Additional information on QrC for Defining a severe asthma super-responder: findings from a Delphi process poster (ERS)

Methods

Panel selection

- In order to develop a robust consensus definition, it was important for the Delphi panel to include individuals with appropriate expertise and experience from a wide variety of countries. Invited panel members were required to have one or more of the following within the last 5 years:
    - Experience in clinical management of severe asthma patients
    - Participation in a severe asthma advisory board or national or international working group
    - Involvement as an author on severe asthma publications in peer-reviewed journals

Modified Delphi process

- A modified Delphi process was employed to reach consensus on the super-responder definition. Following a literature review of response criteria assessed in key phase 3 randomised controlled trials, the steering committee, together with a group of eleven other people with expertise in severe asthma, developed an initial set of statements and questions addressing various response domains including improvements in:
    - Asthma exacerbations
    - Asthma control
    - Quality of life (QOL)
    - Spirometry
    - Reductions in maintenance treatments
- The process consisted of 3 iterative Delphi rounds (R1, R2 and R3) in which statements and questions regarding potential response domains were sent to each panel member electronically.
- Panel members were required to complete the questionnaire within a 2 week period.
- At round closure all responses were analysed in an anonymised format to tabulate frequency of responses for each item to identify consensus.
- Consensus rules for inclusion or exclusion of an item in the definition of a super-responder were consistent throughout all three Delphi rounds.
    - Items receiving >70% agreement in any Delphi round were included or excluded in the definition of a super-responder.
    - Items receiving >50% and <70% agreement were included in the subsequent Delphi round.
    - Items receiving <50% agreement were removed, except where free text comments indicated that the question or statement was confusing, in which case a revised question/statement was included in the next Delphi round. The steering committee also added additional statements or questions to R2 and R3 based on panel member's comments.
- At the commencement of R2 and R3 panel members were provided with summary results from the previous round to facilitate an informed decision on those questions/statements where consensus was not previously achieved.

Results

Delphi R1

- One hundred and fifteen participants (90% specialist pulmonologists or allergists) from 27 countries completed R1.
- Participants were asked to rank potential super-responder (SR) criteria (1= highest; 6=lowest) and the results are listed in **Table 1.**
- A summary of the key statements achieving consensus and those with majority support but not achieving consensus are listed in **Table 2.**

Delphi R2

- Of the 115 participants from R1, 90 (78%) participated (93% specialist pulmonologists or allergists) from 24 countries in R2.
- A summary of the key statements achieving consensus, those with majority support but not achieving consensus as well as statements not achieving consensus are listed in **Table 3.**

Delphi R3

- Of the 90 participants from R2, 81 (90%) participated (94% specialist pulmonologists or allergists) from 24 countries in R3, further demographic details are provided in **Table 4.**
- A summary of the key statements achieving consensus, those with majority support but not achieving consensus as well as statements not achieving consensus are listed in **Table 5**.
- Participants were asked to respond with their agreement to several patient scenarios comprising different combinations of super-responder criteria observed over 12 months, as shown in **Table 6.**

Table 1. Delphi Round 1 results (ranking question)

Ranking	**Potential criteria**
1	Elimination or major reduction in asthma exacerbations
2	Elimination or major reduction in long term (maintenance) oral corticosteroids (OCS)
3	Major improvement in asthma control
4	Improvement in quality of life
5	Improvement in FEV1
6	Major reduction in maintenance inhaler therapy

Table 2. 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%

Table 3. 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%

[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
[4] MCID = minimally clinically important difference

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%

Table 4. Delphi round 3 participant demographic information (81 participants)

		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%
	Other	4	4.9%

[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 Tables.

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	13	16.0

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) $\geq$ 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%

Table 6. Delphi round 3 patient scenario results

	Patient scenarios							
	1	2	3	4	5	6	7	8
Major Criteria								
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%