"Allergen immunotherapy: The growing role of observational and randomized trial "Real-World Evidence"

Giovanni Paoletti, Danilo Di Bona, Derek K. Chu, Davide Firinu, Enrico Heffler, Ioana Agache, Marek Jutel, Ludger Klimek, Oliver Pfaar, Ralph Mösges, Audrey DunnGalvin, Jon Genuneit, Hans Jürgen Hoffmann, Giorgio Walter Canonica

Allergy 2021 Sep;76(9):2663-2672.

Manuscript for submission to *Allergy*

	Count	*Journal limits*
Title	100 characters	120 characters
Short title	47	50 characters
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

Giovanni Paoletti [1^]; Danilo Di Bona [2^]; Derek K. Chu [3]; Davide Firinu [4]; Enrico Heffler [1]; Ioana Agache [5]; Marek Jutel [6]; Ludger Klimek [7]; Oliver Pfaar [8]; Ralph Mösges [9]; Audrey Dunn Galvin [10]; Jon Genuneit [11]; Hans Jürgen Hoffmann [12]; Giorgio Walter Canonica[1]

^ these two Authors equally contributed to this article

1. Personalized Medicine, Asthma and Allergy, Humanitas Clinical and Research Center IRCCS and Department of Biomedical Sciences, Humanitas University, Milan, Italy

2. Department of Emergency and Organ Transplantation, School and Chair of Allergology and Clinical Immunology, University of Bari – Aldo Moro, Bari, Italy

3. Department of Health Research Methods, Evidence and Impact; Division of Immunology and Allergy, Department of Medicine, McMaster University, Hamilton, ON, Canada; The Research Institute of St. Joe's Hamilton, Hamilton, ON, Canada

4. Department of Clinical Sciences and Public Health, University of Cagliari, Italy

5. Department of Allergy and Clinical Immunology, Faculty of Medicine, Transylvania University of Brasov, Brasov, Romania

6. Department of Clinical Immunology, Wroclaw Medical University and "ALLMED" Medical Research Institute, Wroclaw, Poland

7. Center for Rhinology and Allergology, Wiesbaden, Germany

8. Department of Otorhinolaryngology, Head and Neck Surgery, Section of Rhinology and Allergy, University Hospital Marburg, Philipps-Universität Marburg, Marburg, Germany

9. Institute of Medical Statistics and Computational Biology (IMSB), Faculty of Medicine, University of Cologne and CRI – Clinical Research International Limited, Cologne, Germany

10. School of Applied Psychology and Department of Paediatrics & Child Health, University College Cork, Cork, Ireland

11. Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany

12. Department of Clinical Medicine, Aarhus University and Department of Respiratory Diseases and Allergy, Aarhus University Hospital, Aarhus, Denmark

Corresponding author

G. Walter Canonica, MD

Personalized Medicine, Asthma and Allergy

Humanitas Clinical and Research Center IRCCS

Via Alessandro Manzoni 56

20089 Rozzano (MI)

Italy

Tel: +39 02 82 24 37 77

E-mail: giorgio_walter.canonica@hunimed.eu

GWC ORCID: https://orcid.org/0000-0001-8467-2557

GP ORCID: https://orcid.org/0000-0003-3953-9225

DB ORCID: https://orcid.org/0000-0002-9728-3806

HJH ORCID: https://orcid.org/0000-0002-6743-7931

EH ORCID: https://orcid.org/0000-0002-0492-5663

Disclosures

GP reports no conflict of interest;

DDB reports no conflict of interest;

DKC is a CAAIF-CSACI-AllerGen Emerging Clinician-Scientist Research Fellow, supported by the Canadian Allergy, Asthma and Immunology Foundation, the Canadian Society of Allergy and Clinical Immunology and AllerGen NCE Inc. (the Allergy, Genes and Environment Network).

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;

HJH reports no conflict of interest;

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

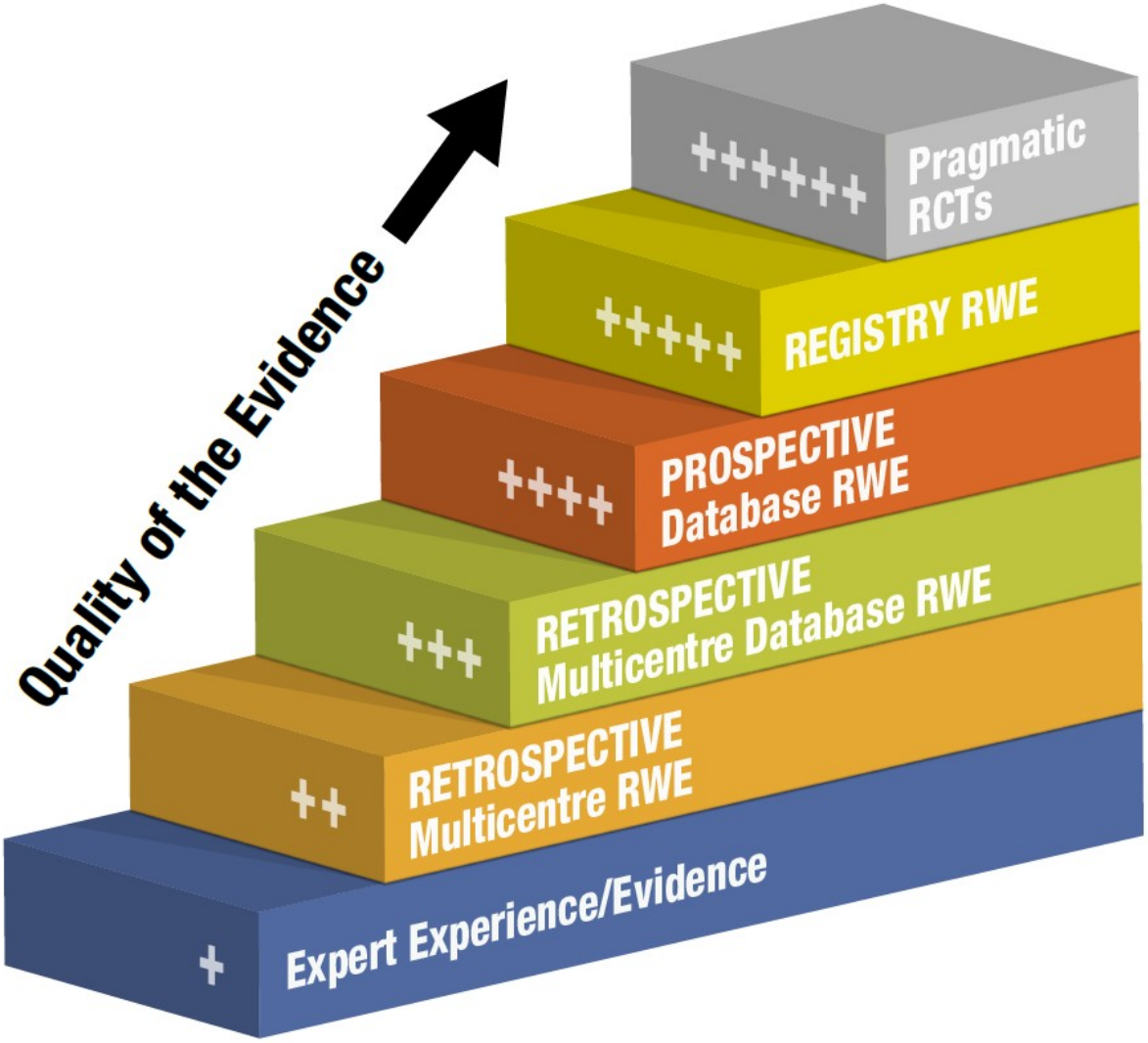
Research and discussions forming the basis for this paper were supported by an unrestricted educational grant from Stallergenes Greer, Antony-France. No author received any support or remuneration from this grant for the development of this manuscript.

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**



138

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*).

.

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.

7. References

1. Arasi S, Corsello G, Villani A, Pajno GB. The future outlook on allergen immunotherapy in children: 2018 and beyond. Ital J Pediatr. Jul 11 2018;44(1):80. doi:10.1186/s13052-018-0519-4
2. Passalacqua G, Bagnasco D, Canonica GW. 30 years of sublingual immunotherapy. Allergy. May 2020;75(5):1107-1120. doi:10.1111/all.14113
3. Noon L. Prophylactic inoculation against hay fever. . Lancet 1911;177:1572–73.
4. Frankland AW. Preseasonal injection treatment in hay fever using aqueous extracts. Int Arch Allergy Appl Immunol. 1965;28(1):1-11. doi:10.1159/000229629
5. Johnstone DE, Dutton A. The value of hyposensitization therapy for bronchial asthma in children--a 14-year study. Pediatrics. Nov 1968;42(5):793-802.
6. Ogawa M, Kochwa S, Smith C, Ishizaka K, McIntyre OR. Clinical aspects of IgE myeloma. N Engl J Med. Nov 27 1969;281(22):1217-20. doi:10.1056/NEJM196911272812204
7. Nelson HS. New forms of allergy immunotherapy for rhinitis and asthma. Allergy Asthma Proc. Jul-Aug 2014;35(4):271-7. doi:10.2500/aap.2014.35.3778
8. Canonica GW, Passalacqua G. Noninjection routes for immunotherapy. J Allergy Clin Immunol. Mar 2003;111(3):437-48; quiz 449. doi:10.1067/mai.2003.129
9. Scadding GK, Brostoff J. Low dose sublingual therapy in patients with allergic rhinitis due to house dust mite. Clin Allergy. Sep 1986;16(5):483-91. doi:10.1111/j.1365-2222.1986.tb01983.x
10. Passalacqua G, Albano M, Fregonese L, et al. Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite-induced rhinoconjunctivitis. Lancet. Feb 28 1998;351(9103):629-32. doi:10.1016/S0140-6736(97)07055-4

11. Roberts G, Pfaar O, Akdis CA, et al. EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. Allergy. Apr 2018;73(4):765-798. doi:10.1111/all.13317
12. Canonica GW, Bousquet J, Casale T, et al. Sub-lingual immunotherapy: world allergy organization position paper 2009. World Allergy Organ J. Nov 2009;2(11):233-81. doi:10.1097/WOX.0b013e3181c6c379
13. Canonica GW, Cox L, Pawankar R, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. World Allergy Organ J. Mar 28 2014;7(1):6. doi:10.1186/1939-4551-7-6
14. Larenas-Linnemann D, Cox LS, Immunotherapy, Allergy Diagnostics Committee of the American Academy of Allergy A, Immunology. European allergen extract units and potency: review of available information. Ann Allergy Asthma Immunol. Feb 2008;100(2):137-45. doi:10.1016/S1081-1206(10)60422-X
15. Bachert C, Larche M, Bonini S, et al. Allergen immunotherapy on the way to product-based evaluation-a WAO statement. World Allergy Organ J. 2015;8(1):29. doi:10.1186/s40413-015-0078-8
16. Muraro A, Roberts G. EAACI Guidelines - Allergen Immunotherapy Guidelines Part 2: Recommendations. Accessed July 2020, https://www.eaaci.org/documents/Part_II_-_AIT_Guidelines_-_web_edition.pdf
17. Pfaar O, Bachert C, Bufe A, Buhl R, Ebner C, Eng P, Friedrichs F, Fuchs T, Hamelmann E, Hartwig-Bade D, Hering T, Huttegger I, Jung K, Klimek L, Kopp MV, Merk H, Rabe U, Saloga J, Schmid-Grendelmeier P, Schuster A, Schwerk N, Sitter H, Umpfenbach U, Wedi B, Wöhrl S, Worm M, Kleine-Tebbe J, Kaul S, Schwalfenberg A. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases: S2k Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Society for Pediatric Allergy and Environmental Medicine (GPA), the Medical Association of

German Allergologists (AeDA), the Austrian Society for Allergy and Immunology (ÖGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Dermatology (DDG), the German Society of Oto- Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC), the German Society of Pediatrics and Adolescent Medicine (DGKJ), the Society for Pediatric Pneumology (GPP), the German Respiratory Society (DGP), the German Association of ENT Surgeons (BV-HNO), the Professional Federation of Paediatricians and Youth Doctors (BVKJ), the Federal Association of Pulmonologists (BDP) and the German Dermatologists Association (BVDD). Allergo J Int. 2014;23(8):282-319. doi: 10.1007/s40629-014-0032-2. PMID: 26120539; PMCID: PMC4479478.)

18. European Medicines Agency; Commitee for medicinal products for human use (CHMP), eds. Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases. CHMP/EWP/18504/2006. London, 20. November 2008

19. Jacobsen L, Niggemann B, Dreborg S, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy. Aug 2007;62(8):943-8. doi:10.1111/j.1398-9995.2007.01451.x

20. Larenas-Linnemann D. How does the efficacy and safety of Oralair® compare to other products on the market? Ther Clin Risk Manag. 2016;12:831-50. doi:10.2147/TCRM.S70363

21. Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Long-lasting effects of sublingual immunotherapy according to its duration: a 15-year prospective study. J Allergy Clin Immunol. Nov 2010;126(5):969-75. doi:10.1016/j.jaci.2010.08.030

22. Dhami S, Nurmatov U, Arasi S, Khan T, Asaria M, Zaman H, Agarwal A, Netuveli G, Roberts G, Pfaar O, Muraro A, Ansotegui IJ, Calderon M, Cingi C, Durham S, van Wijk RG,

Halken S, Hamelmann E, Hellings P, Jacobsen L, Knol E, Larenas-Linnemann D, Lin S, Maggina P, Mösges R, Oude Elberink H, Pajno G, Panwankar R, Pastorello E, Penagos M, Pitsios C, Rotiroti G, Timmermans F, Tsilochristou O, Varga EM, Schmidt-Weber C, Wilkinson J, Williams A, Worm M, Zhang L, Sheikh A. Allergen immunotherapy for allergic rhinoconjunctivitis: A systematic review and meta-analysis. Allergy. 2017 Nov;72(11):1597-1631. doi: 10.1111/all.13201. Epub 2017 Jul 14. PMID: 28493631

23. Bousquet J, Schunemann HJ, Togias A, et al. Next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for allergic rhinitis based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and real-world evidence. J Allergy Clin Immunol. Jan 2020;145(1):70-80 e3. doi:10.1016/j.jaci.2019.06.049
24. Lockey RF. "ARIA": global guidelines and new forms of allergen immunotherapy. J Allergy Clin Immunol. Oct 2001;108(4):497-9. doi:10.1067/mai.2001.118638
25. Calderón MA, Boyle RJ, Penagos M, Sheikh A. Immunotherapy: The meta-analyses. What have we Learned? Immunol Allergy Clin North Am. May 2011;31(2):159-73, vii. doi:10.1016/j.iac.2011.02.002
26. Dhami S, Kakourou A, Asamoah F, et al. Allergen immunotherapy for allergic asthma: A systematic review and meta-analysis. Allergy. Dec 2017;72(12):1825-1848. doi:10.1111/all.13208
27. Di Bona D, Plaia A, Leto-Barone MS, La Piana S, Di Lorenzo G. Efficacy of Grass Pollen Allergen Sublingual Immunotherapy Tablets for Seasonal Allergic Rhinoconjunctivitis: A Systematic Review and Meta-analysis. JAMA Intern Med. Aug 2015;175(8):1301-9. doi:10.1001/jamainternmed.2015.2840

28. Durham SR, Penagos M. Sublingual or subcutaneous immunotherapy for allergic rhinitis? J Allergy Clin Immunol. Feb 2016;137(2):339-349 e10. doi:10.1016/j.jaci.2015.12.1298
29. Passalacqua G, Canonica GW, Bagnasco D. Benefit of SLIT and SCIT for Allergic Rhinitis and Asthma. Curr Allergy Asthma Rep. Nov 2016;16(12):88. doi:10.1007/s11882-016-0666-x
30. Penagos M, Passalacqua G, Compalati E, et al. Metaanalysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. Chest. Mar 2008;133(3):599-609. doi:10.1378/chest.06-1425
31. Jutel M, Agache I, Bonini S, et al. International Consensus on Allergen Immunotherapy II: Mechanisms, standardization, and pharmacoeconomics. J Allergy Clin Immunol. Feb 2016;137(2):358-68. doi:10.1016/j.jaci.2015.12.1300
32. Passalacqua G, Sastre J, Pfaar O, Wahn U, Demoly P. Comparison of allergenic extracts from different origins: the value of the FDA's bioequivalent allergy unit (BAU). Expert Rev Clin Immunol. Jul 2016;12(7):733-9. doi:10.1080/1744666X.2016.1187561
33. Pfaar O, Demoly P, Gerth van Wijk R, et al. Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: an EAACI Position Paper. Allergy. Jul 2014;69(7):854-67. doi:10.1111/all.12383
34. Pfaar O, Agache I, de Blay F, Bonini S, Chaker AM, Durham SR, Gawlik R, Hellings PW, Jutel M, Kleine-Tebbe J, Klimek L, Kopp MV, Nandy A, Rabin RL, van Ree R, Renz H, Roberts G, Salapatek AM, Schmidt-Weber CB, Shamji MH, Sturm GJ, Virchow JC, Wahn U, Willers C, Zieglmayer P, Akdis CA. Perspectives in allergen immunotherapy: 2019 and beyond. Allergy. 2019 Dec;74 Suppl 108:3-25. doi: 10.1111/all.14077. PMID: 31872476.
35. Pfaar O, Alvaro M, Cardona V, Hamelmann E, Mösges R, Kleine-Tebbe J. Clinical trials in allergen immunotherapy: current concepts and future needs. Allergy. 2018

515 Sep;73(9):1775-1783. doi: 10.1111/all.13429. Epub 2018 Apr 16. PMID: 29446469; PMCID:
516 PMC6175179.
517 36. Muraro A, Roberts G. EAACI Guidelines - Allergen Immunotherapy Guidelines Part 1:
518 Systematic Reviews. Accessed July 2020,
519 https://www.eaaci.org/documents/AIT_Guidelines-web_version.pdf
520 37. Muraro A, Roberts G, Halken S, et al. EAACI guidelines on allergen immunotherapy:
521 Executive statement. Allergy. Apr 2018;73(4):739-743. doi:10.1111/all.13420
522 38. Schünemann HJ. All evidence is real world evidence. BMJ Opinion. Accessed
523 September 2020, https://blogs.bmj.com/bmj/2019/03/29/holger-j-schunemann-all-
524 evidence-is-real-world-evidence/
525 39. Gerstein HC, McMurray J, Holman RR. Real-world studies no substitute for RCTs in
526 establishing efficacy. Lancet. Jan 19 2019;393(10168):210-211. doi:10.1016/S0140-
527 6736(18)32840-X
528 40. Bousquet JJ, Schunemann HJ, Togias A, et al. Next-generation ARIA care pathways for
529 rhinitis and asthma: a model for multimorbid chronic diseases. Clin Transl Allergy.
530 2019;9:44. doi:10.1186/s13601-019-0279-2
531 41. US Food and Drug Administration. Real-World Evidence. Accessed September 2020,
532 https://www.fda.gov/science-research/science-and-research-special-topics/real-world-
533 evidence
534 42. Fanaroff AC, Califf RM, Harrington RA, et al. Randomized Trials Versus Common
535 Sense and Clinical Observation: JACC Review Topic of the Week. J Am Coll Cardiol.
536 Aug 4 2020;76(5):580-589. doi:10.1016/j.jacc.2020.05.069
537 43. Corrigan-Curay J, Sacks L, Woodcock J. Real-World Evidence and Real-World Data for
538 Evaluating Drug Safety and Effectiveness. JAMA. Sep 4 2018;320(9):867-868.
539 doi:10.1001/jama.2018.10136

44. Devillier P, Demoly P, Molimard M. Allergen immunotherapy: what is the added value of real-world evidence from retrospective claims database studies? Expert Rev Respir Med. May 2020;14(5):445-452. doi:10.1080/17476348.2020.1733417
45. Haynes B. Can it work? Does it work? Is it worth it? The testing of healthcare interventions is evolving. BMJ. Sep 11 1999;319(7211):652-3. doi:10.1136/bmj.319.7211.652
46. Wahn U, Bachert C, Heinrich J, Richter H, Zielen S. Real-world benefits of allergen immunotherapy for birch pollen-associated allergic rhinitis and asthma. Allergy. Mar 2019;74(3):594-604. doi:10.1111/all.13598
47. Jutel M, Brüggenjürgen B, Richter H, Vogelberg C. Real-world evidence of subcutaneous allergoid immunotherapy in house dust mite-induced allergic rhinitis and asthma. Allergy. Feb 20 2020;doi:10.1111/all.14240
48. Blin P, Demoly P, Drouet M, et al. An observational cohort study of the use of five-grass-pollen extract sublingual immunotherapy during the 2015 pollen season in France. Allergy Asthma Clin Immunol. 2018;14:38. doi:10.1186/s13223-018-0262-9
49. Devillier P, Molimard M, Ansolabehere X, et al. Immunotherapy with grass pollen tablets reduces medication dispensing for allergic rhinitis and asthma: A retrospective database study in France. Allergy. Jul 2019;74(7):1317-1326. doi:10.1111/all.13705
50. Gerstlauer M, Szepfalusi Z, Golden D, Geng B, de Blic J. Real-life safety of 5-grass pollen tablet in 5-to-9-year-old children with allergic rhinoconjunctivitis. Ann Allergy Asthma Immunol. Jul 2019;123(1):70-80. doi:10.1016/j.anai.2019.04.011
51. Janson C, Sundbom F, Arvidsson P, Kampe M. Sublingual grass allergen specific immunotherapy: a retrospective study of clinical outcome and discontinuation. Clin Mol Allergy. 2018;16:14. doi:10.1186/s12948-018-0093-8

564 52. Rajakulasingam RK, Farah N, Huber PAJ, et al. Practice and safety of allergen-specific
565 immunotherapy for allergic rhinitis in the UK national health service: A report of "real
566 world" clinical practice. Clin Exp Allergy. Jan 2018;48(1):89-92. doi:10.1111/cea.13052
567 53. Rhyou HI, Nam YH. Efficacy of Allergen Immunotherapy for Allergic Asthma in Real
568 World Practice. Allergy Asthma Immunol Res. Jan 2020;12(1):99-109.
569 doi:10.4168/aair.2020.12.1.99
570 54. OPCRD. Optimum Patient Care Research Database. Accessed July 2020,
571 https://opcrd.co.uk/
572 55. Farrah K, Young K, Tunis MC, Zhao L. Risk of bias tools in systematic reviews of
573 health interventions: an analysis of PROSPERO-registered protocols. Syst Rev. Nov 15
574 2019;8(1):280. doi:10.1186/s13643-019-1172-8
575 56. Morgan RL, Thayer KA, Santesso N, et al. A risk of bias instrument for non-randomized
576 studies of exposures: A users' guide to its application in the context of GRADE. Environ
577 Int. Jan 2019;122:168-184. doi:10.1016/j.envint.2018.11.004
578 57. Campbell JD, Perry R, Papadopoulos NG, et al. The REal Life EVidence AssessmeNt
579 Tool (RELEVANT): development of a novel quality assurance asset to rate observational
580 comparative effectiveness research studies. Clin Transl Allergy. 2019;9:21. doi:10.1186/
581 s13601-019-0256-9
582 58. Roche N, Campbell JD, Krishnan JA, et al. Quality standards in respiratory real-life
583 effectiveness research: the REal Life EVidence AssessmeNt Tool (RELEVANT): report
584 from the Respiratory Effectiveness Group-European Academy of Allergy and Clinical
585 Immunology Task Force. Clin Transl Allergy. 2019;9:20. doi:10.1186/s13601-019-0255-
586 x

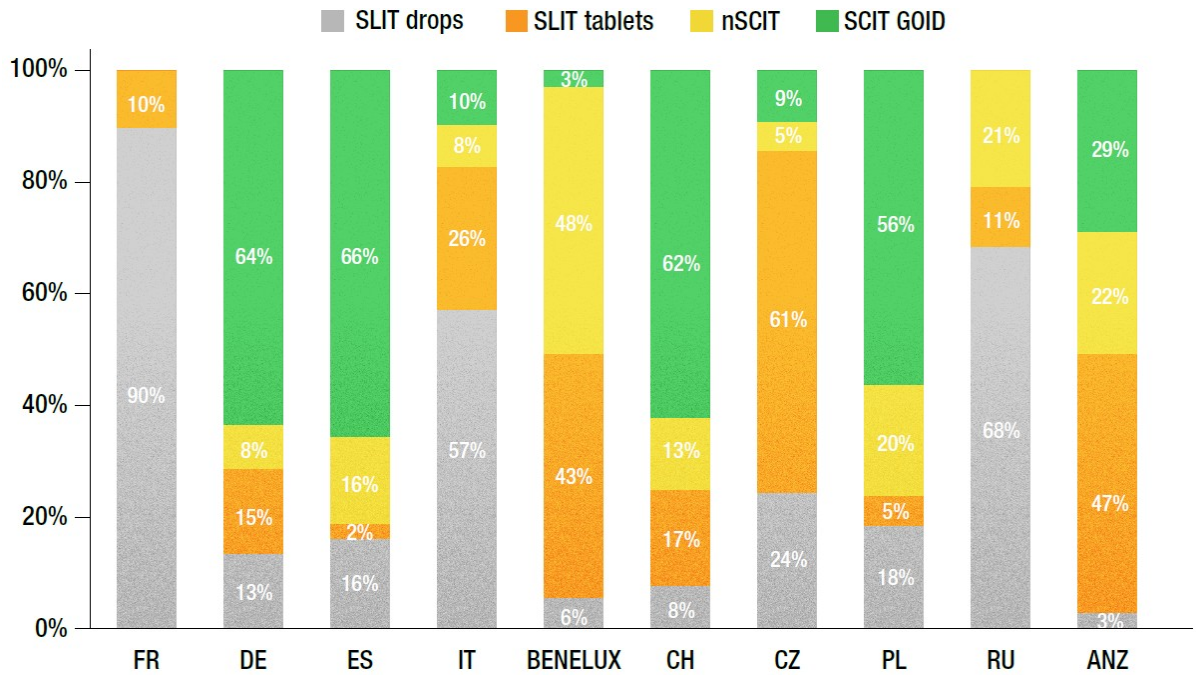
587 59. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in
588 non-randomised studies of interventions. BMJ. Oct 12 2016;355:i4919.
589 doi:10.1136/bmj.i4919
590 60. Dickerman BA, García-Albéniz X, Logan RW, Denaxas S, Hernán MA. Avoidable flaws
591 in observational analyses: an application to statins and cancer. Nat Med. Oct
592 2019;25(10):1601-1606. doi:10.1038/s41591-019-0597-x
593 61. García-Albéniz X, Hsu J, Hernán MA. The value of explicitly emulating a target trial
594 when using real world evidence: an application to colorectal cancer screening. Eur J
595 Epidemiol. Jun 2017;32(6):495-500. doi:10.1007/s10654-017-0287-2
596 62. Roche N, Anzueto A, Bosnic Anticevich S, et al. The importance of real-life research in
597 respiratory medicine: manifesto of the Respiratory Effectiveness Group: Endorsed by the
598 International Primary Care Respiratory Group and the World Allergy Organization. Eur
599 Respir J. Sep 2019;54(3)doi:10.1183/13993003.01511-2019
600 63. Cox LS. Sublingual Immunotherapy for Allergic Rhinitis: Is 2-Year Treatment Sufficient
601 for Long-term Benefit? JAMA. Feb 14 2017;317(6):591-593.
602 doi:10.1001/jama.2017.0128
603 64. Durham SR, Emminger W, Kapp A, et al. SQ-standardized sublingual grass
604 immunotherapy: confirmation of disease modification 2 years after 3 years of treatment
605 in a randomized trial. J Allergy Clin Immunol. Mar 2012;129(3):717-725 e5.
606 doi:10.1016/j.jaci.2011.12.973
607 65. Scadding GW, Calderon MA, Shamji MH, et al. Effect of 2 Years of Treatment With
608 Sublingual Grass Pollen Immunotherapy on Nasal Response to Allergen Challenge at 3
609 Years Among Patients With Moderate to Severe Seasonal Allergic Rhinitis: The GRASS
610 Randomized Clinical Trial. JAMA. Feb 14 2017;317(6):615-625.
611 doi:10.1001/jama.2016.21040

66. Egert-Schmidt AM, Kolbe JM, Mussler S, Thum-Oltmer S. Patients' compliance with different administration routes for allergen immunotherapy in Germany. Patient Prefer Adherence. 2014;8:1475-81. doi:10.2147/PPA.S70326
67. Kiel MA, Roder E, Gerth van Wijk R, Al MJ, Hop WC, Rutten-van Molken MP. Real-life compliance and persistence among users of subcutaneous and sublingual allergen immunotherapy. J Allergy Clin Immunol. Aug 2013;132(2):353-60 e2. doi:10.1016/j.jaci.2013.03.013
68. Senna G, Lombardi C, Canonica GW, Passalacqua G. How adherent to sublingual immunotherapy prescriptions are patients? The manufacturers' viewpoint. J Allergy Clin Immunol. Sep 2010;126(3):668-9. doi:10.1016/j.jaci.2010.06.045
69. Incorvaia C, Mauro M, Leo G, Ridolo E. Adherence to Sublingual Immunotherapy. Curr Allergy Asthma Rep. Feb 2016;16(2):12. doi:10.1007/s11882-015-0586-1
70. Katkade VB, Sanders KN, Zou KH. Real world data: an opportunity to supplement existing evidence for the use of long-established medicines in health care decision making. J Multidiscip Healthc. 2018;11:295-304. doi:10.2147/JMDH.S160029
71. ISAR Study Group. International Severe Asthma Registry: Mission Statement. Chest. Apr 2020;157(4):805-814. doi:10.1016/j.chest.2019.10.051
72. Califf RM, Sugarman J. 2015. Exploring the ethical and regulatory issues in pragmatic clinical trials. Clin Trials. 12:436–441. doi:10.1177/1740774515598334.
73. Avaible from website: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-annex-i-definitions-rev-4_en.pdf
74. *Leopold SS. Editorial: Words and meaning in scientific reporting: consecutive, prospective, and significant. Clin Orthop Relat Res. 2013;471(9):2731-2732. doi:10.1007/s11999-013-3162-9*

637 75. Motheral B, Brooks J, Clark MA, et al. A checklist for retrospective database studies--
638 report of the ISPOR Task Force on Retrospective Databases. Value Health. 2003;6(2):90-97.
639 doi:10.1046/j.1524-4733.2003.00242.x
640 76. Mitchell H. Gail Retrospective Study: Definition. First published: 29 September 2014
641 https://doi.org/10.1002/9781118445112.stat05209)

8. Figures

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

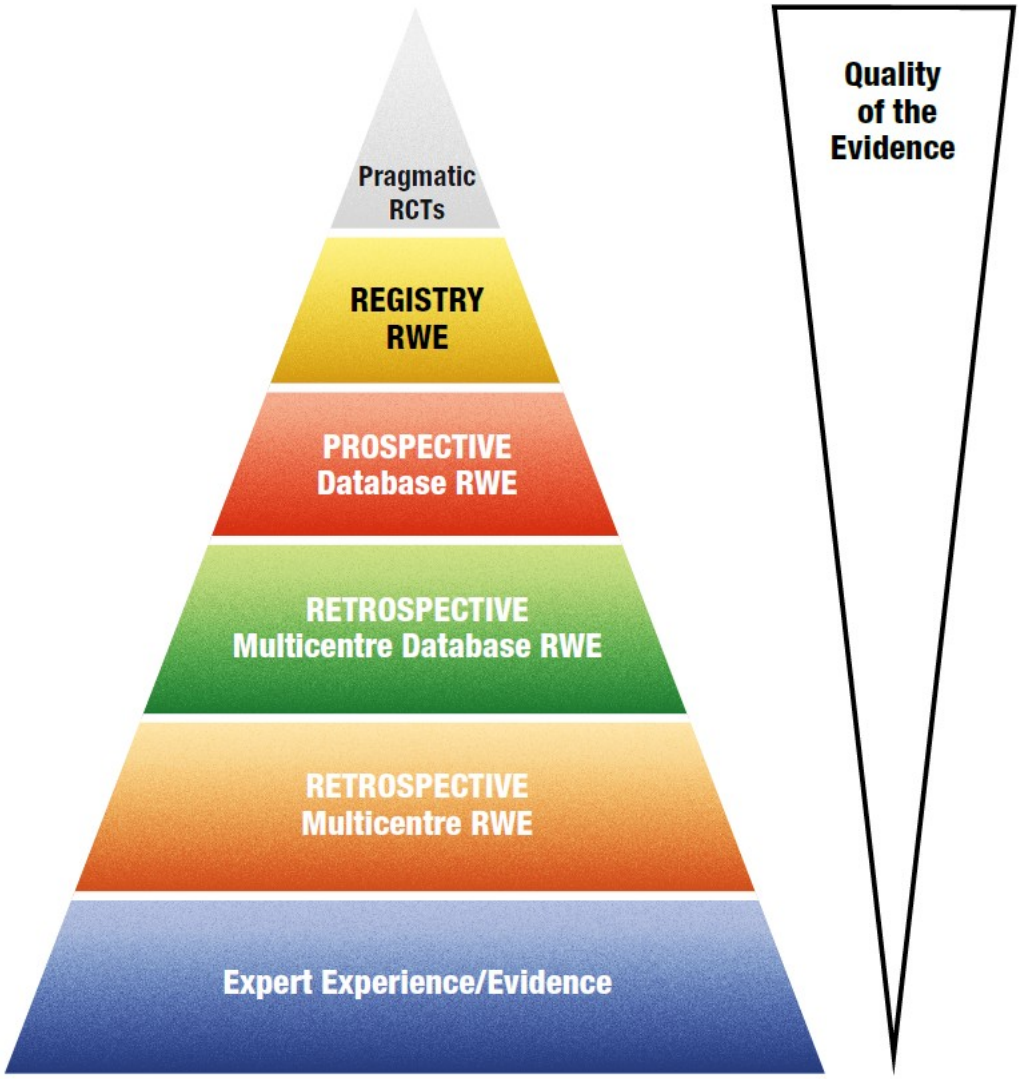


nSCIT, subcutaneous immunotherapy with natural extracts; SCIT, subcutaneous immunotherapy with natural extracts; SCIT GOID, subcutaneous unfractionated allergoid immunotherapy; SLIT, sublingual immunotherapy. FR: France; DE: Germany; ES: Spain; IT: Italy; CH: Switzerland; CZ: Czech Republic; PL: Poland;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

679