

# THE LANCET

## Respiratory Medicine

### Supplementary appendix 2

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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## 1 Summary

Following a two round online Delphi survey an online consensus meeting was held on the 22<sup>nd</sup> November 2021 to discuss outcomes where, according to the pre-agreed definition of consensus, consensus for inclusion in, or exclusion from, the core outcome set (COS) had not been reached. This report summarises these discussions and the resulting core outcome set (table 2).

## 2 Pre-Meeting for people with long COVID and their carers

A one hour pre-meeting for people with long COVID and their carers was held on the 18<sup>th</sup> November. This session was led by the COMET Patient and Public Coordinator and aimed to provide information on core outcome sets and what to expect at the meeting and to offer an opportunity to meet the PC-COS team and to ask questions. Six participants attended the pre-meeting.

## 3 Consensus meeting participants

Thirty-three people attend the consensus meeting, including 4 non-voting members of the study team, 1 observer, 1 facilitator and 27 voting participants, who had completed both rounds of the online Delphi survey, attended the online meeting (15 health professionals/researchers, 12 people with long COVID/their carers). A comparison of the round 2 Delphi scores for these 27 participants, with the scores of the rest of the Delphi participants, did not reveal any major differences.

Some participants were unable to attend for the entire meeting or dropped in and out as a result of internet connection. The final number of voting participants for each outcome are included in this report.

In the online Delphi survey the results in round 2 were presented for three stakeholder groups: people with long COVID and their carers; health professionals or researchers with long COVID; and health professionals caring for people with long COVID or researchers undertaking long COVID research who themselves did not have long COVID. All were invited to express their interest in attending the online consensus meeting. The number of health professionals/researchers with long COVID able to attend was small (n=5). As a result, a decision was made prior to the meeting, without reference to the Delphi results, to have two voting groups only: people with long COVID/their carers; and healthcare professionals/researchers. Health professionals/researchers with long COVID were provided with descriptions of these two groups prior to the meeting and asked which group they felt was more appropriate for them to be in for the purpose of the consensus meeting.

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### Table 1. Consensus meeting participants

	N (%)
<b>Healthcare professionals/Researchers</b>	<b>15 (100)</b>
<b>Delphi stakeholder group</b>	
Health professional (including those who also do research) <sup>1</sup>	10 (67)
Researcher (without any clinical patient care duties) <sup>2</sup>	4 (26)
Health professional with Long COVID/Post-COVID condition <sup>1</sup>	1 (7)
<b>Country of residence</b>	
Belgium	1 (7)
Brazil	1 (7)
Canada	1 (7)
Chile	1 (7)
Ghana	1 (7)
India	2 (13)
Nigeria	1 (7)
Norway	1 (7)
Russia	1 (7)
Sweden	1 (7)
Switzerland	1 (7)
UK	1 (7)
USA	2 (13)
<b>People with long COVID and their carers</b>	<b>12 (100)</b>
<b>Delphi stakeholder Group</b>	
Person with Long COVID/Post-COVID Condition	7 (58)
Family member/caregiver of person with Long COVID/Post-COVID Condition	1 (8)
Health professional with Long COVID/Post-COVID condition <sup>3</sup>	4 (33)
<b>Country of residence</b>	
Belgium	1 (8)
Greece	1 (8)
Ireland	1 (8)
Spain	1 (8)
UK	7 (58)
USA	1 (8)
<sup>1</sup> Health professionals who care for people with long COVID	
<sup>2</sup> Researchers who undertake research in long COVID	
<sup>3</sup> Health professionals who do not provide care for people with long COVID	

#### 4 Outcomes

Twenty six outcomes were rated in round 2 of the online Delphi survey. The pre-agreed definition of consensus (appendix 1) was applied to ratings submitted in round 2 for each of the three stakeholder groups (Supplementary file – consensus matrix). Ten outcomes met the definition for “consensus in” to be

included in the core outcome set and five met the definition of “consensus out” and were excluded from the core outcome set. The remaining 11 outcomes had no consensus. Five outcomes, in four domains, included at least one, but not all, stakeholder groups where 80% or more of participants rated the outcome 7-9 and these were prioritised for discussion at the consensus meeting.

For a further two outcomes,  $\geq 65\%$  and  $< 80\%$  of participants in all stakeholder groups had rated the outcome 7-9 and these were also prioritised for discussion at the consensus meeting.

At the consensus meeting the results for outcomes for discussion in a particular domain were presented together with the outcomes, from the same domain, already included in the COS. Meeting participants were then invited to provide comments for inclusion of outcomes in the COS followed by comments against. After the discussion of an outcome, meeting participants anonymously rated the outcome using the 1-9 scale (1 not that important – 9 critically important). People with long COVID and their carers and health professionals/researchers voted separately. The same definition of consensus was applied i.e. for an outcome to be included in the core outcome set 80% or more of participants in both groups were needed to give a rating of 7-9.

The discussion and rating of outcomes was facilitated by an independent facilitator.

#### 4.1 Outcomes included after R2 of the Delphi

The study team had previously decided (prior to the Delphi) that to maintain some consistency with an earlier COS developed for the acute COVID-19 phase [1], the outcome “recovery” would automatically be included in the COS, to be measured with using the same scale as determined previously [1]. There was some discussion about the use of the recovery scale and that, for long COVID, only partial recovery might be expected. It was also noted that recovery may be non-linear.

Outcomes that reached the definition of consensus in after round 2 of the Delphi survey were presented.

The outcomes voted out after round 2 of the Delphi were also presented. These outcomes included “Reproductive and sexual functioning, symptoms, and conditions”, defined as “new onset or worsening problems with menstrual periods, infertility (i.e., ability to make a baby), desire for sex, ability to have sex, or discomfort during sex”. Meeting participants raised that the population voting may have impacted upon the final result. For example, those who menstruate may have rated the outcome more highly than those who did not. Whilst the Delphi survey asked participants their gender it did not ask whether someone menstruated or not and a review of data by gender may not accurately reflect this.

The research team noted the issues with aspects of this particular outcome and commented that the core outcome set agreed today should be the outcomes that are critical to measure in all research/clinical practice and applicable to all people with long COVID. The core outcome set agreed would represent the minimum that should be measured and that reproductive and sexual function outcomes could and should still be measured in studies where this outcome was relevant to the population and/or intervention.

## 4.2 Outcomes discussed in the consensus meeting

### 4.2.1 Mortality outcomes

One outcome “survival”, was prioritised for discussion in the mortality domain.

#### Survival

Arguments for inclusion made reference to registry studies that demonstrated higher mortality for people with long COVID. It was also noted that this outcome would be easy to measure.

There was some discussion about survival and that how long a participant should be followed up for is important, however this would be determined by the particular study using the COS.

#### Outcome of discussion and rating:

<b>Outcome: Survival</b>	<b>% rating 1-3</b>	<b>% rating 4-6</b>	<b>%rating 7-9</b>
People with long COVID and their carers (n=12)	17	0	83
Health professionals and researchers (n=12)	0	8	92
<b>Result</b>	<b>Outcome included in COS</b>		

#### 4.2.2 Physiological/clinical outcomes

Two outcomes were prioritised for discussion in the physiological/clinical domain. These were described and presented alongside outcomes in the same domain that had reached “consensus in” in the Delphi surveys.

##### Sleep-related functioning, symptoms, and conditions

Arguments for inclusion expressed that this was a common and debilitating symptoms for people with long COVID. Also that sleep functioning is related to neurological functioning and could impact on other symptoms for example fatigue, cognitive function, anxiety etc.

Arguments against noted that other related outcomes including “Nervous system functioning, symptoms, and conditions” and “fatigue or exhaustion” are already included in the COS and so there was a need to focus on what is core and should always be measured. The potential burden to patients and researchers of having a large number of outcomes as core was commented on at this stage. A counter argument was raised that this is a symptom that has a major impact on the patient’s quality of life and that there are ways to assess sleep that are not burdensome so the importance of sleep should be considered outside of the issues of assessment. It was also noted that whilst poor sleep can impact on fatigue and that fatigue can be present without sleep issues.

Meeting participants were reminded at this stage that, even though sleep could potentially form part of a neurological assessment it was important not to assume that this would be the case and to vote on the importance of specifically including sleep-related functioning, symptoms and conditions in the COS.

<b>Outcome: Sleep-related functioning, symptoms, and conditions</b>	<b>% rating 1-3</b>	<b>% rating 4-6</b>	<b>%rating 7-9</b>
People with long COVID and their carers (n=12)	0	25	75
Health professionals and researchers (n=12)	0	36	64
<b>Result</b>	<b>Outcome not included in the COS</b>		

##### Muscle and joint symptoms and conditions

Arguments for inclusion focused on the debilitating nature of muscle and joint symptoms and conditions. In particular muscle pain and its impact on activities of daily living was discussed.

No arguments for exclusion from the COS were put forward.

<b>Outcome: Muscle and joint symptoms and conditions</b>	<b>% rating 1-3</b>	<b>% rating 4-6</b>	<b>%rating 7-9</b>
People with long COVID and their carers (n=12)	0	8	92

Health professionals and researchers (n=12)	8	67	25
<b>Result</b>	<b>Outcome not included in COS</b>		

#### 4.2.3 Life impact outcomes

Two outcomes were prioritised in the life impact domain. “Satisfaction with life, or personal enjoyment” and “social role functioning and relationship problems” were described and presented alongside outcomes in the same domain that had reached “consensus in” in the Delphi surveys.

##### Satisfaction with life, or personal enjoyment - Satisfaction with life, or personal enjoyment, loss of being the person who you were

The outcome description was queried and noted that “loss of being the person who you were” could be seen as something separate. Discussions noted that this was an important outcome but not necessarily critically important as other physical symptoms already included in the COS are likely to have an impact on satisfaction with life and these physical symptoms are more important to measure.

Arguments against were put forward that although an important outcome, including it as critical would increase the participant burden in terms of patient reported outcome measures.

Satisfaction with life, or personal enjoyment	% rating 1-3	% rating 4-6	%rating 7-9
People with long COVID and their carers (n=12)	25	33	42
Health professionals and researchers (n=12)	9	64	27
<b>Result</b>	<b>Outcome not included in COS</b>		

##### Social role-functioning and relationships problems

There was a brief discussion for this outcome, noting that the physical symptoms already included in the COS were more important and that these impact on, for example, someone’s ability/desire to socialise.

Social role-functioning and relationships problems	% rating 1-3	% rating 4-6	%rating 7-9
People with long COVID and their carers (n=12)	42	33	25
Health professionals and researchers (n=12)	9	73	18
<b>Result</b>	<b>Outcome not included in COS</b>		



#### 4.2.4 Resource use outcomes

Two resource use outcomes were prioritised for discussion. No outcomes in this domain had met the definition of “consensus in” after the second round of the Delphi survey.

##### Family/carer burden

Discussions included the importance of family/carer support and the potential of ongoing symptoms to have a big impact on family/carer burden which would be a reason for including it in the COS. Other views were that whilst it was important it was not a core outcome critically important to measure all of the time.

<b>Outcome: Family/carer burden</b>	<b>% rating 1-3</b>	<b>% rating 4-6</b>	<b>%rating 7-9</b>
People with long COVID and their carers (n=12)	25	42	33
Health professionals and researchers (n=12)	0	64	36
<b>Result</b>	<b>Outcome not included in COS</b>		

##### Healthcare resource utilisation

Participants talked about the availability of healthcare resources and the importance of measuring whether an intervention reduced the need for resource use. It was also noted that it was important to document service provision and service use including instances where people seek private treatment and the reasons for this i.e. a service is not available in the area that they live. The importance of capturing the economic cost of social care was also raised.

The arguments against inclusion focused on the researcher burden of capturing the outcome. The study team noted that a cost-effectiveness study would measure these outcomes if it was the objective of the study.

<b>Outcome: Healthcare resource utilisation</b>	<b>% rating 1-3</b>	<b>% rating 4-6</b>	<b>%rating 7-9</b>
People with long COVID and their carers (n=12)	0	8	92
Health professionals and researchers (n=12)	0	27	73
<b>Result</b>	<b>Outcome not included in COS</b>		

## 5 Meeting Feedback

### Pre-Meeting Feedback

An electronic questionnaire was provided for participants to complete in Zoom at the end of the pre-meeting.

A copy of the questionnaire is provided in appendix 2. Participants were asked to respond to questions using a 1 – 5 Likert scale, with 1 anchored to “strongly disagree”, 3 to “neither” and 5 to “strongly agree”.

Question	Mean response (N=6)
I was satisfied with the information provided in this meeting	5.0
I understand what the consensus meeting next week will be about	4.8
I understand my role in the consensus meeting	4.8
I feel encouraged to share my opinion during the consensus meeting	4.8
The length of this pre-meeting was about right	4.7
I felt able to ask questions and have them answered	4.8
I am happy that I attended this pre-meeting	4.7

### Consensus Meeting Feedback

An electronic questionnaire was sent to meeting participants, by email, after the consensus meeting. A total of 14 responses were received one week after the feedback questionnaire was sent (58%, taking into account responses were not expected from the three voting PC-COS investigators present at the meeting). A copy of the questionnaire is provided in appendix 2. Participants were asked to respond to questions using a 1 – 5 Likert scale, with 1 anchored to “strongly disagree”, 3 to “neither” and 5 to “strongly agree”. A free text field was used for any other feedback to be provided.

Question	Mean response - people with long COVID and their carers (N=6)	Mean response – Healthcare professionals and researchers (N=8)
The information that the meeting organisers provided me with in advance of the meeting was helpful	4.2	4.5
I was satisfied with the process used to agree the core outcomes set today	3.5*	4.4
I was satisfied with the way the meeting was facilitated.	4.3	4.8
I felt able to contribute to the meeting†	4.2†	4.6
I felt comfortable in communicating my views	4.0	4.6
The workshop produced a fair result	3.2*	4.4
*Person a disagreed with this statement † Person b disagreed with this statement		

Suggestions for how the meeting could have been improved included increasing accessibility for international participants who did not speak English and repeating the already included outcomes more frequently so that areas covered already could be taken into consideration more easily. One response indicated that more debate was needed. One response also noted that the perceived burden to healthcare professionals/researchers for some outcomes may have affected the vote in that group. However, the study team did reiterate in the meeting that the burden to patients was a major consideration.

## 6 Discussion

Ten outcomes were included, in the core outcome set, after the two round online Delphi survey and one further outcome “survival” was added at the consensus meeting. In addition the outcome “recovery” reported in the published COS for people with COVID 19 [1] is included in the COS as this was considered relevant – the agreed core outcome set of 12 outcomes is reported in Table 2.

**Table 2. Outcomes included in the Core Outcome Set**

Domain	Outcome	Outcome description
Mortality	Survival	How long does someone live
Physiological/Clinical Outcomes	Cardiovascular functioning; symptoms; and conditions	New onset or worsening of problems affecting the heart (e.g. pounding or racing heart) and the blood vessels (e.g., veins or arteries)
	Fatigue or Exhaustion	New onset or worsening in severity or duration of feeling exhausted, having too little energy, or needing more rest
	Pain	New onset or worsening of problems related to uncomfortable feelings in the body that can include sharp or burning pain, dull ache, or stinging or throbbing feeling, pain that comes and goes
	Nervous system functioning; symptoms; and conditions	New onset or worsening of dizziness, fainting, headache, tremors/shaking, seizures/fits, muscle twitching, tingling feelings, decreased sensation, stroke, inability to move part of the body, lack of coordination, or speech difficulty
	Cognitive functioning; symptoms; and conditions	New onset or worsening problems with memory, communication, concentration, or understanding instructions
	Mental functioning; symptoms; and conditions	New onset or worsening problems with emotions and mood, including anxiety/worrying, panic attacks, depression, suicidal thoughts, or post-traumatic stress disorder
	Respiratory functioning; symptoms; and conditions	New onset or worsening problems with lungs or breathing (e.g., shortness of breath, chest tightness. or coughing)
	Post-exertion symptoms	Worsening of symptoms following physical or mental exertion that can last for a prolonged duration
Life Impact Outcomes	Physical functioning; symptoms; and conditions	New onset or worsening problems with physical abilities, including muscle strength, arm/leg shaking or unsteadiness, walking, dressing, or eating
	Work/occupational changes and study	New onset or worsening problems with being able to resume work, study or activities/hobbies
<b>Outcomes included from the COVID-19 COS [1]</b>		
	Recovery	The absence of symptoms related to the illness, the ability to do usual daily activities, and a return

		to a previous state of health and mind (prior to the COVID-19 illness)
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Discussions at the consensus meeting highlighted differing stakeholder viewpoints for some outcomes. This dissonance was particularly marked for muscle symptoms and conditions with 92% of people with long COVID rating the outcome as critically important compared to only 25% of healthcare professionals. Instead the majority of health professionals (67%) considered the outcome important but not critical. Relevant studies may want to measure muscle symptoms and conditions and should be encouraged to do this where it is relevant. Muscle pain specifically was discussed and further consideration should be given to how this relates to the included “pain” and “physical functioning” outcomes. This issue will be taken forward in the next stage of the research where how outcomes should be measured will be agreed.

There was also a difference between stakeholder groups for the outcome “healthcare resource utilisation”, which met the definition of consensus “in” for people with long COVID and their carers but did not for health professionals and researchers. This outcome may often be measured in trials where the funder requires an economic analysis but did not meet the criteria for inclusion in the COS to be measured in all studies.

The next steps will focus on agreeing how each of the twelve outcomes included in the core outcome set should be measured.

## References

1. Tong A, Baumgart A, Evangelidis N, et al. Core Outcome Measures for Trials in People With Coronavirus Disease 2019: Respiratory Failure, Multiorgan Failure, Shortness of Breath, and Recovery. *Crit Care Med.* 2021;49(3):503-516. doi:10.1097/CCM.0000000000004817

## Appendix 1

Pre-defined definition of consensus applied in the consensus meeting

Consensus classification	Description	Definition
Consensus in	Consensus that outcome should be included in the core outcome set	80% or more of participants in each stakeholder group rating the outcome 7-9
Consensus out	Consensus that outcome should not be included in the core outcomes set	Anything else

## Appendix 2

### Pre-Meeting Feedback questionnaire

Question	Response options				
I was satisfied with the information provided in this meeting	1 Strongly disagree	2 Disagree	3 Neither	4 Agree	5 Strongly Agree
I understand what the consensus meeting next week will be about	1 Strongly disagree	2 Disagree	3 Neither	4 Agree	5 Strongly Agree
I understand my role in the consensus meeting	1 Strongly disagree	2 Disagree	3 Neither	4 Agree	5 Strongly Agree
I feel encouraged to share my opinion during the consensus meeting	1 Strongly disagree	2 Disagree	3 Neither	4 Agree	5 Strongly Agree
The length of this pre-meeting was about right	1 Strongly disagree	2 Disagree	3 Neither	4 Agree	5 Strongly Agree
I felt able to ask questions and have them answered	1 Strongly disagree	2 Disagree	3 Neither	4 Agree	5 Strongly Agree
I am happy that I attended this pre-meeting	1 Strongly disagree	2 Disagree	3 Neither	4 Agree	5 Strongly Agree

### Consensus meeting feedback questionnaire

Question	Response options				
The information that the meeting organisers provided me with in advance of the	1 Strongly disagree	2 Disagree	3 Neither	4 Agree	5 Strongly Agree

meeting was helpful					
I was satisfied with the process used to agree the core outcomes set today	1 Strongly disagree	2 Disagree	3 Neither	4 Agree	5 Strongly Agree
I was satisfied with the way the meeting was facilitated.	1 Strongly disagree	2 Disagree	3 Neither	4 Agree	5 Strongly Agree
I felt able to contribute to the meeting	1 Strongly disagree	2 Disagree	3 Neither	4 Agree	5 Strongly Agree
I felt comfortable in communicating my views	1 Strongly disagree	2 Disagree	3 Neither	4 Agree	5 Strongly Agree
The workshop produced a fair result	1 Strongly disagree	2 Disagree	3 Neither	4 Agree	5 Strongly Agree
Is there anything else that could have been done to make the meeting better?	Free Text				
Is there anything else you'd like to tell the study team?	Free text				

Appendix 3 – Summary table of R2 and consensus meeting ratings

Domain	Outcome	Outcome description	% people with long COVID rating 7-9 in the online Delphi	% HCPs/researchers with long COVID voting 7-9 in the online Delphi	% HCPs /researchers voting 7-9 in the online Delphi	% people with long COVID voting 7-9 in consensus meeting	% HCPs voting 7-9 in consensus meeting	Result
Mortality outcomes	Survival	How long does someone live	79	86	90	83	92	Included in the COS
Physiological/clinical outcomes	Sleep-related functioning; symptoms; and conditions	New onset or worsening of problems with falling or staying asleep, need for sleeping medications/aids, excessive sleepiness, or lack of refreshing sleep/poor sleep quality	80	87	75	75	64	Not included in the COS
	Muscle and joint symptoms and conditions	New onset or worsening of joint or muscle problems, such as muscle weakness or joint stiffness or swelling	81	85	60	92	25	Not included in the COS
Life impact outcomes	Satisfaction with life; or personal enjoyment	Satisfaction with life, or personal enjoyment, loss of being the person who you were	80	84	76	42	27	Not included in the COS
	Social role-functioning and relationship	New onset or worsening problems with connecting with others, maintaining friendships and romantic relationship	65	78	76	25	18	Not included in the COS

	s problems							
<b>Resource Use Outcomes</b>	Family/care r burden	Being a burden on caregiver/family or friends/colleagues; impact of sickness on other people in your life	67	77	69	33	36	Not included in the COS
	Healthcare resource utilisation	Seeing more healthcare professionals (e.g., doctor, physiotherapist, psychologist); taking new medications; returning to the hospital or emergency care; including complimentary/alternative medicine (e.g., acupuncturists, naturopaths)	77	81	75	92	73	in the COS