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Defining a Severe Asthma Super-Responder: Findings from a Delphi Process

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What is already known about this topic? Clinicians recognize severe asthma patients in whom biologics and other add-on therapies lead to dramatic improvement, so-called super-responders. However, there is no consensus regarding the most appropriate super-responder definition.

What does this article add to our knowledge? Using a modified Delphi process, we developed a consensus definition of a severe asthma super-responder that includes exacerbation elimination, a large improvement in asthma control, cessation of maintenance oral steroids, having well-controlled asthma, and a large improvement in FEV₁.

How does this study impact current management guidelines? This consensus definition is an important prerequisite for better understanding super-responder prevalence, predictive factors, and the mechanisms involved. Super-response may become an important outcome measure in future studies of add-on therapies for severe asthma.

BACKGROUND: Clinicians are increasingly recognizing severe asthma patients in whom biologics and other add-on therapies lead to dramatic improvement. Currently, there is no agreed-upon super-responder (SR) definition.

OBJECTIVE: To survey severe asthma experts using a modified Delphi process, to develop an international consensus-based definition of a severe asthma SR.

METHODS: The Delphi panel was composed of 81 participants (94% specialist pulmonologists or allergists) from 24 countries and consisted of three iterative online voting rounds. Consensus

on individual items, whether acceptance or rejection, required at least 70% agreement by panel members.

RESULTS: Consensus was achieved that the SR definition should be based on improvement across three or more domains assessed over 12 months. Major SR criteria included exacerbation elimination, a large improvement in asthma control (two or more times the minimal clinically important difference), and cessation of maintenance of oral steroids (or weaning to adrenal insufficiency). Minor SR criteria were composed of a 75% exacerbation reduction, having well-controlled asthma, and

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Abbreviations used

ACQ- Asthma Control Questionnaire

ACT- Asthma Control Test

GINA- Global Initiative for Asthma

MCID- Minimal clinically important difference

OCS- Oral corticosteroid

QOL- Quality of life

R1- Round 1 (etc)

RCT- Randomized control trial

SR- Super-responder

500 mL or greater improvement in FEV₁. The SR definition requires improvement in at least two major criteria. In the future, the SR definition should be expanded to incorporate quality of life measures, although current tools can be difficult to implement in a clinical setting and further research is needed.

CONCLUSIONS: This international consensus-based definition of severe asthma SRs is an important prerequisite for better understanding SR prevalence, predictive factors, and the mechanisms involved. Further research is needed to understand the patient's perspective and to measure quality of life more precisely in SRs.

Key words: Asthma; Biologics; Asthma treatment

A significant minority of people with asthma have severe disease in which asthma remains uncontrolled despite high-dose inhaled corticosteroids and long-acting β -agonists,^{1,2} inhaler technique and adherence optimization, trigger factor avoidance, and comorbidity management.³ Severe asthma imposes a high personal burden including recurrent exacerbations, distressing symptoms, oral corticosteroid (OCS) side effects, impaired quality of life (QoL), and reduced workplace productivity.^{4,5}

Various highly effective add-on therapies have been developed for severe asthma, including monoclonal antibodies targeting type 2 inflammatory pathways,⁶⁻⁸ azithromycin,⁹ and bronchial thermoplasty.¹⁰ In appropriately selected patients, these novel therapies produce a 40% to 50% reduction in asthma exacerbations.⁶⁻⁹ Exacerbation reduction has been the primary outcome measure in key randomized control trials (RCTs) of add-on therapies,⁶⁻⁹ although other highly beneficial effects such as OCS sparing have been demonstrated.¹¹⁻¹³ In contrast, the impacts of novel therapies on lung function and patient-reported outcomes such as asthma control and QOL have been more modest.⁶⁻⁹ Importantly, group data reported in large RCTs may obscure patient subgroups experiencing more dramatic improvements.

Clinicians who treat severe asthma patients with novel add-on therapies are increasingly recognizing a subgroup of patients who experience remarkable clinical benefits. The extent of improvement may be dramatic, much larger than the typical improvements reported in large RCTs. Sometimes referred to as super-responders (SRs), such patients may report that their lives have been transformed. Developing an agreed-upon SR definition is an important prerequisite for defining prevalence, identifying predictive factors, and understanding SRs.

However, there is no agreed-upon definition for SR. In a recent real-world study of mepolizumab-treated patients with severe eosinophilic asthma,¹⁴ the authors defined SRs as those in the upper quartile of asthma control improvement, assessed using the five-item Asthma Control Questionnaire (ACQ-5).¹⁴ Kavanagh and colleagues¹⁵ took a different approach, defining SRs as mepolizumab-treated patients who were exacerbation-free and were free of maintenance OCS at 1 year; a real-world study of benralizumab-treated patients used a similar definition.¹⁶

Rather than using an arbitrary definition, the aim of this study was to develop a consensus-based SR definition that encompassed both objective measures and patient-reported outcomes. We used a Delphi process to survey multiple severe asthma experts from numerous countries. Some results of this study were reported at the European Respiratory Congress 2020.¹⁷

METHODS

We used a modified three-round Delphi method process¹⁸ to develop a consensus definition of an SR (ie, a severe asthma patient reporting remarkable improvement with add-on therapies). The Anonymized Data Ethics and Protocol Transparency Committee provided ethical approval.

Modified Delphi process

The steering committee plus 11 other asthma experts developed initial statements covering asthma exacerbations, control, QOL, spirometry, and maintenance treatment reductions, based on response criteria assessed in phase 3 asthma trials.

The process consisted of three iterative rounds (R1-3) in which statements and questions regarding response criteria were sent to panel members electronically using LimeSurvey (version 3.7.1), a Web-based open source electronic survey tool hosted on Observational Pragmatic Research Institute's server (<https://www.limesurvey.org/>). Panel members ranked response criteria and indicated agreement on a five-point scale (strongly agree, agree, neutral, disagree, and strongly disagree). Participants were encouraged to provide free text comments after each question

. Consensus was defined a priori as agreement (strongly agree plus agree) with a statement or question by 70% or more of panel members. If a statement or question received majority support but consensus was not achieved, it was carried forward to the next round, with modifications based on comments. Statements and questions achieving less than 50% agreement were removed, except when comments indicated misunderstanding, in which case they were revised for the next round. Summary results were provided to panel members after each round to facilitate informed decisions in subsequent rounds. Providing group data after each round is central to the modified Delphi technique, in contrast to the original Delphi technique in which sequential one-on-one interviews occur without knowledge of other panel members' responses. The steering committee added statements and questions to R2 and R3 based on the comments received. Participants had 2 weeks to respond, with reminders sent when necessary.

Delphi R1. Demographic variables and members' experience were documented, plus the initial statements and questions

To target R2 and R3 to those who completed previous rounds, e-mail addresses were collected and stored securely by the project

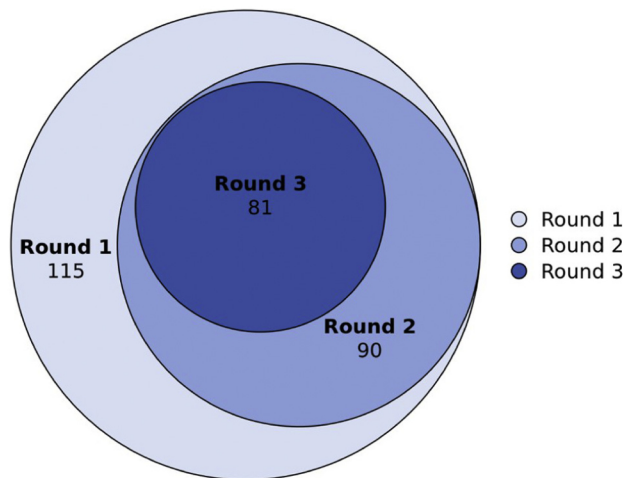


FIGURE 1. Number of Delphi panel participants in each round.

administrator to maintain confidentiality and provide the steering committee with deidentified data only.

Delphi R2. The R2 questionnaire asked whether improvement across two or more or three or more domains was necessary, the duration of exacerbation elimination, the magnitude of a major improvement in asthma control, and whether having well-controlled asthma was necessary. The minimum clinically important difference (MCID) for the ACQ is 0.5,¹⁹ and for the Asthma Control Test (ACT) is 3 points.²⁰ Panel members were asked whether an increase of two, three, or four times the MCID for these questionnaires should define an SR. For Global Initiative for Asthma (GINA)-defined asthma control, panel members indicated whether a one- or two-level improvement should define an SR.

There is no universally accepted MCID for FEV₁ in asthma, although the minimal patient-perceivable improvement is 230 mL.²¹ Hence, panel members were asked if improvement in FEV₁ of 500 mL or greater (slightly more than double 230 mL) might form part of the SR definition.

Many panel members commented that QOL assessments are important but difficult in a clinical environment, and that QOL tools are largely untested in severe asthma. Hence, R2 included additional questions

to assess attitudes regarding several QOL tools.²²⁻²⁶

Delphi R3. Based on feedback, R3 asked about dividing response criteria into major and minor criteria. Several patient scenarios were constructed (

to clarify panel members' responses to combinations of response criteria.

RESULTS

We recruited 115 individuals who participated in R1, 90 of whom participated in R2 and 81 of whom participated in R3 (Figure 1). Participants covered a broad age range and included more men than women (Table I). Ninety-four percent were specialist pulmonologists or allergists; there were smaller numbers of nurses, pharmacists, and researchers. Ninety-five percent were actively involved in severe asthma treatment whereas greater than 80% had been on a severe asthma advisory

TABLE I. Participant characteristics of those who participated in all three Delphi rounds

Participant characteristics	n	%
Age, y		
<35	2	2.5
35-44	22	27.2
45-54	35	43.2
55-64	16	19.8
>65	5	6.2
Not answered	1	1.2
Sex		
Female	25	30.9
Male	56	69.1
Occupation		
Pulmonologist	61	75.3
Allergist	14	17.3
Asthma nurse	2	2.5
Allergist and pulmonologist	1	1.2
Scientist	1	1.2
Clinical researcher	1	1.2
Pharmacist	1	1.2
Treat severe asthma		
Yes	77	95.1
Advisory board, national/international working group (past 5 y)		
Yes	72	88.9
Severe asthma publications (past 5 y)		
Yes	68	83.9
Country of work (n = 24)		
Australia	16	19.8
United Kingdom	15	18.5
Italy	10	12.4
Canada	6	7.4
Greece	5	6.2
United States	5	6.2
Argentina	3	3.7
Denmark	2	2.5
Bulgaria	2	2.5
Finland	2	2.5
Mexico	2	2.5
Others (refer to Table E7 details)	13	16.0

board or national or international working group or had authored a peer-reviewed publication within the past 5 years. Participants worked in 24 countries

Delphi R1

Participants were asked to rank potential SR criteria (1 = highest and 6 = lowest). Table II lists the results. Seven statements were supported by 70% or more of participants (Table III).

Ninety percent agreed that an SR definition requires improvement across at least two domains. This might involve a sustained exacerbation-free period and major improvements in asthma control and QOL. Consensus was achieved that a major reduction or cessation of OCS was important in those treated with long-term OCS, although participants acknowledged that a

TABLE II. Delphi Round 1 ranking question results

Ranking	Potential criteria
1	Elimination or major reduction in asthma exacerbations
2	Elimination or major reduction in long-term (maintenance) oral corticosteroids
3	Major improvement in asthma control
4	Improvement in quality of life
5	Improvement in FEV ₁
6	Major reduction in maintenance inhaler therapy

TABLE III. Delphi Round 1 results

Question/statement	Agreement (% of respondents) (n = 115)
Statements achieving consensus	
Requires evidence of improvement across at least two domains	90%
Requires being completely exacerbation-free for an extended period*	94%
For patients previously treated with long-term OCS, requires a major reduction in or cessation of OCS.	83%
A person might be classified as a super-responder even if unable to cease OCS because of adrenal insufficiency, provided there had been a major reduction in OCS dose and other response criteria had been met.	94%
A major improvement in asthma control is essential to the definition.†	77%
Improvement in quality of life is an important part of the definition.	88.9%
A large improvement in FEV ₁ might be part of the definition but is not essential.‡	78%
Statements with majority support but not achieving consensus	
A 75% reduction in exacerbations is sufficient to define a super-responder	60.2%
In relation to asthma control, there should be a large improvement in both asthma control and well-controlled asthma	61.9%

OCS, oral corticosteroids.

*No consensus for the duration over which this should be assessed.

†Opinion varied regarding how large the improvement should be.

‡Opinion varied regarding how large that improvement should be and whether an FEV₁ greater than 80% predicted was necessary.

person might be an SR even if he or she was unable to cease OCS because of adrenal insufficiency, provided there had been a major reduction in OCS dose and other response criteria had been met. There was consensus that a large improvement in FEV₁ might be part of the SR definition, although FEV₁ improvement was not regarded as being essential to the definition.

A further two statements received majority support but did not achieve the consensus definition: a 75% reduction in exacerbations was required, and there was a need for both a large improvement in asthma control and well-controlled asthma.

However, several issues were unclear, including the duration over which exacerbation elimination should be assessed and the magnitude of a major improvement in asthma control or FEV₁. One-third of participants did not think it was practical to assess

QOL in a clinical environment, whereas others commented that QOL tools are largely untested for severe asthma, and that more research is needed.

Delphi R2

Ninety individuals took part in R2, further refining the SR definition. Consensus was achieved for several additional criteria, as detailed in Table IV: a person should be exacerbation-free for 12 months, and a major improvement in asthma control should equate to two or more times the MCID (ie, an improvement of ≥ 1.0 in ACQ score or an improvement in ACT score of ≥ 6.0 would be necessary to define someone as an SR). If using GINA criteria, two levels of improvement would be required. Consensus was confirmed that people receiving long-term OCS should have been completely weaned from OCS, or to the point of adrenal insufficiency, and that irrespective of baseline, a large improvement in FEV₁ might be a criterion in the definition, but it is not essential.

Four statements were supported by more than 50% of participants but did not achieve the consensus definition. These included the requirement for both a large improvement in asthma control and achieving well-controlled asthma, a 75% or greater reduction in exacerbations, an improvement in FEV₁ of 500 mL, and the need for improvement across three or more domains. These four statements were further evaluated in Delphi R3.

The inclusion of a QOL measure was not supported by a majority, although multiple participants commented that this was an important area that needed more research.

Delphi R3

A total of 81 individuals took part in Delphi R3, which coincided with the arrival of the COVID-19 pandemic in Europe and North America, leading to delays in questionnaire completion. Seventy percent of those who participated in R1 completed all three rounds. Consensus was achieved for several questions and statements, as detailed in Table V: improvement should be across three or more domains, and the creation of major and minor criteria was supported, in which major criteria have greater weight than minor criteria. Consensus was achieved that having a 75% or greater reduction in exacerbations and having well-controlled asthma should be included as minor criteria. A large improvement in FEV₁ should be defined as 500 mL or greater. More than 50% of participants supported including QOL improvement as a minor criterion, but this did not quite achieve the consensus definition. There was strong support for further research into QOL measurement tools that are appropriate for severe asthma.

Finally, participants responded to several patient scenarios composed of different combinations of SR criteria observed over 12 months

There was strong consensus among participants that patient scenarios 1, 4, and 8 described SRs. Most participants also thought that patient scenarios 3, 6, and 7 described patients who might be regarded as SRs, although consensus was not quite achieved. In contrast, a minority of patient participants thought that patient scenarios 2 and 5 described SRs.

The authors therefore propose that an SR definition should include three or more criteria, at least two of which should be major criteria. However, close examination of participant responses to the eight different scenarios suggests that not all

TABLE IV. Delphi Round 2 results

Question/statement	Agreement (% of respondents) (n = 90)
Statements achieving consensus	
A person should be exacerbation-free for 12 mo.	93.3%
The amount of improvement in asthma control as measured by Asthma Control Questionnaire or Asthma Control Test score should be at least twice the minimal clinically important difference.*	70.0%
The amount of improvement in asthma control as measured by Global Initiative for Asthma score should be two levels of improvement.	83.3%
Patients receiving long-term oral corticosteroids should have been completely weaned from oral corticosteroids, or to the point of adrenal insufficiency.	87.8%
A large improvement in FEV ₁ , irrespective of baseline, might be a criterion but is not an essential requirement	93.3%
Statements with majority support but not achieving consensus	
In relation to asthma control, there should be a large improvement in both asthma control and well-controlled asthma	68.9%
A 75% or greater reduction in exacerbations over 12 mo would be sufficient.	64.4%
A large improvement in FEV ₁ should be defined as 500 mL (two times the minimal patient-perceivable improvement).	62.2%
Require improvement across three or more domains	58.9%
Statements not achieving consensus	
A major reduction in maintenance inhaler therapy should be one of the domains.	46.7%
Should a quality of life measure be used in the definition?	44.4%

*An identical percentage of respondents replied "Possibly, but more research is needed." Further data on responses to different quality of life measures and other patient-reported outcomes

TABLE V. Delphi Round 3 results

Question/statement	Agreement (% of respondents) (n = 81)
Statements achieving consensus	
Require improvement across three or more domains	80.3%
Support for using major and minor criteria	75.3%
Major criteria have greater weight than minor criteria.	86.4%
Additional minor criteria:	
≥75% reduction in exacerbations	74.1%
Well-controlled asthma	76.5%
Large improvement in FEV ₁ defined as 500 mL	88.9%
Further research required surrounding quality of life tools	87.7%
Statements not achieving consensus	
Improvement in quality of life as minor criterion	60.5%
Major reduction in maintenance inhaler therapy as minor criterion.	48.2%

minor criteria are ranked equally; greater weight was paid to 75% or more exacerbation reduction and well-controlled asthma than to FEV₁ improvement.

DISCUSSION

This Delphi-based study drew on the knowledge and experience of 81 experts from multiple countries to reach consensus on a definition of severe asthma SR. Consensus was achieved that improvement should be sustained (present for 12 months) and should involve improvement in three or more criteria. Consensus was also achieved for the creation of major and minor criteria, in which major criteria have greater weight than minor criteria. Major criteria were composed of exacerbation elimination, a

major improvement in asthma control and OCS elimination or weaning to the point of adrenal insufficiency. Minor criteria were composed of a 75% reduction in exacerbations, achieving well-controlled asthma, and a 500 mL or greater improvement in FEV₁. The steering committee proposes that an SR should include improvement in three or more criteria, at least two of which should be major criteria (Figure 2).

Exacerbation reduction has been the primary outcome measure in key RCTs of monoclonal antibodies and other add-on therapies.⁶⁻⁹ In selected patients, these therapies reduce asthma exacerbations by 40% to 50% compared with placebo.⁶⁻⁹ A substantial improvement in asthma exacerbations was the highest ranked SR criteria (Table II). Over 90% of panel members agreed that an SR should be completely exacerbation-free for an extended period (Table III); R2 provided support for the proposition that this extended period should be 12 months (Table IV). Exacerbation elimination subsequently became a major criterion. In Delphi R3 a 75% or more reduction in exacerbations was accepted as a minor criterion. Notably, a 75% exacerbation reduction is more than the average exacerbation reduction reported in major RCTs. If exacerbation elimination has been achieved, it is inappropriate to include a 75% exacerbation reduction as an additional minor criterion. This would amount to double-counting, because exacerbation elimination will always include a 75% exacerbation reduction.

Some add-on therapies have a clear OCS-sparing effect.¹¹⁻¹³ The elimination of long-term maintenance OCS or a major reduction in it was the second ranked SR criterion (Table II), and there was also strong support for the notion that a person might be classified as an SR even if unable to cease OCS because of adrenal insufficiency, provided there had been a major reduction in OCS dose and other response criteria had been met.

Improvements in asthma control have not been primary end points in large RCTs of add-on therapies. While some trials have reported greater improvements in asthma control in the active treatment arm than in the placebo arm, the average magnitude of

Improvement should involve 3 or more criteria (at least 2 of which should be major criteria) and should be assessed over 12 months*

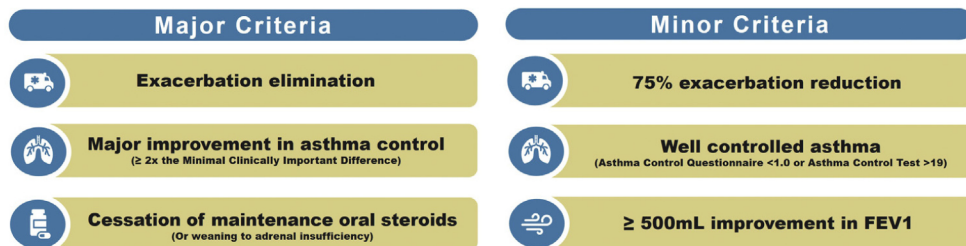


FIGURE 2. Major and minor criteria for defining a super-responder. *If exacerbation elimination has been achieved, it is inappropriate to include a 75% exacerbation reduction as an additional minor criterion. This would amount to double-counting, because exacerbation elimination always includes a 75% exacerbation reduction.

improvement has usually been modest, less than the MCID and of uncertain clinical significance.^{7,8} In the current project, a major improvement in asthma control was the third ranked SR criteria. It achieved consensus in R1, in which 77% of participants agreed that a major improvement in asthma control was essential to the SR definition. The challenge in R2 and R3 was to achieve consensus regarding what constitutes a major improvement in asthma control. Seventy percent agreed in R2 that the magnitude of a major improvement in asthma control should be at least twice the MCID for the ACQ and ACT. Thus, an improvement of 1.0 or greater in ACQ score or an improvement in ACT score of 6.0 or greater would be necessary to qualify as an SR. When using the GINA criteria, over 80% agreed that two levels of improvement would be required, although because GINA allows only three states of asthma control (well-controlled, partly controlled, and uncontrolled), quantifying improvement can be difficult. As noted earlier, group RCT data may obscure the identification of individuals experiencing more dramatic improvements. A recent real-world study of mepolizumab-treated patients with severe eosinophilic asthma defined SRs as those in the upper quartile of asthma control improvement. Such patients had an improvement in ACQ5 score of more than 2.8, well above the MCID.¹⁴ In a real-world study of benralizumab in severe eosinophilic asthma, Kavanagh and colleagues¹⁵ reported improvements of twice the MCID for ACQ6 in 43.1%, the achievement of an ACQ6 of less than 1 at 1 year in 24.6%, and both of these outcomes in 19.2% of patients. We acknowledge that improvements in asthma control will probably vary depending on which asthma control score is used, so there is a need for further research to determine which questionnaires are better able to identify SRs reliably.

Other patient-reported outcomes such as QOL are important to patients but have not been primary end points in large RCTs. Monoclonal antibodies targeting IgE, IL-5, IL-5 receptor, and IL-4/IL-13 receptor generally produce modest average improvements in QOL, often less than the MCID,^{7,8,27} although this may vary according to which QOL instrument is used.⁷ Although consensus was achieved in R1 that improvement in QOL should be an important part of the SR definition, some participants did not think it was practical to assess QOL in a clinical environment, and many commented that QOL tools are largely untested for severe asthma. In R2, we asked specific questions about a number of these QOL tools, including the

Asthma Quality of Life Questionnaire, Severe Asthma Questionnaire, Global Rating of Change scale, visual analog scale, and Work Productivity and Activity Impairment. Many participants were unfamiliar with these tools or unsure about their validity. Including QOL improvement as a minor criterion in the SR definition received support but did not achieve the predefined consensus definition. The need for further research on QOL measurement tools for severe asthma received strong support.

Lung function improvement has been a secondary outcome in many RCTs of add-on therapies. A systematic review of omalizumab concluded that improvements in FEV₁ were small and inconsistent.⁶ Anti-IL-5 therapies produce average improvements in FEV₁ of 80 to 110 mL.⁷ Dupilumab produces average improvements in pre-bronchodilator FEV₁ of 130 to 200 mL (relative to placebo).²⁸ Up to 70% of patients with elevated blood eosinophils and exhaled nitric oxide showed an FEV₁ improvement of 200 mL or greater.²⁸ In R2, consensus was achieved that a large improvement in FEV₁ should be defined as 500 mL or greater. How frequently this degree of improvement occurs in RCTs and registry studies is not clear and warrants further research. We recognize that there will be differing opinions regarding how best to define FEV₁ improvement, whether as an absolute value or a percentage improvement. This issue warrants further investigation.

The Delphi process has multiple strengths. Anonymity of responses and the large number of panel members from multiple countries reduced the risk that a small group, or those from a single region, might exert undue influence. Moreover, providing summary results after each Delphi round allowed panel members the chance to revise their opinions based on group responses. The steering committee decided on an a priori definition of consensus as 70% or greater agreement based on our review of several Delphi studies conducted on asthma. After data collection, we became aware of a systematic review of Delphi studies reporting that 75% agreement was the median threshold to define consensus (range, 50% to 97%).²⁹ However, we did not think it was appropriate to change the definition after data collection had finished. The severe asthma SR definition that emerged from this study included a combination of objective domains (exacerbations, OCS use, and FEV₁) and subjective domains (asthma control). Assessing subjective, patient-reported outcomes forms an important component of managing severe asthma, but it can be difficult in the clinical setting because of

the significant placebo response seen in RCTs. One cannot ignore the risks of overinterpreting subjective improvements in patients treated with add-on therapies, although we think that the SR definition mitigates this risk by requiring large improvements in multiple domains over 12 months. We acknowledge that our study had limitations. The Delphi process is subjective by nature; it is based on opinions, albeit those of experts. We are also conscious that the requirement for improvement in three or more criteria makes it difficult to achieve an SR in patients with relatively unimpaired lung function who are not receiving maintenance OCS. Hence, we think it important for the utility of these SR criteria to be further evaluated in large independent datasets. As an example, we will assess the performance characteristics of the different SR criteria in the International Severe Asthma Registry.³⁰ It will also be important to understand how the different major and minor SR criteria correlate with each other and the extent to which they predict future clinical outcomes.

This international consensus-based definition of severe asthma SRs is an important prerequisite for better understanding factors associated with super-response to therapy and the mechanisms involved. Indeed, it is highly likely that the study of SRs to specific biologic therapies may offer novel insights into asthma pathophysiology and asthma phenotypes. Finally, additional research needs to focus on understanding the patient perspective better and more precisely measuring QOL in SRs.

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