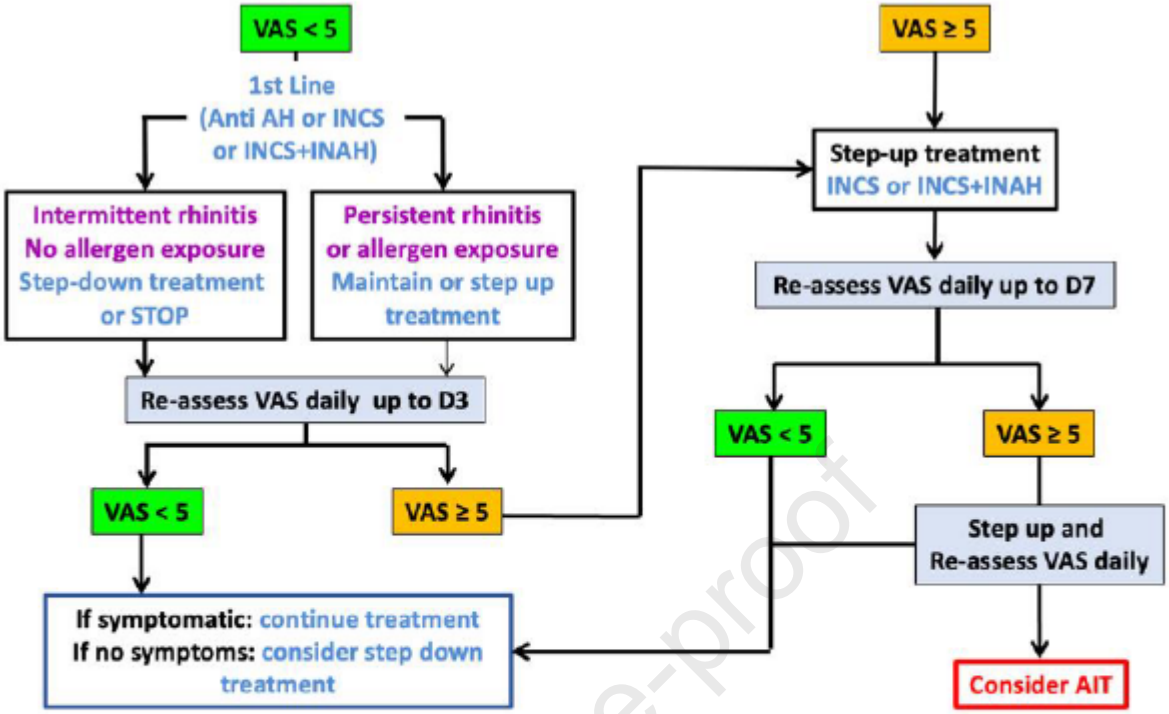

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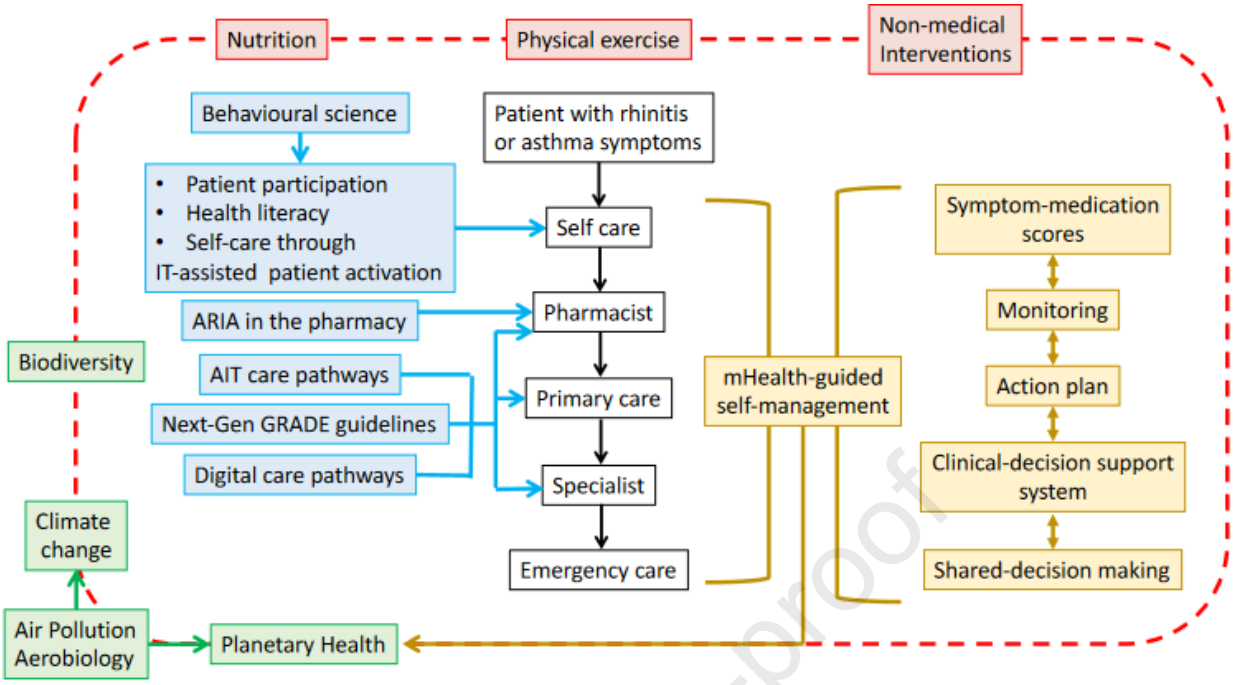

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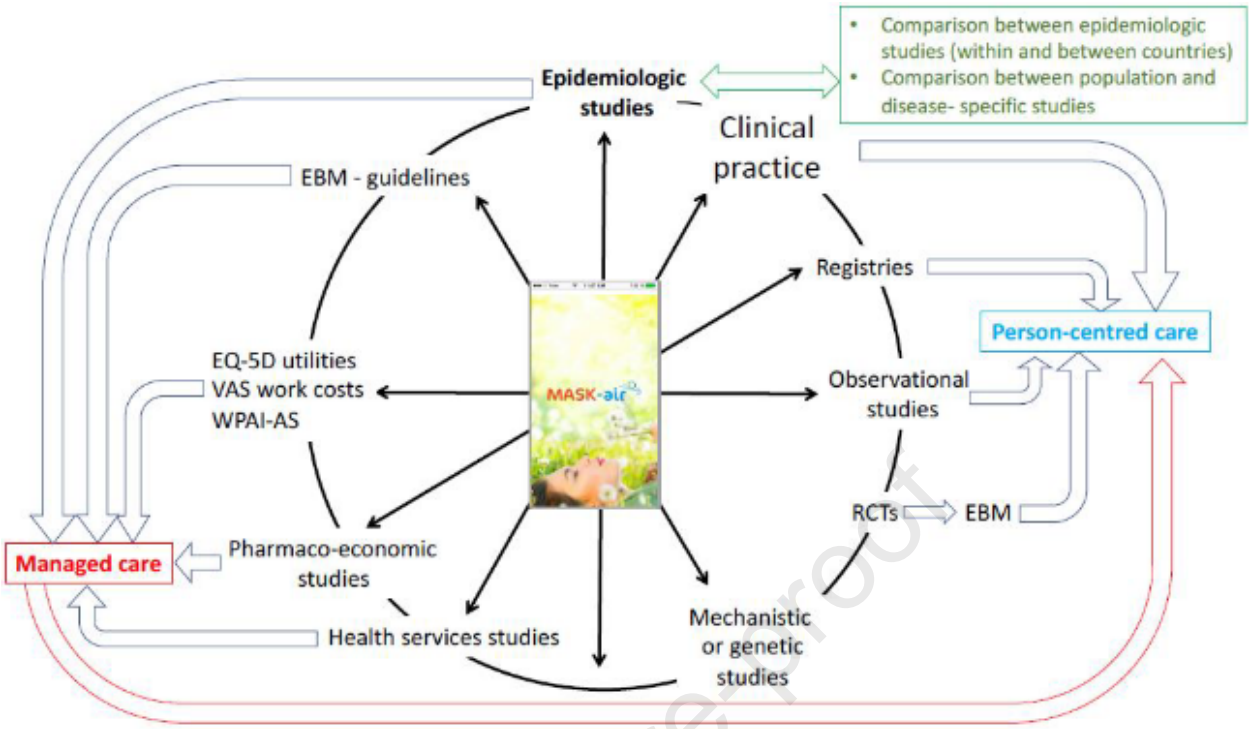

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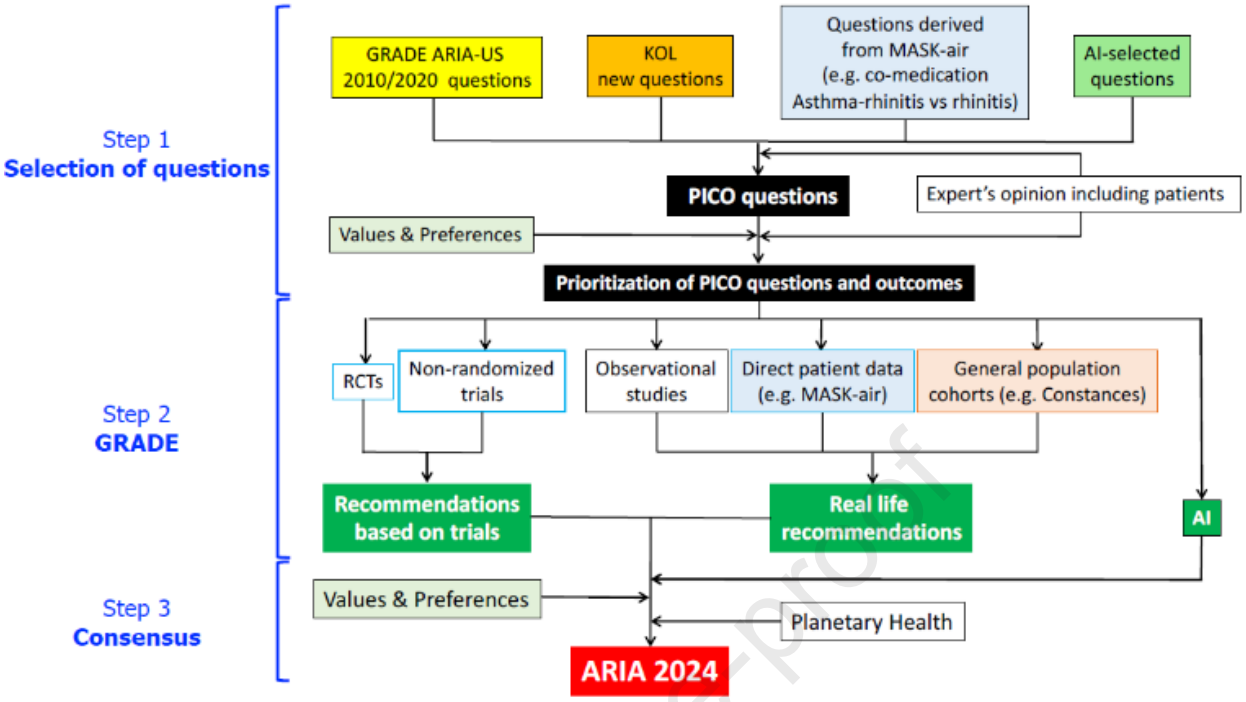

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Table E1: ARIA strategic overview (updated from (E1))

	Acronym & ref	Name	Dates
WHO-associated projects			
	ARIA (E2-E6)	Allergic Rhinitis and its Impact on Asthma	1999-
	WHO Collaborating Center for Asthma and Rhinitis (Montpellier)		2004-14
	GARD (E7)	Global Alliance against chronic Respiratory Diseases, demonstration project	2003-23
	WHO-ITU (E8)	"Be He@lthy, Be Mobile" handbook on asthma and COPD	2017
EU grants and projects			
	GA^{2}LEN (E9)	Global Allergy and Asthma European Network (FP6)	2004-
	MeDALL (E10, E11)	Mechanisms of the Development of Allergy (FP7)	2009-14
	EIP on AHA (E12)	European Innovation Partnership on Active and Healthy Ageing (DG Santé & CONNECT)	2012-20
	Joint Research Center (JRC) Scientific and Policy Reports on Strategic Intelligence Monitor on Personal Health Systems Phase 3 (SIMPHS3) (E13)		2015
	MACVIA (E14)	European Regional Development Fund (ERDF-Région Languedoc-Roussillon)	2016-7
	Twinning (E15)	Transfer of Innovation (DG Santé & CONNECT)	2017-9
	DHE Twinning (E16)	Transfer of innovation in severe asthma (H2020)	2019-20
	POLLAR (E17, E18)	Impact of air Pollution on Asthma and Rhinitis (EIT Health)	2018-9
	CATALYSE (E19)	Climate change (Horizon Europe)	2022-
	MASK@PACA	European Regional Development Fund (ERDF-Région PACA)	2021-2
	Good Practice DG Santé on digital health (DG Santé) (E20)		2018
	Best Practice OECD-DG Santé (E21)		2023
ARIA-EAACI Task Forces and projects			
	Combined symptom-medication scores for allergic rhinitis (CSMS) (E22)		2021
	Digital biomarkers in rhinitis and asthma including electronic daily symptom-control score in asthma (e-DASTHMA) (E23, E24)		2022
	Digital biomarkers in allergen immunotherapy (in press)		2023
	UCRAID (Ukrainian Citizen and refugee electronic support in Respiratory diseases, Allergy, Immunology and Dermatology) (E25)		2023
	INTERAID (International travel electronic support in Respiratory, Allergy, Immunology and Dermatology)		2024

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