

SUPPLEMENTARY MATERIAL

ANNEX 1

MASK-air® 2014-2022

(Mobile Airways Sentinel NetworK for airway diseases)

Table 1. Strategic overview (modified from ¹)

	Acronym & ref	Name	Dates
WHO-associated projects			
	ARIA ²⁻⁶	Allergic Rhinitis and its Impact on Asthma	1999-
	WHO Collaborating Center on Rhinitis and Asthma (Montpellier)		2004-14
	GARD ⁷	Global Alliance against Chronic Respiratory Diseases	2003-
	WHO-ITU ⁸	“Be He@lthy, Be Mobile” handbook on asthma and COPD	2017
EU grants and projects			
	GA ² LEN ⁹	Global Allergy and Asthma European Network (FP6)	2004-
	MeDALL ^{10,11}	Mechanisms of the Development of Allergy (FP7)	2009-14
	EIP on AHA ¹²	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 (SIMP3S) ¹³		2015
	MACVIA ¹⁴	European Regional Development Fund (ERDF-Région Languedoc-Roussillon)	2016-7
	Twinning ¹⁵	Transfer of Innovation (DG Santé & CONNECT)	2017-9
	DHE Twinning ¹⁶	Transfer of Innovation in severe asthma (H2020)	2019-20
	POLLAR ¹⁷	Impact of Pollution on Asthma and Rhinitis (EIT Health)	2018-9
	Catalyse	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) ¹⁸		2018
	Candidate Best Practice OECD-DG Santé		2023

ARIA: Allergic Rhinitis and its Impact on Asthma, CARAT: Control of Allergic Rhinitis and Asthma Test, EAACI: European Academy of Allergy and Clinical Immunology, e-CDSS: electronic clinical decision support system, GA²LEN: Global Allergy and Asthma European Network, GARD: Global Alliance against Chronic Respiratory Diseases, OECD: Organisation for Economic Co-operation and Development, POLLAR: Impact of Pollution on Asthma and Rhinitis, Catalyse: Climate Action to Advance HealthY Societies in Europe, WHO: World Health Organization. ITU: International Telecommunication Union

Table 2. Maturity level of MASK-air® (modified from ¹)

Rhinitis platform	TRL*		Asthma platform	TRL	
App for rhinitis and asthma (MASK-air®): 28 countries, 17 languages, >50,000 users	9	¹⁹⁻²¹	Adaptation of the MASK-air app for severe asthma: DHE SA-TWINNING	8	
PROMs for rhinitis	9		PROMS for asthma	9	²²
CARAT questionnaire for screening and control of rhinitis and asthma, 20 countries	9	²³⁻²⁶	The same questionnaire will be used	9	²³⁻²⁵
e-physician questionnaire for rhinitis (available on the MASK-air website) deployed in 28 countries and 17 languages	9	²⁷	Adaptation of the MASK questionnaire for SA developed by the DHE SA-TWINNING	6	
Electronic clinical decision support system in English for rhinitis	7	²⁸			
Embedding air quality (outdoor air pollution) and pollen data in MASK-air® (POLLAR)	9	¹⁷	Alerts for air pollution and pollens predicting asthma exacerbations	5	
			Alerts for rhinovirus predicting asthma exacerbations	4	^{29,30}
EAACI-ARIACARE-digital network (28 countries, 20 languages)	9		The same network will be used	9	
Symptom-medication score for rhinitis	9	³¹	Daily control-medication score for asthma	5	
			Sensors for pulmonary function	5	
Embedding artificial intelligence in MASK-air®	2			2	

*: Technology Readiness Level (TRL) ³²

PROMs: patient-reported outcome measures, Twinning: Transfer of Innovation, CARAT: Control of Allergic Rhinitis and Asthma Test, POLLAR: Impact of Pollution on Asthma and Rhinitis

Table 3. Methodology and GDPR

	Study name	Ref	Study type	N users	N days	N countries
1	COSMIN guidelines	33	Obs, CS-L	2,497	14,612*	15
2	Test-retest, intra-class coefficient	34	Obs, CS-L	17,780	317,176	25
3	Quality of data (intra-individual response variability)	35	Obs, CS	14,189	205,904	23
2	Independence of data	34	Obs, CS	1,136	5,889	18
4-7	VAS work	14,35-37	Obs, CS	14,189	205,904	18
7,8	EQ-5D	14,37	Obs, CS	1,288	NA	18
6,9	Work Productivity and Activity Impairment Allergic Specific (WPAI:AS)	14,36-38	Obs, CS	1,288	NA	18
10	CARAT	26	Obs, CS	1,086	2,042	22
11	CARAT*	39	<i>Systematic review</i>			
12	PROMs in severe asthma	22	Obs, CS	86	2,349	12
13	MASK-air in old age adults	40	Obs, CS	19,888	349,045	27
14	Combined symptom-medication scores for allergic rhinitis (ARIA-EAACI CSMS)	41	Obs, CS	17,780	317,176	25
15	Electronic daily control-medication score in asthma (e-DATHMA)					
16	Cut-off levels					
17	Mobile health app for monitoring AR and asthma in real life in Lithuanian MASK-air users	42	Obs, L	149	NA	Lithuania
18	Implementation of the MASK-air® app for rhinitis and asthma in old age adults. MASK@Puglia	43	Obs, CS	174	NA	Italy
19	Comparison of anti-histamine reporting by MASK-air, Google Trends and sales in Europe	44	Obs, CS			
20	CDSS (Clinical Decision Support System)	28		NA	NA	NA
21	CHRODIS guidelines	45		NA	NA	NA
22	Geolocation (GDPR)	46		NA	NA	NA
23	GDPR	47		NA	NA	NA

ARIA: Allergic Rhinitis and its Impact on Asthma, CARAT: Control of Rhinitis and Asthma Test, CHRODIS: Joint Action on Chronic Diseases, COSMIN: Consensus-based Standards for the selection of health Measurement INstruments, EAACI: European Academy of Allergy and Clinical Immunology, EQ-5D: EuroQol, GDPR: General Data Protection Regulation, PROM: Patient-reported outcome measure, VAS: visual analogue scale

Obs: Observational study, CS: Cross-sectional study, L: Longitudinal study, NA: not applicable.

*: Systematic review carried out for MASK-air

Table 4. Major achievements

	Study name	Ref	Study type	N users	N days	N countries
Baseline characteristics						
23	Pilot study of mobile phone technology in AR in European countries. The MASK-rhinitis study	⁴⁸	Obs, CS	3,260	NA	20
24	Treatment of AR during and outside the pollen season using mobile technology. A MASK study	⁴⁹	Obs, CS	9,035	70,286	Europe 18
Phenotype of allergic diseases and asthma						
25	Daily allergic multimorbidities	²⁰				
26	Clusters of asthma and rhinitis	⁵⁰	Obs, CS	8,075	297,169	26
27	Rhinitis associated with asthma is distinct from Rhinitis alone	Submitted	Obs, CS+L	3,797	256,839	27
Adherence to treatment of AR using mobile technology						
28	Adherence to treatment of AR using mobile technology	⁵¹	Obs, CS	6,949	NA	21
Real-world data in allergic rhinitis						
29	Treatment of AR using mobile technology with real-world data: The MASK observational pilot study	⁵²	Obs, CS	2,871	39,634	
30	Mobile technology offers novel insights on control and treatment of AR. The MASK study	²¹	Obs, CS	9,122	112,054	23
24	Treatment of AR during and outside the pollen season using mobile technology. A MASK study	⁴⁹	Obs, CS	9,035	70,286	Europe 18
31	Comparison of rhinitis treatments using MASK-air [®] data considering the Minimal Important Difference	⁵³	Obs, CS	10,860	269,837	28
32	Differences in behavioural patterns in AR medication in Europe: A study using MASK-air [®] real-world data	⁵⁴	Obs, CS	13,122	222,024	Europe 18
Real-world data in asthma						
33	Longitudinal severe asthma pilot study	⁵⁵	Obs, CS	13	1,250	Italy
34	Treatment of asthma using mHealth real-world data: The MASK-air observational study		Obs, CS	3,229	70,270	27
35	Adherence to ICS/LABAs in asthma		Obs, CS			
Impact of allergic diseases						
36	Academic productivity in AR: A MASK-air [®] direct data cross-sectional study	⁵⁶	Obs, CS	1,970	13,454	28
4-7	Work productivity	^{14,35-37}	Obs, CS	14,189	205,904	18
Clinical trials						
37	Validation of the MASK-air App for assessment of AR	⁵⁷	RCT	267	7,500	Spain
38	Effect of nasal irrigation on AR control in children; complementarity between CARAT and MASK outcomes	⁵⁸	RCT	76	NA	Greece
Allergen immunotherapy						
39	Effect of AIT in the MASK-air [®] study: proof-of-concept analysis	⁵⁹	Obs, CS	17,780	317,176	25
40	Allergen AIT in MASK-air users in real-life: results of a Bayesian mixed-effects model	⁶⁰	Obs, CS	1,093	42,756	25
41	Daily improvement of allergy control by sublingual AIT: A MASK-air [®] cross-sectional study	Submitted	Obs, CS	217	4,726	14
Aerobiology and air pollution						
42	POLLAR	⁶¹	Obs, CS	3,323	36,440	15
43	POLLAR*	⁶²	<i>Review of methods used in POLLAR</i>			

Obs: Observational, RCT: randomised controlled trial, CS: cross-sectional, L: longitudinal, NA: not available

AIT: Allergen immunotherapy, AR: Allergic Rhinitis, CARAT: Control of Rhinitis and Asthma Test, LABA: Long-acting β_2 agonist, ICS: Inhaled corticosteroids, POLLAR: Impact of air POLLution on Asthma and Rhinitis.

*: Review carried out for MASK-air

5. Patient-centred digital biomarkers for allergic respiratory diseases and asthma

Biomarkers for the diagnosis, treatment and follow-up of patients with rhinitis and asthma are urgently needed. Although some biologic biomarkers exist in specialist care for asthma, they cannot be largely used in primary care. There are no validated biomarkers in rhinitis or allergen immunotherapy (AIT) that can be used in clinical practice. MASK-air® has defined mHealth biomarkers that should make a bridge between the clinical practice, randomised control trials, observational real-life studies and allergen challenges. Using the MASK-air app as a model, a daily electronic combined symptom-medication score for allergic diseases (CSMS) and for asthma (e-DASTHMA) was reported and embedded in a strategy similar to the diabetes approach for disease control. (Table 5).

Table 5. Potential implications of the allergy-CSMS

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 relapse

2- **Randomised Controlled Trials (RCTs):** mHealth biomarkers are currently exploratory end points 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- **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. They allow large simple trials and pragmatic clinical trials to be performed

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

In allergen immunotherapy, the allergy-CSMS can be used to (i) stratify patients (uncontrolled days during the allergen exposure, e.g., pollen season, despite guideline-based treatment in patients adherent to treatment), (ii) propose an early stopping rule, (iii) follow the patient during the treatment and (iv) follow the patient during the after-cessation follow-up period (Figure 1). However, a dual approach can be proposed combining the daily allergy-CSMS with a control test for allergic diseases assessing at least one month of survey.

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ANNEX 2

SILAM

(System for Integrated modeLLing of Atmospheric coMposition)

Table 1. Research and application background

Acronym & ref	Name	Dates
WMO-associated projects		
SDS-WAS	Sand and Dust Storm Warning advisory and Assessment System	2018-
VFSP-WAS	Vegetation Fires and Smoke Pollution Warning advisory and Assessment System	2021-
Relevant (inter-)national grants and projects		
CAMS2-44	Copernicus Atmospheric Monitoring Service, regional AQ forecasting ensemble, leading the pollen forecasting task. European-scale AQ and pollen forecasts, evaluation against the in-situ and satellite data, now- and hind-casting, interim and validated reanalysis.	2021-2027
AUTOPOLLEN	Automatic Pollen detection network. EUMETNET. Development of strategy towards the European real-time automatic pollen and spores monitoring. Elaboration of standards and protocols of operations and model-measurement interactions.	2018-2022
ACCC	Atmosphere and Climate Competence Center flagship project. Academy of Finland. Strategic overview of climate-resilient society, mitigation and adaptation measures at Finnish national and international level. Development of monitoring and modelling approaches, decision support systems.	2020-2024
DEODE	Destination Earth On-Demand Extremes, Horizon Europe. Development and demonstration of Digital Twin.	2022-2024
ENBEL	Enhancing Belmont Research Action to support EU policy making on climate change and health. H2020 Belmont forum. Harmonization and cross-project collaboration towards universal approaches of climate change adaptation and assessment of the impacts on health.	2021-2023
PASYFO	Within the Personal Allergy Symptom Forecasting project, the PASYFO web tool has been created and developed to handle CAMS data downscaled with the SILAM model in Lithuania and Latvia. Connecting the air quality forecasts and personal allergy reports a high-resolution regional system for predicting the personal allergy symptoms of sensitive people in Lithuania and Latvia.	2017-2018
PS4A	The project Advanced study of Pollen, Spores and air pollutants for predicting the human Allergy (PS4A) addresses the next major scientific frontiers: (i) in-depth mechanistic analysis of the pollen production mechanisms, their interplay with environmental factors and pollution, (ii) accounting for individual specifics of allergy sufferers and development of personalised allergy forecasts.	2018-2021
ALL-IMPRESS	Aeroallergens and immunological preparedness for future climate scenarios: implications for public health promotion. The main goal is to evaluate and interpret the interconnection between climate change, aeroallergens and immunological preparedness and to translate findings into the promotion of public health and societal adaptation.	2020-2024
GLORIA	The research results within the Global health risks related to atmospheric composition and weather (GLORIA) project provide science-based new knowledge and insights regarding the role of air pollution, ambient temperature and allergenic pollen as determinants of mortality and morbidity, including asthma, allergic diseases, respiratory infections and adverse pregnancy outcomes. A new assessment of global environmental health impacts is being conducted.	2017-2020
POLLAR	The Impact of Pollution on Asthma and Rhinitis (POLLAR) project aims at providing an integrated software platform solution by combining emerging technologies with machine learning to (i) understand the effects of air pollution in allergic rhinitis and its impact on sleep/apnea, work and asthma, (ii) assess societal consequences, (iii) propose preventive strategies, (iv) develop participative policies and (v) expand knowledge of multimorbidity in chronic diseases.	2019-2020

WMO: World Meteorological Organization

Table 2. Maturity level of SILAM sub-systems

SILAM sub-systems	Applications	TRL
Core atmospheric composition forecasting and assessment	Copernicus Atmospheric Monitoring Service CAMS	9
Emergency decision support	Finnish emergency preparedness framework	9
Aeroallergens forecasting and assessment	Copernicus Atmospheric Monitoring Service CAMS	9
Data assimilation: 3D-VAR	Copernicus Atmospheric Monitoring Service CAMS	9
4D-VAR	Research projects	6
EnKF	Research projects	7
Allergy Risk assessment	Personal Allergy SYstem Forecasting PASYFO	5

TRL: Technology Readiness Level, 3D-VAR / 4D-VAR: 3-dimensional variational data assimilation, EnKF: Ensemble Kalman Filter