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Determination of the minimally important difference in a nasal symptom score in house dust mite allergy

Philippe Devillier¹ | Harald Brüning² | Karl-Christian Bergmann³

¹UPRES EA220, Foch Hospital, University Versailles Saint-Quentin, University Paris-Saclay, Suresnes, France

²Dermakiel, Allergie und Hautzentrum, Kiel, Germany

³Allergy-Centre-Charité, Charité-Universitätsmedizin Berlin, Berlin, Germany

Correspondence

Philippe Devillier, UPRES EA220, Foch Hospital, University Versailles Saint-Quentin, University Paris-Saclay, Suresnes, France.
Email: p.devillier@hopital-foch.org

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Abstract

Background: House dust mite (HDM) allergens are responsible for the most prevalent persistent respiratory allergies. Clinical trials in this field often use a four-component nasal symptom score (T4NSS) as a measure of efficacy.

Methods: The present observational, prospective, multinational, multicenter study determined the minimal important difference (MID) for a T4NSS in children, adolescents, and adults with physician-diagnosed HDM-induced allergic rhinoconjunctivitis (AR). Patients rated the T4NSS daily, a 15-point global rating of change scale (GRCS) and the Rhinoconjunctivitis Quality of Life Questionnaire weekly. The MID was determined primarily by using a regression method with a GRCS threshold of 2.

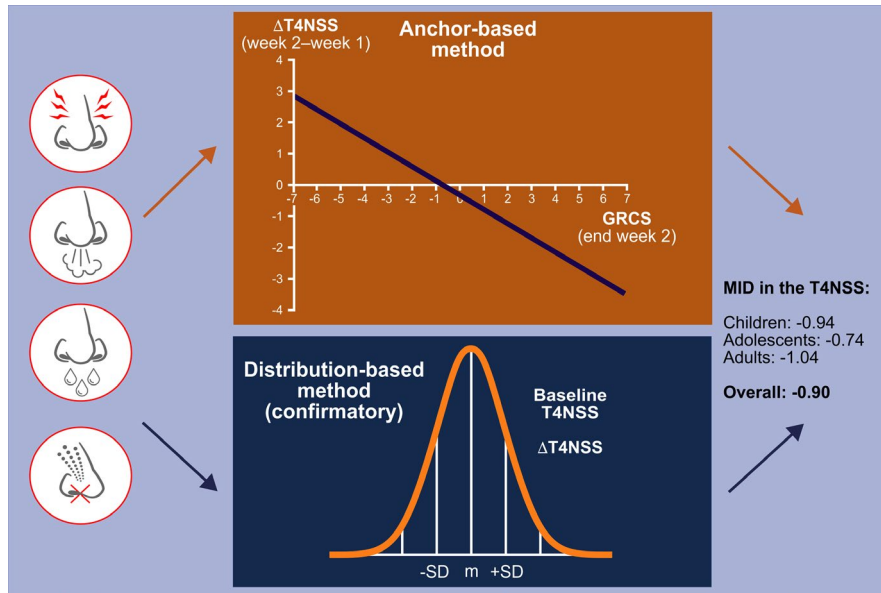
Results: A total of 546 patients (210 adults, 133 adolescents, and 203 children) were included; 92.6% of the patients had moderate-to-severe AR, and 30.1% had concomitant mild asthma. During the first week, the mean $\pm$ standard deviation T4NSS was 5.68 ± 2.76 in adults, 5.34 ± 2.66 in adolescents, and 5.07 ± 2.48 in children. In a GRCS regression analysis, the MID [95% confidence interval] for the T4NSS was $-0.90 [-1.06;-0.75]$ overall ($n = 509$), $-0.94 [-1.19;-0.69]$ in children ($n = 187$), $-0.74 [-1.07;-0.41]$ in adolescents ($n = 125$), and $-1.04 [-1.29;-0.79]$ in adults ($n = 197$). The MID did not differ greatly from one disease severity tertile to another. Confirmatory distribution-based analyses yielded overall MID values of -0.87 for the first week of the study and -0.93 for the week 2-week 1 difference.

Conclusion: The MID for improvement in the T4NSS is at least -0.90 units in children, adolescents, and adults suffering from HDM-induced AR. This value could be rounded up to -1 unit for convenience.

KEYWORDS

house dust mite-induced allergic rhinoconjunctivitis, minimally important difference, nasal symptom score

Abbreviations: AR, allergic rhinoconjunctivitis; ARIA, Allergic Rhinitis and its Impact on Asthma; GRCS, global rating of change scale; HDM, house dust mite; MID, minimal important difference; QoL, quality of life; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; RTSS, rhinoconjunctivitis total symptom score; T4NSS, four-component nasal symptom score; VAS, visual analogue scale; Δ T4NSS, change in the four-component nasal symptom score.



GRAPHICAL ABSTRACT

In patients with house dust mite allergic rhinoconjunctivitis, the minimal important difference for improvement in a four-item nasal symptom score was at least 0.9 units. This value was estimated in children ($n=187$), adolescents ($n=125$), and adults ($n=197$) by both regression analyses using anchors and distribution-based analyses using the standard deviation (SD). The anchors in the regression analyses were either a 15-point global rating of change scale or the age-specific Rhinoconjunctivitis Quality of Life Questionnaires. GRCS: global rating of change scale; MID: minimal important difference; T4NSS: four-component nasal symptom score

1 | INTRODUCTION

Allergic rhinoconjunctivitis (AR) is a highly prevalent condition that can impair respiratory health, quality of life (QoL), sleep, and school/work performance.¹⁻⁵ In clinical trials in AR, it is essential to be able to accurately estimate symptom severity through patient-reported outcomes, such as nasal, ocular, or total symptom scores, a visual analogue scale (VAS) of disease intensity, or a general or disease-specific QoL scale.⁶⁻¹¹ A key parameter in patient-reported outcomes is the minimal important difference (MID), which denotes the smallest score or change in score likely to be important from the patient's perspective.¹² Knowledge of the MID for a particular disease severity score is important for physicians and patients (when seeking to define and achieve clinical effectiveness) and for health authorities (when considering marketing authorization applications and reimbursement decisions). Recently, we determined that the MID in the widely used rhinoconjunctivitis total symptom score (RTSS, comprising four nasal and two ocular symptoms) was 1.1-1.3 in a study of children, adolescents, and adults suffering from grass pollen-induced AR.¹³

Although grass pollen allergy is the most prevalent causative allergen for AR worldwide (affecting 20%-30% of the general population in most countries),¹ house dust mite (HDM) allergens in the domestic (indoor) environment are responsible for the most prevalent persistent respiratory allergies.¹⁴ The symptoms of HDM-induced AR occur persistently throughout the year, albeit with seasonal peaks and troughs.^{15,16} Nasal symptoms predominate in HDM-induced AR, and clinical trials in this field often score a four-component nasal symptom score (T4NSS) as a measure of efficacy. In earlier research,

Barnes et al estimated the MID for a T4NSS in a population of 204 adults with mild-to-moderate seasonal or perennial AR by pooling nine different, small studies.¹⁷ However, the applicability of Barnes et al's results was limited by the facts that (a) the analysis was based on the pooling of nine different, small studies, (b) the analysis was restricted to adults, and (c) the patients were variously allergic to different allergens (and not solely to HDM allergens).

Hence, the primary objective of the present observational, prospective, multinational, multicenter study was to determine the MID for a T4NSS in children, adolescents, and adults with HDM-induced AR

2 | METHODS

2.1 | Overall study design

We performed an observational, prospective, international, multicenter study (EQUINOXE 3) in Germany and France. Allergologists, ENT physicians, pulmonologists, dermatologists, pediatricians, internists, and general practitioners in Germany and France were invited to participate in the study. The physicians were asked to recruit patients suffering from HDM-induced AR (with or without asthma), as described in detail below. Three age groups were studied: children (aged 5-11), adolescents (aged 12-17), and adults (aged 18-65).

2.2 | Study population

The main inclusion criteria were as follows: males or females aged between 5 and 65 years; provision of written consent;

physician-diagnosed, HDM-induced AR for at least the previous 12 months; sensitization to *Dermatophagoides pteronyssinus* or *D farinae* (according to a documented, positive skin prick test and/or a specific immunoglobulin E assay ≥ 0.7 kU/L within the previous 12 months); and a baseline T4NSS of at least 5 out of 12 on the day of the inclusion visit (V)1 and on the two previous days (with nasal congestion score ≥ 2 and rhinorrhoea score ≥ 2 on those three days).

The main exclusion criteria were as follows: pregnancy at the time of inclusion; noncontrolled asthma; a negative nasal HDM challenge test within the last 12 months; and any known disease or medication that might interfere with the questionnaires (eg, an ENT infection preceding the initial visit).

2.3 | Study assessments

The present MID determination used data from a six-month efficacy trial (the results of which have not yet been published) consisting of alternating two-week periods during which patients alternated between a two-week "booklet" (scoring) period and two weeks without scoring. Here, the MID was determined from the data recorded in the very first two-week booklet period (filled out immediately after inclusion), during which the changes in symptoms were highest (as performed in our previous study)¹³ (Figure 1). Each age group was provided with a specific data booklet for the two-week period, during which the patients (or their parents) were asked to rate (a) the T4NSS for symptom severity on a daily basis, (b) a 15-point global rating of change scale (GRCS, see below), and the age-specific Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)^{9,10,18} weekly. The T4NSS comprised four individual nasal symptoms (sneezing, rhinorrhoea, congestion, and itching) scored on the following scale: 0 = absence of symptoms; 1 = mild symptoms; 2 = moderate symptoms; and 3 = severe symptoms.

The GRCS is a standardized, symmetric scale that reflects the patient's perception of the change in his/her symptoms over the previous week.^{13,19} The scale is centered on 0 ("no change") and ranges from -7 ("a very great deal worse") to +7 ("a very great deal better") (see Table 1 in¹³). For a 15-point GRCS, it is accepted that scores of -1, 0, and +1 correspond to an absence of change, and therefore scores of -2 or +2 correspond to the smallest worsening or improvement perceived by the patient.^{6,8,20,21}

The GRCS score obtained at the end of the second week of the "booklet period" (ie, the change in AR symptoms with respect to the first week) was defined as the anchor value for determination of the MID (detailed below).

2.4 | Ethical aspects

In Germany, the study protocol was approved by the local independent ethics committee and registered with the national health authority (Paul-Ehrlich-Institut), the German National Association of Statutory Health Insurance Physicians (Kassenärztliche Bundesvereinigung), and the statutory health insurance body (Gesetzliche Krankenversicherung).

In France, the study protocol was approved by the local independent ethics committee (Comité de Protection des Personnes Paris IDF VIII, Boulogne-Billancourt, France) and was registered with the national health authority (Agence Nationale de Sécurité du Médicament et des Produits de Santé) and the French National Data Protection Commission (Commission Nationale de l'Informatique et des Libertés).

Patients were included after they had (a) received verbal information on the study's objectives and procedures and (b) given their written, informed consent to participation. For under-18 patients, the parents also received study information and had to give their written, informed consent.

2.5 | Sample size

Given that the present study was exploratory, our sample size estimation was not based on a statistical hypothesis. However, on the basis of previous observational studies with similar designs (and in which between 40% and 50% of the questionnaires were returned with valid data), we estimated that the inclusion of approximately 1200 patients would yield a total sample size of 600 and thus about 200 patients per age group (as in our previous study¹³). This total number of patients exceeds the sample size of most other studies of MIDs in this field.

2.6 | Statistical analysis

All statistical analyses were performed with SAS software (version 9.2, SAS Institute Inc, Cary NC, USA). The MID in the T4NSS was primarily determined (for each age group and for the study population as a whole) by using the widely adopted regression method with a GRCS anchor.^{12,22} The relationship between the difference in the mean T4NSSs for the first and second weeks (Δ T4NSS, as the dependent variable) and the change in the GRCS score (the anchor, as the independent variable) can be analyzed using a linear regression, with residual analysis being used to find the best model. The MID for an improvement is then determined as the value of Δ T4NSS that corresponds to a score of +2 on the GRCS regression line.²³ This regression method considers the whole per-protocol study population and, thus is more appropriate than the MID

Inclusion



Days	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Symptoms	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Global rating of change questionnaire														X
RQLQ							X							X

FIGURE 1 Study design for MID determination

TABLE 1 Demographic and clinical characteristics of the study population (n = 546)

	Children aged 5-11 (n = 203)	Adolescents aged 12-17 (n = 133)	Adults aged 18 and over (n = 210)
Females (%)	86 (42.36%)	55 (41.35%)	129 (61.43%)
Age (years)	8.65 ± 1.89	13.82 ± 1.73	36.93 ± 13.01
ARIA classification (n, %):			
Mild intermittent	7 (3.45%)	5 (3.76%)	2 (0.95%)
Moderate-to-severe intermittent	20 (9.85%)	13 (9.77%)	24 (11.43%)
Mild persistent	7 (3.45%)	3 (2.26%)	4 (1.90%)
Moderate-to-severe persistent	164 (80.79%)	109 (81.95%)	177 (84.29%)
Duration of disease at inclusion (years)	3.0 ± 1.75	4.8 ± 3.27	8.9 ± 7.41
T4NSS at the inclusion visit	8.38 ± 1.82	8.40 ± 1.93	8.21 ± 2.13
Average T4NSS for week 1	5.07 ± 2.48	5.34 ± 2.66	5.68 ± 2.76
RQLQ score at the inclusion visit	2.46 ± 1.02	2.59 ± 0.88	2.93 ± 1.04
RQLQ score for week 1 (day 7)	1.89 ± 1.06	2.11 ± 1.18	2.41 ± 1.25
Concomitant co-morbidities (n, %):			
Asthma	84 (41.38%)	33 (24.81%)	43 (20.48%)
Sinusitis	5 (2.98%)	4 (3.92%)	23 (12.64%)
Atopic dermatitis	38 (18.72%)	12 (9.02%)	17 (8.10%)
Food allergy	12 (5.91%)	12 (9.02%)	14 (6.67%)
Taking symptomatic treatments for AR on the day of the consultation (n, %):	150 (73.89%)	102 (76.69%)	134 (63.81%)

Note: Results are given as the number (percentage) or the mean ± SD.

Abbreviations: ARIA, Allergic Rhinitis and its Impact on Asthma; T4NSS, four-component nasal symptom score; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire.

determination based on the mean Δ T4NSS in those patients with a GRCS score of [+2,+3] at the end of the second week^{19,23,24} (ie, only 24 to 27 patients in each of the three age groups). Furthermore, the MID in the T4NSS was estimated with the RQLQ as the anchor using the regression procedure, and a threshold value of 0.53 as the MID in the RQLQ.¹⁵

We also confirmed the MID in the T4NSS in several secondary analyses: (a) a regression analysis as a function of initial disease severity and (b) distribution-based analyses. The distribution-based analyses rely on the statistical distributions of the score (such as the standard deviation (SD)) and seek to identify the smallest change in the score that is not likely to be due to a random variation in the measurement (also referred to as a "minimum detectable change").^{25,26} The distribution-based approach uses different proportions (eg, 0.33 and 0.5) of the SD of the baseline score^{6,25,27-31} or 0.5 SD of the mean change in the score.^{12,25,29}

3 | RESULTS

A total of 296 physicians (122 in Germany and 174 in France) agreed to participate in the study. Valid data for estimation of the MID in the

T4NSS were obtained for 546 patients (210 adults, 133 adolescents, and 203 children).

The baseline characteristics of each age group are shown in Table 1. On the day of the consultation, 92.86% of the patients were rated by the physician as having moderate-to-severe AR (according to the Allergic Rhinitis and its Impact on Asthma classification^{32,33}), and 70.70% were taking symptomatic medications for AR at the time of inclusion. The symptomatic medications for AR taken regularly during the preceding weeks were primarily oral antihistamines (41.69%), nasal corticosteroids (20.76%), and nasal antihistamines (5.48%). Asthma was the most frequent concomitant condition (in 29.30% of the patients overall), especially in children. The proportion of patients with atopic dermatitis fell with age, and the proportion with one or more food allergies rose with age.

3.1 | Estimation of the MID in the T4NSS using a regression method

In the primary assessment, the MID in the T4NSS was determined in a regression analysis vs. GRCS with a threshold of 2 (Table 2). The number of valid booklet datasets for calculating the MID differed

TABLE 2 The MID [95%CI] in the T4NSS, estimated using the regression method for an improvement of + 2 in the GRCS score or of 0.53 in the RQLQ

Regression	Whole population N = 509	Children N = 187	Adolescents N = 125	Adults N = 197
Change in T4NSS vs GRCS	-0.90 [-1.06; -0.75] n = 509	-0.94 [-1.19; -0.69] n = 187	-0.74 [-1.07; -0.41] n = 125	-1.04 [-1.29; -0.79] n = 197
Change in T4NSS vs RQLQ	-0.97 [-1.03; -0.90] n = 511	-0.97 [-1.08; -0.86] n = 198	-1.02 [-1.15; 0.90] n = 119	-0.93 [-1.03; -0.83] n = 194

Abbreviations: GRCS, global rating of change scale; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; T4NSS, four-component nasal symptom score.

from one method to another; there were 509 valid datasets for the primary assessment, 511 for the regression vs. RQLQ, and 546 patients for the distribution-based method (see below). During the first week of the study, the mean $\pm$ SD T4NSS was 5.68 ± 2.76 in adults, 5.34 ± 2.66 in adolescents, and 5.07 ± 2.48 in children. The MID for the T4NSS was -0.90 for all patients ($n = 509$), -0.94 in children ($n = 187$), -0.74 in adolescents ($n = 125$), and -1.04 in adults ($n = 197$). The results of the Δ T4NSS vs. GRCS linear regression analysis were significant for each age group ($P < 0.0001$); Pearson's correlation coefficients for Δ T4NSS vs. GRCS (0.53, 0.56, 0.42, and 0.57, respectively, for the population as a whole, the children, the adolescents, and the adults) were higher than the commonly recommended threshold value of 0.30 (based on Cohen's rules of thumb) for an acceptable association between an anchor and a patient-reported change in score,¹² and even higher than the recently proposed threshold of 0.40.²² In a secondary analysis, the MID was estimated using a T4NSS vs. GRCS regression analysis (as described above) as a function of the initial disease severity. The population was divided into three groups according to the T4NSS at baseline (corresponding to scores of 4-7, 8-9, and 10-12, respectively). The MID values (Table 3) did not differ greatly from one disease severity group to another, since the 95% confidence intervals (CIs) overlapped.

The MID in the T4NSS was also determined in a regression analysis vs. age-specific RQLQ with a threshold of 0.53 (Table 2). The MID for the T4NSS was -0.97 for the population as a whole ($n = 511$), -0.97 in children ($n = 194$), -1.02 in adolescents ($n = 119$), and -0.93 in adults ($n = 198$). Pearson's coefficients for the correlation between T4NSS and RQLQ (0.59, 0.61, 0.61, and 0.55, respectively, for the population as a whole, the children, the adolescents, and the adults) were again higher than the recommended thresholds of 0.30 or 0.40.

3.2 | Estimation of the MID in the T4NSS using distribution-based methods

Using a distribution-based method and a cutoff value of 0.33 SD, the MID [95%CI] in the T4NSS (for week 1) was calculated to be -0.87 in the population as a whole (Table 4). Based on the change in T4NSS between weeks 1 and 2 and a cutoff value of 0.50 SD, the MID was -0.93. Details for the three age groups are also given in Table 4.

4 | DISCUSSION

In the present prospective study of children, adolescents, and adults suffering from HDM-induced AR, we used two regression methods (with the GRCS or the RQLQ as the anchor) and two distribution-based methods to estimate the MID in the T4NSS. In the present observational study, the patients were treated according to normal clinical practice in a "real-life" setting. The main inclusion criteria were a baseline T4NSS ≥ 5 , in order to give sufficient room for improvement and thus avoid floor effects related to low initial disease intensity.

The use of patient-reported measures of change as "external" anchors for estimation of the MID was initiated by researchers at McMaster University (Hamilton, Canada).⁶ The use of a GRCS score as an anchor is not ideal because this metric reflects a patient's subjective assessment of change. However, given the absence of satisfactory objective measurements in AR, the GRCS is currently the most appropriate choice for this disease. Anchor-based methods are generally recommended for estimating MIDs, whereas distribution-based methods are considered to be useful for providing supportive evidence, since this latter approach does not take into account patient assessment.^{6,12} A MID determined with a clinical anchor is sometimes called a minimal clinically important difference.^{22,34} Juniper et al.²³ established the MID in the RQLQ score by applying an anchor-based method to a small group of 28 adult patients with a GRCS score of [+2,+3] for improvement or [-3;-2] for worsening. A threshold of 2 GRCS units was used for the regression method because this value was previously employed to estimate the MID for validated QoL questionnaires in AR²³ and in asthma.^{19,20} Furthermore, recall bias constitutes a limitation for GRCS-based methods. In an attempt to minimize this shortcoming, changes in AR symptoms were assessed with the GRCS over two consecutive weeks. Furthermore, we evaluated the MID of the T4NSS with an RQLQ anchor (given the well-accepted MID for this QoL questionnaire), and the MID values were close to those determined with a GRCS anchor.

The distribution-based method has been criticized because the choice of cutoff (0.33 or 0.50 SDs, for example) does not take account of individual patient assessments and might yield smaller estimates of the MID than the anchor-based method.³⁵ However, it has been considered that an MID of 0.50 SDs is both clinically significant

TABLE 3 The MID [95%CI] for the T4NSS, determined by linear regression vs. the GRCS for overall symptom intensity (threshold: 2) by disease severity group

	Whole population N = 502	Lowest disease severity TN4SS [4-7] N = 173	Middle disease severity TN4SS [8-9] N = 195	Upper disease severity TN4SS [10-12] N = 134
MID (overall)	-0.90 [-1.06; -0.75]	-0.95 [-1.24; -0.65]	-0.96 [-1.26; -0.66]	-0.79 [-1.17; -0.42]
MID in children	-0.94 [-1.19; -0.69]	-1.04 [-1.52; -0.55]	-0.88 [1.33; -0.44]	-0.88 [-1.63; -0.13]
MID in adolescents	-0.74 [-1.07; -0.41]	-0.86 [-1.56; -0.16]	-0.82 [-1.41; -0.23]	-0.52 [-1.26; 0.22]
MID in adults	-1.04 [-1.29; -0.79]	-0.92 [-1.37; -0.46]	-1.22 [-1.85; -0.60]	-0.94 [-1.54; -0.35]

	Whole population	Children	Adolescents	Adults
T4NSS during the first week	N = 533	N = 198	N = 130	N = 205
0.50 SD	-1.36	-1.24	-1.33	-1.38
0.33 SD	-0.87	-0.82	-0.88	-0.91
0.50 SD of the mean change in the T4NSS (first vs. second week)	N = 527 -0.93	N = 196 -0.96	N = 128 -0.96	N = 203 -0.88

TABLE 4 MID for the T4NSS in the population as a whole and in the three age groups, as determined by distribution-based methods (as a function of the proportion of the SD)

and meaningful but not necessarily minimal.¹² It has been suggested that 0.33 SD is a good approximation of the MID taking account of changes in the scores.^{12,27,31,36} Here, we used the distribution-based methods in secondary analyses based both on the T4NSS at the inclusion visit (0.50 SD) and changes in this score between week 1 and week 2 (0.33 SD). The estimates provided by distribution-based methods for the different age groups were all less than 1 (ranging from 0.82 to 0.96). Using a distribution-based approach alone is usually inadequate.³⁴ Concordance between methods is, however, an important factor in confirming the choice of an MID. If the value is rounded to the nearest whole number (as performed conventionally³⁷), the MID for improvement in the T4NSS would be -1 unit. The patients' demographics and baseline status also contribute to the variability in reported MID values. In the present study, we evaluated the MIDs in the T4NSS for children, adolescents, and adults, and the results were similar in all three age groups. Furthermore, the MID values did not differ with disease severity (according to tertiles of the baseline T4NSS).

As mentioned above, the MID in a four-component nasal symptom score (T4NSS) has previously been estimated in a population of 204 adults with mild-to-moderate seasonal or perennial AR (induced by various types of allergens and not just HDMs) by pooling nine different, small studies.¹⁷ The MID in the T4NSS was calculated using (a) anchor-based methods (either in a subset of patients with a GRCS score of +1 or +2 or by linear regression to determine the change in T4NSS associated with a score of 1.50 units in the GRCS) and (b) a distribution-based method (0.20 SD). The GRCS and SD thresholds chosen by Barnes et al were lower than those used in the present study, which might explain why the latter researchers found lower estimates for the MID in the T4NSS (0.28 and 0.23

units using the anchor-based methods and 0.59 units using a distribution-based method). These values are clearly lower than the rounded-up value of 1 T4NSS unit estimated in the present study.

The present study had some limitations. Firstly, the exploratory nature of the present study meant that our sample size estimation was not based on a statistical hypothesis; it was estimated solely with regard to previous studies and the expected questionnaire return rate. The sample size was nevertheless larger than in many other MID studies. Secondly, the large number of investigating centers means that we cannot rule out a risk of heterogeneity in the way that the (standardized) questionnaires were administered by the physicians and/or interpreted by the patients. In an attempt to reduce heterogeneity in the way the questionnaires were administered, we standardized data collection by providing the participants with comprehensive, written instructions on filling out the questionnaires. All the investigators were specialist physicians with expertise in allergic rhinitis management and the ability to explain the booklet's questionnaires to the participants. The study's strengths included its relatively large sample size and its multicenter design in two countries, which thus ensured the generalizability of the data.

The MID for improvement in the T4NSS was at least 0.90 units in children, adolescents, and adults suffering from HDM-induced AR. However, it should be borne in mind that this MID corresponds to a meaningful change on an individual basis and not the intergroup difference in mean scores that is sometimes used to justify the efficacy or non-efficacy of a treatment vs. a placebo or a standard of care in clinical trials [34]. Even when a small proportion of patients responds to treatment (ie, when there is no marked intergroup difference in the mean score), the change in these individuals may be clinically meaningful. In this context, an assessment of the distribution of the responses (ie, changes in the

score equal to or greater than the MID) in each treatment group may provide more detailed information on the treatment effect [22,34].

In placebo-controlled clinical trials of HDM immunotherapy formulations, efficacy is generally evaluated as the difference between the active and placebo treatment arms after several months of treatment.³⁸ Therefore, self-assessment of the symptom change vs. baseline would suffer from memory bias, and the MID can only be used as a clinically relevant reference value for the comparison of the symptom scores between treatment arms during the evaluation period. Although the primary endpoint in an AIT trial is generally the difference between the active and placebo treatment arms in a daily combined symptom and medication score, the symptom and medication scores can even be co-primary endpoints.³⁸⁻⁴⁰ It has been suggested that an absolute MID can be standardized as an effect size in order to evaluate the clinical significance of intergroup differences. For this purpose, the MID is divided by the baseline SD of the whole population.³⁸ In the present study, the value of the mean SD at the inclusion visit (around 1.90) yields an MID (expressed as an effect size) close to 0.45. This value is lower than the intergroup difference vs. placebo in the least-squares means of the symptom scores (0.62 for the 300 IR group and 0.58 for the 500 IR group) in a study of the efficacy of HDM allergen immunotherapy tablets in adults⁴¹—suggesting that AIT indeed had a meaningful impact on symptoms in the latter study. Although the MID in the symptom score in the present study was estimated in the context of standard care (which is quite different from the context of rescue medication use allowed in an AIT trial), we suggest that a difference in the mean T4NSS between AIT and placebo groups of more than 0.45 is clinically meaningful.

In conclusion, our results suggest that the MID for improvement of the T4NSS is at least 0.90 units in children, adolescents, and adults suffering from HDM-induced AR. For convenience, this value could be rounded up to 1 unit.

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CONFLICT OF INTEREST

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AUTHORS' CONTRIBUTIONS

P. Devillier made substantial contributions to study conception and design and data acquisition and analysis. He drafted the article. KC. Bergmann made substantial contributions to study conception and design and data acquisition and analysis. He also revised the article critically for important intellectual content. H. Brüning made substantial contributions to study conception and design and data acquisition and analysis. He also revised the article critically for important intellectual content. All the above-cited individuals approved the version to be published.

ORCID

Philippe Devillier  <https://orcid.org/0000-0001-6054-1886>

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