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| **Authors** | 14 | No limit stated |
| **Keywords** | 5 | 5 listed alphabetically |
| **Abstract** | 205 words | 200 words, unstructured |
| **Word count** | 3179 words | 4500 words |
| **Tables/figures** | 4 | 10 total |
| **References** | 76 | 200 references |

# Allergen immunotherapy: the growing role of observational and randomised trial "real-world evidence"

**Suggested short title:** Real-world evidence for allergen immunotherapy

## EAACI Methodology Committee Recommendations

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**Disclosures**

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**DF** reports no conflict of interest;

**EH** reports personal fees from AstraZeneca, personal fees from Sanofi, personal fees from Novartis, personal fees from Teva, personal fees from GSK, personal fees from Circassia, personal fees from Boehringer Ingelheim, personal fees from Valeas, personal fees from Nestlè Purina, outside the submitted work.

**IA** is Associate Editor for Allergy and Clinical and Translational Allergy.

**MJ** reports personal fees from ALK- Abello, Allergopharma, Stallergenes, Anergis, Allergy Therapeutics, Circassia, Leti, Biomay and HAL during the conduct of the study; personal fees from Astra-Zeneka, GSK, Novartis, Teva, Vectura, UCB, Takeda, Roche, Janssen, MedImmune and Chiesi, outside the submitted work

**LK** is President of the German Society of Applied Allergology (AeDA), President of German Allergy League, Vice-President of German Academy of Allergy and Environmental Medicine and Chair of EAACI ENT section. He has received research grants from Allergy Therapeutics/Bencard, Great Britain/Germany; ALK-Abelló, Denmark; Allergopharma, Germany; ASIT Biotech, Belgium; AstraZeneca, GB/Sweden, Bionorica, Germany; Biomay, Austria, Boehringer Ingelheim, Germany, Circassia, USA; Stallergenes, France; Cytos, Switzerland; Curalogic, Denmark; GlaxoSmithKline (GSK), Great Britain; HAL,

Netherlands; Hartington, Spain; Lofarma, Italy; Mylan, USA; Novartis, Switzerland, Leti, Spain; ROXALL, Germany; Sanofi, France and/or has served on the speaker's bureau or was consulting for the above mentioned pharmaceutical companies.

**OP** has received institutional grants and personal fees from ALK-Abelló, Allergopharma, Anergis S.A., ASIT Biotech Tools S.A., Bencard Allergie GmbH/Allergy Therapeutics, Biomay, Circassia, GlaxoSmithKline; HAL Allergy Holding B.V./HAL Allergie GmbH, Laboratorios LETI/LETI Pharma, Lofarma, Nuvo and Stallergenes-Greer, and personal fees from Indoor Biotechnologies, MEDA Pharma, Mobile Chamber Experts (a GA$^2$LEN Partner), Novartis Pharma and Pohl-Boskamp.

**RM** reports grants and personal fees from Engelhard, during the conduct of the study; personal fees from allergopharma, grants and personal fees from Allergy Therapeutics, grants and personal fees from Bencard, grants and personal fees from Leti, grants and personal fees from Lofarma, grants and personal fees from Stallergenes, grants from Optima, personal fees from Friulchem, grants and personal fees from Hexal, grants and personal fees from Klosterfrau, personal fees from FAES, personal fees from Meda, personal fees from Novartis, personal fees from UCB, grants and personal fees from BitopAG, grants from Hulka, grants from Ursapharm, personal fees and non-financial support from Menarini, personal fees from Mundipharma, personal fees from Pohl-Boskamp, grants from Inmunotek, personal fees from Hikma, personal fees from Sandoz, grants and personal fees from Lek, grants and personal fees from Cassella, personal fees from SanofiGenzyme, non-financial support from SmartPeakFlow, personal fees from Strathos, grants from Aimmune, outside the submitted work; and Ralph Mösges is the director and the owner of Clinical Research International Ltd. and of ClinCompetence Cologne GmbH, two contract research organizations focusing on upper airways diseases.

**ADG** reports personal fees from Aimmune Therapeutics and DBV Technologies outside the submitted work.

**JG** reports no conflict of interest;

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**GWC** has received grants and consultancy fees from A. Menarini, ALK-Abelló, Allergy Therapeutics, AstraZeneca-Medimmune, Boehringer Ingelheim, Chiesi Farmaceutici, Genentech, Guidotti-Malesci, GlaxoSmithKline, Hal Allergy, Merck Sharp & Dome, Mundipharma, Novartis, Orion, Sanofi-Aventis, Sanofi Genzyme/Regeneron, Stallergenes Greer, Uriach Pharma, Teva, Valeas and ViforPharma.

**Acknowledgements**

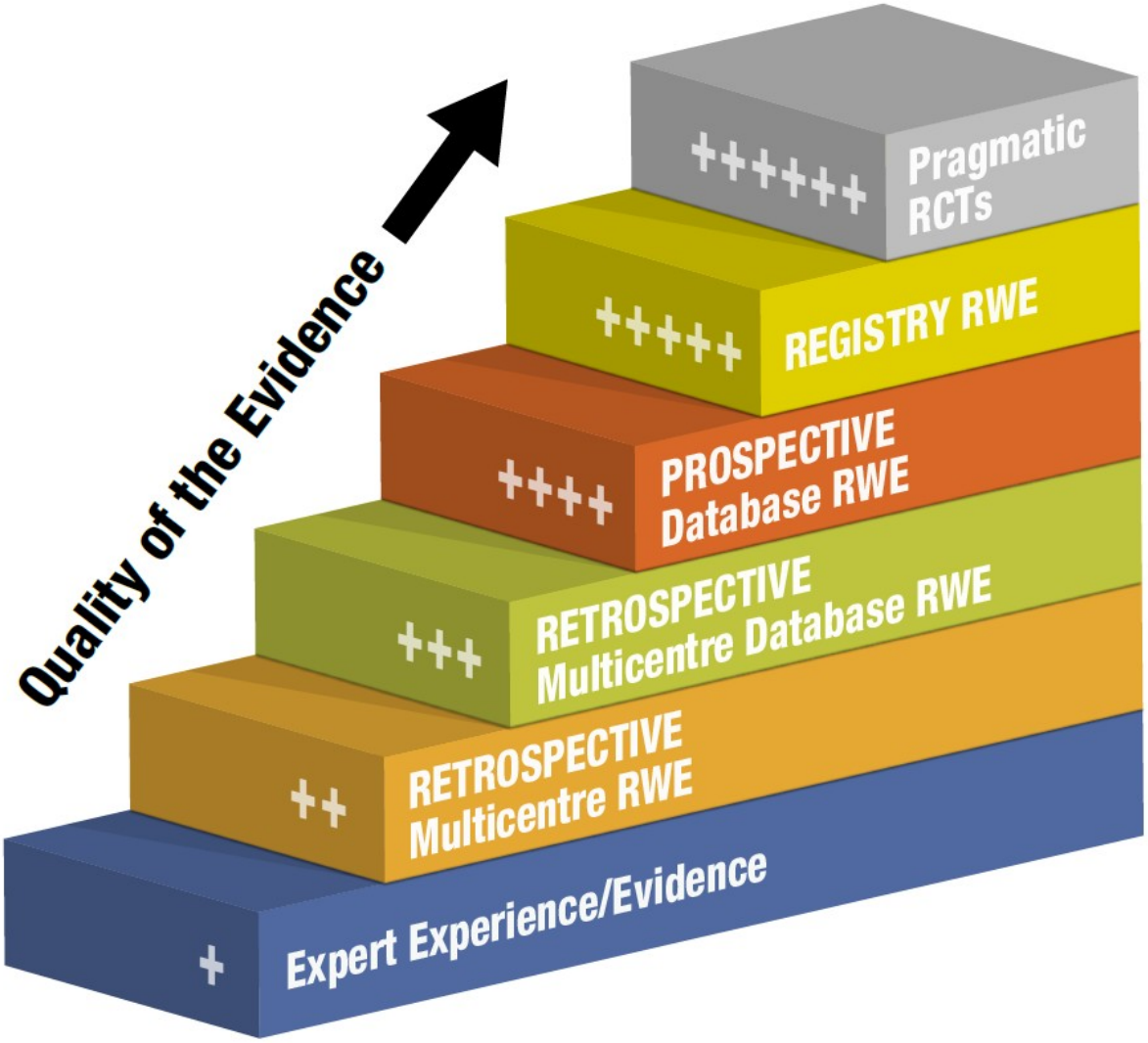
Research and discussions forming the basis for this paper were supported by an unrestricted educational grant from Stallergenes Greer, Antony-France. No author received any support or remuneration from this grant for the development of this manuscript.

**Suggested abstract**

Although there is a considerable body of knowledge about allergen immunotherapy (AIT), there is a lack of data on the reliability of real-world evidence (RWE) in AIT and consequently, a lack of information on how AIT effectively works in real life. To address the current unmet need for an appraisal of the quality of RWE in AIT, the European Academy of Allergy and Clinical Immunology Methodology Committee recently initiated a systematic review of observational studies of AIT, which will use the RELEVANT tool and the Grading of Recommendations Assessment, Development and Evaluation approach (GRADE) to rate the quality of the evidence base as a whole. The next step will be to develop a broadly applicable, pragmatic "real-world" database using systematic data collection. Based on the current RWE base, and perspectives and recommendations of authorities and scientific societies, a hierarchy of RWE in AIT is proposed, which places pragmatic trials and registry data at the positions of highest level of evidence. There is a need to establish more AIT registries that collect data in a cohesive way, using standardised protocols. This will provide an essential source of real-world data that can be easily shared, promoting evidence-based research and quality improvement in study design and clinical decision-making.

**Suggested key words:** allergen immunotherapy, randomised controlled trial, real-world evidence, subcutaneous immunotherapy, sublingual immunotherapy

137 **Graphical abstract**

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## 1. Introduction

Allergen-specific immunotherapy (AIT) is the only treatment with a disease-modifying effect in IgE-mediated allergic diseases, and it can deliver long-term clinical benefits that may persist for years after treatment discontinuation.[1, 2] In 1911, Noon demonstrated the efficacy of subcutaneous injections of a grass pollen extract in patients with hay fever, using an empiric approach.[3] Although Noon's rationale for 'vaccinating' against 'aerogenic toxins' to induce tolerance was incorrect, his research served to demonstrate that subcutaneous administration of pollen extracts was effective in reducing hay fever symptoms, and this early discovery paved the way for the development of AIT. In 1964, Frankland and colleagues took the important step of conducting the first randomised, double-blind, placebo-controlled study of subcutaneous immunotherapy (SCIT),[4] and in 1968, Johnstone and Dutton provided evidence that SCIT could modify the clinical course of respiratory allergy.[5]

For more than 70 years, SCIT remained the only form of AIT available, and it was used empirically until the discovery of IgE by Ishizaka and colleagues in 1965.[6] SCIT is associated with several drawbacks including the need for repeated injections, as well as the risk of systemic adverse reactions.[7] Concerns about safety and the need for a simpler administration regimen drove the search for alternative routes of AIT administration, with the aim of developing effective treatments for allergic rhinitis (AR) and asthma that offered improved convenience, safety and a reduced potential for human error, compared with conventional SCIT. By the early 1980s, several new administration routes had been explored, including the local bronchial and oral routes; however, these were abandoned due to a lack of efficacy in reducing symptoms and an increased risk of side effects.[2, 8]

Sublingual administration of allergen extracts was first investigated in the early 1900s, but it was not until the 1980s that several landmark studies demonstrated the safety and effectiveness of sublingual immunotherapy (SLIT). In 1986, Scadding and colleagues

conducted the first randomised, double-blind, placebo-controlled trial of a sublingual AIT preparation, with results showing that low-dose SLIT was efficacious in relieving symptoms in almost three-quarters of patients with perennial AR due to house dust mite allergens.[9] In 1998, the first mechanistic trial of SLIT demonstrated a downregulation of markers of allergic inflammation, coupled with a significant clinical effect in lowering symptom scores.[10] In the same year, the World Health Organization first recognised SLIT as a viable alternative to the subcutaneous route. Subsequently, European Academy of Allergy and Clinical Immunology (EAACI) guidelines on AIT for AR[11] and two World Allergy Organization (WAO) position papers dedicated to SLIT were published: the first WAO report in 2009 assessed 60 trials,[12] and the second in 2014 included 77 trials.[13] Both SCIT and SLIT have demonstrated good clinical efficacy for the management of AR and asthma, and the availability of both formulations offers clinicians and patients a wide choice of treatment.

## 2. Evaluation of AIT

Evaluating the AIT literature reveals a major limitation, in that many studies are not comparable because they use different types of allergen extracts, doses and dosing regimens, and their study designs, inclusion criteria and outcome assessments often also differ. The broad diversity in composition of AIT products[14] means that efficacy must be demonstrated for each individual product, rather than as a class.[15, 16] In addition, the clinical efficacy of AIT is measured using various scores as primary and secondary study endpoints. The

European Medicines Agency (EMA) stipulates combined symptom and medication scores as primary endpoint. In the future in order to permit the comparison of results from different studies is mandatory a standarditation of clinical endpoints[17,18].

However, due to the wide variety of allergens and compositions of allergen extracts, it is challenging from an organisational or economic perspective to conduct randomised controlled trials (RCTs) with every product.

### 2.1. Overview of current AIT markets

Globally, SLIT appears to be the most common route of administration of AIT, as demonstrated by an analysis of the worldwide market share in 2019 for different AIT formulations; these data show that SLIT tablets and drops combined accounted for 52% of all prescribed AIT products (*Data provided by IQVIA report 2019-formerly IMS*).

Across Europe in 2019, the preferred route of administration of AIT differed widely, with subcutaneous unfractionated allergoid immunotherapy formulations comprising most of the AIT prescriptions in Germany, Poland, Spain and Switzerland, while SLIT predominated in Czechoslovakia, France, Italy and Russia. The proportions of SCIT and SLIT prescriptions were comparable in the Benelux countries. Looking further afield, this was also the case for Australia and New Zealand (**Figure 1**) (*Data provided by IQVIA report 2019-formerly IMS*).

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### 2.2. Current and future evidence base for AIT

Randomised, double-blind, placebo-controlled phase III studies have provided the necessary evidence for registration of several AIT products,[18-22] and there is now a considerable body of knowledge about AIT. However, there remains a need for more high-quality studies and data. In the allergy field, the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines were the first to adopt an evidence-based medicine approach.[23, 24] Since then, several meta-analyses

have been performed to evaluate the efficacy and safety of SCIT or SLIT for the management of asthma and AR in both adult and paediatric populations.[22,25-30] The findings of the individual studies chosen for inclusion in meta-analyses are usually in favour of AIT, but due to differing products, dosages, protocols and treatment schedules, as well as outcome measures, methodological difficulties may prevent meta-analyses from reaching robust and definitive conclusions.[15, 31-35]

A product-by-product analysis and evaluation is mandatory when an AIT treatment is chosen for clinical use, as clearly stated in WAO criteria for the requirements of an AIT product,[15] by EAACI guidelines.[16,17, 36, 37] Scientific societies such as the WAO have also published guidance and criteria to design and run a robust clinical trial of AIT.[12, 13]

Evidence to inform decision-making can range in design from being clinically mechanistic to pragmatic, and randomised or non-randomised. In this regard, some have advocated for the term "real-world evidence" (RWE), although this has some significant limitations; notably, the suggestion that populations in RCTs do not come from the "real world" when clearly they do, albeit often selected.[38] Non-randomised studies (NRS) can be considered a source of complementary evidence to inform clinical practice alongside RCTs.[39] In 2019, ARIA proposed that Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria should be applied to NRS in order to strengthen the conclusions drawn from these data. They also advised that future guidelines for AR and asthma should include testing, refinement and confirmation of guideline recommendations, based on NRS in combination with the GRADE approach.[40]

## 3. Non-randomised studies and real-world evidence

The term RWE has often been invoked as a catchall and led to misuse and confusion. The United States Food and Drug Administration (FDA) has provided some guidance, defining RWE as "clinical evidence regarding the usage and potential benefits or risks of a medical

product derived from analysis of RWD (real-world data). RWE can be generated by different study designs or analyses, including but not limited to, randomised trials, including large simple trials, pragmatic trials, and observational studies (prospective and/or retrospective)."[41] Likewise, the FDA defines RWD as "data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources… for example: electronic health records (EHRs), claims and billing activities, product and disease registries, patient-generated data including in home-use settings, and data gathered from other sources that can inform on health status, such as mobile devices."[41]

Here, we define RWE NRS similarly, encompassing a range of methodologies that include non-interventional studies, patient registries, claims database studies, patient surveys and electronic health record studies. However, not all NRS are RWE and vice versa. A further implication is that real-world data are often collected without the explicit intention of being used for research on safety or effectiveness, but instead are repurposed for use as such. A common misconception is that RCTs only assess treatments that are still in clinical development in a highly selected group of patients; however, in reality, both pragmatic RCTs and NRS (e.g. registries) can assess treatments that are already approved and include broad and diverse patient populations.

Until the 1940s, the development of new treatments relied on NRS. After that time, there was increasing recognition that anecdotal reports based on clinical practice observations were often misleading. This led to a near-total replacement of the prior non-randomised approach with the use of randomised, controlled clinical trials. Indeed, the history of medicine is rife with examples whereby observational data have been misleading even with established clinical practices, and which are only uncovered after the same hypothesis is tested in an RCT.[42] This reinforces the widely-held notion about NRS that no matter how large in scale or sophisticated in analysis, the risk of bias (including mis-specification, selection, reporting,

analysis and confounding, among others) will limit certainty in causal inference. Conversely, proponents of NRS RWE advocate that mechanistic trials may often not be fully representative of real-life situations because they employ strict, protocol-defined inclusion criteria to identify eligible patients – that is to say, directness in the applicability of the studied intervention effects to the applied population. This could mean that some patients with the condition of interest may be excluded based on characteristics such as disease severity, age, comorbidities or the use of concomitant medications. Though there is often no compelling rationale to suspect any modification of the treatment effect in these subpopulations, registries and routinely collected data can facilitate analysis of a broader patient population. However, it must be recognised that any results, whether from mechanistic RCTS, pragmatic RCTS, or NRS RWE, are always extrapolated to the patient at the bedside in clinical practice.

Traditional RCTs may answer a specific question more robustly and have a lower risk of bias, but some may consider them to be limited in applicability at times. In contrast, NRS may be able to evaluate broader and larger populations and thus the results are more generalisable, but may be misleading due to the higher risk of bias. Therefore, both approaches have their inherent pitfalls, and there is clearly a trade-off in choosing one approach over the other. However, it is a fallacy to pit them against each other, rather than viewing them as providing complementary evidence to aid the process of making trustworthy clinical decisions.[38, 39] A balance must be struck between pragmatic RCTs (which can include patient registries and routinely collected data in order to mitigate cost, resource requirements and accessibility) and the long timelines associated with traditional RCTs (**Figure 2**). This is particularly relevant to AIT studies, which may involve follow-up for years after cessation of the treatment course. Furthermore, restrictive enrolment criteria and a concentration of trial sites in certain health

systems make it challenging for some patients to enrol in RCTs, particularly if they have comorbidities or their mobility or cognitive abilities are affected.

In this context, it is important to define the terms 'efficacy' and 'effectiveness'. The former is representative of mechanistic clinical trials, answering the question "Can intervention X improve condition Y?", while the latter applies to pragmatic studies (both randomised and non-randomised), addressing "Does intervention X improve condition Y under practical (or even routine) circumstances?". Efficacy is the extent to which an intervention does more good than harm under ideal circumstances, whereas effectiveness assesses whether an intervention does more good than harm when provided under the usual circumstances of healthcare practice.[43-45] It follows that studies demonstrating efficacy can fail to show effectiveness, for example due to poor implementation. Likewise, studies that fail to show effectiveness do not imply the absence of efficacy, even within the same patient population (**Figure 2**).

Although most NRS of the effectiveness of AIT are retrospective in design and include small numbers of patients, large prescription and claims databases are increasingly being used to enable analysis of greater numbers of patients than was possible in the past, albeit with the caveats in mind described above. For example, Wahn and colleagues conducted a retrospective cohort analysis of a German longitudinal prescription database including patients with birch pollen-associated AR and/or asthma.[46] They demonstrated the benefits of AIT for up to 6 years after treatment cessation, through significantly reduced AR and asthma medication intake, and significantly decreased risk of new-onset asthma medication use on-treatment. A similar analysis by Jutel and colleagues that investigated the effectiveness of allergoid AIT in the treatment of house dust mite−induced AR and/or asthma reported significantly fewer AR and asthma prescriptions in patients on AIT versus control patients (59.7% *vs* 10.8%), and a significantly lower probability of asthma development with up to 6

years of follow−up.[47] However, a limitation of databases such as these is that information on symptom scores is not recorded (i.e. indirectness in GRADE terminology), supporting the need for AIT registries that capture data on both symptoms and medication use routinely.

Another retrospective study included 117 adults with allergic asthma who had used inhaled corticosteroids (ICS) for >1 year in a single tertiary hospital in Korea. It compared the clinical parameters and outcomes between the AIT and non-AIT groups and concluded that irrespective of the type of allergen, long-term maintenance AIT helps to spare ICS dose and achieve better control in patients with allergic asthma.[48-53] The tools used in these studies are reminiscent of the anonymous electronic medical records and patient questionnaires collected within the Optimum Patient Care Research Database (OPCRD) that provide an essential source of data to promote evidence-based research and quality improvement.[54]

In observational research as well as in RCTs, ensuring high-quality methodology is crucial to avoid biases that would compromise the reliability and validity of results. Following the GRADE methodology for evidence appraisal, both RCTs and NRS can start as high-quality evidence. Subsequent considerations of risk of bias, imprecision, indirectness, inconsistency, publication bias, residual confounding, the strength of association and possible dose-response gradients can lead to the level of evidence being downgraded or upgraded. While there are several tools to guide the design of observational research to ensure systematic and rigorous processes, until the creation of the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I)[55, 56] and REal Life EVidence AssessmeNt Tool (RELEVANT),[55, 57, 58] there were no instruments specifically designed for the evaluation of published asthma effectiveness research.

The Cochrane Collaboration's ROBINS-I[59] encourages users to appraise each NRS in its attempt to emulate a hypothetical pragmatic RCT,[60, 61] as doing so can facilitate identification of risks of bias. Similar to the well-known Cochrane RCT risk-of-bias tools, ROBINS-I

covers the seven core domains where internal validity might be threatened. ROBINS-I employs 'signalling questions' to help users judge the risk of bias within each domain. The judgements for each domain carry forward to an overall risk of bias judgement across all domains for the outcome being assessed. RELEVANT was jointly created in 2019 by members of the Respiratory Effectiveness Group and a specific EAACI Task Force through a step-wise approach, and was designed for use in asthma. The final version of this tool consists of 21 quality sub-items (11 of these are considered critical and named 'primary sub-items') distributed across seven methodology and reporting domains: Background, Design, Measures, Analysis, Results, Discussion/Interpretation, and Conflict of Interest.

## 4. Appraising the quality of RWE in AIT

Although RCTs are considered as the gold standard for evaluating treatment efficacy,[62] one of the main limitations of most RCTs in AIT is their short duration (usually 12 months, encompassing one pollen season). Several long-term studies have shown that the effectiveness of AIT and its potential for preventing the onset of asthma and new sensitisations is dependent on its duration of use, with successful outcomes (i.e. disease modification) achieved only after completion of the recommended 3-year treatment course.[63-65] However, RWE from NRS using pharmaceutical prescription databases suggests that AIT treatment effect persistence (i.e. the completion of the 3-year course) is achieved by <40% of patients receiving SCIT, and <10% of patients using SLIT.[66-68] A frequent issue in these trial is patient attrition. Furthermore, adherence to treatment (e.g. the number of SLIT tablets actually taken by patients relative to the prescribed number) is low in routine clinical practice.[69] Taking these factors into account, it is clear that results from RCTs demonstrating AIT efficacy may not always translate into AIT effectiveness and that knowledge translation efforts, as well as methods to enhance adherence, are required.

There is a lack of data on the reliability of RWE (NRS and RCT) studies in AIT and, consequently, a lack of information on how AIT effectively works in real life. To address the current unmet need for an appraisal of the quality of RWE in AIT, the EAACI Methodology Committee has recently initiated a systematic review of observational studies of AIT, which will use the RELEVANT and ROBINS-I tools to determine the risk of bias for the evidence available, and use the GRADE approach to rate the quality of the evidence base as a whole. The purpose of this analysis is two-fold: firstly, to identify robust evidence that can be integrated with the findings from RCTs to provide a more complete picture on which to base clinical recommendations and secondly, in the case of there not being any studies of sufficient quality, to use the available evidence to inform the optimal design of future high-quality research in AIT. The next step will be to develop a broadly applicable and pragmatic "real-world" database using systematic data collection, similar to the OPCRD.[54]

## 5. Looking to the future of RWE: a call to action

Recently, Schünemann published "All evidence is real world evidence",[38] reinforcing the relevance of RCT as part of the real world, the misuse of the term "RWE", the potential role of NRS and the possible bias in collecting or evaluating these data. In this light, the recent manifesto in respiratory medicine highlighted the importance of RWE (NRS and RCT), advocating for the appraisal and inclusion of high-quality, pragmatic studies in large, heterogeneous populations in the development of clinical practice guidelines.[62] In addition to providing information for clinicians, the value of these data is increasingly being recognised by regulatory bodies and other stakeholders.[41, 70]

Registries are considered a particularly valuable source of broadly applicable data. For example, the Severe Asthma Registries[71] have demonstrated their value at a national, regional and international level in providing remarkable data, fruitfully revealing information that was

not detectable in traditional registration trials conducted in highly selected, homogeneous patient populations.

Based on the current knowledge base for RWE and the perspectives and recommendations of authorities and scientific societies, we therefore propose a hierarchy of RWE in AIT (**Figure 3, Table 1**), which places pragmatic trials and registry data at the position of highest levels of evidence.

## 6. Final Remark

Because of their proven importance and value, we conclude with a *Call to Action* to establish more AIT registries, with the aim of collecting data in a cohesive way, using standardised protocols. Particular attention should be paid to patient engagement in these trials to obtain high quality data. This will enable data to be easily shared and provide an essential source of RWE to promote evidence-based research and quality improvement in study design and clinical decision-making.

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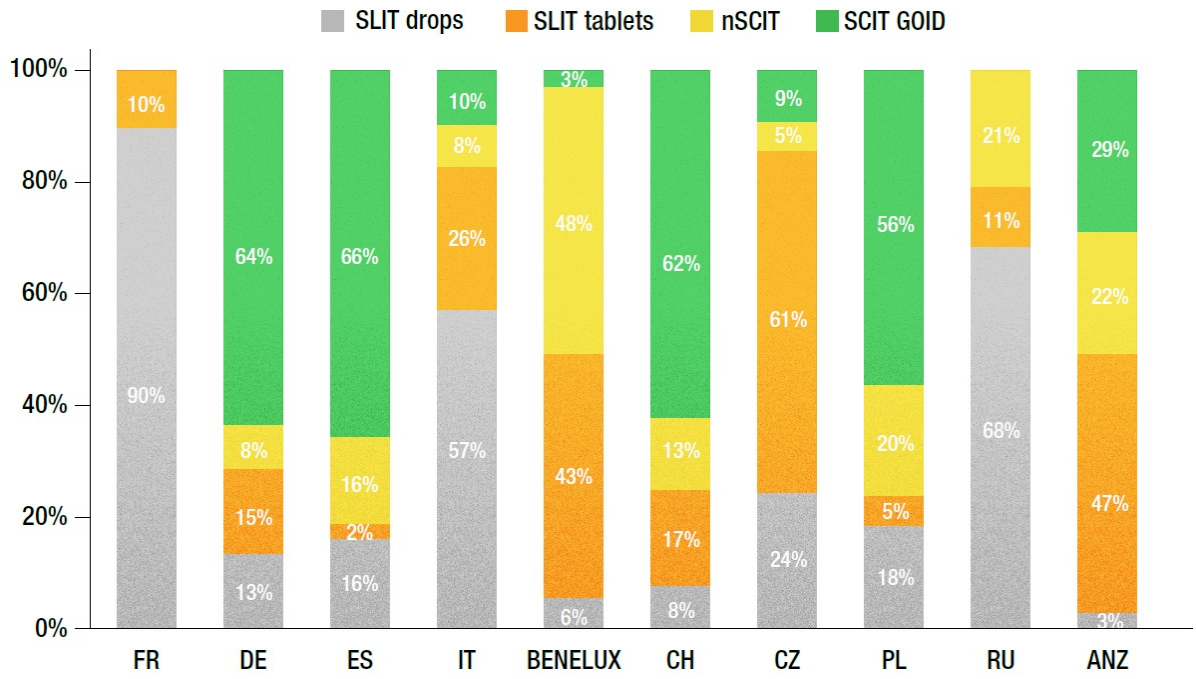
## 8. Figures

**Figure 1.** Sales of AIT in 2019 by route of administration, stratified by selected countries/regions.

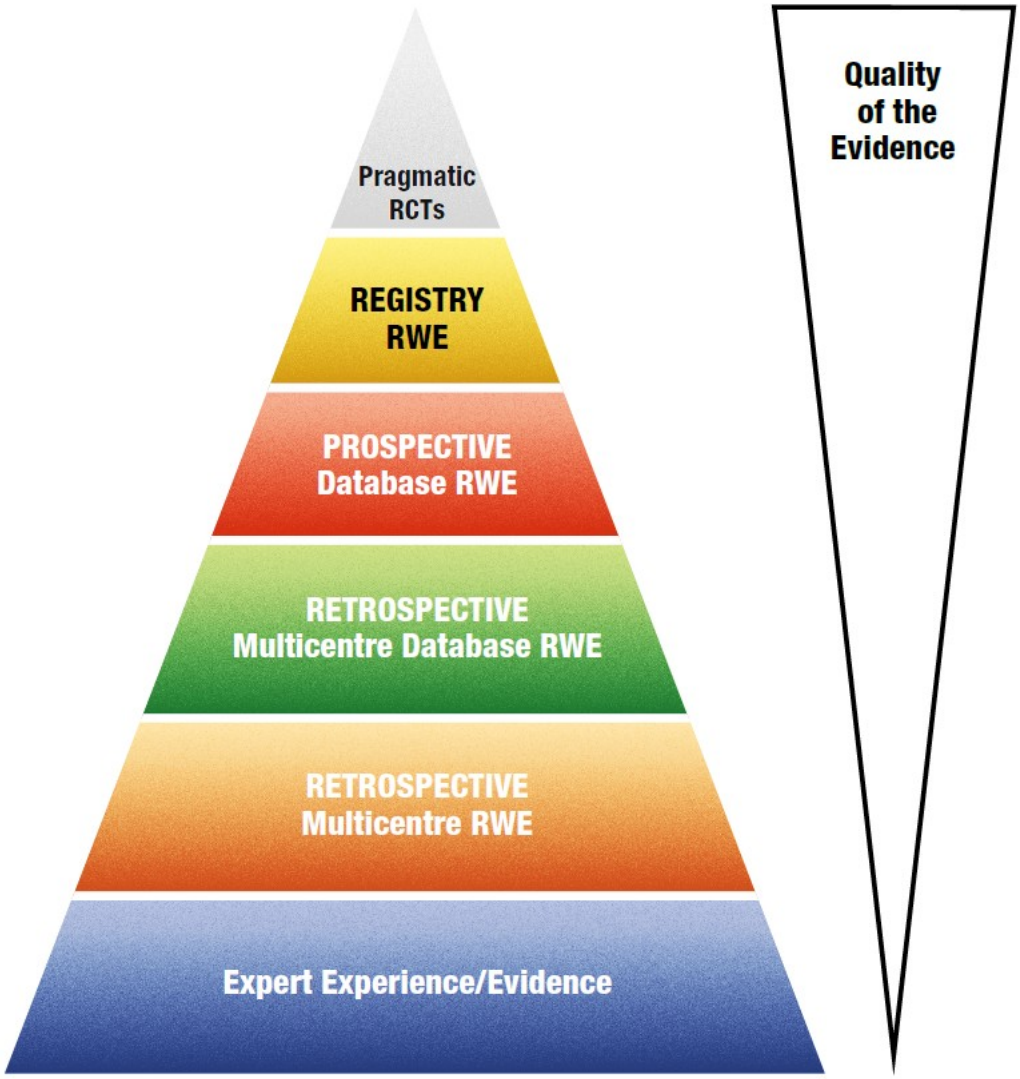



nSCIT, subcutaneous immunotherapy with natural extracts; SCIT, subcutaneous immunotherapy with natural extracts; SCIT GOID, subcutaneous unfractionated allergoid immunotherapy; SLIT, sublingual immunotherapy. FR: France; DE: Germany; ES: Spain; IT: Italy; CH: Switzerland; CZ: Czech Republic; PL: Poland; RU: Russian; ANZ: Australia & New Zealand.

Data source: IQVIA report 2019-formerly IMS.

**Figure 2.** The outer circle includes the heterogeneous patient population eligible for a given treatment under routine care. This population is typically enrolled in pragmatic RT and in observational studies. The inner circle includes a small subgroup of the potentially eligible patients representing a "selected" population devoid of specific characteristics potentially interfering with treatment effect (confounders). This subpopulation is typically included in RCTs (efficacy studies).

**Figure 3.** Proposed Hierarchy of allergen immunotherapy real-world evidence from highest to lowest quality. The definition of the studies is in Table 1.




RCT, randomised controlled trial; RWE, real-world evidence

675 **9.Table**

676 **Table 1**. The definition of the type of studies present in the proposed Hierarchy of allergen
677 immunotherapy real-world evidence.

678

| |
|---|
| **Pragmatic randomised controlled trial:** Trials designed to evaluate the effectiveness of interventions in real-life routine practice conditions, opposite to explanatory trials that aim to test whether an intervention works under optimal situations [72]. |
| **Registry real-world evidence:** An organised system that uses observational methods to collect uniform data relative to real-world setting on specified outcomes in a population defined by a particular disease, condition or exposure [73]. |
| **Prospective database real-world evidence:** is a type of cohort study, where participants are enrolled into the study before they develop the disease or outcome in question in a real-world contest [74]. |
| **Retrospective multicenter Database real-world evidence:** is based on the use of an existing database to respond retrospectively to clinical questions [75]. |
| **Retrospective multicenter real-world evidence:** is a clinical trial conducted at more than one medical center or clinic where, in contrast to a prospective study, the outcome of interest has already occurred at the time the study is initiated [76]. |
| **Expert Experience/Evidence:** is somebody who has a broad and deep competence in terms of knowledge, skill and experiencethrough practice and education in a particular field. |

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