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Criteria used by health professionals on the selection of allergen immunotherapy in real clinical practice: Methodology

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ABSTRACT

Background: Allergen immunotherapy (AIT) is today the only etiological therapy for respiratory allergic diseases, including allergic rhinitis, allergic conjunctivitis, and allergic asthma. Even though interest in real-world data has recently increased, publications mainly focus on short-term and long-term efficacy and safety of AIT. Indeed, information is still lacking regarding the "key parameters" or "drivers of prescription" used by doctors to prescribe AIT or by the patients to accept AIT as treatment for their respiratory allergic disease. Examining these factors is therefore the main goal of the CHOICE-Global Survey: "Criteria Used by Health Professionals on the Selection of Allergen Immunotherapy in Real Clinical Practice: An international academic electronic survey".

Methods: We present the methodology of the CHOICE-Global Survey, an academic, prospective, multicenter, observational, transversal, web-based e-survey, conducted in real-life clinical settings designed to collect data from 31 countries representing 9 global different socio-economic and demographic regions. In the present document, we describe the survey, how it was conceived and developed, how data are stored and analyzed, and the different steps that will provide this information to the allergy community.

Conclusions: The CHOICE-Global Survey will be able to provide, from an academic point of view, information on the drivers of prescription of AIT in real-life practice and improve understanding regarding the key parameters considered by doctors and patients for such therapy.

Keywords: Allergen immunotherapy, Clinical practice, Drivers, Prescription, Survey

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BACKGROUND

Allergen immunotherapy (AIT) has been used for more than a century as part of the treatment of allergic diseases. It is the only etiological therapeutic intervention currently available worldwide.

The disease modifying potential of AIT has been proven for IgE-mediated allergic rhinitis, rhinoconjunctivitis and asthma in children, adolescents, and adults.[1,2]

The clinical efficacy and safety of AIT for both subcutaneous and sublingual immunotherapy (SCIT and SLIT, respectively) have been documented in multiple systematic reviews and meta-analyses of double-blinded placebo-control randomized clinical trials (DBPCRCTs) for respiratory allergy.[3] Different clinical outcomes and laboratory parameters have been successfully evaluated.[4] Thus, AIT is a well-established favorable option of treatment endorsed by practicing physicians, academic groups, regulatory agencies, and health authorities.

During the last decades, there has been an emerging interest on "real-world data" (RWD) which allows us to complement the information generated by the "gold standard" DBPCRCTs.[5] RWD has been obtained for the efficacy and safety of AIT from real-life clinical settings, following the national/regional clinical parameters of practice of AIT.[6] The clinical and socio-economic outcomes evaluated support the efficacy of AIT in all studies.[7,8]

However, there is still information lacking regarding the "key parameters" or "drivers of prescription" used by doctors to prescribe AIT or by the patients to accept AIT as treatment for their respiratory allergic disease. This novel information would help clinicians, academics, researchers, and regulatory groups to better understand and optimize the use of AIT, in real-life settings.

In an independent academic manner, we set up an electronic survey to determine and prioritize those "drivers of prescription" in different regions of the world. Two electronic surveys, one for prescribing doctors and one for patients receiving AIT were designed to obtain this information. Minor adjustments according to local/regional practical uses of AIT were implemented as well.

This "global electronic survey" was designed to identify these "drivers of prescription" for AIT for respiratory diseases (allergic rhinitis/rhinoconjunctivitis and/or allergic asthma) caused by IgE-dependent-hypersensitivity reactions to aeroallergens in several countries.

In this paper, the methodology developed to perform this global prospective electronic survey, called CHOICE-GLOBAL for "Criteria Used by Health Professionals on the Selection of Allergen Immunotherapy in Real Clinical Practice: An international academic electronic survey" is described.

METHODS

Design

This is a prospective, multicenter, observational, transversal, web-based e-survey, conducted in real-life clinical settings designed to collect data for a minimum of 12 consecutive months, starting from the date of inclusion of the first patient in each country. Doctors' and patients' anonymity was preserved during the study. Due to SARS-CoV-2 pandemic sanitary international restrictions, not all the participating countries have the same start date of data collection.

Electronic survey

Two on-line questionnaires were designed:

1. **Doctors' Questionnaire (DQ)**: This is the first questionnaire to be completed, and the survey participating doctor should fill it in only once. It includes 24 questions, and its completion takes 4–5 min. Through the DQ we collect information about the doctor who is prescribing AIT, such as their specialty, clinical experience on AIT and on clinical allergy, setting of practice (public or private, available facilities and auxiliary staff), number of patients with respiratory allergy under their care, number of them under AIT, and commonly used diagnostic tools and procedures. Some questions were designed to identify doctors' preferences related to AIT such as: preferred route and type of AIT, type of schedule and, above all, the main criteria for prescribing AIT. Detailed information may be found in Supplementary Appendix A.
2. **Patient's questionnaire (PQ)**: This questionnaire should be completed by the prescribing

doctor only once for each patient starting AIT. It includes 27 questions, and its completion takes 7–8 min. Apart from socio-demographic data (age, gender, education, occupation), it comprises information related to current allergic diseases (asthma, rhinitis, urticaria, atopic dermatitis, conjunctivitis and food, drug, or hymenoptera allergy), patient's allergic profile (allergen sensitization), current allergy treatment, previous AIT (if any, route, and composition), details of the current prescribed AIT (disease indication and severity, composition, route, treatment schedule), relevance of certain aspects of the patient's profile and of the AIT prescription, and expectation of benefits. Detailed information can be found in Supplementary Appendix B.

DQ and PQ were prepared in accordance with the "checklist for reporting results of internet e-surveys, CHERRIES".[9] The questionnaires use a skip logic pattern, allowing participating doctors to avoid certain sections according to their responses in preceding questions. The questions are presented in a fixed order and most of them have a close-ended format having drop down list answers, aiming to avoid open answers as much as possible. An optional free text box ("others") is supplied in some of the questions to avoid missing unexpected information. Most of the questions are designed to be answered in a compulsory manner.

Questions were modified slightly or "tailored" in accordance with recommendations by national Ethic Committees or requests by each participating country, but there were no changes in the main body of the survey.

Both questionnaires need to be completed online in English. Translation into national languages was also provided for those doctors who didn't feel comfortable enough to thoroughly understand specific questions in English.

A beta test was performed by all national coordinators – real users of the software application – to assess and confirm the usefulness of the questionnaires and the feasibility of using them in real life settings for this larger-scale survey.

Working groups

1. **Executive Team**: It is composed of a group of international allergists and academics with extensive experience in AIT. They were responsible for: i) designing the project, ii) elaborating the e-questionnaires (DQ and PQ), iii) identifying and contacting allergy key opinion leaders with interest in AIT, iv) adapting the questionnaires to local clinical practices (when needed), v) facilitating all national logistics and providing requested documentation, vi) collecting information in an independent data-base and, vii) developing the project in a global scale.
2. **Data-base Managers**: It is composed of a group of independent allergists responsible for: i) providing codes for each participating doctor and patients, ii) answering questions and queries from participant physicians, iii) creating recruitment reports at regular time interval to monitor study evolution, iv) closing and cleaning data-base and v) providing all raw data to an independent third party (statisticians) for further analysis.
3. **National Coordinators**: They are allergists in each country responsible for: i) identifying local doctors prescribing AIT willing to take part in the survey, ii) coordinating local logistics and iii) implementing strategies to boost participation, at a local level and iv) obtaining survey's local/national ethical approval.
4. **Participating Doctors**: They are registered doctors currently practicing clinical allergy who are prescribing AIT as part of regular clinical practice treatment. These colleagues are recruited by the corresponding national coordinator(s) by direct phone calls, emails, open academic meetings, etc. No participating fees are paid. All participating doctors are to be acknowledged and those from centers contributing larger numbers of patients are given the option to be named as co-authors in upcoming publications. A unique 5-digit code is allocated to each participating doctor by the data-base manager. The first 2 digits identify the country of origin and the last 3 the individual doctor's code number. Only data managers know to which doctor a specific code is associated, and they do not share such information with other members of the working group.

Patients included in the survey

This survey includes data from patients with respiratory allergy of all ages who initiate AIT with pollen, house dust mite, animal dander, and/or moulds as either SCIT, SLIT-drops, or SLIT-tablets according to real-life clinical standards of practice.

Patients could be included in this survey if previous AIT courses had been performed. Patients undergoing more than one AIT could be included, by completing 1 PQ for each new AIT prescription.

Patients under AIT with Hymenoptera venoms or food could not be included in the survey.

Global participation

Doctors and patients from 31 countries representing 9 global different socio-economic and demographic regions are included in this survey. The participating countries and the general plan for the timeline of the study are shown in Fig. 1. Due to the lack of interest, political local issues, or the request of honorarium of participating doctors, some other invited countries were not included in this international cohort.

AIT products

This survey is not intended to study any specific medication or any investigational medicinal product. No commercial names of AIT products or AIT product identification are recorded in any of the questionnaires. Therefore, pharmacovigilance data are not collected or reported in this survey.

Blinding design

Doctors' anonymity is crucial in this survey, where professional criteria and other sensitive information are collected. Therefore, data are collected anonymously and without any traceability. For this purpose, 2 separate databases have been created. The first database contains names and contact details of participating doctors, together with an individual numerical identification code for the survey. The second database includes only the survey information extracted from the 2 questionnaires. The Survey's Data Managers are the only persons with access to the first database, enabling contact with any study doctor if clarification regarding data is needed.

Database

The SurveyMonkey® online instrument is used for this survey. This program allows the

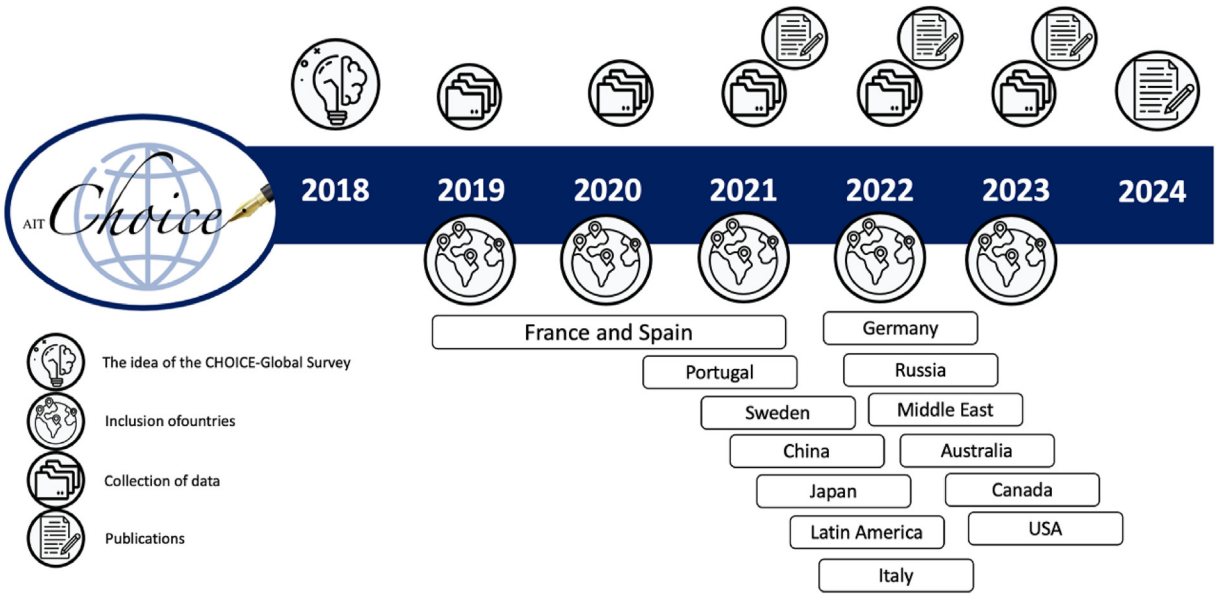

Fig. 1 CHOICE-Global: participating regions/countries. Legend – The first development begun in 2018. Since then, countries are included, and data collected (2019–2023). Papers will be published during the study, and the final manuscript is planned to be prepared in 2024. Latin America countries include Argentina, Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Panama and Peru. Middle East countries include Jordan, Lebanon, Kuwait, Kingdom of Saudi Arabia, Qatar and United Arab Emirates

participating doctors to store all data collected on a centralized electronic database. The SurveyMonkey® facility operates some of the most advanced technology for Internet security commercially available today. Secure Sockets Layer (SSL) technology protects user information using both server authentication and data encryption, ensuring that user data is safe, secure, and available only to authorized persons. SurveyMonkey® is PCI-DSS compliant.

Steps of CHOICE-global survey

The different steps of the CHOICE-Global Survey are shown in Fig. 2.

Legal and ethics framework

Directives and specific national laws in force in the participating countries and any regulatory national requirements are followed. Each national coordinator is responsible for contacting and gaining approval from their corresponding ethics committees.

Statistical methods

Statistical analyses will be carried out by an independent third-party using SPSS. Firstly, a general analysis of the DQ and PQ questionnaires will be performed to identify data entry errors, inconsistencies between variables. Once the database is cleaned, it will be locked.

Prior to any analysis, generation of new variables or classifications of interest, based on the data collected in the questionnaires will be established including analysis of multiple combinations of variables/groups with multiple answers. A descriptive analysis will provide the basic global information of the survey with a fusion of data from both DQ and PQ. Tables of frequency to analyze associations between two variables, contrasting the percentage differences with the statistical tests required according to established objectives (Chi-square, Fisher, McNemar, Odds Ratios) will be prepared. For the comparison of the distributions of quantitative variables, adequate techniques of analysis of the variance will be applied.

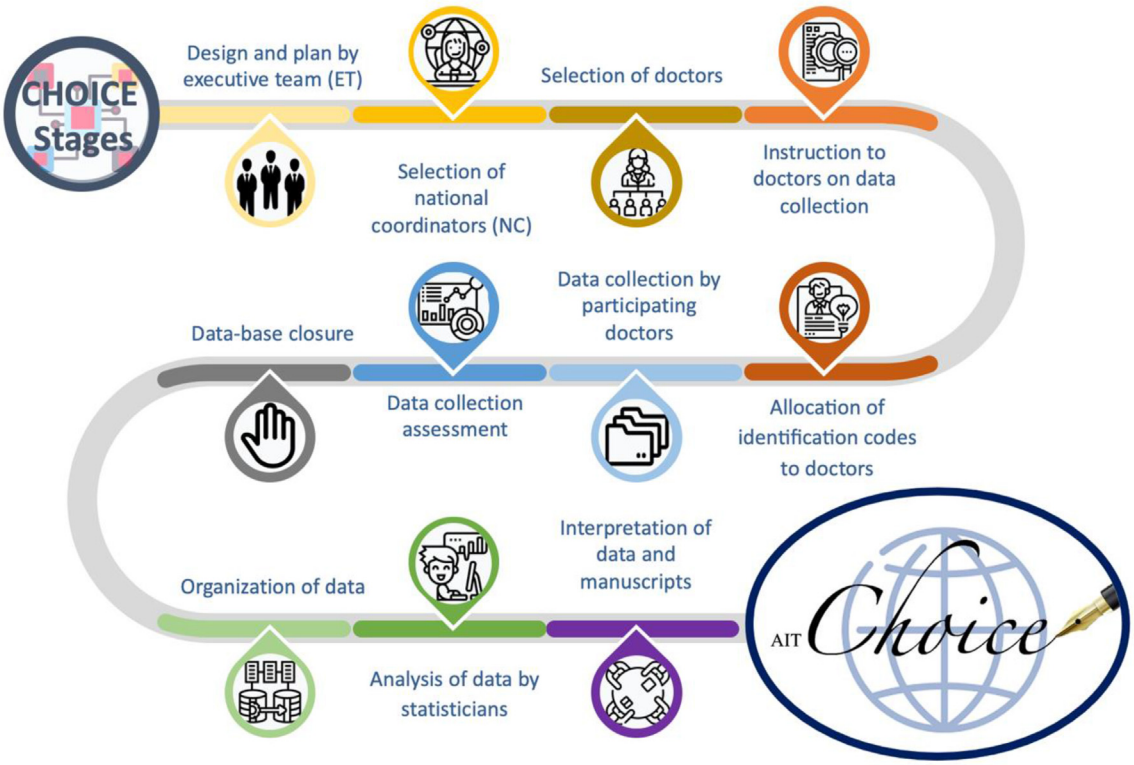

Fig. 2 CHOICE-global: Survey's working flow diagram (steps)

Multivariate analysis with relevant objective variables will be carried out, with logistic regression and decision trees. Unsupervised cluster analysis, to obtain a typology or profile of patients according to the variables that will be determined for their interest and/or their significance in the previous statistical analysis, will also be considered.

Database managers won't change throughout the study. Data are stored on the online SurveyMonkey® platform and, once surveys are completed in each country, downloaded, and stored on an encrypted file on a computer connected to a secured server of the Allergy Unit of the University Hospital of Montpellier (France) and on another one of the Hospital Infantil Universitario Niño Jesús of Madrid (Spain), by each one of the two data managers. Global analysis will only be done by the same independent third party. For local publications, national coordinators will be able to request access to the data of their own country.

Sample size of the survey

There is no sample size established, as this is an explorative pilot survey. Nevertheless, an estimation of the sample size has been carried out: including around 270 doctors, providing information on 18–20 patients each (more than 5000 patients) will provide an overall accuracy of 0.014 (<1.5%). To obtain an error lower than 5% in the estimation of a given country, a minimum of 400 patients per country is required.

Data quality assessment

The survey's data managers carry out a monthly systematic review of the database, searching for inconsistencies, such as duplicated data entry, missed information or any other kind of potential error. They generate a query and contact the corresponding survey's participating doctor responsible for that questionnaire for clarification. When a mistake is identified, and after double checking, the mistake can be removed, and the correct data can be introduced into the database. Tracked changes of all errors detected are recorded as well.

Financial issues

To cover the basic expenses necessary for the survey's development, an unrestricted educational grant was requested to several AIT companies, that had no access to the survey data. Neither the participating doctors nor the patients receive economic compensation. Therefore, it is the altruistic wish to contribute to science and to the improvement of our knowledge on the drivers of prescription for AIT, which moves all participants to participate in this academic project.

CONCLUSIONS

The CHOICE-Global Survey will be able to provide, from an academic point of view, information on the drivers of prescription of AIT in real-life practice and help better understand the key parameters considered by doctors and patients for such therapy.

Abbreviations

AIT, Allergen immunotherapy; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; DBPCRCTs, double-blinded placebo-control randomized clinical trials; RWD, real-world data; CHOICE, Criteria Used by Health Professionals on the Selection of Allergen Immunotherapy in Real Clinical Practice: An international academic electronic survey; DQ, Doctors' Questionnaire; PQ, Patient's questionnaire; SSL, Secure Sockets Layer.

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Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed yet during the current study. Data will be available at the completion of the study.

Authors' contributions

DC, PRR, PR, CV, CM, TBC, PD and MAC all equally contributed to the present work, through substantial contributions to the conception or design of the work; drafting the work and revising it critically for important intellectual content; agreement to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Ethics approval and registration

The Ethical Committee of the University Hospital of Montpellier approved the current study (2019_IRB-

MPL_09-02). The Study was registered on ClinicalTrials (NCT04038268). Depending on local legislations, approval will be obtained for each state requiring it in the future.

Consent for publication
All Authors reviewed and approved for publication the final version of the paper.

Declaration of competing interest
The Authors declare that there is no conflict of interest for the present paper.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2023.100749.

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