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

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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: 3,257

This article has an online data supplement, which is accessible from this issue's table of content online at https://www.jaci-inpractice.org/

DECLARATION OF INTERESTS

John W. 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 J. 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.

Michael E. 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, personal fees from Restorbio, personal fees from Equillium, personal fees from Genzyme, grants and personal fees from Cohero Health, grants, personal fees and non-financial support from Teva, personal fees and non-financial support from Boehringer Ingelheim, grants, personal fees and non-financial support from AstraZeneca, personal fees from GSK, outside the submitted work; .

David B. Price reports grants from AKL Research and Development Ltd, grants and personal fees from AstraZeneca, grants and personal fees from Boehringer Ingelheim, grants from British Lung Foundation, grants and personal fees from Chiesi, personal fees from Cipla, personal fees from GlaxoSmithKline, personal fees from Kyorin, personal fees from Merck, grants and personal fees from Mylan, personal fees from Mundipharma, grants and personal fees from Novartis, grants and personal fees from Regeneron Pharmaceuticals, grants from Respiratory Effectiveness Group, grants and personal fees from Sanofi Genzyme, 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, personal fees from Airway Vista Secretariat, personal fees from EPG Communication Holdings Ltd, personal fees from FIECON Ltd, personal fees from Fieldwork International, personal fees from OM Pharma SA, personal fees from PeerVoice, personal fees from Phadia AB, personal fees from Spirosure Inc, personal fees from Strategic North Limited, personal fees from Synapse Research Management Partners S.L, personal fees from Talos Health Solutions , personal fees from WebMD Global LLC, 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 92.61% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); 5% shareholding in Timestamp which develops adherence monitoring technology.

ABSTRACT (250/250 words)

Background: Clinicians are increasingly recognising severe asthma patients in whom biologicals 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 in order to develop 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 requires improvement in at least 2 major criteria. In the future, the SR definition should be expanded 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.

HIGHLIGHTS BOX

1. **What is already known about this topic?** Clinicians recognise severe asthma patients in whom biologicals and other add-on therapies lead to dramatic improvement, so called 'super-responders'. However, there is there is no consensus on the most appropriate super-responder definition.
2. **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.
3. **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.
4. **Key words:** asthma, biologics, asthma treatment

ABBREVIATIONS

ACQ	Asthma Control Questionnaire
~~ACQ~~	~~Asthma Control Questionnaire~~
ACT	Asthma Control Test
ADEPT	Anonymised Data Ethics and Protocol Transparency
AQLQ	Asthma Quality of Life Questionnaire
FEV1	Forced Expiratory Volume in the first second
GINA	Global Initiative for Asthma
GRC	Global Rating of Change
MCID	Minimal Clinical Important Difference
MPPI	Minimal Patient Perceivable Improvement
OCS	Oral Corticosteroids
QOL	Quality of Life
R1	Round 1
R2	Round 2
R3	Round 3
RCT	Randomised Control Trial
SAQ	Severe Asthma Questionnaire
SR	Super-Responder
VAS	Visual Analogue Scale
WPAI	Work Productivity and Activity Impairment

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 (583 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. Summary results were provided to panel members after each round to facilitate informed decision 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/questions to R2 and R3 based on comments received. Participants had two weeks to respond, with reminders sent when necessary.

<u>Delphi R1</u>

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 suggests 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 (1437words)

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. It should be emphasized that if exacerbation elimination has been achieved it is not appropriate to include a 75% exacerbation reduction as an additional minor criterion. This would amount to 'double-counting', given that exacerbation elimination will always include a 75% exacerbation reduction.

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 with

77% of participants agreeing that a major improvement in asthma control was essential to the SR definition. The challenge in R2 and R3 was to achieve consensus on what exactly 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 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, over 80% agreed that 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 based on our review of several Delphi studies conducted in asthma. After data collection, we became aware of a systematic review of Delphi studies which reported that 75% agreement was the median threshold to define consensus (range 50 – 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 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. 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 one another and the extent to which they predict future clinical outcomes.

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

358 research needs to focus on better understanding the patient perspective and more precisely
359 measuring QOL in SRs.

360

ACKNOWLEDGEMENTS

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.

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475 **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%
	55-64 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%
	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
OCS: Oral Corticosteroids; FEV1: Forced Expiratory Volume in the first second.	

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TABLE 3: Delphi Round 1 results summary

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.~~1~~[1]	94%
For patients previously treated with long term OCS, requires a major reduction 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.~~2~~[2]	77%
Improvement in quality of life (QOL) is an important part of the definition.	88.9%
A large improvement in FEV1 might be part of the definition but is not essential.~~3~~[3]	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; QOL: Quality of Life; FEV1: Forced Expiratory Volume in the first second. [1]No consensus for the duration over which this should be assessed; [2] Opinion varied on how large the improvement should be; [3] Opinion varied on how large that improvement should be, and whether an FEV1 >80% predicted was necessary.	

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~~1~~ [1] ~~No consensus for the duration over which this should be assessed~~

~~2~~ [2] ~~Opinion varied on how large the improvement should be~~

~~3~~ [3] ~~Opinion varied on how large that improvement should be, and whether an FEV1 >80% predicted was necessary~~

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TABLE 4: Delphi Round 2 results summary

Question/statement	*Agreement (% of respondents), N = 90*
Statements achieving consensus	
A person should be exacerbation free for 12 months.	93.3%
The amount of improvement in asthma control as measured by ACQ or ACT score should be at least twice the MCID[4]	70.0%
The amount of improvement in asthma control as measured by GINA score should be two levels of improvement	83.3%
Patients on long term OCS should have completely weaned off OCS, or to the point of adrenal insufficiency.	87.8%
A large improvement in FEV1, irrespective of baseline, might be one of the criteria, 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 months would be sufficient.	64.4%
A large improvement in FEV1 should be defined as 500ml (2 times the MPPI)[5]	62.2%
Require improvement across 3 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 QOL measure be used in the definition?[6]	44.4%

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[4] MCID = minimally clinically important difference
[5] MPPI = Minimal Patient Perceivable Improvement
[6] An identical % of respondents replied "possibly, but more research is needed". Further data on responses to different QOL measures and other patient reported outcomes such as work productivity can be found in the Supplementary Table E2. .

ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; FEV1: Forced Expiratory Volume in the first second; GINA: Global Initiative for Asthma; MCID: Minimal Clinical Important Difference; MPPI: Minimal Patient Perceivable Improvement; OCS: Oral Corticosteroids; QOL: Quality of Life. [4]An identical % of respondents replied "possibly, but more research is needed". Further data on responses to different QOL measures and other patient reported outcomes such as work productivity can be found in the Supplementary Table E2.

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TABLE 5: Delphi Round 3 results summary

Question/statement	*Agreement (% of respondents, N = 81*
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: a) ≥75% reduction in exacerbations b) 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%
FEV1: Forced Expiratory Volume in the first second; QOL: Quality of Life.	

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FIGURE LEGENDS

FIGURE 1: Number of Delphi panel participants in each round

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

FEV1: Forced Expiratory Volume in the first second. *If exacerbation elimination has been achieved it is not appropriate to include a 75% exacerbation reduction as an additional minor criterion. This would amount to 'double-counting', given that exacerbation elimination will always include a 75% exacerbation reduction.

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

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*A complete list of members of the Delphi Panel may be found in the acknowledgements section.

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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This article has an online data supplement, which is accessible from this issue's table of content online at https://www.jaci-inpractice.org/

DECLARATION OF INTERESTS

John W. 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 J. 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.

Michael E. 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, personal fees from Restorbio, personal fees from Equillium, personal fees from Genzyme, grants and personal fees from Cohero Health, grants, personal fees and non-financial support from Teva, personal fees and non-financial support from Boehringer Ingelheim, grants, personal fees and non-financial support from AstraZeneca, personal fees from GSK, outside the submitted work; .

David B. Price reports grants from AKL Research and Development Ltd, grants and personal fees from AstraZeneca, grants and personal fees from Boehringer Ingelheim, grants from British Lung Foundation, grants and personal fees from Chiesi, personal fees from Cipla, personal fees from GlaxoSmithKline, personal fees from Kyorin, personal fees from Merck, grants and personal fees from Mylan, personal fees from Mundipharma, grants and personal fees from Novartis, grants and personal fees from Regeneron Pharmaceuticals, grants from Respiratory Effectiveness Group, grants and personal fees from Sanofi Genzyme, 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, personal fees from Airway Vista Secretariat, personal fees from EPG Communication Holdings Ltd, personal fees from FIECON Ltd, personal fees from Fieldwork International, personal fees from OM Pharma SA, personal fees from PeerVoice, personal fees from Phadia AB, personal fees from Spirosure Inc, personal fees from Strategic North Limited, personal fees from Synapse Research Management Partners S.L, personal fees from Talos Health Solutions , personal fees from WebMD Global LLC, 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 92.61% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); 5% shareholding in Timestamp which develops adherence monitoring technology.

ABSTRACT (250/250 words)

Background: Clinicians are increasingly recognising severe asthma patients in whom biologicals 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 in order to develop 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 requires improvement in at least 2 major criteria. In the future, the SR definition should be expanded 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.

HIGHLIGHTS BOX

1. **What is already known about this topic?** Clinicians recognise severe asthma patients in whom biologicals and other add-on therapies lead to dramatic improvement, so called 'super-responders'. However, there is there is no consensus on the most appropriate super-responder definition.
2. **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.
3. **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.
4. **Key words:** asthma, biologics, asthma treatment

ABBREVIATIONS

ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
ADEPT	Anonymised Data Ethics and Protocol Transparency
AQLQ	Asthma Quality of Life Questionnaire
FEV1	Forced Expiratory Volume in the first second
GINA	Global Initiative for Asthma
GRC	Global Rating of Change
MCID	Minimal Clinical Important Difference
MPPI	Minimal Patient Perceivable Improvement
OCS	Oral Corticosteroids
QOL	Quality of Life
R1	Round 1
R2	Round 2
R3	Round 3
RCT	Randomised Control Trial
SAQ	Severe Asthma Questionnaire
SR	Super-Responder
VAS	Visual Analogue Scale
WPAI	Work Productivity and Activity Impairment

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 (583 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. Summary results were provided to panel members after each round to facilitate informed decision 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/questions to R2 and R3 based on comments received. Participants had two weeks to respond, with reminders sent when necessary.

<u>Delphi R1</u>

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 suggests 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 (1437words)

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. It should be emphasized that if exacerbation elimination has been achieved it is not appropriate to include a 75% exacerbation reduction as an additional minor criterion. This would amount to 'double-counting', given that exacerbation elimination will always include a 75% exacerbation reduction.

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 with

77% of participants agreeing that a major improvement in asthma control was essential to the SR definition. The challenge in R2 and R3 was to achieve consensus on what exactly 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 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, over 80% agreed that 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 based on our review of several Delphi studies conducted in asthma. After data collection, we became aware of a systematic review of Delphi studies which reported that 75% agreement was the median threshold to define consensus (range 50 – 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 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. 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 one another and the extent to which they predict future clinical outcomes.

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

355 research needs to focus on better understanding the patient perspective and more precisely
356 measuring QOL in SRs.

357

ACKNOWLEDGEMENTS

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.

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472 **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%
	55-64 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%
	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
OCS: Oral Corticosteroids; FEV1: Forced Expiratory Volume in the first second.	

510 **TABLE 3: Delphi Round 1 results summary**

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.[1]	94%
For patients previously treated with long term OCS, requires a major reduction 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.[2]	77%
Improvement in quality of life (QOL) is an important part of the definition.	88.9%
A large improvement in FEV1 might be part of the definition but is not essential.[3]	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; QOL: Quality of Life; FEV1: Forced Expiratory Volume in the first second. [1]No consensus for the duration over which this should be assessed; [2] Opinion varied on how large the improvement should be; [3] Opinion varied on how large that improvement should be, and whether an FEV1 >80% predicted was necessary.	

511

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513 **TABLE 4: Delphi Round 2 results summary**

Question/statement	*Agreement (% of respondents), N = 90*
Statements achieving consensus	
A person should be exacerbation free for 12 months.	93.3%
The amount of improvement in asthma control as measured by ACQ or ACT score should be at least twice the MCID[4]	70.0%
The amount of improvement in asthma control as measured by GINA score should be two levels of improvement	83.3%
Patients on long term OCS should have completely weaned off OCS, or to the point of adrenal insufficiency.	87.8%
A large improvement in FEV1, irrespective of baseline, might be one of the criteria, 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 months would be sufficient.	64.4%
A large improvement in FEV1 should be defined as 500ml (2 times the MPPI)	62.2%
Require improvement across 3 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 QOL measure be used in the definition?	44.4%
ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; FEV1: Forced Expiratory Volume in the first second; GINA: Global Initiative for Asthma; MCID: Minimal Clinical Important Difference; MPPI: Minimal Patient Perceivable Improvement; OCS: Oral Corticosteroids; QOL: Quality of Life. [4]An identical % of respondents replied "possibly, but more research is needed". Further data on responses to different QOL measures and other patient reported outcomes such as work productivity can be found in the Supplementary Table E2.	

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TABLE 5: Delphi Round 3 results summary

Question/statement	*Agreement (% of respondents, N = 81*
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: a) ≥75% reduction in exacerbations b) 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%
FEV1: Forced Expiratory Volume in the first second; QOL: Quality of Life.	

FIGURE LEGENDS

FIGURE 1: Number of Delphi panel participants in each round

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

FEV1: Forced Expiratory Volume in the first second. *If exacerbation elimination has been achieved it is not appropriate to include a 75% exacerbation reduction as an additional minor criterion. This would amount to 'double-counting', given that exacerbation elimination will always include a 75% exacerbation reduction.

Figure 1

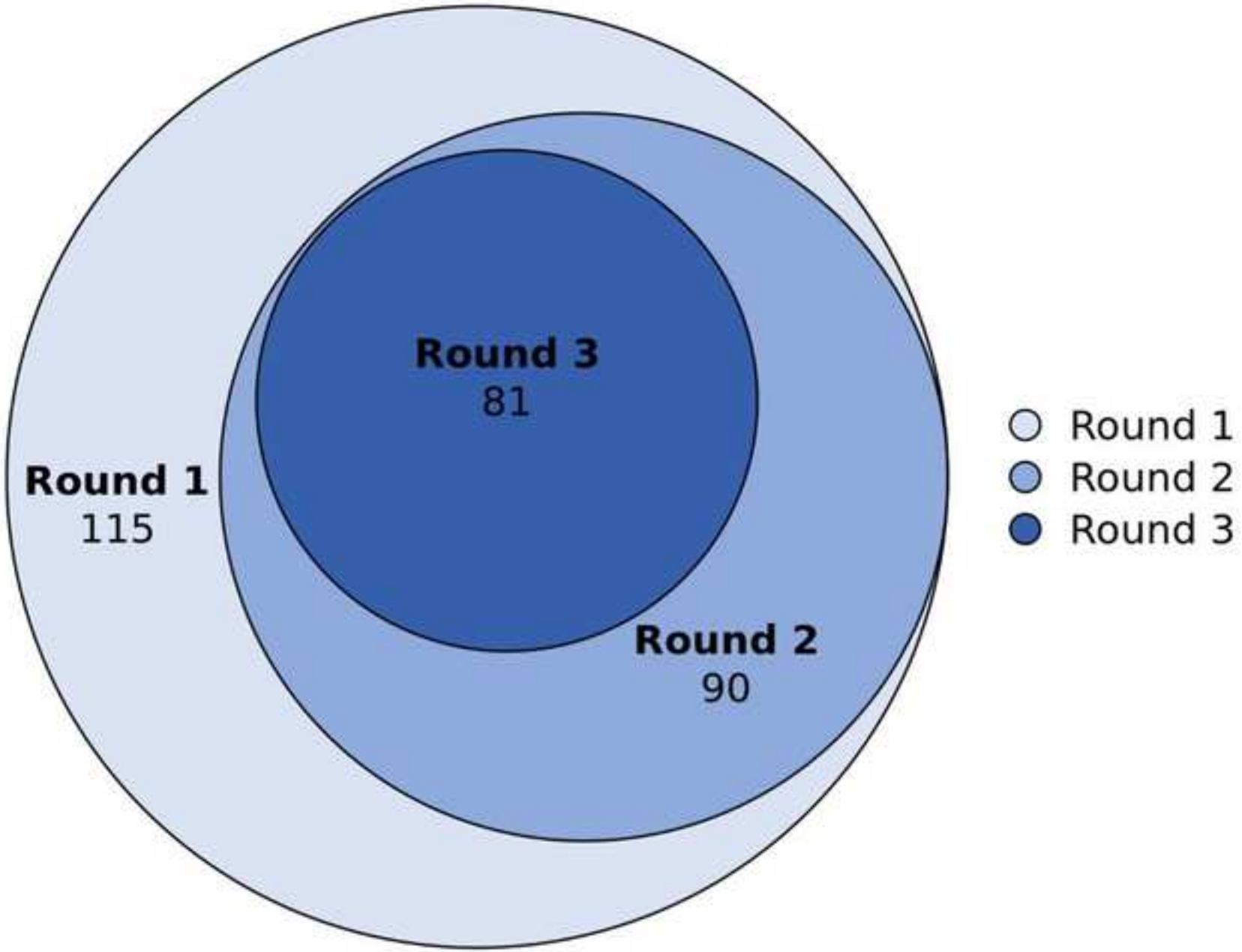
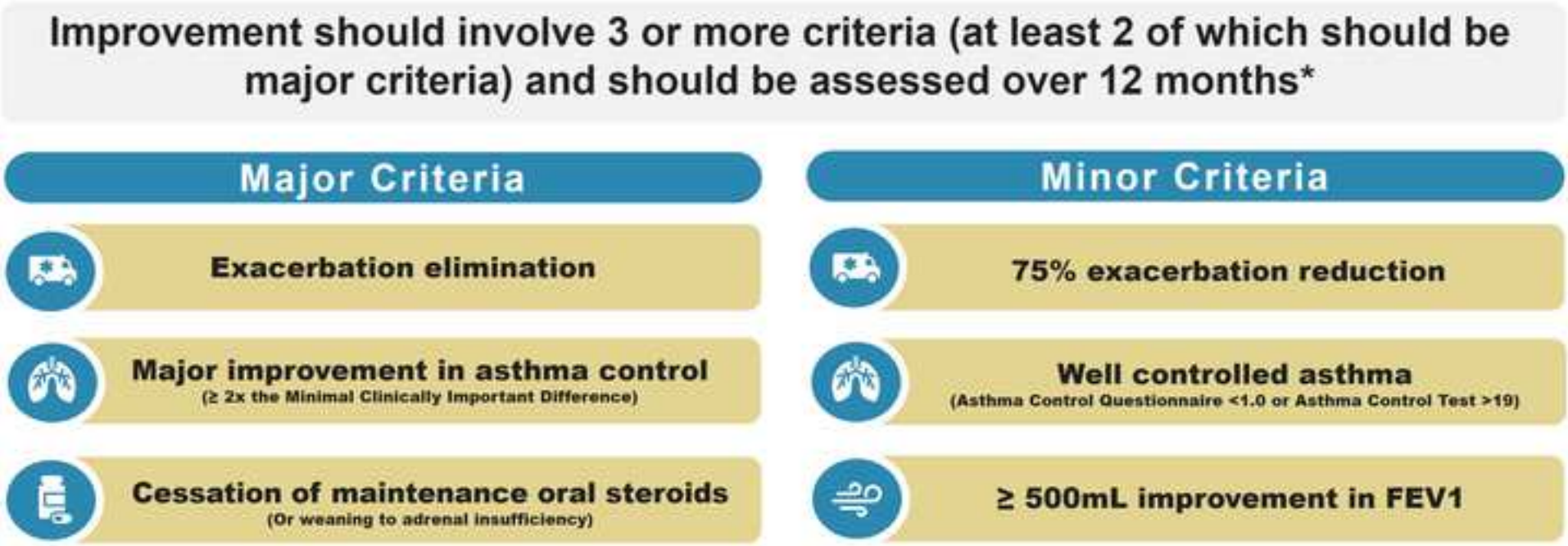


Figure No.2



SUPPORTING INFORMATION

Supplementary Table E1. Panel selection criteria

Invited panel members with appropriate expertise were required to meet ≥1 of the following criteria within the last 5 years:	
1	Experience in management of severe asthma
2	Participation in a severe asthma advisory board or national/international working group
3	Author on a peer-reviewed severe asthma publication

Supplementary Table E2. Delphi panel participants comments

Round 1	
Question	**Comments**
For how long should a person be exacerbation free to be regarded as a super-responder?	It depends on their pre-biologic state if they've gone from 6 to 2 as I have seen thats a significant response
	conditional on continued medication use
	18 months
	24 months or more
	More than 2 years
	24mths
	I think depends on how much they exacerbated before. If 4 exacerbtaion and they haven't had one in 12 months then that is significant. If they only had 2 exacerabtions then perhaps a longer period of time eg 2 years might be a more appropriate duration. So I would think at least 12 months.
	It's important to consider the severity of exacerbation rather their number
	24 months
	12 months ideally more
	indefinite
	depends on how many exacerbations they were having pre-biologic; minimum 2 months in the most severe
In relation to asthma control, consider which of the following	ACQ I think was validated in patients with mild/moderate asthma so it likely doesnt hold firm with patients eligble for biologics. Also the last question is becoming redundant with the SYGMA data. I also

statements about the definition of a super-responder you agree with. A super-responder should be defined by:	really feel the ACQ doesnt capture severe to non severe reductions in disease status. So I do think ACQ is not that reliable.
	OCS tapering/stop is a fundamental requirement to be taken into consideration
	should be any of these- not mutually exclusive
	This is fine but not sufficient to define a super responder
	PAtients can start a biologic agent with exacerbactions and mild symnptoms
	Should reflect abolition or near abolition of airways inflammation and therefore very low risk of significant disease exacerbation
	Inclusion of major improvement or even normalization of lung function (FEV1) could also be considered in the criteria for the definition.
	the criteria should be as easy as possible, that's why I would prefer to only go with the well controlled, no matter how great the improvement was, surely making very sure one starts off with a severe asthmatic patient.
	Despite objectivity of the questionnaire, symptoms could be influenced by co-existing comorbidity eg nasal symptoms / obesity / fixed airflow limitation which makes it challenging to achieve ACQ<1.0. So change in magnitude would be more appropriate.
	Lung function should also have improved if initially abnormal
	some of the mepo studies didn't show a huge improvement in the acq so I think even if they dropped their ACQ to <1 i would see that as a sign of being a great result. additionally if they are on a biologic and they drop from at least 2 to <1 , that is a significant improvement anyway.

	These questionnaires have their limitations, particularly ACQ, not developed for severe asthma, largely for allergic asthma, which severe asthma is usually not
	some super responders still score highly due to poor specificity of some questions
	the quantification of large improvement would be the challenge
	A super-responder should be someone who started out with significant symptoms with dramatic improvement on the biologic agent.
	To me this definition also needs to incorporate exacerbation burden.,
	Large improvement in control must be defined espacially if the pt is just well controlled
	In most cases I would describe as super responders we have seen a dramatic improvement in ACQ but in those with longstanding fixed airflow obstruction they may still be limited in activities with breathlessness on exertion despite an otherwise life-changing response.
How do you usually assess asthma control in your severe asthma patients?	SNOT-22, St George
	both ACQ and ACT
	mAQLQ
	CARAT
	both ACT and ACQ
	Oral corticosteroid dose per year (mg)
If a large improvement in ACQ score should be part of the definition of a super-responder, how large should	Maybe combining improvement of >50% AND the score < 1
	care needs to be taken in interpreting this as a stand alone: an improvement of greater than one may be achieved simply by performing a review prior to initiation of therapy

that improvement be? Bear in mind that the minimally clinically important difference (MCID) in the ACQ score is 0.5.	would use absolute score
	This depends to some extent on what the startoing position was and the pre-existing rate of exacerbations. therefore freedom from exacerbations may be required for a patient with only a low starting ACQ
	it depends where they start: some have low symptoms but still exacerbate. So I think 0.5
	more the final number than the change
	> 0,5
	ACQ<1 irrespective of initial plus min improvement of 0.5
If a large improvement in ACT score should be part of the definition of a super-responder, how large should that improvement be (bearing in mind the MCID is 3 points)?	3
	ACT should be 20 or higher
	Passing from uncontrolled to controlled in the quicker time and maintaining for 1 year
	depends on their baseline ACT
In patients who were on long term oral corticosteroids (OCS) prior to commencing a biological or other targeted therapies, which of the following statements should form part of the definition of a super-responder?	Super responder to me does mean a complete wean off OCS.
	Either 100% reduction or lowest dose possible due to AI
	Unless they have adrenal insufficiency
	anything less than 100% is simply down titration to the lowest dose of ICS which maintains control
	wean down to minimum "adrenal replacement dose" i.e. 5-7.5 mg pred/d
	unless the patient has a secondary adrenal insufficiency (after complete withdrawal of OCS), implicating a need for chronic treatment with hydrocortisone as substitution therapy (but not for asthma)
	Many other factors like a city hospital admissions or hospital visits

	Implies that response has obviated the need for steroid treatment which is always no more than partially efficacious
	often cannot come completely off if have been on for many years
	Completely weened OR on systemic steroids due to HPA axis suppression
	if only 75% or less OCS reduction, it is a responder, but not a super-responder.
	if steroids cannot be completely withdrawn and need to be kept exclusively due to adrenal insufficiency even 4-5 mg may be aceptable
	Complete withdrawal may not be possible to due adrenal suppression, hence not necessary the exclusion criteria for super-responder
	often unable to wean below 5mg due to adrenal suppression
	100% reduction may not be possible due to adrenal insufficiency
	Except if they require OCS for adrenal insufficiency ie those on OCS for adrenal insufficiency only but not for asthma can also be super responders
	ideally weaned off
	In most cases this is a complete weaning off OCS but this can be limited by adrenal insufficiency so difficult to mandate a 100% reduction. I would suggest a complete weaning off OCS for their asthma.
	100% or 75% depending of the initial dose and the duration in year of ocs
	Not completely as still may have exac that are easy to control but need OCS
	If they are clinically much improved, then even a 50% reduction would be good. The reduction should be taken in context of how they are doing clinically
	Well established in other disease groups that RAI is not a marker of treatment failure.

If a person were unable to completely cease OCS because of adrenal insufficiency, would it be reasonable to define them as a super-responder, provided other criteria had been met, and provided there had been a major reduction in OCS dose?	In this other criteria, tests or investigation to identify clear patients with adrenal insufficiency should be addressed
	This inability to completely cease OCS should be documented as due to clearly adrenal issues (an extra-pulmonary reason in this context). Moreover, the patient may have whatever non-respiratory reason that necessitates treatment with OSC.
	Adrenal insufficiency is transient. I have not known of continuous AI, it only obliges the treating physician to taper slowly, but complete stop of OCS after 2-3 months should not be detained by AI.
	I would consider switch patient on mineralo only steroids to access weather I can wean patient completely off the gluco part of it
	at least 50% steroid reduction
	depends on time frame - with long slow wean (years) may be able to completely come off pred
	Generally pass to cortone acetate
	I would advice not to consider rare conditions (as adrenal insufficiency) in the major definition criteria of a super responder
A large improvement in quality of life (QOL) should be part of the definition of a super-responder.	ACQ is partially effective on this item
	it is quality of life which affects patients most
	QOL is difficult to capture; the current tools such as ACT and ACQ are imperfect. If the patient describes his / her evolution as "spectacular" or "phantastic", no need for questionnaires and MCIDs.
	This is the most important outcome measure to define a super-responder IMO. It has to be from the patients perspective.

	Since exacerbations most strongly impact on any asthmatic's QOL, and reflect the amount of inflammation in the airways, the two go hand in hand.
	At present, the use of QOL is limited to research centers, and not widely used in clinical practice. In such case, symptom control and improvement seen in super responders are captured by ACT, ACQ
	QOL can be dependant on co-morbid disease function
	A doubling or even tripling the MCID would be needed to satisfy the definition of a super-responder (as it was the case with the ACT score improvement).
	Quality of life specifically due to asthma is difficult to assess in these patients as imparied quality is usually related to the adverse effects of steroids. Thus a non-disease specific QOL tool such as SF-36 should be employed along with an asthma QOL tool
Should other patient-reported outcomes be part of the definition of a super-responder?	Yes but to be honest this is a space which needs serious attention and novel thought.
	asthma-related limitations in physical acitivity
	But we do not have yet a validated one to be used in clinical practice
	?SAQ
	perhaps relating to ability to work or not have activities impaired
	Medication usage/reduction
	Self-evaluation of the evolution / control of asthma by the patient (using a VAS)
	Definitely, as other aspects
	The Severe Asthma Questionnaire
	less use of reliever therapy improvement in lung function

	Hospital/ ICU admissions as most observed cases of super responders in our cohort had aggressive history of hospitalization
	ability to exercise and terminate sickleave
	The super responders will often give very positive reports about the effectiveness of the mAb
	1) Lung function improvement (previously mentioned; 2) positive changes in the biomarkers: e.g. peripheral or sputum eosinophil depletion etc.
	going back to work full time
	A simple VAS-scale could substitute more complicated QoL measurements, or may be the miniAQLQ. 15 questions, patients like to do it, because the improvement is marvelous.
	Pulmonary function increase above 300 ml in FEV1s Being able to almost not need SABA rescue
	Use of SABA medication
	Could consider additional responses in chronic sinonasal diseases
	Potentially life style issues such as being able to return to work, resume previous activities etc
	?FEV1 (we have seen some amaing responses to FEV1)
	Patient reported SABA use to be considered
	I think the patient rated response to therapy ie their impression of how well they are doing should be included as part of the responder definition. Most of these patient report remarkable improvements.
	Efficacy drug also on major comorbidity
	improved biomarkers
	Improvement of comorbilities

	Possibly - reduce inhaled meds significantly
	difficult to capture in a clinical setting
	Pulmonary function tests improvement Health Care resources reduction
Please list which patient-reported outcomes should be part of the definition of a super-responder?	ACT, ACQ or some other tally of symptom control. And, of course, patient-reported exacerbations (or the lack thereof).
	OCS, Quality of life scoring, ED/GP visits, macroeconimic costs,
	mMRC, AQLQ, WURSS-21
	Symptom score, quality of life, limitations in physical acitivity
	See above
	WPAI
	ACQ-6, AQLQ, SAQ
	Medication usage/reduction
	Self-report and evaluation of the response by the patient as "excellent" or at least "much better".
	Hodpital admission OCS reduction
	Not only systemic OCS reduction, also ICS/LABA/LAMA reduction Also health care contact # during the past year Improvement in lung function
	SAQ

	severe exacerbations (hospitalizations, ER visits, use of OCs), symptoms control (ACT), lung function, quality of life, reduction of chronic OCs
	Hospital admissions, ICU admissions, near fatal attacks
	AQLQ
	Pulmonary function test data. Use of rescue medication
	exercise ability and sickleave
	Since commencing treatment my asthma is 1) Much worse 2) somewhat worse 3) about the same 4) somewhat better or 5) much better. I use this self-reported as part of AMR and all the super responders choose 5)
	increase in everyday activity
	Exercise tolerance Weight loss Sleep quality Return to work/activities
	Improvement in symptoms, as well as PROM scores: e.g. St George Respiratory Questionnaire (SGRQ), EQ-5D for health-related quality of life etc. Doubling or tripling the MCID (if the latter exist validated).
	Validated ones
	going back to work full time or even part time if had been on disability

	Ask the patient if they feel markedly improved, moderately improved, slightly improved, no change or worse. Ask patients if the add on therapy has transformed their asthma - SA, agree, neutral, disagree, SD
	ACT
	GINA, VAS, (mini-AQLQ)
	AQLQ ACT
	Improved QOL.
	improvement in LF particulalry in PEFR variability
	Use of SABA
	return to work Return to sport / exercise patient satisfaction assessment
	lung function, and improvement in biomarkers (could be both FeNO and eosin)
	definitely exacerbation frequency symptom control
	questionnaires related to steroid adverse effects
	AQLQ/SAQ and potentially WPAI or equivalent
	Significant reduction in symptoms Ability to undertake activities that were previously limited

	no daily symptoms, no exercise related symptoms, no exacerbations for 12 months at least
	some patients although they don't have an improvement in their ACT stated that they were able to claim stairs, walk for a prolonged distance and even run for the first time in many years after starting biologic. These parameters are not measured in ACT and others.
	Patient reported SABA use (inhaled and/or nebulized)
	ACQ/Work,productivity/SF36
	QoL, exacerbations, medication use
	Asthma control Number and severity of exacerbation Reduction >75% of oral CS dose Improvment of comorbidity
	self-reported symptom burden, functional capacity.
	improvement in sinusitis symptoms Decrease in sputum Improved exercise tolerance
	Blood/sputum Eos if anti-IL5 Improvement in allergic rhino conjunctivitis is on Omalizumab + ideally reduction in Eos
	Abily to perform previous actities interrupted because of uncontrolled severe asthma Reduction of BMI because of more exercise and less OCS
	Improvement rinitis or sinusitis Improvement physical exercise

	Infrequent requirement for SABA
	large increase in ability to perform physical exercises, climbing, bush waking swimming,tennis
	physical activity improvement, reduction of symptoms, AQLQ
	Use of rescue meds Activity
	consider CAT
	AQLQ or mini AQLQ
	Diurnal and nocturnal Symptoms (control) Use of rescue medication Self- prescribed systemic corticosteroids Laboral absentism due to asthma
A large improvement in FEV1 is an important part of the definition of a super-responder.	not only abolute value in FEV1 but, more important, the full recovery of reversibility after bronchodilation test
	As surrogate mater of modulation of airways remodeling
	May have fixed airflow obstruction
	young folk with severe disease may have normal or near normal lung function
	Is a secondary criterion.
	Not all superresponders have an improvement in FEV1 , include as a secondary outcome not primary outcome (also depends on the type of biologic used)
	A degree of permanent airways obstruction owing to remodelling changes may prevent full reversal of the FEV1 but still reflect an excellent reversal of the ongoing inflammation

	I have not seen it in my cohort, thus can not comment on including it in the definition
	depends on the baseline FEV1
	I think this is a sub-group of super responders. I have plenty of people who have had major QOL & ACQ responses and exacerbation free as well as off maint OCS who have had the minimal FEV1 improvement of 100-200ml. The ones that have significant improvements in lung function are a bit rarer
	In severe asthma, obstruction in spirometry may be irreversible at least partly.
	Although I do strongly believe exacerbation rate is prime, followed by patient related outcomes, we cannot leave lung function out of the equation.
	this should be defined as an increase of 300 ml or more and / or 20 % or more from baseline
	If abnormal to start with
	Unless previous FEV1 was not very significantly impaired
	Most patients do not have a significant change in FEV1 or have preserved lung function to begin with therefore I don't think this should be included. Symptomatic improvement is often completely discordant with changes in lung function as well which is another reason not to include lung function.
	FEV1 may be relatively preserved, albeit at the cost of chronic steroids. If the biologic allow for tapering of steroids while maintaining FEV1, that patient should still be considered a super-responder.
	If lung function is reduced, ie < 70%, a clinically relevant increase in FEV1 seems important
	In those with persistent variability and reversibility pre-treatment I would agree.
	As the initial fev1 is not a criteria for all biologics consider it as an additional minor criteria
	A large improvement of FEV1 should be considered only in patients without indirect signs of remodelling and not be part of the super-responder definition for all patients.

	Only as an "or" statement - so, if someone has a huge improvement in FEV1 but doesn't quite meet other criteria, they might still qualify as a super-responder. But, an increase in FEV1 should not be required for all.
A large improvement in FEV1 might be part of the definition of a super-responder but is not essential.	if have improvement in other domains
	maintenance of an "acceptable" FEV1 value with dyspnea not being disabling ?
	If significant bronchial obstruction persists, the patient should not be classified as super-responder.
	asthma is a multifacetted disease: response to therapy will need to be measured in a variety of ways of which FEV1 is one
	See previous comment.
	1) it should be FEV1/FVC, and 2) the large improvement only counts for those starting off very low. however, there are severe asthmatics -more so in children- with frequent exacerbations, but not too back LFT in-between acute asthma episodes.
	Perhaps this is better as significant improvement in FEV1 is not as common as other outcomes.
	If not a LARGE improvement, it should be essential at least a MCID
	especially for those with normal lung funciton to start with (brittle asthma is still important)
	this is a reasonable criterion but depends largely on the reduction of the frequency of the exacerbation unless the patient has airway remodeling
In relation to improvement in FEV1, consider which of the following statements do you agree with. A	any of above
	I think we shouldn't consider % predicted but % best personal value
	Patients can (rarely) start a biologic agent with normal pulmonary function

super-responder should be defined by:	in patients with long standing disease and significant airways damage, achieving >80% may be an impossibility
	Patients with long-standing (severe) asthma might never attain normal lung function (FEV1). e.g. impaired lung growth in childhood due to (severe) asthma
	Not to be used as a primary outcome, FEV1 may not define super responders
	In a 6 months period of time
	There may be a dramatic response on reduction of exacerbations and per oral glucocorticoids but change in FEV1 may be minimal.
	See previous comment - I think having multi-dimensional components in the definition will lead to complexity - the definition should be based on steroid reduction (maintenance treatment / exacerbation reduction) and asthma control
	would prefer FEV1/FVC (e.g. in my home town at 2000m height, quite some have personal best for FVC of 120%.... so the ratio is a better indicator for airflow obstruction than the FEV1 by itself). Now... it is also true that in severe asthma FVC often goes down probably because of distal airway closing, and then the relation tends to normalize again, though this is not a good sign.... ups, what to decide best. Sorry to be confusing, but these are my thoughts. If you want to stick with FEV1: then consider instead of predicted 'personal best'.
	A patient who has remodelled airways may improve 30 % or 600 ml and not be still completely normal but undoubtly is a super-responder
	Super responders might only have minimal improvement in FEV1

	I would want to say large degree improvement in FEV1 even if <80% but not sure what that degree would be. ?An arbitrary number.
	I would not include an FEV1 criteria, however if we do then I pick the improvement in FEV1 regardless of whether lung function normalizes
	Do not think FEV1 should be part of this criteria
With which of the following statements do you agree? Major improvement or elimination of exacerbations is:	I think defining elite responder in such binary terms is too difficult to get too.
	Exacerbations most closely reflect uncontrolled airways inflammation
	To me the most important.
	super responder should have response in almost every domain considered . exacerbations , FEV1s, PRO , control etc .
	In an OCS-dependent patient who is no longer exacerbating frequently because he/she is on chronic OCS, getting the OCS off or down may be the main driver behind starting a biologic. So, they may show a decrease in OCS as their responder criteria rather than decrease in exacerbation.
With which of the following statements do you agree? A major reduction or cessation of long term OCS is:	Unless dependent on systemic steroids and cannot stop.
	I would consider someone who becomes less symptomatic or asymptomatic but is unable to significantly reduce maint OCS as a partial responder
	Depends whether the patient has been titrated down previously and will take some time to proceed to steroid cessation
	For the definition of a super-responder

With which of the following statements do you agree? A major improvement in asthma control is:	This issue arises repeatedly. A super-responder should be symptom and exacerbation-free with normal or nearly normal lung function in the absence of systemic corticosteroids. It doesn't matter whence the patient has come but arriving at this destination defines a super response.
	Asthma control as measured by the current imperfect PRO tools (ACT and ACQ).
With which of the following statements do you agree? A major improvement in QOL is:	Quality of life can be affected by comorbidities.
	As reported by the patient Do not use the AQLQ! which is skewed towards allergen-driven symptoms, whereas more than 50% of adult patients with late-onset severe asthma are not allergic; therefore, the AQLQ questions do not capture the full improvement of QOL in these patients.
	QoL most closely reflects the frequency and severity of exacerbations which in turn reflects the amount of airways inflammation
	Co-morbidities. Colonised lung disease and/or ABPA remain symptomatic but less exacerbations and Tx burden
	There may be other factors in the short term compromising QOL
With which of the following statements do you agree? A significant improvement in FEV1 is:	Not essential. Important but need to be aware of ARM.
	Reduced FEV1 may be partially reve owing to airways remodelling changes
A definition of a super-responder should be based on evidence of improvement across at least two domains.	Based on the improvement across ALL the essential domains.
	Exacerbations and OCS use
	Abolition of exacerbations is the key outcome
	Why not even across at least three domains?

	Two DEFINED domains - steroid exposure and symptoms
	Suggestion: maximum 1 exacerbation (not severe) over the past 12 months, and evidence of improvement across at least 2 of the other domains (GINA, LFT, QoL or VAS).
	I think the improvement should be in every domain
	I think it has to be at least three domains - typically exacerbations, OCS use/exposure and control/QOL. Lung function is not as important. Improving in 3/3 or 2/2 domains that pertain to the specific patient is essential. All domains should universally improve. I usually also include SABA use as one of the things I follow. Partial responders improve in some but not all domains. The bar should be higher for super responders. Remember this should entail a nearly miraculous response to therapy.
	At least 3
Round 2	
A definition of a super-responder should be based on evidence of improvement across how many domains?	I think we can rank and score each domain e.g. a reduction in OCS is arguably superior to FEV1 improvement. Rank 1: exacerbation reduction and/or OCS reduction Rank 2: asthma control and/or quality of life Rank 3: FEV1 / FENO improvement and each has its own score.
	Not more than 5.
	Think 2 and probably needs some form of hierarchical thinking - oy experience is that when the key targets of steroid reduction and exacerbation reduction are completely met, many of the other domains align

	Exacerbations, off maintenance steroids, and major improvement in asthma symptoms control
	The definition should encompass several domains: OCS use, severe exacerbations, bronchial obstruction and PRO (symptoms, mainly).
	Asthma exacerbations and asthma control are sufficient
	Surely this depends on how many domains had the capacity for improvement?
	I think that asthma exacerbations and control are key domains that must be met. OCS reduction is also very important, but not defining.
	At least 2 domains
	Exacerbation plus one of symptom control, asthma-related QoL or functional capacity, and FEV1
	two or more
	the three domains of asthma exacerbations, OCS use (or Maintenance therapy reductions), and QOL are major aspects that are appreciated and felt by patients for improvement
	at least exacerbations, control and QoL
	A suggestion: we could establish major and minor criteria: superresponder is 2 major criteria or 1 major and 2-3 minor Major = 1) ≥90% reduction in severe exacerbations 2) Weaning off OCS (or till adrenal insufficiency: this should be clearly defined how to suspect and confirm that) Minor = ≥75% reduction in severe exacerbations, major improvement in asthma control, in QoL, in FEV1 or major reduction in controller therapy Be careful to define exacerbations well, we had a long discussion here, to not confuse between a flare of asthma symptoms that can easily be controlled by SMART approach, and asthma crisis (aggressive rise

	in symptoms, not controllable with simple rescue therapy, needing OCS or hospitalization). Exacerbation is then used to cover all this, the first part is a 'mild exacerbation' and the last 'severe exacerbation'. We decided we prefer to call the second one: asthmatic crisis, so we all know what we are talking about, and also for non-specialists to not confuse when to apply SMART and when not.
	To be a super-responder my feeling would be there should be a significant response across a borad range of outcome measures, hence three or more
	For example, steroid and exacerbation elimination should be enough to define a super-responder
	The outcomes might be inter-related, eg.less exacerbation or less symptoms and therefore less OCS and better QoL
	the maintenance of a small dose of OCS does not configure a super response.
	Reduction in exacerbations, reduction/ elimination in OCS and improvement in QOL in my opinion are the main 3
	Not convinced all domains carry equal significance and perhaps more relevant to split into essential (exacerbation or OCS reduction) and supportive (ACQ, SAQ, FEV1) criteria.
	Besides the clinical criteria (exacerbations reduction, OCS elimination, asthma control) it would be desirable to include one biological (blood, sputum Eos reduction, FENO in dupilumab). According to this, 1 biological and 2 clinical criteria.
	Two domains would cover patients with fixed airway disease and/or colonised lung disease, other comorbidities that could cause symptoms scores to be elevated.
	reduction in SABA requirements,major improvement in QOL and decreased use of OCS.
	super responder in the area of severe asthma is really about oral CS / asthma control / QoL

Even if someone has not been completely exacerbation free, should a 75% or greater reduction in exacerbations be sufficient to classify someone as a super-responder?	A surprising number of these statements refer to the magnitude of change from baseline. For me, the definition of "super responder" has more to do with the outcome achieved and not the magnitude of change. It is, after all, the clinically important result. If the patient has no asthma-related symptoms, few or no exacerbations (0 is not reliably achievable because it's hard to account for random viral URI's) and normal lung function, I will continue with the current strategy. But if there is a persisting symptom or exacerbation tendency, I might still change therapies no matter how great the improvement from baseline has been.
	This is clearly a responder but the term super responder should be reserved who do extremely well - ie systemic steroids no longer required (allowing for HPA axis suppression)
	Super respondents should be exacerbations free (90% reduction)
	A super-responder should be free of severe exacerbations. Maybe we could tolerate occasional severe exacerbations related to, for instance, bronchial infection.
	I think it depends on the number- 4 to 1 a year would be impressive.
	Only if exacerbatios are< 2 per year
	I think this depends on the time frame you are referring to.
	I think if someone exacerbates (especially moderate / severe exacerbation) even once a year that person is not a 'super' responder, Super-response should be like water on fire.
	may be in a 6 month period of evaluation, but in a 12 month it should be 100% free
	I would consider a 75% reduction to be not far of the reduction we saw in the clinical studies. Should super-response be a good way beyond this?

	In some ways this may be a reflection of how common do we think a super-responder is - if it is really rare then complete freedom from exacerbation is probably the way to go.
	A decrease from 4 exacerbations to 1 exacerbation is reasonable to classify as a super-responder on further reflection
	It depends on baseline exacerbation rate eg. 2 per year with OCS burst to zero exacerbation vs 5-6 exacerbation per year down to 1 per year. I would argue the later is just as important.
	it depends on the frequency of previous year , if someone goes from 8 to 1 is a superresponder for example
	could be a responder but not necessarily super
	I agree since in most of the studies, exacerbation reductions ranges around 70%
	There is no evidence biologics can prevent AHR from occurring - my real world experience is that patients on biologics are all susceptible to viral AE
For how long should a person be exacerbation free to be regarded as a super-responder?	I think that 12 months should be enough but it should be from month +6 to +18 of first dose. A severe Asthma patient can have a severe exacerbation during the first month when medication is just starting to act.
	12M is the most accepted look back period for exacerbation and includes all four seasons (shorter periods become season dependent).
	I am not convinced that every exacerbation needs to be eliminated
	Longer periods may be desirable but many payors will be looking for a trial off treatment to check for spontaneous resolution after 1 year: an exacerbation my thus be induced by purposeful withdrawal, although exacerbations in this context could be excepted

	Annual rates allow better comparison with other therapies
	If a 75% reduction in exacerbations is enough, a long period of being exacerbation free is not needed to be a super responder.
	More than 12 months it´s not necessary since the behavior of asthma is seen in a 12 month period
In relation to asthma control, a super-responder should be defined by having:	I don't like either of these options. My preferred answer is an ACQ less than 1. Period. If the patient started at 1.3, the magnitude of change is small but I can't ask for much better than an ACQ of 1. As in my previous comments, it's the destination and not the journey that makes up my definition of super responder.
	Same argument as for definition - we are trying to define those specific patients who fixed with these therapies - clearly others are responders but not super responders
	To be considered a super-responder a patient must be able to live without limiting symptoms. The magnitude of the response is not so important. The goal is to maintain symptoms well-controlled.
	Some of my patients have ACQs on average of 4-5; therefore a reduction to 2 in 6 months for example is excellent. Again I think this depends on the time frame you are referring to. I think in 12 months you would need both ACQ<1 and large improvement, but within the first 12 months I think it is reasonable to have either.
	This is tricky and depends on the other domains that go into definition of SR. If the main criterion is exacerbation, then EITHER here can be a good secondary criterion. But if we look at control only, It becomes illogical to classify someone as SR if they had ACQ<1 before AND after treatment.
	Either option will entitle centers and physicians not relaying on ACQ measurements, as well
	two domains!

	should define what is a 'large improvement'
	Again think if we are talking about super-responder we need to be looking for a response above ad beyond, therefore we should be taking someone with poorly controlled symptoms and getting rid of them. Hence ACQ <1 and large improvement
	Magnitude of response depends on baseline ACQ. Usual response is defined by changes required for continuation treatment based on local criteria. Super responders defines those with superior response so it should be well controlled asthma in someone with very high symptom burden prior to initiating biologic
	the option B cound mean that a patient started treatment from a partially controlled to a controlled point. But partial control in not a criteria for severe asthma
	ACQ <1 is a more objective indicator than "large" improvement, control by ACQ is defined <1.5 so, a super responder would be that patient reaching <1
	Pts with pulmonary comorbidity & extra-pulmonary comorbidity that can influence symptom scores will not have a ACQ < 1
If a large improvement in ACQ or ACT score is part of the definition of a super-responder, how large should that improvement be?	I would to see an ACQ of less than 1.5 (regardless of magnitude of improvement). Super respondents should be symptoms free or very largely reduce (minimum)
	Again, it is not so important the magnitude of the response. It is essential to keep the patient free of symptoms. For instance, if a patient improves ACT from 9 to 18, this patient remains uncontrolled and, in consequence, an eventual switch should be considered.

	ACT score should not be used as it also asks for patient's self reported perceptions of asthma control which can be misleading I wouldnt use this as a measure at all
	Again this is important in relation with the other dimensions of the definition of SR.
	ACQ - though this questionaire only validated in mild asthma patients and still includes ventolin as rescue medication. This may need revising with ICS/LABA PRN using increasing.
	We are not speaking about responder, but SUPERresponder.
	2x MCD is likely too small of a difference but 4x would be hard to operationalise (particularly with ACT), so 3x is now my choice
	2 or more
	Large improvement shouldn't be included because if a patient has an score of 6 points, if you want to be very strict requiring 4 times the MCID, that would be 2 points of improvement, in that case the ACQ after treatment would be 4, the patient would remain uncontrolled
	equal or greater than two times the MCID
	I feel an improvement measured in a percentage of commencing score is a better marker of improvement
What level of improvement in GINA score would be sufficient to define a super-responder, on the basis that anyone receiving a biologic will be uncontrolled (GINA levels of asthma	GINA might not be sensitive enough to separate super responders from a positive but non spectacular improvement
	I'm not convinced this is a good outcome measure to assess response to biologics at all.
	Again, the definition is about what is achieved, not the magnitude of change.
	Again, it is not so important the magnitude of the response. It is essential to keep the patient free of symptoms.

control are uncontrolled, partly controlled and controlled)?	Again depends on the room for improvement
	Again this depends on the time frame. I would accept one level for the first 12 months but 2 levels after that.
	One level can be enough IF control is the second dimension, Otherwise two level (i.e., everyone should be fully controlled)
	I do not think the GINA control level is sensitive enough. I would not include the GINA control level as criterium
	Practically, two levels of improvement would mean uncontrolled improving to controlled
	GINA levels less practical in day to day practice compared to the scores from ACQ or ACT
	Usually a patient candidate to a biologic treatment is uncontrolled, so, to be controlled that would be 2 levels of improvement
	I find GINA to be somewhat unspecific
In patients who were on long term oral corticosteroids (OCS) prior to commencing a biological or other targeted therapies, should patients have completely weaned off OCS (i.e 100% reduction), or to the point of adrenal insufficiency, to be defined as a super-responder?	In a patient under a monoclonal antibody, a complete weaning of OCS is essential. If that is not possible with a particular mAb, then we have to consider switch.
	as some patients will not wean for reasons other than asthma control
	"To the point of adrenal insufficiency" will need to be defined
	Maintenance OCS for asthma is not evidence based and associated with severe adverse effects and increased mortality
	completely agree, biological treatment should try to reach 100% of reduction or to the point of adrenal insufficiency
	It seems clear to me that biologicals are measured in their effectiveness as a steroid sparing agent

	50% or greater reduction sufficient
	Definition of "to the point of adrenal insufficiency" should be given
In relation to improvements in quality of life, should a quality of life measure be used to define a super-responder?	This is a key patient centred outcome measure, perhaps most important to patients
	If easy to use and is validated
	Given we can capture QoL properly in real-world practice
	I agree with the notion that Qol measures do not have strong signal to noise ratio here. The focus should be on exacerbation, control, and potentially FEV1
	QoL is very important and should be included, but not so easy to measure. Questionnaires are quite long and most protected $$.
	quality of life evaluation isn't more powerful than control questionnaires and it is time consuming
	Too much cross over from comorbidities
Would it be appropriate to use the Asthma Quality of Life Questionnaire (AQLQ - 15 questions) to assess quality of life in patients?	the AQLQ is not designed for severe asthma.
	Reasonable to measure this but should not be part of definition
	Quite long, shorter QoL instrument would be preferable
	think that sgrq would be more sensitive
	exactly, I think this is the most suitable one.. or the mini-AQLQ?.
	More research is needed with respect to AQLQ utility in defining superresponders
	It’s not well validated in severe asthma
	shows low sensitivity to changes
	Only for research purposes
	As a research question - yes, in clinical reality it is an expensive exercise

	sure, but i dont believe AQLQ should be part of evaluation
	most of the improvement in quality of life is due to the weaning off of prednisone and less side effects from steroids which is not captured in asthma quality of life questionnaires
	SAQ should be used
Would it be appropriate to use the Severe Asthma Questionnaire (SAQ) to assess quality of life in patients?	The SAQ has been developed specifically for severe asthma patients
	The evidence of compelling difference from AQLQ remains to be further evaluated - and at this stage should not be part of definition
	after validation of the SAQ
	The SAQ is relatively new and needs more validation
	probably this might be the best tool, as it is specifically designed for severe asthma. I have no experience with it, though.
	Appropriate to use but no established MID so agree further research needed.
	Not a more robust indicator than ACQ that is more universal and easy to apply
	Would probably be more accurate than using the ACQ which does not capture SA symptoms particularly well however PBS requires ACQ
If a large improvement in quality of life score is part of the definition of a super-responder, how large should the improvement be?	Same comments. It's not the magnitude of change.
	don't think should be part of definition
	A larger multiple of MCID I think would be necessary for a quality of life metric
	equal or more than two times the MCID
	Match symptom score - however a percentage of commencement score improvement would be better
	simple and easy to use with a wide scale

Could the Global Rating of Change (GRC) scale be a useful tool in defining a super-responder?	The GRC would need more research in severe asthma
	risking of using to many scores, we use the Euro Qol healthscale (VAS)
	cant rely on perceptions
	Never heard of this scale, I think I am not the only one
	Subjective ratings like GRC are at the risk of placebo effect and heterogeneity of the feeling of improvement which varies fro individual to individual.
	agree it would be useful in combination with other measures, depending on its validity
	This sounds very subjective - which is absolutely correct as it is the patient's view which is key - however there is a strong placebo effect which may confound this? If we are dealing with super-response should we more objective
	it is a useful parameter but may depend on patient's perception that can be altered
	May have a role alongside other measures but highly subjective.
	Even when it would be also an indicator of failure, it is an scale not used in pivotal studies, so more research would be needed
	Not familiar with GRC to comment
	all measures are a rough estimate of what is important
Could the Visual Analogue Scale (VAS) be a useful tool in defining a super-responder?	A VAS is less sensitive than a Borg scale. The SAQ global score uses a Borg scale so the addition of a VAS would add no value.
	Is it validated in severe asthma?
	Very generic instrument, not able to merely capture asthma symptoms

	I think I prefer the specific questionnaires. As we shall have no placebo-group to compare against,I am afraid these general/global scoring systems shall be very sensitive to bias: one HAS to feel better when using a very costly treatment.
	Similar comments to the GRG
	patient perception may alter the response
	Potentially if used as supportive information alongside other metrics.
	it´s easy to apply and easily available
	VAS is a useful response tool for specific questions so its benefit would be dependant on the question using the VAS
	stick to objective criteria!!!!
Work productivity was suggested as a potential area for evaluating super-responders, do you agree (using the Work Productivity and Activity Impairment (WPAI) questionnaire as a potential instrument)?	WPAI may be a helpful outcome measure but I'm not convinced it should form part of the definition of a super-responder.
	Many barriers to this area some of which are disease related and others not - should not be part of definition
	No, this tool is relevant, but has not been validated to capture specific changes in asthma control and is probably not sensitive enough
	Very difficult to measure productivity loss accurately and it will be an equity challenge given that not everyone is working (or working full time). Work time loss is also affected by the specifics of work environment (e.g., whether the individual can work from home etc affects their time loss).
	This is a parameter that we are keen to see improve and would be of interest topayers

	an important aspect of impairment of the severe asthmatic patient, with economic consequences. Important tool in our discussion with authorities to get more budget assigned to severe asthma.
	Potentially this may have a role
	I don't think it needs to be included in the definition of a super responder; it can be used clinically when assessing response to biologics
	Agree useful if used as supportive information alongside other key metrics but should not be used in isolation to defund a super responder
	Not validated in every country, wouldn't be applicable in developing countries
	The damage to work productivity in severe asthma was done many years prior to commencing the biological. Some of my patients have entered the work/study arena but most have long since stopped looking for employment
	but of course only in workers !
Consensus was reached in round one that a large improvement in FEV1 might be one of the criteria used to define a super-responder. What is the appropriate definition of a large improvement in FEV1?	Think this is very vague - depends on starting point, degree of fixed airflow obstruction and other factors - having a cut point is fraught with challenges and I would resist having in definition
	What is really important is to keep FVE1 above 80%, if possible. Low FEV1 is a well-known risk factor for future exacerbations.
	depends on how low the baseline FEV1 is too
	Depends what the starting FEV1 is.
	There will be many who have lesser change in FEV1 but will be picked up by other parameters
	some folk may have irreversible lung disease and demosntrate little reversibility (there was no comment box in the last question)

	only as a minor criterium
	I think that an improvement of at least 3times MCID should be used. That would be 300ml and improvements in fev1 are not frequent
	it depends to the natural history of that patient asthma. Severe compromised asthmatics may obtain a great improvement from smaller volumes
	I think >230 mls
	I would favour a percentage change or total volume change in the definition
	strongly agree because if a patient reaches 500 mL of improvement surely it would have impact in every aspect of the disease
	More feeling than anything else
	It depends on pre-tratment FEV1.
	2 times MPPI would actually be 460ml - not a round number but I would be happy to accept 460ml
Round 3	
Is the following patient a super-responder? Please read the patient scenario below. Pre-treatment: exacerbation prone, poor asthma control but not on continuous OCS.After 12 months of treatment: zero exacerbations in 12 months,	FEV1 responder should be 200 mL
	think the key here is how many exacerabtions (4 to zero not that impressive?)
	Minimal improvement in FEV1 could either reflect good baseline FEV1 or chronic airway remodelling. Neither of those would prevent me classifying patient as a super-responder.
	probaby so i have voted yes. Improvement or the ability to improve lung function is a function of age and airway remodelling. A young person may not improve much: an old person with a long history of asthma may not be able to improve because of remodelling

major improvement in asthma control (at least 2 x MCID), now has well controlled asthma (assessed by ACQ or ACT), FEV1 improved by 150ml.	Either they are on continuous OCS or have required sufficient OCS burden in steroid bursts over the last 12 months
	It depends on the degree of the persisting bronchial obstruction and its reversibility.
	While we do not have three domains here because of FEV1, I would qualify this patient as a super-responder because the abnormal domains have normalized.
	This seems like a good response but not a super one! If the patient had been on OCS before but not after it could have been a strong indication of super response. Right now there is not enough evidence to call this pattern super response.
	I'm disappointed that the Delphi process did not allow a step back. I feel strongly that a super responder is defined by freedom from exacerbations, good control and normal or nearly normal lung function. The definition is about the patient's state of asthma on therapy and not the change from baseline. Can we try this in a future Delphi????
	Zero "severe" exacerbation
	He/she is a good responder independently on FEV1
	exac free as a major domain for the label of 'super responder'
	I think a major improvement in three domains is needed to be a super-responder. Major improvement in each domain to me is: -control: increased and now good -exacerbations: a reduction of at least 75% -OCS: cessation of maintenance use -lung function: improvement of 2 x MCID.

	AS REACHED A SIGNIFICANT INCREASE IN ALL PARAMETERS
	I generally don't believe that significant improvements in FEV1 should be required for a super response. In my clinical practice a fair number of patients have preserved lung function but very poor control and exacerbations leaving them little improvement for significant FEV1 improvements and in fact in clinical trials FEV1 changes were modest therefore I don't consider FEV1 a major criteria for super response.
	Improvement is not necessarily related to T2 therapy, reduction in exacerbations or improvement in asthma control could be due to more follow-up visits rather than a true effect. FEV1 improvement could be the natural variation of the test (spirometry)
	Improvement across multiple domains and achieved control with no exacerbations. FEV1 improvement supports super responder status but not required for it (particularly when baseline lung function is not known - this could now be normal)
	Pretreatment level of exacerbations may be important ie ?6 ?4
Is the following patient a super-responder? Please read the patient scenario below. Pre-treatment: exacerbation prone, poor asthma control but not on continuous OCS.After 12 months of treatment: zero exacerbations in 12 months, major improvement in asthma	think the key here is how many exacerabtions (4 to zero not that impressive?)
	ACQ and ACT are not that specific to asthma small airways pathology. The patient might still deconditioned / obese leading to breathless symptoms, and may use SABA habitually rather than as really needed. The 2xMCID improvement is good considering those issues though could consider 3xMCID given some UKSAR data. Thoughts on FEV1 change as above.
	One would want to recheck for missed comorbidities causing symptoms
	It depends on the impact of comorbidities (obesity, anxiety...) on the questionnaires but, in general terms, symptoms should be controlled.

control (at least 2 x MCID) but has not achieved well controlled asthma (assessed by ACQ or ACT), FEV1 improved by 150ml.	Not sure I understand this question as states major imp in asthma control, but not by questionnaire? I presume that means they started at 3 and improved to 1.8 on ACQ but still not controlled?
	Asthma control is an obligatory variable
	The super-responder should have both major asthma control improvement and have achieved well-controlled asthma
	As above. What's the current state of asthma? Can we distinguish between a super improver and a super responder?
	hypotetically the patients started from a very low asthma control and reached a not yet controlled status, In may opinion is a good clinical response by not sufficient as superresponder
	THIS IS A RESPONDER
	This kind of patient could be consedered as a good responder, not super
	I think a significant improvement in asthma control with an achievement of criteria for well controlled asthma is the hallmark of super response. This is the most likely factor to improve after asthma exacerbations. I would consider this patient a partial responder (good enough but not super).
	Improvement is not necessarily related to T2 therapy, reduction in exacerbations could be due to more follow-up visits rather than a true effect. Improvement in asthma control by ACQ or ACT is needed to have an objetive measure. FEV1 improvement (150 mL) could be the natural variation of the test (spirometry).
	Difficult to judge without some further details of pre-treatment exacerbation frequency and ACQ.
	Not a super responder
	Depends on whether other comorbidities are driving symptoms. I would be inclined to answer yes.

	The scenario is no accurate enough. In my personal practice, it depends on the trajectory of ACQ since I know the patient. So, if I rephrase "is ACQ mandatory to define super-response: potentially no, if pre treatment ACQ was extremely high"
	improved in 3 domains
Is the following patient a super-responder? Please read the patient scenario below. Pre-treatment: exacerbation prone, poor asthma control but not on continuous OCS.After 12 months of treatment: zero exacerbations in 12 months, major improvement in asthma control (at least 2 x MCID) but has not achieved well controlled asthma (assessed by ACQ or ACT), FEV1 improved by 500ml.	agree as above
	asthma still not well controlled
	same as above case
	It depends on the impact of comorbidities (obesity, anxiety...) on the questionnaires but, in general terms, symptoms should be controlled. This clinical scenario could be a partial response.
	Difficult subjective versus objective - but high score in ACQ could be dysfuntional breathing - not asthma
	its hard to imagine no improvement in QOL with a 500 ml improvement in lung function!
	Asthma control is an obligatory variable
	While the asthma control domain has not completely normalized, the major improvement coupled with the large FEV1 improvement and lack of exacerbation is compelling
	As above.
	hypotetically the patients started from a very low asthma control and reached a not yet controlled status, In my opinion it is a very good clinical response according to FEV1 improvement even if I would expect to compare with the the history of his lung function
	THIS IS A RESPONDER ((A PARTICULAR PHENOTYPE: RESPIRATORY FUNCTION)

	I am torn about this one because I believe improvements in control as the hallmark of a super response. Not too sure what to say here. The FEV1 improvement is substantial. My first thought was "Does this actually happen in real life OR would this patient really have a significant improvement in control as well?" I have not seen too many patients with such an improvement in FEV1 that have a partial response in terms of control.
	it has 2 clinical criteria: exacerbations AND asthma control by 2xMCID, AND at least one biological/physiological criteria: large improvement on FEV1
	Significant improvement across multiple domains
	Not a super responder as not well controlled shown in ACQ but did improve in FEV1
	As above re comorbidities. Huge FEV1 improvement would present paradox as to why ACQ/ACT has not reached controlled thresholds
	improved in 3 domains
	Significant improvement across at least 3 domains even though ACQ or ACT not normalised
Is the following patient a super-responder? Please read the patient scenario below. Pre-treatment: exacerbation prone, poor asthma control and has been on continuous OCS for 2 years.After 12 months of treatment: zero exacerbations in 12	FEV1 improvement 200 mL
	probably has a significant amount of fixed aireways disese
	a huge steroid sparing effect here too
	It depends on the degree of the persisting bronchial obstruction and its reversibility.
	Clear three domain improvement
	So, did the ACT go from 5 to 11? Not a super responder....
	Zero "severe" exacerbation

months, able to cease continuous OCS, major improvement in asthma control (at least 2 x MCID), now has well controlled asthma (assessed by ACQ or ACT), FEV1 improved by 150ml.	The patients reached the optimal responde in both exacerbation and OCS discontinuation . Moreover reached minor end points , In my opinion it is a very good clinical response
	AS REACHED A SIGNIFICANT INCREASE IN ALL PARAMETERS
	Yes, for the reasons I described above. I am not too concerned about changes in FEV1.
	Even when the patient has 3 clinical criteria, lacking of a biological (Eos, FEV1, FENO, etc) or physiological criteria (FEV1) may not be considered super responder
	Both QOL and FEV1 improvement
	improved in 5 domains
Is the following patient a super-responder? Please read the patient scenario below. Pre-treatment: exacerbation prone, poor asthma control and has been on continuous OCS for 2 years.After 12 months of treatment: zero exacerbations in 12 months, able to cease continuous OCS, but only minor improvement in asthma control. FEV1 improved by 150ml.	is difficult to concile the improvements in exacerbations and OCS with por control
	Minor improvement in Sx context of coming off OCS to me is a good response.
	two domains of no great improvement: however is clearly a responder
	most patients don't get much of a change in FEV1
	It depends on the impact of comorbidities (obesity, anxiety...) on the questionnaires but, in general terms, symptoms should be controlled. This clinical scenario could be a partial response.
	still great response but symptoms and lung function change is minimum so still ongoing disease burden
	Asthma control is an obligatory variable
	The elimination of corticosteroids makes up for the only minor improvement in asthma control
	it means that the patient still have some daily symtoms (consequently is non a superresponder) or he started from a not so bad control
	THIS IS A RESPONDER

	This is another one of those cases that seems improbable. Most patients with improvements in exacerbations and cessation of OCS would likely have a concordant improvement in control. I agree that this is a super responder because I stratify response on the basis of importance. 1. Reduction in exacerbation. 2. OCS reduction. 3. Asthma Control. 4. Improvement in QOL/patient perception that they have improved. 5. FEV1 change.
	only 2 clinical criteria reached
	good responder but not "super"!
	No OCS and improved FEV1 and no exacerbation shows supper response as difficult to come of OCS usually
	OCS cessation is a symptom driver, check adrenal function
	same comment; depends on the trajectory of ACQ values
	improvement in 3 domains
Is the following patient a super-responder? Please read the patient scenario below. Pre-treatment: exacerbation prone, poor asthma control and has been on continuous OCS for 2 years.After 12 months of treatment: zero exacerbations in 12 months, able to cease continuous OCS, but only minor improvement in	considerably improved but not controlled. Other comorbidities may be contributing which have been inadequately adressed
	It depends on the impact of comorbidities (obesity, anxiety...) on the questionnaires but, in general terms, symptoms should be controlled. This clinical scenario could be a partial response.
	please define minor improvement ACT
	Asthma control is an obligatory variable
	Clear three domain improvement
	Asthma control (symptoms) measured by questionnaires is not always specific for asthma.
	3 out of 4 is enough to me!

asthma control. FEV1 improved by 500ml.	the patient could be a superresponder according to the basal asthma control value
	THIS IS A RESPONDER (A PARTICULAR PHENOTYPE: RESPIRATORY FUNCTION)
	For the reasons outlined above I would agree that this is a significant response. Of course, my answer differs from the exact same scenario above with the patient that did not have chronic OCS use. I made a different judgement here because on a weighted basis I believe the ability to reduce OCS is extremely important increasing my likelihood of defining this as a super response when coupled with the exacerbation reduction and concomitant lung function change.
	it could be because the patient has 2 clinical criteria (exacerbations and OCS reduction) and a physiological (FEV1 by 500 mL)
	Improvement across multiple domains - exacerbations/OCS use and FEV1
	maybe perception problem with ACT!
	As above
	As above
	Indeed we are speaking of ACQ5 not 7. FEV1 is not necessarily compensating ACQ if this is what this question intends to suggest
	improved in 3 domains . OFF STEROIDS
Is the following patient a super-responder? Please read the patient scenario below. Pre-treatment: exacerbation prone, poor asthma	is a good responder not a super
	Looking back on our super-responders on Mepo (many dating back to early CTIMPs) they fluctuate between 0 and 1 exacerbation per year, in part reflecting seasonal influenza etc and low threshold for some doctors to prescribe burst OCS in any severe asthma patient who coughs.

control and has been on continuous OCS for 2 years.After 12 months of treatment: exacerbations have reduced from 4 per year to 1 per year, able to cease continuous OCS, major improvement in asthma control (at least 2 x MCID), now has well controlled asthma (assessed by ACQ or ACT), FEV1 improved by 150ml.	we should allow at least one exacerbation per year in the frequent exacerbator (eg non eosinophilic for those on anti IL5)
	No exacerbations should be permitted in super-responders. It´s very important to determine the nature of the exacerbations (infectious/non-infectious), because infectious exacerbations may fall outside the action of mAbs.
	still exacerbating and modest change in lung function
	Improvement in FEV1 may depend also on for how long the patient has had asthma. If she has had asthma for 20 years, changes in spirometry may be irreversible.
	the presence of stiil one exacerbation suggest a good even if not complete response
	based on asthma control domain in this instance
	THIS IS A RESPONDER (A PARTICULAR PHENOTYPE: EXACERBATORS)
	This patient has met all the significant changes in measurable asthma outcome measurements. Although they still have exacerbations the ability to cease OCS use while still achieving control and improvements in FEV1 is significant. This makes me wonder if the criteria should be slightly different for OCS dependent asthma patients since they are at the extreme end of disease severity. Should the definition of response differ for these patients?
	I consider necessary the addition of a biological criteria to complete the definition of super responder
	People will still have odd exacerbations but minor ones not requiring admission
	Substantial improvements in three other domains.
	improved in 5 domains, despite the fact that had 1 exacerbation
	good or very good responder not a super

Is the following patient a super-responder? Please read the patient scenario below. Pre-treatment: exacerbation prone, poor asthma control and has been on continuous OCS for 2 years.After 12 months of treatment: exacerbations have reduced from 4 per year to 1 per year, able to cease continuous OCS, major improvement in asthma control (at least 2 x MCID), now has well controlled asthma (assessed by ACQ or ACT), FEV1 improved by 500ml.	significant improvement accross three domains
	No exacerbations should be permitted in super-responders with the exception of infectious exacerbations.
	too criteria met
	the presence of stiil one exacerbation suggest a good even if not complete response
	THIS IS A RESPONDER (A PARTICULAR PHENOTYPE: RESPIRATORY FUNCTION)
	This one if a home run! There is one exacerbation but if the duration of therapy exceeds a year perhaps even that will go to zero. In addition, it is inevitable for severe patients to have viral induced exacerbations. In my experience, the exacerbations occur but are not quite as severe which is an important factor to consider.
	Significant improvement across multiple domains and ceased maintenance OCS with dramatic reduction in exacerbation frequency
	improved in 5 domains, despite the fact that had 1 exacerbation
In round 1 and round 2 participants provided comments about the need for "major" and "minor" responder criteria (i.e. a hierarchy among the criteria). Do you agree that it is	Reductions in exacerbation rate and reduction in systemic corticosteroid dose are the most important major criteria. Improvement in asthma control (ACQ or ACT)? Improvement in lung function (FEV1) is a minor criterion.
	This especially relates to changes of OCS. Total cessation or going from >10mg to 5mg or less has a substantial impact. Numerical reduction in exacerbation even not to elimination is also significant.

useful to divide response criteria into major and minor criteria?	super responder must improve exacerbations. (0) , control , FEV1, and stop or reduce OCS if AI precludes complete withdrawl if one criteria is not met should be a very good responder, 2 criteria not met partido responder
	If that were to be done then for me OCS prescription and exacerbations would be the major criteria. The possible advantage of major and minor criteria is that might allow for more flexibility in response.
	some factor incorporating duation of disease and patient age would be helpful
	Major criteria should encompass exacerbations, need for OCS and Symtoms.
	FEV1 value in absolute value is not so important as in percentage adherence to therapy depends also on patient reported outcomes how to achieve a consensus on hierarchy?
	Either a patient responds according to stated criteria or does not. If the aetiology of the non-responsiveness could be defined, that would be different.....
	too complicated, won't be used,
	exacerbations, maintenance OCS are major criteria ACQ, and FEV1 are minor criteria
	I believe the four dimensions should be seen on equal basis: Exacerbation risk, FEV1, asthma control, OCS
	FEV1 improvement ACT basal value Quality of life

	it would be potentially simpler to define three or 4 domains - exacerbations, OCS, symptom control, lung function with agreed criteria for each one, there should not be any presumption that these are necessarily equally weighted - this could be answered over time
	Definitely. That makes it much easier to in essence provide a weighted response - ie provide guidance about what markers of response are more valuable than others.
	if not major and minor, at least: 1 biological criteria (could be major criteria) and 2 clinical (minor)
	There should be a cumulative factor for criteria.
	coming off steroids and> 50% reduction in exacerbations should be major
	Each criteria could be classified as major or minor depending on magnitude of response. Super responder could be then be determined by, for example, satisfying 2 major + X minor criteria.... et ACQ - improvement for ?2MCID is "minor", >2MCID and normalised is major. FEV1 improvement can be similar quantified.
Do you agree that major criteria should have a greater weight than minor criteria in the assessment of a potential Super-Responder?	But one major criteria could have the same weight than 2-4 minor criteria
	Absolutely. You should mandate a significant change in major criteria and accept a more modest change in minor criteria when defining response. This would be highly beneficial to clinicians as they make decisions about therapeutic changes. Developing a tool that gives you a score that can be tracked over time would be amazing but perhaps too lofty a goal.
	biological criteria should be more important in terms of effectiveness
	but depends on the criteria
	please note that 150 mls in a 1.88 m 20 yr male is pretty minimal but the same change in a 70 yr old 1.50 m female could be really important

Even if someone has not been completely exacerbation free, should a 75% or greater reduction in exacerbations be a minor criterion for classifying someone as a super-responder?	The problem is that to be considered 75%+ a patient must have 4 exacerbations and for example 7 down to 2 a greater absolute reduction than 4 to 1 would not be similarly rated. We could do a hybrid and say that an absolute reduction of 4 or 75% should be regarded as a minor criterion. In the same way, perhaps a larger absolute reduction could be considered a major criterion - say 7 to 1 or absolute change of 6. For consideration.
	superresponders should not have exacerbations or be reduced 90%
	I like this. Other possibility is defining 1 exacerbation/year as the minor criteria.
	Instead of 'widening' the term, one can think of defining more terms that will accommodate the meanings. E.g. super-responder, high-responder (and super-duper responder or 'healed' ;-), etc
	It could be a criterion for classifying a patient as responder, but we are talking about super-responders.
	is a major one
	I struggle a bit with the major / minor concept - some of the minor criteria may not be due to the introduction of the biologic therapy. I have no issue with having a group of patients who have a good and important clinical response to biologic treatment, but they do not have a "super" reponse as defined below I think the term super-responder should be retained for someone who has been a frequent user of rescue steroids or has required maintenance systemic steroids and after biologic therapy does not require systemic steroids
	This should be a major criteria (complete exacerbations free or 75% reductions)
	Also the severity of exacerbation should be considered
	suggest 75% or greater exac free as a single criterion rather than major and minor?

	It is not realistic to expect 100% reduction in exacerbations with the current biologic since the mechanisms between exacerbations vay and none of the drugs cover all possible drivers of exacerbations.
	yes because exacerbations are not necessarily eosinophilic, so 75% could be acceptable, if there is a way to evaluate the nature of exacerbations it could be stated a 100% reduction in eosinophilic exacerbations
	I would suggest to add the criteria <0.5 g/year
	i would say >60% reduction eg going from 3 to 1
	The proposal is that major and minor criterion are scored. It would be helpful to know whether a total score would indicate a super responder and what that total score would be in order to determine the criteria.
In relation to asthma control, should having well controlled asthma (e.g ACQ<1.0) be a minor criterion for defining a super-responder?	depends on baseline values
	In my opinion, it should be a major criterion.
	"A responder" refers rather to a change in a criterion under question. On the other hand, ACQ<1 as a target could also be considered.
	for me is a major
	major one
	Not a minor criterion but an essential major criterion.
	again, suggest either/or ACQ greater than 2MCID or less than 1.0
	ACQ is a widely used tool
	Should be well controlled, maybe not <1. But going from ACQ of 4 to 3 does not seem very helpful.
	Would this not be major - or an improvement of >2?

	This could be major improvement if someone have highly elevated ACQ pre-treatment, think it should be coupled with change from baseline.
The current tools for assessing quality of life can be difficult to implement in a clinical setting and it has been suggested further research is needed. Do you agree further research is needed surrounding quality of life tools?	Agree. I do not think any of these have enough evidence to use currently in a super-responder definition.
	I think a consensus can be reached on the basis of the existing knowledge.
	I think SAQ certainly needs more validation and I remain to be persuaded that it provides additional discriminatory value to AQLQ.in this population I do not see any difficulty using mini-AQLQ in a clinical setting
	In a clinical setting VAS would be very easy to use. I would encourage further research on this.
	I have been using the SAQ, mini AQLQ in my clinic and tracking measurements but I am not sure what the right answer is. I would be very interested in participating in research about using SAQ to track QOL changes in response to biologics in severe asthma. We desperately need a way to track PROs in severe asthma. I generally just ask my patients what their impression is of whether the medication is working. Could we use something as simple as a patient rated response to therapy where patients are asked on a graded scale how much better they believe they are?
	those are tools not universally reported
	I feel current QOL assessment tools are only partially well received by SA pts. They do capture the very sick and the very well controlled well though
	I think WPAI in workers is usable
	i think these shoud have less weight. Very subjective
	Not in this context of defining super-responders. Its a separate question that deserves to answered on its own merit.

	QoL is a really hard thing to measure. different people score very differently. one of our patients on a transplant list had fantastic QoL....
Consensus has not been reached surrounding the use of quality of life measurements to define a super responder. Taking into consideration the fact that some participants are uncertain about how quality of life should best be assessed, do you think an improvement in quality of life should be a minor criterion?	The assumption that QoL can only improve may be flawed. There is some inconvenience in modern asthma therapies. Some patients fear needles. In some countries, continuing access to subsidised treatments requires a standard to be met and this may impact QoL. Rhinitis may flare if asthma focssed therapy leads to reduction in OCS. OCS reduction itself can be associated with symptoms or change in QoL. If QoL is to be a criterion then failure to improve QoL should be markedas a negative in a composite scoring system
	provided it takes into consideration both aspects of asthma control and the benefits of coming off steroids and other adverse effects of medications
	QOL seems to correlate with ACQ5
	disagree . patient reported outcomes and QoL is THE criteria for the patient
	We have asthma control as a validated PROM in asthma in our definition. QoL beyond control will make things noisy. Biased responses to achieve the desired treatment recommendation can be a possibility.
	If there is no current consensus on how best to assess quality of life in patients with severe asthma, then it should not be used to define a super responder. however, this could change as further research is undertaken.
	I think QOL is really important but because we have no way to consistently measure it I am on the fence about whether it should be included now or down the road when we have more data.
	with a validated and universally reported tool
	QOL may be hard to restirct to asthma alone in patients with multiple diseases.

	Only a minor criterion if a significant change in score
	It is an important aspect of assessing response but determining the right tool that is feasible in practice is needed
Consensus was reached in round one that a large improvement in FEV1 might be one of the criteria used to define a super-responder. What is the appropriate definition of a large improvement in FEV1?	The only caution about this is by setting an absolute volume rather than % it would make it more difficult for someone who is small or old to have a 500mL change in FEV!
	500 ml or normal Fev1s
	I would only place as a minor criteria. Some patients have good FEV1 between exacerbations (i.e. at baseline) and some fixed remodelling - neither could realistically improve by 500mls. Also lung function is generally done without true bronchodilator washout in the real world.
	please see previous comments about the ability to improve FEV1 due to age or duration of disease
	What about normalisation of the FEV1? Would not be observed in those with irreversible remodelling changes.
	Lung function is by definition variable in this population and needs to take into account multiple factors including background treatment - again, if someone has a good (but not super response as previously outlined in my earlier comments) a change in lung function may be part of that improvement - however the defining issue regarding super response is no systemic steroids
	Please notice that at least part of the patients with severe asthma have developed irreversible obstruction and thus even if the response to a specific medication would be very good, improvement in FEV1 may be minimal.
	this should be another (major) domain in the definition - other domains being exacerbations, OCS, symptom control. This is clearly an important outcome for the patient and spirometry is

	feasible/necessary to monitor these patients. The fact that a lower proportion of patients may achieve this endpoint compared to say exacerbations does not imply this to be any less important (one could argue quite the contrary).
	IT DEPENDS ON ASBOLUTE VALUE. I SUGGEST TO CONSIDER A SUPER-RESPONDER ONLY IF FEV1 AND FEV1/FVC RETURN ABOVE DEL LOWER LIMIT OF NORMALITY (COMPLETE REVERSIBILITY).
	Most patients don't get more than a 200ml improvement in FEV1 therefore I think 500ml is very high. If it was a major criteria I would be more interested in arguing for a lower number like the 230ml suggested below. Perhaps a more modest cut off should be considered? Why aren't you going with 2x MCID or 200ml?
	Improvement in pulmonary function (FEV1) is not and objective of T2 therapy because inflammation is not always related to airway disfunction, so 500 mL could be a super response
	It would be a significant sign of drug efficacy. I believe these patients are rare and probably represent a patient that had treatment resistant eosinophilic airway inflammation susceptible to aIL5.
	Very long hesitation
A definition of a super-responder should be based on evidence of improvement across how many domains?	Improvement across at least two major domains
	Perhaps major in 2 and minor in 1 (or major in 3)?
	May be a score of 2 for each major and of 1 for each minor with a score of 6 or more demonstrating a super responder?
	No symptoms, no steroids and no permanent airways obstruction.
	asthma control is superior to FEV1

	I would keep this simple based on the known primary effect of these treatments - reduction in systemic steroids exposure
	three domains: 1 biological/physiological and 2 clinical

Supplementary Table E3. Delphi round 1 questions

The question types consisted of 6 or 3 point Likert scales (strongly agree, agree, neutral, disagree, strongly disagree). Multiple choice, ranking and open ended questions were also included in the questionnaires. Participants were encouraged to use the free text fields to provide qualitative feedback to inform further decision making. Nine demographic questions were included to obtain relevant background information to justify their inclusion in this Delphi exercise.

Question	**Response options**
Do you treat severe asthma patients?	Yes
	No
How many severe asthma patients do you normally see in a typical month?	
How many patients do you currently have on treatment with a biological?	
What is your age?	Under 35 years
	35 - 44 years
	45-54 years
	55-64 years
	65 years and over
	Prefer not to say
What is your gender?	Male
	Female
	Prefer not to say
In which country do you practice?	
Which of the following best describes your current occupational group?	General practice/primary care
	Allergist
	Respiratory medicine specialist/pulmonologist
	Asthma nurse
	Other
Have you participated in a severe asthma advisory board or national/international working group in the last 5 years?	Yes
	No

How many peer reviewed publications on severe asthma have you authored in the last 5 years?	Nil
	1-5
	6-10
	More than 10
	Prefer not to say
Being completely exacerbation free for an extended period should be part of the definition of a super-responder.	Strongly agree
	Agree
	Neutral
	Disagree
	Strongly disagree
	Don't know
For how long should a person be exacerbation free to be regarded as a super-responder?	6 months
	12 months
	Not a relevant criteria
	Don't know
	Other
Even if someone has not been completely exacerbation free, should a 75% or greater reduction in exacerbations be sufficient to classify someone as a super-responder?	Strongly agree
	Agree
	Neutral
	Disagree
	Strongly disagree
	Don’t know
With which of the following questionnaires are you familiar?	ACQ
	ACT
	GINA
	None of the above
In relation to asthma control, consider which of the following statements about the definition of a super-responder you agree with. A super-responder should be defined by:	Well controlled asthma (e.g.ACQ < 1.0) regardless of the magnitude of improvement
	Well controlled asthma (e.g.ACQ < 1.0) AND a large improvement in control
	A large degree of improvement even if the person does not have well controlled asthma

	Unsure
	Make a comment on your choice here:
	If you have any comments on this issue please enter these in the adjacent box.
How do you usually assess asthma control in your severe asthma patients?	ACQ
	ACT
	GINA
	Other - please describe briefly
If a large improvement in ACQ score should be part of the definition of a super-responder, how large should that improvement be? Bear in mind that the minimally clinically important difference (MCID) in the ACQ score is 0.5.	1.0 or greater
	2.0 or greater
	3.0 or greater
	At least a 50% improvement in ACQ score
	An improvement in ACQ is not important in defining a super-responder
	Don't know
	Other - please describe briefly
If a large improvement in ACT score should be part of the definition of a super-responder, how large should that improvement be (bearing in mind the MCID is 3 points)?	6 points or greater
	9 points or greater
	12 points or greater
	An improvement in ACT is not important in defining a super-responder
	Don't know
	Other - please describe briefly
If a large improvement in GINA score should be part of the definition of a super-responder, how large should that improvement be (bearing in mind the GINA levels of asthma control are uncontrolled, partly controlled and controlled)?	One level of improvement
	Two levels of improvement
	An improvement in GINA score is not important in defining the super-responder
	Don't know
	Other - please describe briefly

In patients who were on long term oral corticosteroids (OCS) prior to commencing a biological or other targeted therapies, which of the following statements should form part of the definition of a super-responder?	Patients should have completely weaned off OCS (I.e. 100% reduction)
	OCS reduction 75% or greater
	OCS reduction 50% or greater
	Other
	Unsure
	If you have any comments on this issue please enter these in the adjacent box.
If a person were unable to completely cease OCS because of adrenal insufficiency, would it be reasonable to define them as a super-responder, provided other criteria had been met, and provided there had been a major reduction in OCS dose?	Strongly agree
	Agree
	Neutral
	Disagree
	Strongly disagree
	Don't know
	If you have any comments on this issue please enter these in the adjacent box.
A large improvement in quality of life (QOL) should be part of the definition of a super-responder.	Agree
	Agree but not practical in a clinical environment
	Neutral
	Disagree
	Don't know
	If you have any comments on this issue please enter these in the adjacent box.
Should other patient-reported outcomes be part of the definition of a super-responder?	Yes
	No
	Don't know
	If you have any comments on this issue please enter these in the adjacent box.

Please list which patient-reported outcomes should be part of the definition of a super-responder?	Please write your answer here:
A large improvement in FEV1 is an important part of the definition of a super-responder.	Strongly agree
	Agree
	Neutral
	Disagree
	Strongly disagree
	Don't know
	If you have any comments on this issue please enter these in the adjacent box.
A large improvement in FEV1 might be part of the definition of a super-responder but is not essential.	Strongly agree
	Agree
	Neutral
	Strongly disagree
	Disagree
	Don't know
	If you have any comments on this issue please enter these in the adjacent box.
In relation to improvement in FEV1, consider which of the following statements do you agree with. A super-responder should be defined by:	FEV1>80% predicted regardless of the magnitude of improvement
	Large degree of improvement in FEV1 AND FEV1>80%
	Large degree of improvement in FEV1 even if the FEV1 is <80%
	Unsure
	If you have any comments on this issue please enter these in the adjacent box.
With which of the following statements do you agree? Major improvement or elimination of exacerbations is:	Essential to the definition of a super-responder
	Important but not essential
	Not important
	Don't know

	If you have any comments on this issue please enter these in the adjacent box.
With which of the following statements do you agree? A major reduction or cessation of long term OCS is:	Essential in those previously on long term OCS
	Important but not essential
	Not important
	Don't know
	If you have any comments on this issue please enter these in the adjacent box.
With which of the following statements do you agree? A major improvement in asthma control is:	Essential to the definition of a super-responder
	Important but not essential
	Not important
	Don't know
	If you have any comments on this issue please enter these in the adjacent box.
With which of the following statements do you agree? A major improvement in QOL is:	Essential to the definition of a super-responder
	Important but not essential
	Not important
	Don't know
	If you have any comments on this issue please enter these in the adjacent box.
With which of the following statements do you agree? A significant improvement in FEV1 is:	Essential to the definition of a super-responder
	Important but not essential
	Not important
	Don't know
	If you have any comments on this issue please enter these in the adjacent box.
A definition of a super-responder should be based on evidence of	Strongly agree
	Agree
	Neutral

improvement across at least two domains.	Disagree
	Strongly disagree
	Don’t know
	If you have any comments on this issue please enter these in the adjacent box.
The following potential criteria might be used to define a super-responder. Rank these from most important to least important.	Asthma control (major improvement or achievement of well controlled asthma)
Please number each box in order of preference from 1 to 6	Exacerbations (elimination or major improvement)
	Major improvement in FEV1
	Major improvement in QOL
	Long term OCS use (elimination or major reduction)
	Maintenance inhaler therapy (major reduction)

Supplementary Table E4. Delphi round 2 questions

Should a major reduction in maintenance inhaler therapy be one of the domains for defining a super responder? ***Note: Consensus was reached in round one regarding the first 5 domains which might be used to define a super-responder: Asthma exacerbations - major reduction or elimination, OCS - major reduction or elimination, asthma control – major improvement, quality of life improvement and FEV1 improvement.***	Strongly agree
	Agree
	Neutral
	Disagree
	Strongly disagree
A definition of a super-responder should be based on evidence of improvement across how many domains? ***Domains: Asthma exacerbations - major reduction or elimination, OCS - major reduction or elimination, asthma control – major improvement or quality of life improvement or FEV1 improvement.***	One domain
	Two domains
	Three or more domains
	Make a comment on your choice here:
Even if someone has not been completely exacerbation free, should a 75% or greater reduction in exacerbations be sufficient to classify someone as a super-responder? ***Note: In round one 94.07% of participants stated being completely exacerbation free for an extended period of time should be part of the definition of a super-responder. 60.17% of***	Strongly agree
	Agree
	Neutral
	Disagree
	Strongly disagree
	Make a comment on your choice here:

participants stated a 75% or greater reduction in exacerbations is sufficient to classify someone as a super-responder.	
For how long should a person be exacerbation free to be regarded as a super-responder? ***Note: In round one 62.71% of participants stated participants should be exacerbation free for 12 months to be defined a super-responder.***	12 months
	18 months
	24 months
	Make a comment on your choice here:
In relation to asthma control, a super-responder should be defined by having: ***Note: In round one 61.86% of participants stated a super-responder should be defined as having well-controlled asthma (e.g ACQ<1.0) AND a large improvement in asthma control.***	Well-controlled asthma (e.g ACQ<1.0) AND a large improvement in asthma control
	EITHER well-controlled asthma (e.g ACQ<1.0) OR a large improvement in asthma control
	Make a comment on your choice here:
If a large improvement in ACQ or ACT score is part of the definition of a super-responder, how large should that improvement be? ***Note: In round one 19.61% participants defined a super-responder as an ACQ score improvement of 2 times the minimal clinically important difference (MCID) and 47.06% participants stated an ACT score improvement of 2 or more times the MCID.***	Two times the MCID
	Three times the MCID
	Four times the MCID
	Make a comment on your choice here:
What level of improvement in GINA score would be sufficient to define a super-responder, on the basis that	One level of improvement
	Two levels of improvement
	Make a comment on your choice here:

anyone receiving a biologic will be uncontrolled (GINA levels of asthma control are uncontrolled, partly controlled and controlled)? ***Note: In round one 55.56% of participants defined a super-responder as having two levels of improvement in GINA score.***	
In patients who were on long term oral corticosteroids (OCS) prior to commencing a biological or other targeted therapies, should patients have completely weaned off OCS (i.e 100% reduction), or to the point of adrenal insufficiency, to be defined as a super-responder? ***Note: In round one 90.86% of participants agreed that patients who were unable to completely cease long term OCS due to adrenal insufficiency can still be defined as a super-responder, provided there had been a major reduction in OCS use.***	Strongly agree Agree Neutral Disagree Strongly disagree Make a comment on your choice here:
In relation to improvements in quality of life, should a quality of life measure be used to define a super-responder?	Yes definitely Possibly, but more research is needed No Don't know Make a comment on your choice here:
Would it be appropriate to use the Asthma Quality of Life Questionnaire (AQLQ - 15 questions) to assess quality of life in patients?	Yes definitely Possibly, but more research is needed No Don't know Make a comment on your choice here:

Would it be appropriate to use the Severe Asthma Questionnaire (SAQ) to assess quality of life in patients? ***Note: The SAQ asks how difficult aspects of health related quality of life are in the last 2 weeks because of asthma symptoms or side effects of treatment. The questionnaire measures response across the following domains social life, personal life, leisure activities, housework, work or education, family life, depression, irritability, anxiety, sleep and appearance.*** ***The SAQ has 2 parts and provides 2 scores. The SAQ has 16 questions which are scored using a 7 point Likert scale ranging from very, very difficult (1) to no problem (7), with responses averaged to form a SAQ score . The SAQ-global score is produced from a single 100 point scale from 0 to 100, where 0 equates to no quality of life, 100 equates to perfect quality of life.***	Yes definitely
	Possibly, but more research is needed
	No
	Don't know
	Make a comment on your choice here:
If a large improvement in quality of life score is part of the definition of a super-responder, how large should the improvement be?	Two times the MCID
	Three times the MCID
	Four times the MCID
	Make a comment on your choice here:
Could the Global Rating of Change (GRC) scale be a useful tool in defining a super-responder? ***Note: The Global Rating of Change (GRC) scale is a single item***	Strongly agree
	Agree
	Neutral
	Disagree
	Strongly disagree

questionnaire used to quantify a patient's improvement or deterioration over time following a treatment. This is achieved by asking the patient to indicate to what extent they perceive a change has occurred. The GRC incorporates a 10 point scale which prompts patients to describe how they feel since starting their new asthma treatment (5 =a great deal better, 0 =No change, -5 = a great deal worse).	Make a comment on your choice here:
Could the Visual Analogue Scale (VAS) be a useful tool in defining a super-responder? ***Note: The Visual Analogue scale (VAS) is a psychometric measuring instrument which uses a continuous scale to measure a patient's subjective experience of a disease. It comprises of a 10cm long segment, which prompts patients to indicate their perception of their symptoms by marking a point along the segment.***	Strongly agree Agree Neutral Disagree Strongly disagree Make a comment on your choice here:
Work productivity was suggested as a potential area for evaluating super-responders, do you agree (using the Work Productivity and Activity Impairment (WPAI) questionnaire as a potential instrument)? ***Note: The Work Productivity and Activity Impairment (WPAI) questionnaire can be used to measure***	Strongly agree Agree Neutral Disagree Strongly disagree Make a comment on your choice here:

impairments in both paid work and unpaid work. ***The WPAI is a patient reported quantitative assessment which examines the amount of absenteeism, presenteeism and daily activity impairment and has been adapted to measure work productivity loss amongst patients with specific health problems.***	
Would you agree that a large improvement in FEV1, irrespective of baseline FEV1 might be one of the criteria used to define a super-responder but is not an essential requirement (rationale being not everyone has an impairment in FEV1 who has severe asthma)?	Strongly agree
	Agree
	Neutral
	Disagree
	Strongly disagree
Consensus was reached in round one that a large improvement in FEV1 might be one of the criteria used to define a super-responder. What is the appropriate definition of a large improvement in FEV1? Previous studies have reported that a Minimal Patient Perceivable Improvement (MPPI) in FEV1 is 230ml (Santanello et al, ERJ 1999).	500ml (2 times MPPI)
	750ml (3 times MPPI)
	Not feasible
	Make a comment on your choice here:

Supplementary Table E5. Delphi round 3 questions

Is the following patient a super-responder? Please read the patient scenario below. ***<u>Pre-treatment:</u> exacerbation prone, poor asthma control but not on continuous OCS.*** ***<u>After 12 months of treatment</u>: zero exacerbations in 12 months, major improvement in asthma control (at least 2 x MCID), now has well controlled asthma (assessed by ACQ or ACT), FEV1 improved by 150ml.***	Agree Neutral Disagree Make a comment on your choice here:
Is the following patient a super-responder? Please read the patient scenario below. ***<u>Pre-treatment:</u> exacerbation prone, poor asthma control but not on continuous OCS.*** ***<u>After 12 months of treatment</u>: zero exacerbations in 12 months, major improvement in asthma control (at least 2 x MCID) but has not achieved well controlled asthma (assessed by ACQ or ACT), FEV1 improved by 150ml.***	Agree Neutral Disagree Make a comment on your choice here:
Is the following patient a super-responder? Please read the patient scenario below. ***<u>Pre-treatment:</u> exacerbation prone, poor asthma control but not on continuous OCS.*** ***<u>After 12 months of treatment</u>: zero exacerbations in 12 months, major improvement in asthma control (at least 2 x MCID) but has not achieved well controlled***	Agree Neutral Disagree Make a comment on your choice here:

asthma (assessed by ACQ or ACT), FEV1 improved by 500ml.	
Is the following patient a super-responder? Please read the patient scenario below. ***<u>Pre-treatment</u>: exacerbation prone, poor asthma control and has been on continuous OCS for 2 years.*** ***<u>After 12 months of treatment:</u> zero exacerbations in 12 months, able to cease continuous OCS, major improvement in asthma control (at least 2 x MCID), now has well controlled asthma (assessed by ACQ or ACT), FEV1 improved by 150ml.***	Agree Neutral Disagree Make a comment on your choice here:
Is the following patient a super-responder? Please read the patient scenario below. ***<u>Pre-treatment:</u> exacerbation prone, poor asthma control and has been on continuous OCS for 2 years.*** ***<u>After 12 months of treatment:</u> zero exacerbations in 12 months, able to cease continuous OCS, but only minor improvement in asthma control. FEV1 improved by 150ml.***	Agree Neutral Disagree Make a comment on your choice here:
Is the following patient a super-responder? Please read the patient scenario below. ***<u>Pre-treatment</u>: exacerbation prone, poor asthma control and has been on continuous OCS for 2 years.*** ***<u>After 12 months of treatment:</u> zero exacerbations in 12 months, able to cease***	Agree Neutral Disagree Make a comment on your choice here:

continuous OCS, but only minor improvement in asthma control. FEV1 improved by 500ml.	
Is the following patient a super-responder? Please read the patient scenario below. ***<u>Pre-treatment</u>: exacerbation prone, poor asthma control and has been on continuous OCS for 2 years.*** ***<u>After 12 months of treatment</u>: exacerbations have reduced from 4 per year to 1 per year, able to cease continuous OCS, major improvement in asthma control (at least 2 x MCID), now has well controlled asthma (assessed by ACQ or ACT), FEV1 improved by 150ml.***	Agree Neutral Disagree Make a comment on your choice here:
Is the following patient a super-responder? Please read the patient scenario below. ***<u>Pre-treatment:</u> exacerbation prone, poor asthma control and has been on continuous OCS for 2 years.*** ***<u>After 12 months of treatment</u>: exacerbations have reduced from 4 per year to 1 per year, able to cease continuous OCS, major improvement in asthma control (at least 2 x MCID), now has well controlled asthma (assessed by ACQ or ACT), FEV1 improved by 500ml.***	Agree Neutral Disagree Make a comment on your choice here:
In round 1 and round 2 participants provided comments about the need for "major" and "minor" responder criteria (i.e. a hierarchy among the criteria).	Agree Neutral Disagree Make a comment on your choice here:

Do you agree that it is useful to divide response criteria into major and minor criteria?	
Do you agree that major criteria should have a greater weight than minor criteria in the assessment of a potential Super-Responder?	Agree
	Neutral
	Disagree
	Make a comment on your choice here:

The steering committee would like to propose that criteria achieving clear consensus in round 1 and round 2 should become major criteria, while those that received some support, but did not achieve consensus acceptance or rejection, might still be useful as minor criteria. This is outlined in Table below. In the questions that follow you will have the opportunity to vote on each of these proposed minor criteria.

Major criteria (score 2 for each)	**Proposed minor criteria (score 1 for each)**
100% reduction in exacerbations (assessed over 12 months or more)	≥ 75% and < 100% improvement in exacerbations
Previously on long term OCS; now weaned completely off OCS, or to the point of adrenal insufficiency	
Large improvement in asthma control	Well controlled asthma
	Large improvement in QOL
	Large improvement in FEV1
	Major reduction in maintenance inhaler therapy

Even if someone has not been completely exacerbation free, should a 75% or greater reduction in exacerbations be	Agree
	Neutral
	Disagree

<table>
<tr><td>a minor criterion for classifying someone as a super-responder?
Round 2 – 64.44% of participants stated a 75% or greater reduction in exacerbations is sufficient to classify someone as a super-responder.</td><td>Make a comment on your choice here:</td></tr>
<tr><td rowspan="4">In relation to asthma control, should having well controlled asthma (e.g ACQ<1.0) be a minor criterion for defining a super-responder?
Round 2 - there was strong support for a large improvement in asthma control, but the combination of well controlled asthma AND a large improvement in control did not quite achieve consensus (68.89% support).</td><td>Agree</td></tr>
<tr><td>Neutral</td></tr>
<tr><td>Disagree</td></tr>
<tr><td>Make a comment on your choice here:</td></tr>
<tr><td rowspan="4">The current tools for assessing quality of life can be difficult to implement in a clinical setting and it has been suggested further research is needed. Do you agree further research is needed surrounding quality of life tools?
<table>
<tr><td>Quality of life measurement tool</td><td>Round 2 responses</td></tr>
<tr><td>Severe Asthma Questionnaire</td><td>61.11% of participants stated more research is required</td></tr>
<tr><td>Asthma Quality of Life Questionnaire</td><td>51.11% of participants stated more research is required</td></tr>
<tr><td>Work productivity and activity impairment questionnaire</td><td>46.67% of participants suggested this can be used as a potential instrument</td></tr>
</table></td><td>Agree</td></tr>
<tr><td>Neutral</td></tr>
<tr><td>Disagree</td></tr>
<tr><td>Make a comment on your choice here:</td></tr>
</table>

	Visual analogue scale	38.89% of participants consider this a useful tool in assessing treatment response
	Global Rating of Change scale	41.11% of participants consider this a useful tool in assessing treatment response
Consensus has not been reached surrounding the use of quality of life measurements to define a super responder. Taking into consideration the fact that some participants are uncertain about how quality of life should best be assessed, do you think an improvement in quality of life should be a minor criterion?		Agree Neutral Disagree - it should not be part of the definition of a super-responder. Don't know Make a comment on your choice here:
Consensus was reached in round one that a large improvement in FEV1 might be one of the criteria used to define a super-responder. What is the appropriate definition of a large improvement in FEV1? ***Previous studies have reported that a Minimal Patient Perceivable Improvement (MPPI) in FEV1 is 230ml (Santanello et al, ERJ 1999). Round 2 – 62.22% of participants stated an improvement of 2 times the MPPI in FEV1 might be one of the criteria used to define a super-responder.***		500ml (2 times MPPI) 750ml (3 times MPPI) Not feasible Make a comment on your choice here:
Should a major reduction in maintenance inhaler therapy be a minor criterion for defining a super-responder? ***Round 1 – 55% of participants ranked a major reduction in maintenance inhaler***		Agree Neutral Disagree

therapy as the least important domain in defining a super-responder.	
A definition of a super-responder should be based on evidence of improvement across how many domains? ***Domains: Asthma exacerbations - major reduction or elimination, OCS - major reduction or elimination, asthma control – major improvement or quality of life improvement or FEV1 improvement.*** ***Round 2 – 58.89% of participants stated a super-responder should be based on evidence of improvement across three or more domains.***	One domain
	Two domains
	Three or more domains
	Make a comment on your choice here:

Supplementary Table E6. Delphi panel participants country of work 'other' (n=13)

Country of work = other	**Number**	**%**
Belgium	1	1.2%
Colombia	1	1.2%
Estonia	1	1.2%
Spain	1	1.2%
France	1	1.2%
Kuwait	1	1.2%
Netherlands	1	1.2%
New Zealand	1	1.2%
Portugal	1	1.2%
Saudi Arabia	1	1.2%
Singapore	1	1.2%
Taiwan	1	1.2%
UAE	1	1.2%

Supplementary Table E7. Delphi Round 3 patient scenario results summary

	Patient scenarios							
Major Criteria	1	2	3	4	5	6	7	8
Exacerbation elimination	yes	yes	yes	yes	yes	yes	no	no
Control (Large improvement)	yes	yes	yes	yes	no	no	yes	yes
OCS eliminate/major reduction	N/A	N/A	N/A	yes	yes	yes	yes	yes
Minor criteria								
Exacerbation ≥75% reduction	N/A	N/A	N/A	N/A	N/A	N/A	yes	yes
Well controlled asthma	yes	no	no	yes	no	no	yes	yes
FEV1 500ml improvement	no	no	yes	no	no	yes	no	yes
Consensus agreement	85.2%	16.1%	51.9%	90.1%	42.0%	65.4%	55.6%	79.0%