Defining a severe asthma super-responder: findings from a Delphi process

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January 30, 2024

Abstract

Background: Clinicians are increasingly recognising severe asthma patients in whom biologicals and other add-on therapies lead to dramatic improvement. Because there is no agreed upon super-responder (SR) definition at present, we surveyed severe asthma experts using a modified Delphi process in order to define an international consensus-based definition of a severe asthma 'super-responder'. Methods: The Delphi panel comprised 81 participants (94% specialist pulmonologists or allergists) from 24 countries and consisted of 3 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 3 or more domains assessed over 12 months. Major SR criteria included exacerbation elimination, a large improvement in asthma control ([?] 2x the minimal clinically important difference) and cessation of maintenance of oral steroids (or weaning to adrenal insufficiency). Minor SR criteria comprised a 75% exacerbation reduction, having well controlled asthma and a 500mL or greater improvement in FEV1. The SR definition needs to incorporate quality of life measures, though 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 super responders is an important prerequisite for better understanding super-responder prevalence, predictive factors and the mechanisms involved. Further research is needed to understand the patient perspective and measure quality of life more precisely in super-responders.

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Short running title: Defining a severe asthma super-responder

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Funding support : This project was supported by in kind contributions from Observational and Pragmatic Research Institute and the University of Queensland Faculty of Medicine. No pharmaceutical companies were involved in study design or execution.

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Word count for the body of the manuscript: 3,057

This article has an online data supplement, which is accessible from this issue's table of content online at https://onlinelibrary.wiley.com/journal/13989995

ACKNOWLEDGEMENTS

Funding support : This project was supported by in kind contributions from Observational and Pragmatic Research Institute and the University of Queensland. No pharmaceutical companies were involved in study design or execution.

The Delphi Panel members who have contributed to this study are listed below.

Delphi Panel: Adel Mansur, Aikaterini Detoraki, Alan Altraja, Alan James, Alexandra Nanzer-Kelly, Andréanne Côté, Andrew Menzies-Gow, Andriana Papaioannou, Anne-Maree Cheffins, Arnaud Bourdin, Bassam Mahboub, Brian Lipworth, Carlos Andrés Celis-Preciado, Carlos Torres-Duque, Caterina Bucca, Celeste Porsbjerg, Charlotte Ulrik, Chris Corrigan, Christian Taube, Claude Farah, Constance Katelaris, David Langton, Dermot Ryan, Désirée Larenas-Linnemann, Eleftherios Zervas, Enrico Heffler, Flavia Hoyte, Francesca Puggioni, George Christoff, Giorgio Walter Canonica, Giovanna Elisiana Carpagnano, Giuseppe Guida, Gregory Katsoulotos, Guy Brusselle, Hitashi Rupani, Hubertus Jersmann, Ian Clifton, Jaideep Dhariwal, James Fingleton, Jane Duke, Janet Rimmer, Jo Douglass, João Fonseca, Job van Boven, John Corless, John Harrington, Jorge Maspero, José Luis Miguel, Kanok Pipatvech, Karrinda Kenny, Kenneth Chapman, Konstantinos Kostikas, Lauri Lehtimäki, Li Ping Chung, Liam Heaney, Liang-Wen Hang, Louis-Philippe Boulet, Luis Perez-de-Llano, Luisa Ricciardi, Majdy Idrees, Manlio Milanese, Maria Elisabetta Conte, Maria Teresa Costantino, Mariko Koh Siyue, Mark Fitzgerald, Mark Hew, Matthew Peters, Ming-Ju Tsai, Mitesh Patel, Mohammad Hashim Khan, Mohsen Sadatsafavi, Mona Al-Ahmad, Mona-Rita Yacoub, Mónica De Gennaro, Naghmeh Radhakrishna, Nicola Alexander Hanania, Nikolaos Papadopoulos, Njira Lugogo, Norma Linaker, Nunzio Crimi, Paddy Dennison, Parameswaran Nair, Patrick David Mitchell, Paul O'Byrne, Paul Pfeffer, Paula Kauppi, Pauline Hughes, Peter Middleton, Peter Wark, Philip Bardin, Pin-Kuei Fu, Praveen Akuthota, Rekha Chaudhuri, Ricardo Campos, Riyard Al-Lehebi, Roberta Parente, Rovira Francisco, Sally Wenzel, Santus Pierachille, Shrikant Pawar, Stelios Loukides, Stephen Fowler, Tara Mackenzie, Thomas Brown, Tze Lee Tan, Unnur Björnsdóttir, Vanessa McDonald, Veronica Lawriwskyj, Vibeke Backer, Violina Vasileva, Ying-Chun Chien, Zinta Harrington.

DECLARATION OF INTERESTS

John Upham reports personal fees from AstraZeneca, personal fees from GlaxoSmithKline, personal fees from Sanofi, personal fees from Boehringer Ingelheim, personal fees from Novartis, outside the submitted work.

Chantal Le Lievre has nothing to disclose.

David Jackson reports personal fees from AstraZeneca, personal fees from GlaxoSmithKline, personal fees from Boehringer Ingelheim, personal fees from Teva, personal fees from Napp, personal fees from Chiesi, personal fees from Novartis, grants from AstraZeneca, outside the submitted work.

Matthew Masoli reports personal fees from Novartis, personal fees from AstraZeneca, outside the submitted work; .

Micahel Wechsler reports grants and personal fees from Novartis, grants and personal fees from Sanofi, personal fees from Regeneron, personal fees from Genentech, personal fees from Sentien, grants, personal fees and non-financial support from Teva, personal fees and non-financial support from Boehringer Ingelheim, grants and personal fees from GlaxoSmithKline, personal fees from Restorbio, personal fees from Equillium, non-financial support from Merck, personal fees from Genzyme, personal fees from Pulmatrix, personal fees from Cohero Health, personal fees and non-financial support from AstraZeneca, outside the submitted work; .

David Price reports grants from AKL Research and Development Ltd, personal fees from Amgen, grants and personal fees from AstraZeneca, grants and personal fees from Boehringer Ingelheim, grants from British Lung Foundation, grants and personal fees from Chiesi, grants and personal fees from Circassia, personal fees from Cipla, personal fees from GlaxoSmithKline, personal fees from Kyorin, personal fees from Merck, grants and personal fees from Mylan, grants and personal fees from Mundipharma, grants and personal fees from Napp, grants and personal fees from Novartis, grants and personal fees from Pfizer, grants and personal fees from Regeneron Pharmaceuticals, grants from Respiratory Effectiveness Group, grants and personal fees from Sanofi Genzyme, grants and personal fees from Teva, grants and personal fees from Theravance, grants from UK National Health Service, grants and personal fees from Zentiva (Sanofi Generics), non-financial support from Efficacy and Mechanism Evaluation programme, non-financial support from Health Technology Assessment, outside the submitted work; and stock/stock options from AKL Research and Development Ltd which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore) and 5% shareholding in Timestamp which develops adherence monitoring technology.

ABSTRACT (235/250 words)

Background : Clinicians are increasingly recognising severe asthma patients in whom biologicals and other add-on therapies lead to dramatic improvement. Because there is no agreed upon super-responder (SR) definition at present, we surveyed severe asthma experts using a modified Delphi process in order to define an international consensus-based definition of a severe asthma 'super-responder'.

Methods : The Delphi panel comprised 81 participants (94% specialist pulmonologists or allergists) from 24 countries and consisted of 3 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 3 or more domains assessed over 12 months. Major SR criteria included exacerbation elimination, a large improvement in asthma control ([?] 2x the minimal clinically important difference) and cessation of maintenance of oral steroids (or weaning to adrenal insufficiency). Minor SR criteria comprised a 75% exacerbation reduction, having well controlled asthma and a 500mL or greater improvement in FEV1. The SR definition needs to incorporate quality of life measures, though 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 super responders is an important prerequisite for better understanding super-responder prevalence, predictive factors and the mechanisms involved. Further research is needed to understand the patient perspective and measure quality of life more precisely in super-responders.

KEY WORDS

asthma, biologics, asthma treatment

INTRODUCTION (391 words)

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

Various highly effective add-on therapies have been developed for severe asthma. These therapies include monoclonal antibodies targeting type 2 inflammatory pathways [6–8], azithromycin[9] and bronchial thermoplasty [10]. In appropriately selected patients, these novel therapies produce a 40-50% reduction in asthma exacerbations [6–9]. Indeed, exacerbation reduction has been the primary outcome measure in key RCTs of add-on therapies [6–9], though other highly beneficial effects such as OCS sparing have also been demonstrated[11–13]. In contrast, the impacts of novel therapies on lung function and patient reported outcomes such as asthma control and quality of life (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 recognising 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', such patients may report that their lives have been 'transformed'. Developing an agreed super-responder (SR) definition is an important prerequisite for defining prevalence, identifying predictive factors and understanding SRs.

However, there is no agreed SR definition. In a recent real-world study of mepolizumab treated patients with severe eosinophilic asthma, the authors defined SRs as those in the upper quartile of asthma control improvement, assessed using the 5-item asthma control questionnaire (ACQ)-5 [14]. Kavanagh and colleagues took a different approach, defining SRs as mepolizumab-treated patients who were exacerbation-free and off maintenance OCS at one year[15]; 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. A Delphi process was used to survey multiple severe asthma experts from numerous countries. Some of the results of this study were reported at the European Respiratory Congress 2020 [17].

METHODS (550 words)

A modified 3-round Delphi method process [18] was used to develop a consensus definition of a "super-responder" i.e. severe asthma patients reporting a remarkable improvement with add-on therapies. The Anonymised Data Ethics and Protocol Transparency (ADEPT) Committee provided ethical approval (reference ADEPT0220). Panel selection criteria are outlined in the online Supplementary Table E1.

Modified Delphi process

The steering committee plus eleven 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, R2 and R3) in which statements/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 (Supplementary Table E7). Consensus was defined *a priori*as agreement ('Strongly Agree' plus 'Agree') with a statement/question by [?]70% of panel members. If a statement/question received majority support, but consensus was not achieved, it was carried forward to the next round, with modifications based on comments. Statements/questions achieving <50% agreement were removed, except where comments indicated misunderstanding, in which case they were revised for the next round. Results were provided to panel members after each round to facilitate informed decision in subsequent rounds. The steering committee added statements/questions to R2 and R3 based on comments received. Participants had two weeks to respond, with reminders sent when necessary.

Delphi R1

Demographic variables and members' experience were documented, plus the initial statements/questions (Supplementary Table E2). In order to target R2 and R3 to those who completed previous rounds, email addresses were collected and stored securely by the project administrator to maintain confidentiality and provide the steering committee with de-identified data only.

Delphi R2

R2 questionnaire asked whether improvement across [?]2 or [?]3 domains was necessary, the duration of exacerbation elimination, the magnitude of a "major improvement" in asthma control and whether having well-controlled asthma was also necessary. The minimum clinically important difference (MCID) for the Asthma Control Questionnaire (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-times, three-times or four-times the MCID for these questionnaires should define a SR. For GINA-defined asthma control, panel members indicated if a one-level or two-level improvement should define a SR.

There is no universally accepted MCID for FEV1 in asthma, though the minimal patient perceivable improvement is 230mL [21]. Hence, panel members were asked if improvement in FEV1 of [?]500mL (slightly more than double 230mL) 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 (as detailed in the Supplement Table E3) to assess attitudes to 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 (as detailed in the Supplementary section Table E4), in order to clarify panel members responses to combinations of response criteria.

RESULTS (846 words)

We recruited 115 individuals who participated in R1, of whom 90 participated in R2 and 81 participated in R3 (Figure 1). Participants covered a broad age range and included more men than women (Table 1). Ninety four percent were specialist pulmonologists or allergists, with smaller numbers of nurses, pharmacists and researchers. Ninety five percent were actively involved in severe asthma treatment, while over 80% had been in a severe asthma advisory board or national/international working group or had authored a peer-reviewed publication within the last 5 years. Participants worked in 24 countries (details in Supplementary Table E5).

Delphi R1

Participants were asked to rank potential SR criteria (1= highest; 6=lowest). The results are shown in Table 2. Seven statements were supported by 70% or more of participants (Table 3).

Ninety percent agreed that a 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, though participants acknowledged that a person might be 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. There was consensus that a large improvement in FEV1 might be part of the SR definition, though 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, and the need for both a large improvement in both 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, while 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 4: 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 i.e. an improvement of [?]1.0 in ACQ score or an improvement in ACT score of [?]6.0 is necessary to define someone as an SR. If using GINA criteria, two levels of improvement would be required. Consensus was confirmed that people on long term OCS should have completely weaned off OCS, or to the point of adrenal insufficiency, and that a large improvement in FEV1, irrespective of baseline, might be one of the criteria in the definition, but 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% reduction in exacerbations, an improvement in FEV1 of 500ml 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, though multiple participants commented that this was an important area that needed more research.

Delphi R3

Eighty-one 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 3 rounds. Consensus was achieved for several questions/statements as detailed in Table 5: improvement should be across [?]3 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 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 [?]500ml. Including QOL improvement as a minor criterion was supported by more than 50% of participants but 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 comprising different combinations of SR criteria observed over 12 months, as shown in Supplementary Table E6.

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, though 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 a SR definition should include [?]3 criteria, of which at least two should be major criteria. However, close examination of the participant responses to the eight different scenarios

suggest that not all minor criteria are ranked equally with greater weight paid to [?]75% exacerbation reduction and well-controlled asthma than to FEV1 improvement.

DISCUSSION (1270 words)

This Delphi-based study drew on the knowledge and experience of eighty-one experts from multiple countries to reach consensus on a severe asthma SR definition. Consensus was achieved that improvement should be sustained (present for 12 months) and should involve improvement in 3 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 comprised exacerbation elimination, a major improvement in asthma control and OCS elimination or weaning to the point of adrenal insufficiency. Minor criteria comprised a 75% reduction in exacerbations, achieving well controlled asthma and a 500mL or greater improvement in FEV1. The steering committee proposes that a SR should include improvement in 3 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 40-50% compared to placebo[6–9]. Indeed, a substantial improvement in asthma exacerbations was the highest ranked SR criteria (Table 2), with over 90% of panel members agreeing that a SR should be completely exacerbation-free for an extended period (Table 3), with R2 providing support for the proposition that this 'extended period' should be 12 months (Table 4). 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 the major RCTs.

Some add-on therapies have a clear OCS sparing effect[11–13]. Elimination or major reduction in long term maintenance OCS was the second ranked SR criteria (Table 2), and there was also strong support for the notion that a person might be classified as a 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 endpoints 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, though the average magnitude of improvement has usually been modest, less than the MCID and of uncertain clinical significance[7,8]. In the current project, major improvement in asthma control was the third ranked SR criteria, achieving consensus in R1. Consensus was reached 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 in ACQ score or an improvement in ACT score of [?]6.0 would be necessary to qualify as a super-responder. If using the GINA criteria, two levels of improvement would be required, though because GINA only allows 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 super-responders 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 real-world study of benralizumab in severe eosinophilic asthma, Kavanagh and colleagues reported improvements of twice the MCID for ACQ6 in 43.1%, the achievement of an ACQ6 [?]1 at 1 year in 24.6%, and both of these outcomes in 19.2% of patients[15]. 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 reliably identify super-responders.

Other patient reported outcomes such as QOL are very important to patients but have not been primary endpoints 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], though this may vary according to which QOL instrument is used [7]. Though 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 AQLQ, SAQ, GRC scale, VAS and WPAI; 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 quite achieve the pre-defined 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 80-110 mL[7]. Dupilumab produces average improvements in pre-bronchodilator FEV1 of 130-200mL (relative to placebo)[28]; up to 70% of patients with elevated blood eosinophils and exhaled nitric oxide showed an FEV1 improvement of [?] 200 mL [28]. In R2, consensus was achieved that a large improvement in FEV1 should be defined as [?] 500mL; how frequently this degree of improvement occurs in RCTs and registry studies is not clear and warrants further research. We recognise that there will be differing opinions on 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% agreement; a recent systematic review of Delphi studies reported that 75% agreement was the median threshold to define consensus (range 50 – 97%) [29]. 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 can be difficult in the clinical setting, given the significant placebo response seen in RCTs. One cannot ignore the risks of over-interpreting subjective improvements in patients treated with add-on therapies, though we think that the SR definition mitigates this risk somewhat by requiring very large improvements in multiple domains over 12 months. We acknowledge our study has limitations: the Delphi process is subjective by nature, being based on opinions, albeit those of experts. We are also conscious that the requirement for improvement in [?]3 criteria makes it difficult to achieve a SR in patients with relatively unimpaired lung function who are not on maintenance OCS. Hence, we think it important that the utility of these SR criteria are further evaluated in large independent datasets.

In conclusion, 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. Lastly, additional research needs to focus on better understanding the patient perspective and more precisely measuring QOL in SRs.

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TABLE 1: Participant characteristics of those who participated in all three Delphi rounds

		Number	%
Age			
	<35 years	2	2.5%
	35 - 44 years	22	27.2%
	45-54 years	35	43.2%
	years	16	19.8%
	> 65 years	5	6.2%
	Not answered	1	1.2%
Gender			
	Female	25	30.9%
	Male	56	69.1%
Occupation			
	Pulmonologist	61	75.3%
	Allergist	14	17.3%
	Asthma nurse	2	2.5%
	Allergist & 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 (last 5 yrs)	Yes	72	88.9%
Severe asthma publications (last 5 yrs)	Yes	68	83.9%
Country of work (N=24)			
	Australia	16	19.8%

		Number	%
	United Kingdom	15	18.5%
	Italy	10	12.4%
	Canada	6	7.4%
	Greece	5	6.2%
	USA	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 supplementary Table E6 for further detail)	13	16.0

TABLE 2: 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 (OCS)
3	Major improvement in asthma control
4	Improvement in quality of life
5	Improvement in FEV1
6	Major reduction in maintenance inhaler therapy

TABLE 3: Delphi Round 1 results summary

Question/statement
Statements achieving consensus
Requires evidence of improvement across at least two domains
Requires being completely exacerbation free for an extended period.11No consensus for the duration over which this should
For patients previously treated with long term OCS, requires a major reduction or cessation of OCS.
A person might be classified as a super-responder even if unable to cease OCS because of adrenal insufficiency, provided the
A major improvement in asthma control is essential to the definition.22Opinion varied on how large the improvement shoul
Improvement in quality of life (QOL) is an important part of the definition.
A large improvement in FEV1 might be part of the definition but is not essential.33Opinion varied on how large that impro
Statements with majority support but not achieving consensus
A 75% reduction in exacerbations is sufficient to define a super-responder
In relation to asthma control, there should be a large improvement in both asthma control AND well controlled asthma

TABLE 4: Delphi Round 2 results summary

Question/statement
Statements achieving consensus
A person should be exacerbation free for 12 months.
The amount of improvement in asthma control as measured by ACQ or ACT score should be at least twice the MCID11MC

Question/statement
The amount of improvement in asthma control as measured by GINA score should be two levels of improvement
Patients on long term OCS should have completely weaned off OCS, or to the point of adrenal insufficiency.
A large improvement in FEV1, irrespective of baseline, might be one of the criteria, but is not an essential requirement
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
A 75% or greater reduction in exacerbations over 12 months would be sufficient.
A large improvement in FEV1 should be defined as 500ml (2 times the MPPI)22MPPI = Minimal Patient Perceivable Impr
Require improvement across 3 or more domains
Statements not achieving consensus
A major reduction in maintenance inhaler therapy should be one of the domains.
Should a QOL measure be used in the definition?33An identical % of respondents replied "possibly, but more research is ne

TABLE 5: Delphi Round 3 results summary

Question/statement	*Agreement (% of respondents, N = 8*
Statements achieving consensus	
Require improvement across 3 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 Well controlled asthma	74.1% 76.5%
'Large' improvement in FEV1 defined as 500ml	88.9%
Further research required surrounding QOL tools	87.7%
Statements not achieving consensus	
Improvement in quality of life as a minor criterion	60.5%
Major reduction in maintenance inhaler therapy as a minor criterion.	48.2%

FIGURE LEGENDS

FIGURE 1: Number of Delphi panel participants in each round

FIGURE 2: Major and minor criteria for defining a super-responder

Figure 1

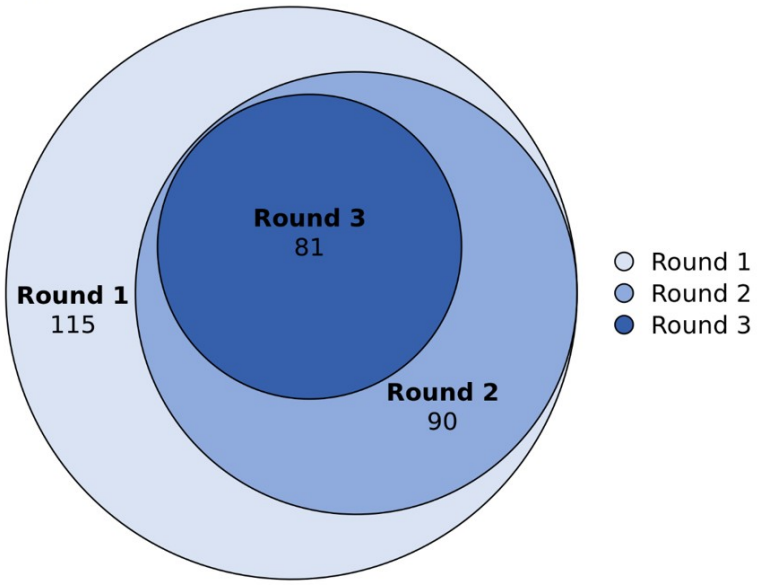

Figure 2