Transfer of innovation on allergic rhinitis and asthma multimorbidity in the elderly (MACVIA-ARIA) - EIP on AHA Twinning Reference Site (GARD research demonstration project)

J. Bousquet, I. Agache, M. R. Aliberti, R. Angles, Isabella Annesi-Maesano, J. M. Anto, S. Arnavielhe, E. Asayag, E. Bacci, A. Bedbrook, et al.

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Abbreviations: AHA, Active and Healthy Aging; AIT, specific immunotherapy; AR, allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma; CARAT, Control of Allergic Rhinitis and Asthma Test; EIP, European Innovation Partnership; EU, European Union; HIT, Health information technology; ICT, information and communications technology; MACVIA, Contre les MAladies Chroniques pour un VIellissement Actif; MASK, MACVIA-ARIA Sentinel NetworK; NAR, non allergic rhinitis; SCUAD, Severe chronic upper airways disease; VAS, visual analogue scale.

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Abstract

The overarching goals of the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA) are to enable European citizens to lead healthy, active and independent lives whilst ageing. The EIP on AHA includes 74 Reference Sites. The aim of this study was to transfer innovation from an app developed by the MACVIA-France EIP on AHA reference site (*Allergy Diary)* to other reference sites. The phenotypic characteristics of rhinitis and asthma multimorbidity in adults and the elderly will be compared using validated information and communication technology (ICT) tools (i.e. the *Allergy Diary* and CARAT: Control of Allergic Rhinitis and Asthma Test) in 22 Reference Sites or regions across Europe. This will improve the understanding, assessment of burden, diagnosis and management of rhinitis in the elderly by comparison with an adult population. Specific objectives will be: (i) to assess the percentage of adults and elderly who are able to use the *Allergy Diary*, (ii) to study the phenotypic characteristics and treatment over a 1-year period of rhinitis and asthma multimorbidity at baseline (cross-sectional study) and (iii) to follow-up using visual analogue scale (VAS). This part of the study may provide some insight into the differences between the elderly and adults in terms of response to treatment and practice. Finally (iv) work productivity will be examined in adults.

KEYWORDS
Allergy, *Allergy Diary*, asthma, European Innovation Partnership on Active and Healthy Ageing, rhinitis

1 | INTRODUCTION

Rhinitis, the most common chronic disease in Europe, often starts early in life, persists across the life cycle and causes a high disease burden in all age groups.[1] Rhinitis and asthma multimorbidity is common[1] and the two diseases should be considered jointly. The symptoms of allergic rhinitis (AR) can cause considerable morbidity in terms of physical and emotional comfort and functional capacity. Work productivity is one of the major societal impacts of AR.[2,3] Sleep impairment is common in AR[4,5] and is associated with severe nasal symptoms.[6]

By 2020, rhinitis will affect at least 20% of the old-age population.[7-11] Rhinitis in this age group has phenotypic specificities and treatment modalities including poly-medication. The effects of polypharmacy may contribute to congestion and dryness.[12] Sex may also be a confounding factor in the elderly. The phenotypic characteristics and treatment of rhinitis in the elderly depend on ageing (physiology, immunology), socio-cultural barriers, environmental factors (urban vs rural), allergic and non-allergic multi-morbidities,[13,14] drug availability and affordability, specific side effects to drugs in this age group,[15] and health systems as well as type of care. However, rhinitis burden in the elderly is an under-recognized and under-treated problem.[8] Important demographic changes are expected in the European population. It is therefore crucial to study the phenotype and treatment of rhinitis-asthma multimorbidity in this age group in different European regions in order to (i) provide new concepts and hypotheses and (ii) offer new diagnosis and management strategies to reduce health and social inequalities.

Measures of AR control include symptom scores, control scores and patients' self-administered visual analogue scales (VAS).[11,16-23] VAS, a psychometric response scale for subjective characteristics or attitudes, has been successfully used in many diseases including AR. Severe chronic upper airway disease (SCUAD) defines uncontrolled AR patients despite optimal pharmacotherapy.[24] The Control of Allergic Rhinitis and Asthma Test (CARAT)[25-28] is the only self-administered questionnaire to quantify the control of both AR and asthma concurrently. It consists of 10 questions on upper and lower airway symptoms, sleep interference, activity limitation, and the need to increase medication over a 4-week period. CARAT meets all items of the COSMIN (COnsensus-based Standards for the selection of health Measurement INstruments) checklist.[29-31] CARAT was developed and validated in Portugal and has been translated and culturally adapted in over 25 languages and nine countries (Belgium, Brazil, France, Germany, Greece, India, Italy, the Netherlands and Ukraine). Web and smartphone versions have been developed, and an open model of distribution contributes to its dissemination.

European Innovation Partnerships (EIPs) bring together all relevant actors at European Union (EU), national and regional levels to: (i) step up research and development efforts; (ii) coordinate investments in demonstration and pilots; (iii) anticipate and fast-track any necessary regulation and standards; and (iv) ensure that any breakthroughs are quickly brought to the market. The goals of the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA) are to enable European citizens to lead healthy, active and independent lives whilst ageing. The EIP on AHA includes 74 Reference Sites.

MACVIA-France (Fighting chronic diseases for active and healthy ageing in France) is a reference site of the EIP on AHA.[32,33] It initiated the project "Integrated Care Pathways for airway diseases (AIRWAYS ICPs)".[34,35] AIRWAYS ICPs aims to develop multi-sectoral ICPs for rhinitis and its multi-morbidities in the elderly, implementing emerging technologies for individualized and predictive medicine.[35] A patient-centred mobile application (app for iOS and Android smartphones) has been developed.[6,36] This app (*Allergy Diary*) uses VAS scores and enables the daily assessment of rhinitis and asthma control by patients themselves.[37,38] It will also include a Clinical Decision Support System (CDSS).[22] The *Allergy Diary* is available for free download in 21 countries and 16 languages and has already been tested by over 8,000 users of all ages. Real-time data from users' smartphones can be stored and retrieved in a functional database. This EIP on AHA Synergy project has been developed between Action Groups of the EIP on AHA to build bridges for innovation in AHA.[39] The *Allergy Diary* also includes CARAT.

Regional organizations engaged in the EIP on AHA were proposed to apply for a grant in order to facilitate the transfer of innovative practices (Twinning) for implementation in other regions (http://www.scale-aha.eu/news.html). The aim of this initiative is to facilitate the deployment of large-scale digitally-enabled innovative solutions for health and care delivery to the ageing population. It therefore contributes to the European Scaling Up Strategy of the EIP on AHA, already initiated by MACVIA-ARIA.[40]

2 | OBJECTIVES OF THE MACVIA-ARIA TWINNING

The transfer of innovative practices (Twinning) aims to transfer and implement (i) the *Allergy Diary* developed by MACVIA-LR[37,38] and (ii) CARAT[25-28] to the different EIP on AHA Reference Sites. Other tools may also be used.

The longer-term aim of the Twinning is (i) to provide care pathways for individualized and predictive medicine for rhinitis and asthma multimorbidity in the elderly,[36] (ii) to extend the study to sleep impairment in AR and asthma and (iii) to assess interactions of allergen exposure and air pollution. Moreover, the Twinning will allow Reference Sites from different areas of Europe to interact. This will increase knowledge, enable the transfer of know-how and support the establishment of local structured thematic networks on respiratory diseases sharing tools, indicators and knowledge that are available in the EU context (Table 1).

Although the vast majority of Reference Sites will work on the main aim of the Twinning (rhinitis and asthma multimorbidity in the elderly), some will have a different Twinning process to reinforce the project (Table 2).

As the study will last 1 year—to account for differences in allergen exposure—the starting data are not necessarily the same in all countries and new Reference Sites can join the Twinning within the next 6 months.

TABLE 1 Objectives of the twinning

General objectives
To compare phenotypic characteristics of rhinitis and asthma multimorbidity in adults and the elderly using validated ICT tools (*Allergy Diary* and CARAT) in EIP on AHA Reference Sites across Europe to better understand, diagnose and manage rhinitis and assess its burden in the elderly
Specific objectives
To assess the percentage of adults and elderly who are able to use the *Allergy Diary*:
Cross-sectional study: The study will include all users recruited by Reference Sites over a period of 1 year. All baseline characteristics will be analysed. Phenotypic characteristics and treatment of rhinitis and asthma multimorbidity in the elderly will be compared with those of adults
Longitudinal study: The study will include all users recruited by Reference Sites over a period of 1 year who have reported more than 1 day of VAS. VAS scores will be analysed. This part of the study may provide some insight into the differences between the elderly and adults in terms of response to treatment and practice
To better understand the methodological problems in this new type of observational study, and particularly age-dependent problems with ICT

TABLE 2 Complementary activities of the twinning

- Andalucia will contribute to the mHealth assessment strategy and will test the quality of the mobile health app (*Allergy Diary*) (http://www.calidadappsalud.com/en).
- Northern Ireland will test another aspect of rhinitis and asthma multimorbidity (Fit at work with rhinitis) as uncontrolled allergic and non-AR has a major impact on work productivity.[2,41-45]
- Porto4Ageing will also contribute to (i) the implementation of CARAT in the Allergy Diary app for European countries with completed cultural adaptation processes (the Netherlands, Belgium, Germany, Greece, Ukraine, Italy, France)[25-28] and (ii) the analysis of long-term longitudinal variability of CARAT scores and its associations with the MASK VAS.
- The HealthRegion CologneBonn will help with the ethical aspects of the Twinning.
- The Trentino reference site will explore the advocacy of MACVIA study results within the Trentinosalute 4.0 Competence Centre on digital health.

3 | ORIGINATOR AND ADOPTER ORGANISATIONS

There are two types of organizations involved (Table 3):

- The "Organization transferring the innovative practice" (originator organization): the organization with the experience and know-how developed in a particular field of intervention, awarded Reference Site status in the 2016 call and included in the innovative practices repository of the EIP on AHA (https://ec.europa.eu/eip/ageing/repository_en).
- The "Organization adopting the innovative practice" (receiving/adopter organization): the organization that will receive the innovative practice and deploy/implement it in its territory. This is the organization that was awarded Reference Site status in the 2016 call and that will benefit from the experience and know-how developed by the "organization transferring an innovative practice" in a particular field of intervention.

There will also be Reference Sites that will help to perform the Twinning. The MACVIA-ARIA Twinning mainly includes Reference Sites but certain other sites are also included (Figure 1).

All Reference Sites wishing to join the MACVIA-ARIA Twinning at a later stage are welcome.

In France, Italy, Germany, Lithuania, Poland, Portugal and Turkey, the Twinning will be carried at a national level with the Allergy Society and national health authorities of the country.

4 | MACVIA-ARIA TWINNING METHODOLOGY

4.1 | Tools

The *Allergy Diary* will be used in all centres except for Andalucia. It is currently available on cell phones and also on tablets for health-care professionals in English (*Allergy Diary Companion*).[37,38] Translations are pending. It includes EQ-5D,[46] the WPAI-AS questionnaire[47-49] and, in some countries, CARAT[26,28,50] (when available in electronic form).

4.1.1 | Allergy diary

App (ANDROID and IOS)

The *Allergy Diary* collects information on AR symptoms experienced (nasal and ocular), disease type (intermittent/persistent), how symptoms impact users' lives, and type(s) of AR treatment used (Table S1, Appendix S1).[6]

Geolocalized users assess their daily symptom control using the touchscreen functionality on their smart phone to click on five consecutive VAS (i.e. general, nasal and ocular symptoms, asthma and work) (Appendix S2).

Medications are also recorded daily (Appendix S3). Mobile phone messaging facilitates the management of AR, providing prompts to assess disease control, take medication, and visit a health care provider if appropriate.

The system was initially deployed in 15 European countries and in 15 languages (translated and back-translated, culturally adapted and legally compliant). It is now also available in Australia, Brazil, Canada, Mexico, Switzerland and Turkey. The system is currently being prepared for the Czech Republic.

Several observational studies have been carried out using the *Allergy Diary*.

- The *Allergy Diary* (Android and iOS) is user-friendly and has been tested for AR and conjunctivitis in over 5,000 users. The simple baseline questionnaire administered by cell phones allows the identification of phenotypic differences between *a priori* defined rhinitis and asthma multimorbidity groups and proposes novel concepts on AR.[6]
- The VAS reporting has been validated (Caimmi et al., submitted).
- Work productivity can be assessed daily (VAS) and there is a highly significant correlation between rhinitis control and work.[39]
- A cross-sectional observational study enables the differentiation of treatment strategies in AR (Bousquet et al., in preparation).
- Over 5% of *Allergy Diary* users are ≥65 years of age.

4.2 | Outcomes

In this observational study, all subjects will fill in the following:

- Baseline characteristics (Table 5).
- EQ5D[46] which can be used in the elderly.
- Treatments (Appendix S3).
- Four consecutive VAS measurements (general, nasal and ocular symptoms, asthma) (Appendix S2).

In addition, adults will fill in:

- The Work Productivity and Activity Impairment Allergic Specific Questionnaire (WPAI-AS)[47,51] (Appendix S4).
- VAS for work (Appendix S2).

TABLE 3 Originator and adopters of the Twinning

Originator
1. MACVIA-France
J Bousquet, S Arnavielhe, A Bedbrook, C Cartier, P Demoly, G Onorato, R Jaquet, D Laune, F Viart
Adopters
2. Andalucia
AM Carriazo, J Ferrero
3. Aragon
R Angles
4. Campania
M Illario, M Triggiani, C Stellato, A Vatrella, G De Feo
5. Catalonia
A Dedeu Baraldès, M Olivé Elias, JM Anto, V Cardona, J Mullol, A Valero
6. City of Helsinki
T Haahtela, T Strandberg, E Valovirta, J Salimaki, S Toppila-Salmi, J Karjalainen, T Vasankari
7. Coimbra
J Malva, A Todo Bom, C Robalo-Cordeiro, M Morais Almeida, MT Veríssimo, A Mota-Pinto
8. Heraklion
EP Prokopakis
9. HealthRegion CologneBonn
R Mösges, L Klimek, T Bieber, A Zurkuhlen, O Pfaar, T Zuberbier, KC Bergmann
10. Life Tech Valley
I Lieten, PW Hellings, C Bachert
11. Liguria
G Passalacqua, E Bacci, L Bertorello
12. Lodz
P Kuna, M Bochenska-Marciniak, M Kupczyk, P Lacwik
13. Medical Delta
NA Guldemond, NH Chavannes, R Gerth van Wijk, WJ Fokkens
14. Milan Metropolitan - Bergamo Province
M Romano, M Sorlini, AC Pozzi, D Lauri, F Corti, G Levato, M Nalin, I Baroni
15. NHS 24
A Sheikh, A Custovic
16. Northern Ireland
I Young, E Colgan
17. Olomouc
V Kolek, Z Gutter, M Sova
18. Pays de la Loire
A Magnan, J Hajjam, L Colas
19. Porto
J Fonseca, M Costa, AM Pereira
20. Puglia
MT Ventura
21. Regione Piemonte
C Bucca, G Moda, G Rolla, A Romano, V Tibaldi
22. Region of Southern Denmark
C Bindslev-Jensen, E Eller, C Wanscher
23. Région Nouvelle Aquitaine
I Bosse
24. Turkey (Global Alliance against Chronic Respiratory Diseases Regional Network)
A Yorgancioglu, B Gemicioglu, C Cingi, O Kalayci, F Kalyoncu
25. ARIA Sweden
M Wickman, E Melén
26. ARIA Lithuania
A Valiulis, R Dubakiene, R Emuzyte, V Kvedariene
27. Australia
S Bosnic-Anticevich, RE O'Hehir
28. Brazil
AA Cruz
29. Mexico
D Larenas-Linnemann
30. Argentina
JC Ivancevich

4.2.1 | Printing of app data using a computer

Patients cannot give access of their electronic data to a HCP due to privacy policies. However, they can print the daily control of their disease as well as their medication details that they filled in in the *Allergy Diary*. The procedure is as follows (Figure 2):

4.2.2 | CARAT

CARAT will be implemented in the *Allergy Diary* app for European countries with completed cultural adaptation processes (the Netherlands, Belgium, Germany, Greece, Ukraine, Italy, France). Every 2-4 weeks, participants with rhinitis and asthma will be prompted to fill in the CARAT questionnaire.

4.2.3 | The physician's questionnaire

For some patients, physicians will fill in a questionnaire that includes the questions of the *Allergy Diary* and of CARAT (Table 4).

The questionnaire will be filled in directly using the ARIA website.

4.3 | Ethics

The terms of use have been translated into all languages and customized according to the country's legislation. They allow the use of the results for research purposes. The example of the UK terms of use is given in Appendix S5.[39] The data are anonymized except for

FIGURE 1 Twinning of the *Allergy Diary* in EIP on AHA Reference Sites (15-11-2016) [Colour figure can be viewed at wileyonlinelibrary.com]

the geolocalized data that are never totally anonymous. The European Commission's Article 29 Working Party stated that geolocation information is personal data (http://ec.europa.eu/newsroom/just/item-detail.cfm?item_id=50083) and that information can only be collected, shared, or stored with people's express consent. This is the case for MASK as users agree on geolocation in the terms of use of the app. Moreover, geolocation is optional and the user can allow it or not on his/her cell phone. Geolocation can be removed at any time. The problem of privacy due to geolocation was examined by the lawyers of each of the countries in which MASK has been launched and it was found to be in accordance with the existing laws. Moreover, geolocation is not used in the data mining process neither is the phone IP.

The Allergy Diary is a CE1 medical device and does not require ethical approval. An ethical agreement has been approved by a German ethics committee for the questionnaire. This ethical agreement will serve for all EU countries.

A participation agremeent to be signed by the patient has been proposed.

4.4 | Possible biases

As in any other observational study, the absence of randomization may be a source of relevant biases.[52] However, observational studies reflect "real-world" use and practice more closely than randomized control trials (RCTs) in terms of the heterogeneous patient populations included and medical interventions.[53] They can provide clinically relevant information not necessarily provided by RCTs. Given the limitations of an observational study approach, it is important to optimize their study design to maximize their validity. In particular, known causes of bias and confounding should be measured.[53]

However, this initiative was not designed to compare questionnaires with apps. A bias might be introduced because app users provide self-reported information in an uncontrolled setting. However, a recent systematic review has assessed the impact that smartphone and tablet apps as a delivery mode have on the quality of survey questionnaire responses compared to any other traditional alternative delivery mode. The review showed that apps might not affect data equivalence as long as the intended clinical application of the survey questionnaire, its intended frequency of administration and the setting in which it was validated remain unchanged.[54]

4.5 | Timeframe for procurement/implementation until 2018

- The adopters will use freely available existing tools including (i) the *Allergy Diary* (Apple app Store and Google Play Store) and (ii) the questionnaire filled in by physicians.
- The *Allergy Diary* is available in 21 countries (Austria, Australia, Belgium, Brazil, Canada, Denmark, Finland, France, Germany, Greece, Italy, Lithuania, Mexico, the Netherlands, Poland, Portugal, Spain, Sweden, Switzerland, Turkey and the UK) and languages (national languages plus Catalan and Finnish Swedish). It can be implemented immediately. For other countries, translation, back-translation, cultural adaptation and legal compliance all require approximately 3-6 months.
- The phenotype, EQ-5D (MAFEIP[39,55]) and AR/asthma medication lists (IMS list customized for each country) are included in the *Allergy Diary*.

4.6 | Action/implementation plan

Three protocols can be implemented (Table 5).

4.6.1 | Deployment of the app to the different Reference Sites (RS)

Immediate and free access (Apple app Store and Google Play Store) is available for 21 countries, from 3 to 6 months for other countries.

4.6.2 | Centres participating in the Twinning

Each Reference Site will select physicians (with training in allergy) who work in out-patient clinics, in hospitals and/or in private practice. A combination of both practices would be optimal. All physicians will be volunteers for the study. There will be no compensation.

1- Open the Allergy Diary app and choose "Show Data on Computer" in the main menu

2- Go to www.macvia-aria-allergy-diary.com/data on your PC/Laptop (enter this URL in the address bar of the browser from your PC/Laptop)

3- Scan the QR code with the Allergy Diary app

4- The screen with your personal data can be seen

5- And you can also print these data (see figure below).

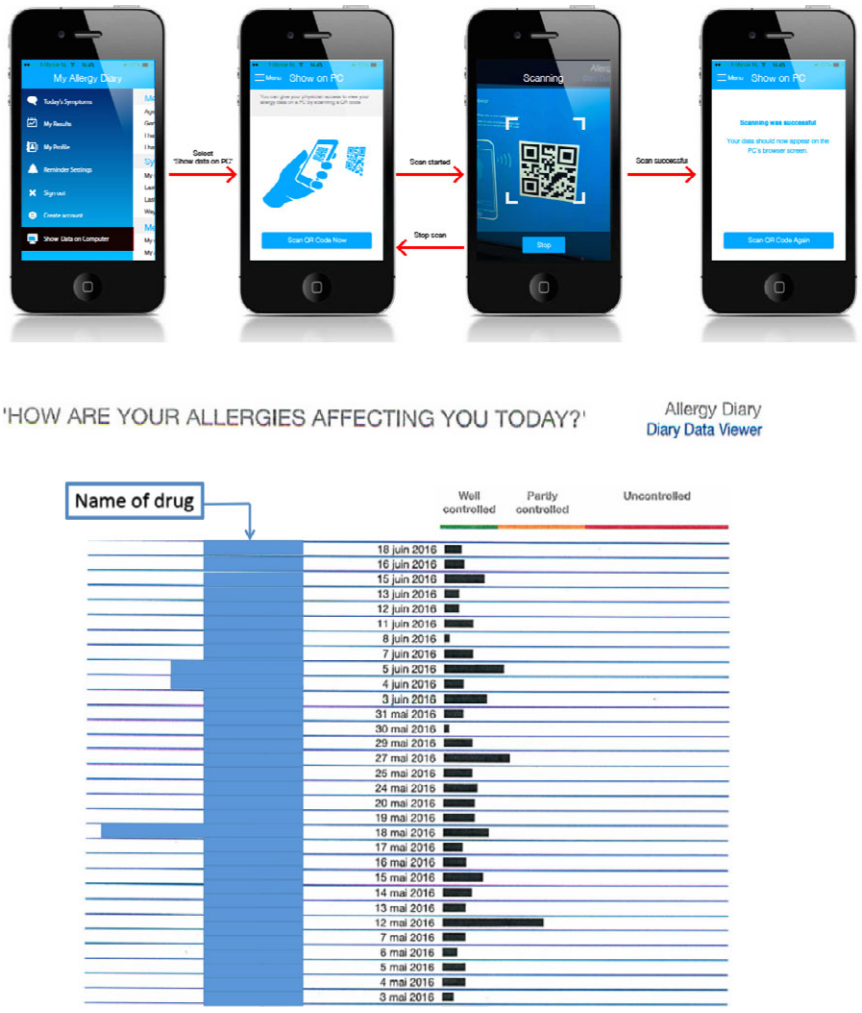

FIGURE 2 Transfer of patient information on a computer and printed information

4.6.3 | Enrolment of users (the elderly) with rhinitis

If possible, each Reference Site will enrol 50 elderly persons (≥65 years) able to use the *Allergy Diary* and 100 adults (<65 years) using the longer protocol. If possible, the number of users will be increased. At the end of the year, each reference site will receive an overview of the data collected in its site. Each physician is expected to enrol at least 10 adults and 5 old age persons.

The duration of enrolment is 12 months to account for variability in allergen exposure during the year. Thus, the study can be initiated in Reference Sites from 1 January, 2017 to 1 July, 2017.

4.6.4 | Study protocol

Two different protocols can be used (and probably mixed in the same region) depending on the decision of the physician.

- Protocol 1: The physician enrolling the user asks the patient to use the *Allergy Diary* and checks that this has been done and that the user has agreed to be geolocalized. This latter point is of importance as it will help to analyse differences between regions. Both specialists and physicians working in primary care can participate in the Twinning.
- Protocol 2 (allergists)
    - Only patients who have not registered to the app will be enrolled.
    - The physician enrolling the user will complete the questionnaire and will profile his/her patient in a computer by answering an online questionnaire (ARIA-EUFOREA website)
    - The physician will end the profile by adding a random alpha-numerical code to his/her patient profile (as we process during

TABLE 4 Questionnaire to be filled in by the physician

(A)

MACVIA- ARIA ***Physician's Questionnaire***				**Date : _ /_/_**
1- Date of birth	LIST WITH YEARS_ /_/_			
2- Sex			**Male**	**Female**
			○	○
3- The patient is suffering from				
Current allergic rhinitis				☐
Current asthma (within the past 3 months)				☐
Conjunctivitis				☐
Non-allergic rhinitis				☐
Asthma previously in life				☐
Current atopic dermatitis				☐
4- Impact of allergic symptoms				
		Yes	**No**	**Don't know**
Symptoms affect sleep		○	○	○
Symptoms restrict daily activities		○	○	○
Symptoms restrict work or participation in school		○	○	○
Symptoms are troublesome		○	○	○
5- CARAT Questionnaire *Question 5- A) should be read to the patient with the patient choosing the answer. There should be no "interpretation": the physician should not fill in the questionnaire on behalf of the patient.* **A) Due to your allergic respiratory diseases (asthma, rhinitis, allergies) in the last four weeks, on average, how many times did you have:**				
	Never	**Up to 2 days per week**	**More than 2 days per week**	**Almost every day**
Blocked nose?	○	○	○	○
Sneezing?	○	○	○	○
Itchy nose?	○	○	○	○
Runny nose?	○	○	○	○
Shortness of breath/dyspnoea?	○	○	○	○
Wheezing in the chest?	○	○	○	○
Chest tightness during physical exercise?	○	○	○	○
Tiredness/limitations in doing daily tasks?	○	○	○	○
Waking up in the night?	○	○	○	○
5- CARAT Questionnaire *Question 5- B) should be read to the patient with the patient choosing the answer. There should be no "interpretation": the physician should not fill in the questionnaire on behalf of the patient.* **B) Due to your allergic respiratory diseases (asthma, rhinitis, allergies) in the last four weeks, how many times did you:**				
	I'm not taking any medicine	**Never**	**Less than 7 days**	**7 or more days**
Increase the use (dosage or frequency) of your medicine?	○	○	○	○
6- Allergic sensitization has been diagnosed (within the past 5 years) by:				
Skin test				○
Specific IgE				○
Skin test + Specific IgE				○
Not diagnosed				○
7- Positive test for:				
House dust mites				☐
Alder				☐
Hazel				☐
Grass pollen				☐

clinical study). This code will be manually registered by the patient on his/her smartphone at the downloading step of the app.

- Hence, physicians' profile data and patients' self-recorded symptoms data will be reconciled for analysis.
- The physician will ask the person to use the *Allergy Diary* and will check onsite that this has been done and that the user has agreed to be geolocalized.

- Protocol 3: Fit at work: Some enterprises (NHS Northern Ireland, Hôpital de Valenciennes, France) are participating in an analysis of work productivity.

For the three protocols, there is potential for direct benefit for the patients and the physicians.

As an example, during the patient's next visit, the physician will see a graph indicating the level of control, the compliance to the treatment and the treatments actually taken by the patient.

Moreover, the first results of the Allergy Diary are extremely interesting.[3,6] Unpublished data show that the care pathways of patients with AR and asthma multimorbidity should be reconsidered as most patients self-medicate.

TABLE 4 (Continued)

(B)	
Cypress pollen	☐
Birch pollen	☐
Other tree pollen	☐
Parietaria pollen	☐
Ragweed pollen	☐
Cat	☐
Dog	☐
Other inhalant allergen	☐
Food allergen	☐
Don't know	☐
8- Prescribed treatment	
(Scrolling list) Add "no treatment" in the scrolling list	
9- The patient currently receives immunotherapy for :	
House dust mites	☐
Alder	☐
Hazel	☐
Grass pollen	☐
Cypress pollen	☐
Birch pollen	☐
Other tree pollen	☐
Parietaria pollen	☐
Ragweed pollen	☐
Cat	☐
Dog	☐
Other inhalant allergen	☐
None	☐
10- Current immunotherapy is administered by:	
SCIT	☐
SLIT drops	☐
SLIT tablets	☐
Oralair	☐
Grazax	☐
11- Date of initiation of immunotherapy	
Month/Year (Scrolling list)	
12- Education	
Secondary school or less	○
Sixth form or college	○
Bachelor degree	○
Postgraduate	○
Missing	○
13- Work Status	
Currently full time employed	○
On light duty or some restricted work assignment or part time	○
Paid leave/sick leave	○
Unemployed because of other reason	○
Student (school, college, university)	○
Keeping house/homemaker	○
Retired	○
On disability	○
Missing	○

4.6.5 | Real-time analysis of the data

The analysis will be based on the pilot study of the *Allergy Diary* (manuscript submitted and manuscript in preparation), and real-time analysis across the different Reference Sites will be available.

5 | EXPECTED OUTCOMES OF THE TWINNING ACTIVITIES

1. *Phenotypic characteristics*: The *Allergy Diary* collects information on AR symptoms and allergic multi-morbidities experienced (nasal and ocular, asthma), on how symptoms impact users' lives, and on the type(s) of AR and asthma treatments used. The study provides a unique opportunity (i) to investigate the phenotype of rhinitis and asthma multimorbidity in the elderly in Europe, (ii) to study differences with other age groups using data on file and (iii) to make comparisons across countries.
2. *Treatment of rhinitis and asthma multimorbidity and disease control*: The control of rhinitis appears to differ depending on the age group. The study will show differences (i) with other age groups using data on file and (ii) between regions, allowing optimization of care pathways.
3. *Use of the EQ-5D* allows quality-of-life and utilities data to be assessed. It is a MAFEIP tool.[39,55]

TABLE 5 Protocols of the Twinning

	Protocol 1 Short version	Protocol 2 Long version	Protocol 3 Fit at work
Allergy Diary	+	+	+
EQ5D, WP-AIAS	Optional	+	+
Physician's questionnaire		+	Optional
Ethical committee	Not needed	Obtained	Needed if physician's questionnaire
Participation agreement	Terms of use of app	Participation agreement form signed by patients	
Recruitment	Any user. Persons attending clinic visits can be included	Persons with rhinitis from clinics with a diagnosis of AR made by a specialist (with skin tests and/or specific IgE)	Users in settings participating in the "Fit at work" protocol

4. *Comparison between regions* (or countries depending on the health system)
5. Comparison between rural and urban environments.
6. *Care pathways*: the results of the study will be used to develop region-specific care pathways (AIRWAYS ICPs) using a personalized medicine approach. Self-management strategies will be of great importance.
7. *Knowledge and know-how transferred*: The epidemic wave of rhinitis in adults (over 25% of the European population) is now reaching the elderly. It is essential to better characterize, understand and manage this disease that affects social life and causes serious discomfort for sufferers. A pan-European view of the problem will allow a cost-effective and socially acceptable management of this disease. The *Allergy Diary*, developed by the MACVIA France Reference Site, is freely available for subjects in most European countries. The app will be deployed by the Reference Site Collaborative Network for transfer of knowledge.[40,56]
8. Rhinitis and asthma multimorbidity exemplifies why a lifecourse approach to AHA is the key to effective interventions that are sustainable for the public health systems.

6 | FUTURE DEVELOPMENTS

- Sleep is impaired in rhinitis and asthma[4,5] and the Allergy Diary has been found to accurately assess sleep impairment.[6] More data are needed and the app is being improved to include sleep-related questions.
- To correlate Allergy Diary data with allergen exposure using classical methods such as pollen counts or Google Trends-derived methods.[57]
- To better understand the links between AR and pollution in order to provide preventive and treatment strategies to reduce AR burden.

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