# EAACI Guidelines on Allergen Immunotherapy: House dust mite-driven allergic asthma

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# Abbreviations

ACEI = Angiotensin Converting Enzyme Inhibitor

ACT = asthma control test

ACQ = asthma control questionnaire

AD = atopic dermatitis/eczema

AEs = adverse events

AHR = airways hyperreactivity

AID = autoimmune diseases

AIT = allergen immunotherapy

AQLQ = asthma quality of life questionnaire

AR = allergic rhinitis

ARIA = Allergic Rhinitis and its Impact on Asthma

BAP = bronchial allergen provocation

BB = beta blockers

DBPC = double blind placebo controlled

EAACI = European Academy of Allergy and Clinical Immunology

FEF 25-75 = forced expiratory flow at 25-75% of the pulmonary volume

FEV1 = Forced Expiratory Volume in 1 Second

GINA = Global Initiative for Asthma

GRADE = The Grading of Recommendations Assessment, Development and

Evaluation

HCP = healthcare professional

HDM = house dust mites

ICS = inhaled corticosteroids

MEF 25 = Maximal Expiratory Flow at 25% of Forced Vital Capacity

MEF 50 = Maximal Expiratory Flow at 50% of Forced Vital Capacity

MEF 75 = Maximal Expiratory Flow at 75% of Forced Vital Capacity

PD20 = Provocative Dose Causing a 20% Drop in FEV1

QoL = quality of life

RCTs = randomised control trials

ROB = risk of bias

SLIT = sublingual allergen immunotherapy

SCIT = subcutaneous allergen immunotherapy

SmPC: Summary of product characteristics

WAO = World Allergy Organisation

WHO = World Health Organisation

# ABSTRACT

Allergen immunotherapy (AIT) has been in use for the treatment of allergic disease for more than 100 years. Asthma treatment relies mainly on corticosteroids and other controllers recommended to achieve and maintain asthma control, prevent exacerbations, and improve quality of life. AIT is underused in asthma, both in children and in adults. Notably, patients with allergic asthma not adequately controlled on pharmacotherapy (including biologics) represent an unmet health need.

The European Academy of Allergy and Clinical Immunology has developed a clinical practice guideline providing evidence-based recommendations for the use of house dust mites (HDM) AIT as add-on treatment for HDM-driven allergic asthma. This guideline was developed by a multi-disciplinary working group using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. HDM AIT was separately evaluated by route of administration and children and adults: subcutaneous (SCIT) and sublingual AIT (SLIT), drops and tablets. Recommendations were formulated for each.

The important prerequisites for successful treatment with HDM AIT are 1) selection of patients most likely to respond AIT and 2) use of allergen extracts and desensitization protocols of proven efficacy.

To date, only AIT with HDM SLIT-tablet has demonstrated a robust effect in adults for critical endpoints (exacerbations, asthma control and safety). Thus, it is recommended as an add-on to regular asthma therapy for adults with controlled or partially controlled HDM-driven allergic asthma (conditional recommendation, moderate quality evidence). HDM SCIT is recommended for adults and children and SLIT drops are recommended for children with controlled HDM-driven allergic asthma as the add-on to regular asthma therapy to decrease symptoms and medication needs (conditional recommendation, low quality evidence).

##  I. Introduction, background

Asthma represents a major health burden, currently affecting around 350 million people globally, with a projected increase to 400 million within the next 30 years [1-5]. It is responsible for considerable morbidity (hospitalisation and unscheduled healthcare) as well as direct and indirect costs (72.2 billion Euro annually in the European Union), and mortality. The major economic impact is due to indirect costs, absenteeism and decreased economic productivity [6-9].

Assessing the role of allergic sensitization in asthma pathophysiology is an important step in disease work-up because such patients might benefit from allergen immunotherapy (AIT) as add-on to pharmacological asthma therapy. The proportion of asthmatic patients with allergen sensitisation varies between 30 to 79% in children [10-12] and from 30 to 60% in adults [13-15], depending on the end points evaluated (sensitization or symptomatic allergic disease). Although type 2-driven inflammation is crucial in allergic asthma, the complexity of the underlying pathophysiological mechanisms means that there are a number of endotypes [15-19]. Assessment of endotypes is key for individualised management, including optimised allergen immunotherapy (AIT).

Remarkably, and probably due to the lack of robust evidence, no diagnostic tool or algorithm has been developed to discriminate between HDM driven allergic asthma and asthma with HDM sensitisation. At present the diagnosis relies on the proof of HDM sensitisation together with a detailed clinical history showing typical symptoms of asthma induced by HDM exposure (Figure 1 and Box 1). Sequential longitudinal assessments over a one-year period to confirm the difficult diagnosis of HDM induced asthma is an approach which might be advocated. In addition, the gold standard could be perfect asthma control in a HDM free environment [20].

**Figure 1. HDM-driven** **allergic asthma diagnosis**

*An accurate diagnosis of HDM-driven allergic asthma includes (i) evidence of allergic sensitisation to HDM and (ii) confirmation of HDM exposure as the main driver of asthma symptoms and control by history. Potentially, allergen provocation (airway hyperreactivity (AHR)) testing may be required.*

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| **Box 1: Nomenclature and Terms [21-24**] |
| ***Anaphylaxis:*** Severe, potentially life-threatening systemic hypersensitivity reaction characterised by rapid onset, life-threatening airway, breathing, or circulatory problems and usually, although not always, associated with skin and mucosal changesAllergen immunotherapy (***AIT):*** Procedure inducing tolerance to a specific allergen by repetitive administration of an allergen ***Adverse event (AE):***  Reaction triggered by AIT administration; can be local or systemic; systemic AE has four degrees of severity Airway hyperreactivity (***AHR):*** Exaggerated response of the airways to specific (allergen) and nonspecific stimuli, which results in airway obstruction Allergic rhinitis (***AR):*** inflammation of nasal mucosa induced upon exposure to an allergen together with the proof of immunological sensitisation to that allergen ***Asthma control:*** evaluated over the past four weeks (GINA 2018): * **controlled asthma** has daytime symptoms less than 2/week, no night-time awakenings, reliever is needed for symptoms less than 2/week and there is no activity limitation due to asthma;
* **partially controlled asthma**: failure to meet 1-2 of these criteria;
* **uncontrolled asthma**: failure to meet 3-4 of these criteria

***Asthma future risk:*** includes the risk of exacerbations, fixed airway obstruction and adverse reactions to medications used to control asthma; lung function measurement is an important part of the assessment of future risk***HDM driven allergic asthma:*** typical symptoms of asthma (wheezing, cough, dyspnoea and chest tightness with evidence of reversibility) with exposure to HDM together with the proof of immunological sensitisation to HDM *Local reaction* (***LR):*** inflammatory response confined to the contact siteQuality of life (***QoL)***: the individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals (WHO). In studies usually assessed by a standardised validated questionnaire estimating the impact of symptoms on daily activities*Subcutaneous immunotherapy* (***SCIT):*** subcutaneous, injectable route of HDM administration***Severe asthma:*** asthma that requires treatment with high-dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming ‘‘uncontrolled’’ or that remains ‘‘uncontrolled’’ despite this therapy (ATS/ERS consensus statement); severe asthma status is valid only after correct diagnosis of asthma and after all comorbidities and adherence to treatment are properly addressed*Sublingual immunotherapy* (***SLIT):*** sublingual (drops or tablets) route of HDM administration  |

It is now recognised that house dust mites (HDM), such as *Dermatophagoides (D) pteronyssinus* or *D. farinae*, are the source of the most important indoor allergens associated with asthma worldwide and lead to the development of high-titre allergen specific IgE. Substantial evidence associates allergic conditions such as asthma, allergic rhinitis (AR), atopic dermatitis (AD) with exposure to HDM or other indoor allergens [25-32]. Data from longitudinal investigations suggest that the development of sensitisation to HDM occurs before polysensitisation [33-35].

The rationale for AIT is the modification of the underlying allergic disease mechanisms triggering a sustained clinical effect based on allergen-specific tolerance, suppression of inflammation and multicomponent clinical improvement [21,36,37].

HDM AIT is currently administered in allergic asthma via either the subcutaneous (SCIT) or sublingual (SLIT) route, the latter with two alternatives: drops and tablets. Alternate routes, such as intralymphatic, are currently under investigation. Similar mechanisms of induction of allergen-specific IgG4, induction of IgE blocking IgG antibodies, T cell tolerance and decrease in Th2 response are described both for SCIT and SLIT [36,37].

A limited number of studies have been specifically designed to evaluate the efficacy and safety of HDM AIT in allergic asthma. Most data come from retrospective subgroup analyses from AIT trials in AR from which patients with concomitant asthma were analysed. According to the European Medicine Agency guidance published in 2015, clinical trials of AIT in asthma should start as add on therapy which has to be considered in the evaluation of the primary endpoint (e.g. evaluation in the context of a stepwise reduction of controller medication). Lung function, composite scores, number of exacerbations or reduced need for controller medication could be considered as primary endpoints [38]. The main issues with outcomes such as exacerbation is the rate of the events, which are infrequent in mild to moderate allergic asthma. Absence of daily symptoms and exacerbations define asthma control but these criteria may respond differently to any specific intervention [39]. Thus, asthma outcomes recommended by health authorities might have different relevance compared to those reported in real life by patients with allergic asthma [23,40].

The Global Initiative for Asthma (GINA) 2018 report recommends the assessment of two domains: control, which includes current symptoms and future risk of exacerbations, progressive loss of lung function and/or fixed airflow limitation and treatment issues, such as adherence and adverse effects. Achieving control of asthma is the major goal in current asthma management. Pharmacological and non-pharmacological strategies are adjusted in a continuous cycle that involves assessment, treatment and review [22]. According to GINA there is potentially a benefit associated with AIT in asthma if allergy plays a prominent role, e.g. asthma with allergic rhinoconjunctivitis [36]. In people with asthma and allergic sensitisation, SCIT is associated with a reduction in symptom scores and medication requirements, and improved allergen- specific and non-specific AHR. In patients sensitised to HDM, with AR and persistent asthma requiring ICS, with FEV1 >70% predicted and with exacerbations despite taking Step 2 therapy, GINA suggests that SLIT can be considered as an add-on therapy (Evidence B) [22]. In 2008 Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines [41] gave both SCIT and SLIT a conditional recommendation in allergic asthma due to moderate or low quality of evidence. However, ARIA 2008 guidelines were published before the publication of the trials specifically designed to evaluate the efficacy and safety of HDM AIT in allergic asthma. HDM AIT should be integrated into the general management of allergic asthma.

## II. Scope and purpose of the guideline

This Guideline has been prepared by the European Academy of Allergy and Clinical Immunology’s (EAACI) Taskforce on AIT for Allergic Asthma and is part of the EAACI Guidelines on Allergen Immunotherapy [42].

The aims of this Guideline are to provide evidence-based clinical recommendations for indications and contraindications to HDM AIT as add-on treatment for HDM-driven allergic asthma and to identify gaps in knowledge and/or implementation, unmet needs and future perspectives.

This Guideline does not address the prevention of HDM-driven allergic asthma, which is covered in the EAACI Guidelines on Allergen Immunotherapy Chapter: Prevention of allergy [43]. It also does not address the potential long-term benefit of HDM AIT (after AIT cessation) due to lack of evidence. AIT with other allergens for allergic asthma (grass, trees, cat) will be addressed in a separate paper.

The primary audiences of these recommendations are clinical allergists, respiratory physicians, paediatricians and other healthcare professionals (e.g. doctors, nurses, and pharmacists) working across a range of primary, secondary and tertiary care settings managing patients with allergic asthma. Industry representatives, health care managers or policy-makers may also find this Guideline useful.

## III. How to use these guidelines

1. Disclaimer

The EAACI Guideline for HDM AIT for allergic asthma is not intended to impose a standard of care. It provides the framework for rational decisions in the management of allergic asthma using AIT by clinicians, patients, third-party payers, institutional review committees and other stakeholders.

Statements regarding the underlying values and preferences as well as qualifying remarks accompanying each recommendation are an integral part of the Guideline and aim to facilitate more accurate interpretation. They should never be omitted or ignored when quoting Guideline recommendations.

1. Interpretation of strong and conditional recommendations (table 1)

Table 1: Interpretation of GRADE recommendations [44,45]

|  |  |  |
| --- | --- | --- |
| **Implications**  | **Strong recommendation**  | **Conditional (weak) recommendation**  |
| **For patients**  | Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.  | The majority of individuals in this situation would want the suggested course of action but many would not.  |
| **For clinicians**  | Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.  | Recognise that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.  |
| **For policy makers** The recommendation can be adapted as policy or performance measure in most situations  | Policy making will require substantial debate and involvement of various stakeholders. Documentation of appropriate (e.g. shared) decision-making processes can serve as performance measure.  |

**IV. Methodology**

# A. Blended approach

1. GRADE assessment of the existing evidence of HDM AIT in asthma [44-46].
2. Individual assessment of major randomised control trials (RCTs) and previous meta-analyses for HDM AIT in asthma
3. Individual assessment of open studies, real-life studies, observational studies, surveys

# B. Evaluation of the body of evidence

1. By delivery route of HDM AIT (SCIT, SLIT drops, SLIT tablets)
2. Stratified for paediatric and adult populations

## C. Clinical questions and outcomes for HDM-driven allergic asthma

The following questions were identified for this guideline:

1. Should HDM SCIT versus no SCIT be used for treatment in paediatric patients with HDM-driven allergic asthma?
2. Should HDM SCIT versus no SCIT be used for treatment in adult patients with HDM-driven allergic asthma?
3. Should HDM SLIT drops versus no SLIT drops be used for treatment in paediatric patients with HDM-driven allergic asthma?
4. Should HDM SLIT drops versus no SLIT drops be used for treatment in adult patients with HDM-driven allergic asthma?
5. Should HDM SLIT tablets versus no SLIT tablets be used for treatment in paediatric patients with HDM-driven allergic asthma?
6. Should HDM SLIT tablets versus no SLIT tablets be used for treatment in adult patients with HDM-driven allergic asthma?

As per GRADE methodology we classified outcomes into critical, important and of low importance according to the classification of asthma outcomes in major RCT HDM AIT asthma trials as requested by the regulatory bodies (table 2)

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| Table 2: Classification of outcomes for HDM AIT for HDM-driven allergic asthma  |
| Critical  | Exacerbations  | Number of exacerbations/number of patients  |
| Number of patients with at least 1 exacerbation  |
| Time to first asthma exacerbation upon ICS reduction/withdrawal  |
| Asthma control  | ACQ score  |
| ACT  |
| “in-house” definitions  |
| Corticosteroid sparing effect  | % decrease in ICS dose for asthma control  |
| Safety  | Systemic reactions (WAO grading)  |
| Important  | Symptom score  | “in-house” definitions  |
| Medication score  | “in-house” definitions  |
| Quality of life  | AQLQ  |
| Lung function  | Small airways\* (% or absolute improvement of MEF 25, MEF 50, MEF 75, FEF25-75)  |
| Allergen specific AHR (increase in PD20 allergen)\*\*  |
| Safety  | Local reactions (WAO grading)  |
| Low importance  | Lung function  | Improvement in FEV1\* (% or absolute)  |
| Non-specific AHR (increase in PD20 methacholine, histamine)\*\*  |
| Comments: \*As most of AIT trials in asthma enrolled subjects with normal lung function the expected benefit on FEV1 is of low importance; in contrast the effect on small airways is important given the systemic effects of AIT \*\* According to the biologic effect the impact on allergen specific AHR is expected to be significant (important outcome) compared to the effect on non-specific AHR (low importance outcome)  |

**D. Evidence review**

Evidence summaries for each question were prepared by a methodologist using GRADE Pro GDT (www.gradepro.org). The GRADE approach was specifically used for this Guideline to bring it into line with other asthma guidelines [36]. The panel members reviewed the summaries of the evidence and provided feedback when appropriate. Evidence summaries are based on the systematic review conducted for this Guideline [47]. In addition, an updated search strategy was performed by delivery route (SCIT, SLIT drops and SLIT tablets) and for the paediatric and adult populations. The methods of the Cochrane Collaboration (www.handbook.cochrane.org) were adopted with the risk of bias at the outcome level assessed using the Cochrane Collaboration’s risk of bias tool [44]. The certainty of the supporting evidence (also called confidence in the estimates of effects or quality of evidence) was assessed by applying the GRADE framework for interventions [45,46]. The certainty of the evidence was categorised as high, moderate, low or very low based on consideration of risk of bias, directness of evidence, consistency and precision of the estimates, and other considerations. Low and very low certainty evidence indicates that the estimated effects of interventions are very uncertain, and any further research is very likely to influence current recommendations. The GRADE Pro GDT (www.gradepro.org) software was used to assess the certainty of evidence. Evidence on values and preferences and cost of AIT was also considered.

**E. Formulating the recommendations**

As per GRADE methodology the summary of judgments is provided for each recommendation. This includes evaluation of the importance of the problem, desirable and undesirable effects, certainty of evidence, values, balance of effects, resources required, certainty of evidence of required resources, cost-effectiveness, equity, acceptability and feasibility.

**F. Document revision**

Each member of the EAACI allergic asthma AIT guideline task force reviewed the final Guideline draft and approved the document. The document was revised to incorporate the pertinent comments suggested by the external reviewers.

**G. Stakeholders involvement**

The EAACI task force on AIT for allergic asthma included members from a wide range of countries, professional backgrounds (allergy, paediatrics, internal medicine, pulmonology, basic and clinical immunology, primary care) and patient representatives. The whole allergy community, connected specialities and representatives of AIT vaccine manufactures were given the opportunity to review and comment on the draft guideline; where appropriate revisions were made.

**H. Conflict of interest**

In accordance with EAACI policy, everyone who is intellectually involved in the project (i.e., considered for guideline authorship) disclosed all potential conflict of interest in writing at the beginning, middle and end of the project.

**I. Other considerations**

Appropriate representation of all stakeholders, peer review by invited experts from a full range of organisations, countries, and professional backgrounds and editorial independence were ensured. Identifying gaps, barriers and facilitators was an important part of the process. All stakeholders had an opportunity to comment on the draft guideline publicised on the EAACI Website for a 3-week period (November 2018) to allow any omissions or errors in the evidence-base to be highlighted. The development of AIT for Allergic Asthma was funded and supported by EAACI. The funder did not have any influence on the guideline production process, on its contents nor on the decision to publish.

The review of this guideline is planned for 2022 but will be brought forward if there are any prior major developments in the evidence.

### V. Evaluation of the body of evidence

1. **GRADE assessment of the existing evidence**

The summary of evidence (SOF) and evidence profiles are presented in Annexe A (supplementary online material).

1. **Individual assessment of major RCTs and previous meta-analyses**

A. HDM SCIT

Wang et al. investigated children and adults with HDM allergic asthma in a randomised double-blind, placebo-controlled (DBPC) trial funded by ALK-Abelló. They reported exacerbations defined by the number of courses of oral corticosteroids required to restore asthma control. No significant difference was found between the SCIT and placebo groups. A difference in favour of SCIT for decreased exacerbation frequency and severity as well as overall symptoms measured with a self-evaluation questionnaire [48] was observed.

In an open randomised clinical trial in children with asthma funded by Allergopharma, SCIT with a mite allergoid added to pharmacotherapy permitted a reduction in the dose of ICS needed to maintain disease control compared with pharmacotherapy alone [49].

In a randomised DBPC trial funded by Allergopharma the minimal ICS dose for asthma control was evaluated as the secondary outcome for 4 doses of HDM SCIT versus placebo in 146 adult patients with asthma. The interventions were given for approximately 7 months. A statistically significant decrease in ICS dose was only observed in the highest dose SCIT group. While average Asthma Control Test (ACT) scores improved in all dose groups, the only statistically significant change was recorded for the medium SCIT dose [50].

Three small prospective DBPC trials funded by Laboratorios LETI assessed HDM efficacy and safety of HDM AIT in adults with allergic asthma [51-53]. In two studies allergen-specific AHR evaluated with bronchial allergen provocation (BAP) was the main outcome, with symptom and medication scores as secondary outcomes. In the study of Basomba, clinical scores were the primary outcomes [53]. All trials reported a significant increase in BAP PD20 FEV1 and improvement in symptom and medication scores. One trial also reported a significant improvement in quality of life (AQLQ) [52]. BAP was not influenced by a placebo effect.

In an open study evaluating 42 children with HDM allergic asthma SCIT, there was a significant improvement in BAP PD20 FEV1. Interestingly, BAP differentiated between responders (60.7%) and non-responders. Although all SCIT treated children reported subjective improvement in their symptoms, only the responders required less medication after SCIT [54].

Several studies assessed the immunological and functional effects of HDM SCIT in adults with mild allergic asthma, these provide indirect evidence for the efficacy of SCIT. In a randomised DBPC study (Alvarez et al). 26 asthmatic subjects were randomised to receive liposome-entrapped *D. pteronyssinus* via SCIT (n=12) or placebo (n=11). An allergen bronchial challenge was performed at the beginning (T0) and after 1 year of treatment (T12). The day before and 24 hour after the allergen provocation, patients were challenged with methacholine (Mch) and blood and sputum samples were obtained. Dose-response curves to Mch were evaluated in terms of Mch-PD20, slope (Mch-DRS) and level of plateau. Blood and sputum eosinophils and serum levels of eosinophil cationic protein (ECP) and intercellular adhesion molecule-1 (ICAM-1) were measured. At T12, previous to the allergen challenge, the active group showed higher values of both FEV1 and Mch-PD20 and lower values of Mch-DRS. At T12, before the allergen challenge, serum ECP levels increased in the placebo group and blood eosinophils showed a trend towards lower numbers in the active group. The immediate response and the changes in Mch-DRS values, sputum eosinophils and serum ECP levels, following the allergen challenge were attenuated in the active group [55].

B. HDM SLIT drops

In the Cochrane SR and meta-analysis by Normansell et al., a wide but varied reporting of largely unvalidated asthma symptom and medication scores precluded a meaningful meta-analysis. A general trend suggested a benefit for SLIT over placebo but variation in scales made the results difficult to interpret [56]. In addition, this SR evaluated SLIT for all allergens and did not differentiate between drops and tablets. The meta-analysis by Compalati et al. identified 12 randomized, DBPC studies that assessed HDM SLIT in patients with AR or asthma (382 patients with AR and 476 with allergic asthma). They reported a large overall benefit for SLIT for symptom scores and decrease in rescue drug use. However, authors found considerable inter-study heterogeneity [57]. Kim et al. evaluated seven studies for symptom score and six with reported medication score. The strength of evidence was high for improving asthma symptoms and moderate for reducing asthma medication [58]. However, most of the studies included small numbers of patients, for example Yukselen 11 SLIT vs 10 placebo, Lue 10 children on SLIT and 10 on placebo, Pajno 24 children with 12 on SLIT, Hirsch 30 children, Tari 58 children with both rhinitis and asthma, Bahçeciler 15 children with rhinitis and asthma. The larger studies included were by Niu et al. which included 97 children, 49 on SLIT and by Ippoliti et al. including 86 children, 47 on SLIT. The meta-analysis of Liao et al. included 11 open or double-blind studies with a total of 454 children with asthma/rhinitis who were sensitised to HDM, ranging from 15 to 109 patients. A large overall reduction in asthma symptom scores but not in medication scores was found; significant inter-study heterogeneity was reported [59].

The RCT study of Wang funded by Stallergenes Greer, which included 484 asthmatic adults (SLIT n= 308 and placebo n= 157), evaluated as the primary efficacy outcome asthma control and a well-defined ICS dose step-down. Although asthma control was achieved by a slightly greater proportion of patients in the active treatment group than in the placebo group, the primary efficacy criterion was not met because of a higher than expected asthma control rate in the whole study population. In view of the wide range of ICS daily doses used by the patients, a *post hoc* analysis by asthma severity was performed. This revealed significant clinical benefits in actively treated subjects with moderate, persistent asthma at baseline (401-800 micrograms budesonide) with better achievement of well-controlled asthma and totally controlled asthma, a higher percentage of patients with an ACQ score < 0.75 and a greater mean reduction in ICS use [60].

In another DBPC trial funded by Stallergenes Greer, adults with asthma were randomised to receive active treatment (n=322) or placebo (n=162) during 52 weeks. The incidence of exacerbations was similar between the active and placebo groups there was no effect on lung function or on the quality of life (QoL) [61].

C. HDM SLIT tablets

Clinical efficacy of the SQ HDM SLIT-tablet in asthma has been evaluated in adults in three DBPC randomised trials funded by ALK [62,64,65]. Each trial had a different asthma related end-points: ICS dose decrease, average asthma symptom score and time to first asthma exacerbation upon ICS dose decrease.

In a large randomized DBPC study, Mosbech et al [62] included 604 subjects with controlled (ACQ <1) and partially controlled (ACQ 1-1.5) mild to moderate asthma and a history of HDM AR. Participants were randomised to receive 3 active doses of a HDM SLIT-tablet or placebo. The primary end-point was the lowest ICS dose needed to maintain asthma control. The difference in the decrease of ICS dose between active and placebo at the end of trial assessment period was 81µg. The benefit was observed only for the highest dose (6 SQ-HDM). A *post hoc* analysis showed that subjects with a daily ICS dose of 400–800 μg and partly controlled asthma at randomisation experienced a significantly higher treatment benefit for the highest dose in terms of ICS dose decrease (327 µg), AQLQ and ACQ compared to the rest of the trial population [63].

A randomized DBPC study of Nolte et al. evaluated HDM asthma as secondary endpoint in allergen exposure chamber. Eighty-three subjects received two different active doses and 41 received placebo. Both doses of 12 and 6 SQ-HDM for 24 weeks resulted in a statistically significant improvement versus placebo in reported average asthma symptom score during allergen challenge, with greater efficacy of the 12 SQ-HDM dose [64].

In the randomised DBPC study of Virchow et al [65] the primary end point was time to first moderate or severe asthma exacerbation during a 6-month ICS reduction period. The trial included 834 adults with HDM-driven allergic asthma. After 7–12 months of treatment with the HDM SLIT-tablet (6 SQ-HDM [n=275] and 12 SQ-HDM [n=282]) or placebo (n=277), daily ICS use was reduced to 50% for 3 months, followed by complete ICS withdrawal for 3 months for the remaining subjects who had not experienced an asthma exacerbation during the previous study phases. The trial included 834 adults with HDM not well-controlled allergic asthma (ACQ score of 1–1.5) and HDM AR, with a need for daily ICS treatment equivalent to budesonide 400–1200 micrograms. There was a significant risk reduction in the time to first asthma exacerbation versus placebo, as observed by hazard ratios of 0.69 and 0.66 for 6 SQ-HDM and 12 SQ-HDM, respectively. Treatment with 12 SQ-HDM resulted in a 34% risk reduction compared to placebo. This study showed that the addition of HDM SLIT improved time to first moderate or severe asthma exacerbation during ICS reduction, with an estimated absolute reduction at sixmonths of nine to 10 percentage points. The reduction was primarily due to an effect on moderate exacerbations.

Combined clinical safety data from the SQ-HDM tablet trials indicate that it is well tolerated, and the observed safety and tolerability profile corresponds with the observed profile for other SLIT products.

As a result of these trials the HDM SLIT tablet is recommended for HDM-induced allergic asthma not well controlled by ICS and associated with mild to severe HDM induced AR, when the patients’ asthma status is carefully evaluated before the initiation of treatment. GINA 2018 recommends SLIT with HDM as an add-on therapy (Evidence B) in patients with exacerbations despite taking Step 2 therapy to decrease mild and moderate asthma exacerbations.

In the paediatric population the randomised DBPC trial of Pham-Thi et al, funded by Stallergenes Greer, included 111 children, 55 on AIT. It showed no additional benefit of SLIT tablets 300 IR to improve lung function or decrease symptoms or medication use after 18 months of treatment [66].

3. **Individual assessment of open studies, real-life studies, observational studies, surveys**

A recent prospective, multi-centre, non-interventional study evaluated 220 patients (117 adults, 103 children) with HDM allergy receiving SCIT with allergoid preparation. Organ-specific key symptoms and the use of concomitant anti-allergic medication were assessed at baseline and after 12 and 24 months. 63% of adults and 64% of children had bronchial symptoms and they decreased significantly at 12 and 24 months in parallel with the use of symptomatic medication. During the 24-month study period, AEs were observed in 3.4% adults and in 6.8% children. All local AEs related to the study drug (erythema, swelling, and pain at the injection site). Serious AEs were reported in three adults and one child: a grade-II anaphylactic reaction (one adult) controlled by oral antihistamines (no hospitalisation) classified as "definitely," three others as not (2) or possibly (1) drug-related [67].

A sub-analysis by Trebuchon of 736 paediatric patients included in a previous retrospective, observational, multicentre study reported a significant decrease in symptoms and medications with HDM SLIT drops [68]. In a prospective, open, parallel group, controlled study the efficacy of three year of SLIT in addition to pharmacotherapy (62 children) was compared with pharmacotherapy alone (28 children) [69]. Ozdemir and colleagues reported significant decreases in the dose and duration of ICS treatment in the SLIT group with 52.4% of subjects able to discontinue ICS. Di Rienzo followed up over a 10 year period 60 children, 35 receiving SLIT versus 25 who received pharmacotherapy only; in this open non-randomised trial the authors reported significant long-lasting effect on symptoms and medication at the end of 4-5-year SLIT [70].

A health-economic, piggy-back analysis of SCIT was conducted based on a RCT performed by Allergopharma that enrolled 65 children and adolescents with controlled allergic asthma. Both costs and cost-effectiveness of HDM SCIT were evaluated based on total medication costs, incremental medication costs and treatment effects (measured as lung function). A bootstrap analysis was performed to validate the results. Compared to the control group with standard asthma medication alone, a steady decline in medication costs was be observed in the intervention group (SCIT plus standard asthma medication) one year after commencing SCIT. This cost trend became statistically significant 3 years after starting SCIT. The calculated potential savings in the SCIT group correlated with an improved lung function. The distribution of the bootstrap results revealed that the probability of SCIT having a superior effectiveness (measured by changes in peak flow results) is around 90% [71].

SQ HDM SLIT-tablet cost-effectiveness was evaluated in a hypothetical cost utility analysis, based on the results of a European phase III randomised controlled trial in HDM allergic asthma uncontrolled by ICS [65]. The model included data collected from 559 patients from 13 countries. SQ HDM SLIT-tablet plus pharmacotherapy was estimated to generate 6.16 quality-adjusted life years (QALYs) per patient at a cost of €5,658, compared with 5.50 QALYs at a cost of €2,985 for placebo plus pharmacotherapy. This equated to an incremental cost of €2,673, incremental QALYs of 0.66 and an incremental cost-effectiveness ratio (ICER) of €4,041. The ICER was, therefore, substantially lower than the €40,000 willingness-to-pay threshold per QALY adopted for the analysis. Deterministic sensitivity analyses indicate the results are most sensitive to the utility score of SLIT during years 2 and 3 of treatment [72].

Another observational, retrospective, and multicentre study carried out in Spain on 419 adult patients diagnosed with HDM AR and/or asthma showed a significant decrease in all quantified resources after a single year of SCIT. Direct costs were decreased by 64% and indirect costs by 94%. Estimated savings for the public National Health System of using SCIT were 5.7 times the cost of immunotherapy [73].

### VI. Recommendations

We present recommendations for AIT in allergic asthma only for HDM since it is the major allergen for allergic asthma and it has the most robust evidence.

**HDM SCIT**

**Question:** Is HDM SCIT recommended for children and adults with HDM-driven allergic asthma?

## Recommendations

1. HDM SCIT is recommended for children and adults with controlled HDM – driven allergic asthma as an add-on treatment to regular therapy to decrease symptoms and medication use

Conditional recommendation, low quality evidence (Table 3)

1. HDM SCIT is recommended for adults with controlled HDM-driven allergic asthma as the add-on treatment to regular therapy to decrease allergen specific AHR and to improve QoL.

Conditional recommendation, low quality evidence (Table 3)

## Values and preferences

This recommendation places a higher value on the risk of intervention with SCIT and a lower value on the benefit of decreasing symptom and medication use and decreasing allergen specific AHR (Table 3).

## Remarks

1. There is significant heterogeneity of HDM SCIT studies: different preparations (extracts and modified forms like allergoid), different delivery systems such as liposome-encapsulated allergen, different protocols included DBPC or non-DBPC studies, different end-points, etc. Thus product by product evaluation is recommended to inform the clinical judgement and only products with proof of efficacy should be used.
2. To date, no HDM SCIT study evaluated reduction in asthma exacerbations or improving asthma control as its primary outcome because they were performed before GINA guidelines promoted these endpoints as primary goals for asthma management. Additionally EMA only published guidance on AIT in 2015. However decreased symptoms and medication use can be considered as a surrogate for asthma control [23]. The decrease in specific AHR might lead to less allergen driven asthma exacerbations [74]. Of note the number of studies that demonstrated a significant effect on the early and, most importantly, the late phase of allergen induced bronchial reaction are very limited.
3. There is limited evidence on potential direct or indirect cost-saving effect by adding HDM SCIT to regular asthma treatment.
4. Asthma control and lung function should be assessed regularly (preferably before each SCIT injection); a minimum 30 minutes observation after therapy at the office is recommended; SCIT should be administered by healthcare professionals (HCPs) with proper training in AIT, under proper conditions to manage severe bronchospasm or a systemic anaphylactic reaction.

Table 3: Judgement of HDM SCIT in decreasing asthma symptoms and medication in children or in adults as add-on treatment to regular asthma therapy in controlled asthma

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Importance  | No  | Probably no  | **Probably yes**  | Yes  |   | Varies  | Don't know  |
| Desirable effects  | Trivial  | **Small**  | Moderate  | Large  |   | Varies  | Don't know  |
| Undesirable effects  | Large  | **Moderate**  | Small  | Trivial  |   | Varies  | Don't know  |
| Certainty of evidence  | Very low  | **Low**  | Moderate  | High  |   |   | No included studies  |
| Values  | **Important uncertainty or** **variability**  | Possibly important uncertainty or variability  | Probably no important uncertainty or variability  | No important uncertainty or variability  |   |   | No known undesirable outcomes  |
| Balance of effects  | Favours the comparison  | Probably favours the comparison  | Does not favour either the intervention or the comparison  | **Probably favours the intervention**  | Favours the intervention  | Varies  | Don't know  |
| Resources required  | Large costs  | Moderate costs  | Negligible costs and savings  | **Moderate savings**  | Large savings  | Varies  | Don't know  |
| Certainty of evidence of resources required  | **Very low**  | Low  | Moderate  | High  |   |   | No included studies  |
| Cost-effectiveness  | Favours the comparison  | Probably favours the comparison  | Does not favour either the intervention or the comparison  | **Probably favours the intervention**  | Favours the intervention  | Varies  | No included studies  |
| Equity  | Decreased  | Probably decreased  | **Probably no impact**  | Probably increased  | Increased  | Varies  | Don't know  |
| Acceptability  | No  | Probably no  | **Probably yes**  | Yes  |   | Varies  | Don't know  |
| Feasibility  | No  | Probably no  | **Probably yes**  | Yes  |   | Varies  | Don't know  |

Due to lack of evidence no recommendation can be provided for the use of HDM SCIT to decrease exacerbations, improve asthma control and lung function or to decrease non-specific AHR.

# HDM SLIT drops

**Question:** Are HDM SLIT drops preparations recommended in children or adults with HDM-driven allergic asthma?

## Recommendations

1. HDM SLIT drops are recommended for children with controlled HDM-driven allergic asthma as an add-on treatment to decrease symptoms and medication use

Conditional recommendation, low quality evidence (Table 4).

## Values and preferences

This recommendation places a high value on decreasing asthma symptoms and medication as well as on the ease of administration at home with potential of decreased resource utilisation (Table 4).

## Remarks

1. Asthma control and lung function should be assessed regularly.
2. The subgroup of patients with moderate asthma might have a better benefit but more safety data are needed.
3. In children the potential benefits could include the ICS sparing effect.

Table 4: Judgment of HDM SLIT drops in decreasing asthma symptoms and medication in children while added to regular asthma treatment for controlled asthma

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Importance  | No  | Probably no  | Probably yes  | **Yes**  |   | Varies  | Don't know  |
| Desirable effects  | Trivial  | **Small**  | Moderate  | Large  |   | Varies  | Don't know  |
| Undesirable effects  | Large  | Moderate  | **Small**  | Trivial  |   | Varies  | Don't know  |
| Certainty of evidence  | Very low  | **Low**  | Moderate  | High  |   |   | No included studies  |
| Values  | Important uncertainty or variability  | Possibly important uncertainty or variability  | **Probably no important** **uncertainty or** **variability**  | No important uncertainty or variability  |   |   | No known undesirable outcomes  |
| Balance of effects  | Favours the comparison  | Probably favours the comparison  | Does not favour either the intervention or the comparison  | **Probably favours the intervention**  | Favours the intervention  | Varies  | Don't know  |
| Resources required  | Large costs  | Moderate costs  | Negligible costs and savings  | Moderate savings  | Large savings  | Varies  | **Don't know**  |
| Certainty of evidence of resources required  | Very low  | Low  | Moderate  | High  |   |   | **No included studies**  |
| Cost-effectiveness  | Favours the comparison  | Probably favours the comparison  | Does not favour either the intervention or the comparison  | Probably favours the intervention  | Favours the intervention  | Varies  | **No included studies**  |
| Equity  | Decreased  | Probably decreased  | **Probably no impact**  | Probably increased  | Increased  | Varies  | Don't know  |
| Acceptability  | No  | Probably no  | Probably yes  | **Yes**  |   | Varies  | Don't know  |
| Feasibility  | No  | Probably no  | Probably yes  | **Yes**  |   | Varies  | Don't know  |

Due to lack of evidence, no recommendation can be provided for the use of HDM SLIT drops in adults with HDM-driven allergic asthma to decrease exacerbations, improve asthma control or to decrease specific and non-specific AHR.

## HDM SLIT tablets

**Question:** Are HDM SLIT tablets recommended for children and adults with HDM-driven allergic asthma?

## Recommendations

HDM SLIT tablets are recommended for adults with controlled and partially controlled HDM-driven allergic asthma as an add-on treatment to regular therapy to decrease exacerbations and to improve asthma control.

Conditional recommendation, moderate quality evidence (Table 5).

## Values and preferences

This recommendation places the high value on decreasing asthma exacerbations and improving or maintaining asthma control while decreasing the ICS dose and on the ease of administration at home with potential decreased resource utilisation (Table 5).

## Remarks

1. Asthma control and lung function should be assessed regularly
2. Patients with partially controlled asthma or with a history of severe asthma exacerbations during the last 12 months should be carefully monitored

Table 5: Judgment of HDM SLIT tablets for decreasing asthma exacerbations and improving asthma control while added to regular asthma treatment

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Importance  | No  | Probably no  | Probably yes  | **Yes**  |   | Varies  | Don't know  |
| Desirable effects  | Trivial  | Small  | **Moderate**  | Large  |   | Varies  | Don't know  |
| Undesirable effects  | Large  | Moderate  | **Small**  | Trivial  |   | Varies  | Don't know  |
| Certainty of evidence  | Very low  | Low  | **Moderate**  | High  |   |   | No included studies  |
| Values  | Important uncertainty or variability  | Possibly important uncertainty or variability  | **Probably no important** **uncertainty or** **variability**  | No important uncertainty or variability  |   |   | No known undesirable outcomes  |
| Balance of effects  | Favours the comparison  | Probably favours the comparison  | Does not favour either the intervention or the comparison  | Probably favours the intervention  | **Favours the intervention**  | Varies  | Don't know  |
| Resources required  | Large costs  | Moderate costs  | Negligible costs and savings  | **Moderate savings**  | Large savings  | Varies  | Don't know  |
| Certainty of evidence of resources required  | Very low  | Low  | Moderate  | High  |   |   | **No included studies**  |
| Cost-effectiveness  | Favours the comparison  | Probably favours the comparison  | Does not favour either the intervention or the comparison  | Probably favours the intervention  | **Favours the intervention**  | Varies  | No included studies  |
| Equity  | Decreased  | Probably decreased  | **Probably no impact**  | Probably increased  | Increased  | Varies  | Don't know  |
| Acceptability  | No  | Probably no  | Probably yes  | **Yes**  |   | Varies  | Don't know  |
| Feasibility  | No  | Probably no  | Probably yes  | **Yes**  |   | Varies  | Don't know  |

Due to lack of evidence no recommendation can be provided for the use of HDM SLIT tablets for children or for adults to improve asthma lung function or quality of life or to decrease specific and non-specific AHR.

### VII. Safety, precautions, contraindications

HDM AIT is a safe adjunct treatment for controlled HDM-driven allergic asthma in children and adults. However, it should be noted that most of the safety data are derived from AR studies enrolling patients with controlled asthma and with FEV1 > 70% predicted. Limited data for adverse events are available for patients only with allergic asthma or for patients with moderate or severe asthma.

Uncontrolled asthma is the major independent risk factor for both severe and fatal adverse reactions and is therefore a major contraindication for both HDM SCIT and SLIT. Patients with severe but controlled HDM-severe asthma may be eligible for HDM AIT in selected cases with careful monitoring. Other contraindications and precautions are listed in Tables 6 and 7. The Summary of Product Characteristics (SmPC) should also be checked for product specific precautions and contraindications that may differ between preparations.

|  |  |
| --- | --- |
| **Table 6 Contraindications and precautions for HDM AIT in patients with HDM-driven allergic asthma**  |  |
|  | Remarks | Key reference |
| HDM AIT is contraindicated in uncontrolled asthma | Due to safety concerns.    | Epstein 2016 [76], Calderon 2017 [77], Rodriguez del Rio 2017 [78], Normansell 2015 [56], Pitsios 2015 [79], Cox 2011 [80], Lockey 2001 [81], Bernstein 2004 [82] |
| HDM SLIT tablet may be considered with caution in partially controlled asthma | HDM AIT might be beneficial especially in patients with partly controlled HDM-driven allergic asthma with studies demonstrating improved asthma control and quality of life. HDM SLIT tablet in adults with asthma not well controlled by ICS or combination products did not increase the risk of major adverse events (AEs) [65]; however, FEV1 less than 70% of predicted value or severe asthma exacerbation within 3 months before randomization were key exclusion criteria.  | Mosbech 2014 [63]Virchow 2016 [65] |
| AIT should not be initiated in pregnancy (but can be continued in pregnancy) | Safety of initiation and continuation of SCIT and SLIT during pregnancy analysed in 4 studies totalling 422 women demonstrated no increased incidence of prematurity, hypertension/proteinuria, congenital malformations or perinatal deaths during pregnancy and no foetal complications following systemic AEs while receiving AIT [83]  | Pitsios 2015 [79] Oykhman 2015 [83]. |
| AIT should not be initiated in patients with active or uncontrolled autoimmune disorders (AID) | The CONSIT survey reported on patients undergoing AIT with AID. Major problems were infrequent [78] | Pitsios 2015 [79] Rodriguez del Rio 2017 [78]  |
| AIT should not be initiated in patients with active malignancies  |   | Pitsios 2015 [79]  |
| AIT may be considered with caution in patients with controlled asthma under treatment with beta-blockers (BB) or ACE inhibitors (ACEI) | Only in specialised settings due to increased refractoriness to treatment of anaphylaxis with epinephrine. The CONSIT survey reported on patients undergoing AIT under BB or ACEI. Major problems were infrequent [78] | Rodriguez del Rio 2017 [78]  |
| AIT is not recommended in patients with immune deficiencies, active infections and infestations and uncontrolled diseases like diabetes, inflammatory bowel disease, gastric ulcer etc. | The CONSIT survey reported on patients with immune deficiencies or under immune suppressants receiving AIT. Major problems were infrequent [78] | Pitsios 2015 [79] Rodriguez del Rio 2017 [78]  |

|  |
| --- |
| **Table 7: Recommendations for risk management of HDM AIT in HDM-driven allergic asthma**  |
| HDM SCIT for HDM-driven allergic asthma  | * Signed informed consent
* Supervised administration by a healthcare professional (HCP) trained in the evaluation of patients with allergic conditions in a setting facilitating proper management of systemic reactions
* Assessment of the patient’s current health status before the administration of SCIT to determine whether there have been any recent changes in the patient’s health that may require modifying or withholding treatment (e.g., uncontrolled/symptomatic asthma or exacerbation of allergy symptoms
* Observation for at least 30 minutes after injection
* Patient education for management and reporting late reactions
 |
| Home based HDM-SLIT for HDM-driven allergic asthma  | * Signed informed consent
* Supervised initiation by a HCP trained in the evaluation of patients with allergic conditions in a setting facilitating proper management of systemic reactions
* Observation for at least 30 minutes after the first dose
* Patient education and written instructions on how to recognize and manage adverse reactions and when to contact the HCP for adverse reactions, treatment gaps, or other events that may affect treatment (e.g. new medication or illness), how to manage missed doses and the situations when they should withhold SLIT
* In cases of oral inflammation, such as mouth ulcers, lichen planus, stomatitis aphthosa or dental extractions, administration of SLIT should be temporarily discontinued until there is complete healing of the oral cavity. Dental flossing and gum hygiene can be associated with gum bleeding. It is recommended that the patient delay the administration of SLIT for a few hours after cessation of gum bleeding. It is suggested to resume SLIT 24 hours after a dental cleaning procedure.
* Recommendations for when to withhold SLIT dose to avoid potential situations when systemic allergic reactions may be more likely should also be provided.
* Regular follow-up care with a HCP trained in the evaluation of patients with allergic conditions to monitor safety.
 |

**VIII. Special considerations**

## A. Provocation tests for selecting patients with HDM-driven allergic asthma for HDM AIT or efficacy assessment

In some AIT trials bronchial allergen provocation tests with HDM were used as the inclusion criteria or as the endpoints (primary or secondary) [38]. Based on the concept of “united airways” nasal and conjunctival allergen provocations can be performed under some circumstances, especially in high risk patients [84, 85]. The drawback of provocation testing is that it may not reflect natural exposure. Standardisation and availability for daily practice (including safety issues) still need to be refined [84,86].

## B. Duration of AIT

Although there is evidence for efficacy after the first year of HDM AIT [63,65 87,88], the current practice is three years of treatment for both SCIT and SLIT aiming at achieving long term efficacy. In asthma there does not appear to be an additional benefit of five-year-therapy compared to three-year-therapy [89,90].

**C. Criteria for HDM-AIT cessation**

After one year of AIT the efficacy for HDM-driven allergic asthma should be evaluated. Unfortunately, there is no consensus on efficacy criteria specific for allergic asthma. Thus, the same approach as for asthma controller medication should be applied [22, 38]. If efficacy is not proven after one year, cessation of AIT therapy should be considered. The indication for treatment, allergic status of patients, association between HDM-sensitisation and asthma symptoms, treatment compliance, etc. should be re-analysed to assess the non-responsiveness to AIT. There are no evidence to allow any recommendations to be made on a shift to another product neither with regard to route of administration, protocol of desensitisation nor company specific preparations.

### D. Categories not covered by recommendations

This Guideline formulated recommendations only for HDM AIT. All the other allergens, including polysensitised and polyallergic patients, will be covered in a second paper.

### E. Biomarkers

To date, there are no biomarkers that sufficiently predict response to HDM-AIT that can be used to decide on initiation or cessation of HDM AIT in HDM-driven allergic asthma.

## F. Combination with biologics

Several trials have been performed with pre-administration or co-administration with omalizumab to improve the safety of SCIT up-dosing [81]. Evidence is lacking to recommend co-administration of biologics and HDM AIT for HDM-driven allergic asthma.

**IX. Discussion**

**A. Unmet needs for HDM AIT in HDM-driven allergic asthma**

## Measuring outcomes

Most of the clinical trials of AIT in asthma evaluated clinically relevant parameters such as symptom and medication scores (with an emphasis on the corticosteroid sparing effect). A limited number of trials have used established asthma outcomes such as validated asthma control questionnaires (e.g. ACQ), lung function parameters besides FEV1, or exacerbation rates (generally defined by requirement for oral corticosteroids or hospitalisations); they have showed negative or mixed results. There is a clear need for better designed studies of HDM AIT in HDM-driven allergic asthma using harmonised and validated clinical outcomes. Respiratory physicians should be included in the trial design.

The frequency and the number of exacerbations, decreased need for controller medication and possibly lung function with a special focus on small airways, should be considered as primary endpoints. Co-primary end-points such as corticosteroid- sparing and decrease in exacerbations should also be considered.

## Methodological difficulties

Several challenges were encountered in developing this guideline.

Firstly, we faced different patient population (paediatrics versus adults) and different allergens with significant variations in standardisation and potency and routes for HDM AIT. Thus, a decision was made to formulate separate research questions for each patient population and HDM AIT route according to biological plausibility and pharmacological effects.

Secondly, guideline panel members identified multiple outcomes to assess desirable and undesirable effects of HDM AIT. Although, guideline panel members rated the importance of the outcomes in HDM-driven allergic asthma, additional work needs to be continued to define patient important outcomes for patients.

Thirdly, multiple RCT reported findings using different approaches. For instance, while some RCTs reported findings in mean and standard deviation, other reported results as median and interquartile ranges. Pre-specified outcomes varied hugely. Ideally a meta-analysis should have access to individual patient data. To summarize the body of evidence, data were transformed using validated approaches and available data.

## B. Barriers, facilitators, gaps and audit criteria

A subgroup of patients with HDM-driven allergic asthma may benefit most from HDM AIT. The important prerequisites for successful HDM AIT are 1) use of allergen extracts of proven efficacy and 2) selection of patients most likely to respond to this causal therapy. The major barriers and facilitators as well as audit criteria are presented in Table 8. Generally, a holistic approach to patients is required with joint commitment of various stakeholders to offer the patients optimal care [92,93,94].

|  |
| --- |
| **Table 8: Barriers, facilitators and audit criteria for HDM AIT in HDM-driven allergic asthma**  |
| **Barriers**  | **Facilitators**  | **Audit criteria**  | **Resource implications**  |
| Insufficient evidence primarily for asthma population  |  Large RCTs and real-life studiesfocused on HDM-driven allergic asthma population | Updated AIT indications based on new evidence. | Joint efforts and harmonisation of different stakeholders |
| Insufficient evidence for the paediatric population | Large RCTs and real-life studiesfocused on paediatric population | Updated AIT indications based on new evidence. | Revised, realistic paediatric investigation plan (PIP) |
| Differences in the evidence for efficacy and safety between different HDM AIT products due to product quality and standardisation and study designs | Improved product standardisation. Harmonisation of production process and study design. Head-to-head comparison between products. | Proportion of patients treated with products for which there is product specific evidence of efficacy and safety | Joint efforts and harmonisation of different stakeholders |
| The application of HDM AIT in asthma is limited due to efficacy and safety concerns | Higher quality large phase 3 DBPC trials with validated outcome measures, patient centred outcomes and post-marketing data | Proportion of patients with HDM-driven allergic asthma successfully treated with HDM AITProportion of patients treated with HDM AIT for HDM-driven allergic asthma who suffer from an adverse event | Joint efforts and harmonisation of different stakeholders |
| Definition of HDM-driven allergic asthma as a lower airways condition, ignoring the frequent association with AR and/or AD and disease endotypes | Revised definition of HDM-driven allergic asthma to include the one airways disease concept and asthma endotypes | Proportion of patients prescribed HDM AIT for the one airways disease (AR and allergic asthma) Proportion of patients with HDM-driven allergic asthma treated according to their endotype | More research for better understanding of the disease mechanism and implementing a new disease taxonomy |
| Low awareness and knowledge of AIT potential by the general public and healthcare professionals outside allergy speciality, e.g. paediatricians, respiratory physicians, ENT, dermatology, primary care physicians | Joint commitment and coordinated actions among academia, patient organisations, regulators, industry to find solutions that properly answer the health expectations of the allergic patients | Proportion of patients prescribed AIT for allergic asthma  | Alignment between various stakeholders |
| Availability and affordability | Pharmacoeconomics studies and implementation of better reimbursement policies | Prescription and reimbursement rate | Change in priority perception of healthcare system |
| Improved patient selection | Better selection of responders using diagnostic tools for accurate identification of clinically relevant patient’s sensitization profile | Proportion of patients who do not benefit from HDM AIT  | More research in disease mechanisms and diagnostic tools |
| Adherence to HDM AIT | Educational programmes, more convenient HDM AIT regimens | Proportion of patients who drop-out from HDM AIT  | Allocation of funds for education. Harmonisation between stakeholders |
| Outcomes reporting in individual RCTs   | Randomised controlled trials reported findings as, for instance, median and interquartile rank.  | Transform data using properly formulas and approaches  | Harmonisation between researchers.  |

|  |  |
| --- | --- |
| **Table 9: Gaps in evidence for HDM AIT in HDM-driven allergic asthma and plan to address**  |  |
| **Gaps in evidence**  | **Plan to address**  | **Priority**  |
| Identifying and standardising relevant outcome measures (control, exacerbation, lung function, composite scores)  | Investigate and validate optimal outcome measures in adults and children.  | High |
| Stratification of patients (HDM as driver of asthma control, adherence, severity)  | Well-designed RCT, example for personalised medicine  | High  |
| Determining long-term efficacy of HDM AIT in HDM-driven allergic asthma (after treatment cessation)  | Well-designed RCT and real-life studies focusing on long-term efficacy of AIT in asthma  | High |
| Cost-effectiveness of HDM- AIT in HDM-driven allergic asthma | Sectoral and generalised cost-effectiveness analysis Long-term perspective as HDM AIT can modify the disease and thereby influence long-term cost  | High |
| Alignment of studies with guidance from regulatory bodies. | Work in partnership with regulatory bodies to continually review trial methodology and outcomes. | High |
| Identification of clinically relevant biomarkers of sensitisation beyond SPT/IgE in order to select responders to HDM AIT  | Proof of concept studies evaluating patient selection based on provocation tests and/or biomarkers including components and other measures | High |
| Impact of allergic multi- morbidities (allergic rhinitis, atopic dermatitis, etc)  | Studies evaluating the global effect of HDM AIT on allergic multi- morbidities  | High  |
| Impact of multi-morbidity (autoimmunity, diabetes, obesity, smoking) and the impact of age (>60 and <5) and age of onset (early onset (childhood; < 18 years); adult onset (between 18 and 40 years) or late onset (> 40 years). | Well-designed RCT and real-life studies focusing on HDM AIT in asthma with co-morbidities | Medium |
| Impact of severity of asthma including suboptimal lung function  | Well-designed RCT and real-life studies focusing on HDM AIT in HDM-driven allergic asthma stratified by severity, including severe and uncontrolled asthma | High |
| Impact of observational period after HDM AIT dose on safety | Well-designed RCT and real-life surveys assessing impact of different observational periods  | Medium |
| Validation of different regimens | RCTs and real-life studies testing different approaches in HDM AIT in terms of dose, duration and route | Medium |

### C. HDM AIT positioning in the context of general asthma management

The administration of HDM AIT should not interfere with or substitute for pharmacological asthma treatment as recommended by various asthma guidelines. It should be considered only when asthma is driven by HDM allergy and is controlled providing the perspective of stepping-down controller treatment while decreasing the future risk of asthma exacerbations and drug-related adverse events. Another option that needs further exploration is whether adding AIT to pharmacological treatment in partially controlled asthma can facilitate achieving asthma control. More safety data are required to support this approach (Figure 2).

**Figure 2: Integration of HDM AIT in the stepwise management of HDM-driven allergic asthma based on the level of asthma control**. *HDM -AIT is recommended for controlled HDM-driven allergic asthma with the expectation to be able to step-down controller treatment while maintain asthma control, given the fact, that the HDM allergen is identified as relevant trigger. For partially controlled asthma adding HDM AIT while stepping-up pharmacological treatment might facilitate achieving asthma control. Due to safety concerns HDM- AIT should not be used for uncontrolled asthma. Caution is necessary if HDM-AIT treatment decisions are made in patients with severe controlled HDM-driven allergic asthma*.

#### X. Key points and conclusion

The treatment of HDM-driven allergic asthma both in adults and children relies on the use of corticosteroids and other controllers recommended to achieve and maintain asthma control and to prevent exacerbations, loss of lung function and improve quality of life. The addition of the first HDM AIT product approved specifically for asthma, the HDM SLIT tablet, has fuelled optimism for the potential benefits of HDM AIT in some patients with HDM-driven allergic asthma, especially if appropriate responder phenotypes can be identified. However, in some countries where there is no reimbursement for HDM AIT, economic constraints may mean that these options are not accessible. It is important to explore the short and long-term health economic effect of AIT in asthma due to its potential disease modifying effect.

## Conclusion. Key points

1. Patients with HDM-driven allergic asthma not adequately controlled on available pharmacotherapy present an unmet health need.
2. AIT targets the underlying mechanisms in allergic asthma by modifying the immunological response to allergen towards tolerance.
3. HDM AIT may add to the anti-inflammatory action of ICS to promote asthma control and decrease the risk of exacerbations.
4. Success of HDM AIT in HDM-driven allergic asthma is largely dependent on proper selection of patients with HDM sensitisation and symptoms driven by specific allergen exposure plus the use of allergen extracts of proven efficacy.
5. To date, only AIT with HDM SLIT-tablet has been demonstrated to show robust effects in adults on critical end-points (exacerbations, asthma control and safety).
6. AIT should only be initiated and monitored by health care professionals with the appropriate competencies which will require an investment in training

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