Core Outcome Set for Research and Clinical Practice in Post COVID-19 Condition (Long COVID): An International Delphi Consensus Study 'PC-COS'

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Contributions: DM and TN conceived the idea for the study. PW led the methodological team. DM, TN, PW and DMN designed the study protocol and were responsible for the day to day running of the project. NSe, CP, AK and JC undertook the literature review, identified outcomes and categorised them for inclusion in the online Delphi survey. NSe coordinated the data revision process. NH, SLG and NSe developed the online Delphi surveys and contributed to the day to day management of the project. DM, TN, WDG, NSc, JP, PO, CA, AT, JS, DMN and PW participated in the project methodology discussions throughout the duration of the project. SLG and NH undertook the data analysis and organised the consensus meeting. JP coordinated the translation of study materials and smooth communication with the WHO. JVD provided the lead for WHO administrative aspects of the study. FS and AA provided invaluable patient perspectives throughout the study. DM drafted the manuscript; all authors reviewed and approved the final manuscript.

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Abstract

Background

Recent data suggest that many people experience Post COVID-19 Condition (Long COVID) following the acute phase of the SaRS CoV-2 infection. At present there is no agreement on what patient health outcomes should be measured in Post COVID-19 Condition. We aimed to identify core outcomes for Post COVID-19 Condition that stakeholders considered critical to assess in all research studies and clinical practice.

Methods

We conducted a multi-step study: (1) review of outcomes reported in studies of Post COVID-19 Condition to develop a list of potential core outcomes; (2) outcomes were then grouped, using the COMET taxonomy, to present in a consensus process; (3) a two-round online international modified Delphi consensus process, including 3 stakeholder groups ('people with Post COVID-19 Condition and their carers', 'healthcare professionals and researchers' and 'healthcare professionals and researchers with Post COVID-19 Condition) to prioritise outcomes; and (4) an international online consensus meeting to finalize the core outcome set. Consensus 'in' was defined, a priori, as 80% or more of each stakeholder group rating an outcome as critical ('7-9' on a 9-point scale). Patient engagement and global outreach activities were undertaken at all stages of the project.

Findings

1535 participants from 71 countries, representing six continents, were involved in the online modified Delphi process, with 1148 participating in both rounds (75% completion rate). Eleven of 24 outcomes met consensus 'in' criteria after the two Delphi rounds and consensus meeting: fatigue or exhaustion; pain; post-exertion symptoms; work/occupational and study changes; survival; and "functioning, symptoms and conditions" for each of the following outcomes: cardiovascular, respiratory, nervous system, cognition, mental and physical. 'Recovery' outcome was added 'a-priori' as a part of previously published COS on COVID-19.

Interpretation

This international study resulted in the development of a COS for Post COVID-19 Condition using a rigorous methodology. The generated consensus-based list of core outcomes should be assessed in clinical research and practice settings. The next step for the development of this COS will be to determine which measurement instruments best measure these outcomes.

Introduction

Coronavirus disease 2019 (COVID-19) may have a wide variety of consequences, including persistence of symptoms for many months after the acute phase. Different names have been suggested for this phenomenon, including Long COVID, Post-Acute Sequelae of SARS-CoV-2 infection (PASC), and or post-COVID syndrome.

The World Health Organization (WHO) uses the term post COVID-19 condition and a recent WHO consensus process defines it as a "condition that occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time."[1]

With a rapid increase in the number of studies investigating post COVID-19 condition, there are many different outcomes evaluated. Such heterogeneity is a common problem across medical research hampering the ability to compare and contrast research, and conduct meta-analyses to inform evidence-based decision making e.g. regarding effective treatments. To address this issue and help ensure that critical outcomes are consistently assessed, Core Outcome Sets (COS) are increasingly being developed. A COS is defined as "an agreed standardised collection of outcomes which should be measured and reported, as a minimum, in all [clinical] trials for a specific clinical area"[2]. COS are also suitable for use in other types of research and clinical practice [3].

There is an urgent need to develop a COS for post COVID-19 condition to ensure that critically important outcomes are measured and reported in a consistent manner. Herein, we report on the development of a COS for post COVID-19 condition in adults for use in clinical research and practice.

Methods

This project was undertaken by an international and multidisciplinary group of experts and people with lived experience of COVID-19 and their carers, under the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) umbrella, in collaboration with the Core Outcome Measures in Effectiveness Trials (COMET) Initiative and the World Health Organization (WHO). An International Steering Committee with members from six continents, including healthcare professionals, researchers, methodologists, WHO representatives, and people with post COVID-19 condition and their carers, were actively involved in the design and conduct of this project. The 'core group' responsible for the study methodology and management included DM, TN, DMN and PW who act as guarantors.

Development of the COS included three stages: 1. A review of outcomes reported in studies of post COVID-19 condition in order to develop a list of outcomes for stakeholder consideration, 2. A two round online modified Delphi consensus process to rate the importance of these outcomes for a COS, and 3. An online interactive consensus meeting to review and agree upon the final COS. These steps are described in further detail below.

The study protocol has been developed a priory. The project was registered a priori (https://www.comet-initiative.org/Studies/Details/1847) with funding by the National Institute for Health Research (NIHR) (Grant COV-LT2-0072) supporting the second stage of the process. Ethical approval for the study was given by the UK Health Research Authority and by the South West - Cornwall & Plymouth Research Ethics Committee (REC number 21/SW/0109).

The intended COS was developed for adults (>=18 years of age) and applies to post COVID-19 condition in both clinical research and practice settings. Throughout the COS development process, the terms post COVID-19 condition and Long COVID were used interchangeably.

Developing a list of outcomes

An extensive list of outcomes, informing the COS consensus process, was created using data from a living systematic review [4], clinical trial protocols and additional studies, including a patient-led survey [5], and a list of additional references suggested by experts involved (Table S1). The search strategy used in the living systematic review was restricted to publications and protocols written in English and is presented elsewhere [4]. Selected studies published beyond the systematic review search period (till 17 March 2021), as well as other systematic reviews, narrative reviews and opinion papers were also reviewed. Research protocol data were extracted from two clinical trials registries, the National Library of Medicine's Clinical Trials.gov and International Clinical Trials Registry Platform (ICTRP), and reviewed by one of four independent reviewers (NSe, AK, CP, JC). All reported outcomes were extracted verbatim.

Unique outcomes from the list were classified using an existing taxonomy by Dodd *et al* (Table S2), with iterative review and discussion by the methodology group, 'core group' and the project steering committee to generate a list of outcomes presented in Round 1 of the modified Delphi consensus process. The final list of outcomes was approved by the International Steering Committee.

Stakeholder groups

Stakeholders were classified into the following three groups: 'people with post COVID-19 condition and family members/caregivers', 'healthcare professionals and researchers without post COVID-19 condition' and 'healthcare professionals and researchers with post COVID-19 condition'. Prerequisites for participation for healthcare professionals and researchers were experience of treating people with post COVID-19 condition and research in the field of post COVID-19 condition, respectively.

Modified Delphi Consensus Process

The consensus process involved a two round online modified Delphi process in which participants were asked to rate each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) scale [6], a 9-point scale that is commonly divided into 3 categories for COS projects: Not Important (1 – 3), Important but Not Critical (4 – 6), and Critical (7 – 9). An option of "unable to rate" was also provided together with the ability to add text-based comments for each outcome.

The Delphi and all participant information materials were available in English, Chinese, Russian, French and Spanish. The Delphi survey was delivered using DelphiManager software (http://www.comet-initiative.org/delphimanager).

Relevant stakeholders were invited to take part in the Delphi process either by direct email, including a direct link to the join the consensus process, from the study team or from relevant patient or professional organisations. Patients from "Long COVID clinical services" were also sent email invitations. Calls for participation were also disseminated via international and local patient organisations and large private "Long COVID" social media groups (Table S3). Relevant stakeholder group descriptions and a contact email were also provided on a study website (https://www.pc-cos.org). These additional stakeholders received Delphi registration links after eligibility confirmation by study team members (NSe, AK) and, if needed, discussion with the 'core group'.

Reminder emails were sent to registered participants, who had not yet completed the survey, at 1 week and 2 weeks after survey launch. In the first Delphi round participants were given information describing the objective of a COS and this project, and then provided with the list of outcomes (accompanied with text providing a simple description for each outcome (Table S4)) and were asked to rate their importance for inclusion in the COS. Participants were also asked to suggest any additional important outcomes. Any additional outcomes submitted were reviewed by the 'core group' to ensure no redundancy with original outcomes before inclusion in the second round.

In the second round of the Delphi process, participants were shown their prior rating from the first round, together with ratings of each of the three stakeholder groups (presented as the distribution of 1-9 ratings for each outcome) and asked to consider this information and again rate the outcome using the 1-9 scale. Only participants rating 50% or more of the outcomes in the first round were invited to the second survey. All outcomes from the first round were carried through to the second round. Reminder emails, highlighting the importance of completing the second round, were sent at regular intervals to participants who had not submitted their responses.

Definition of consensus on outcome inclusion/exclusion

A priori consensus for inclusion of an outcome in the COS was defined as 80% or more of participants, in each stakeholder group, rating an outcome 7-9 (critically important).

Consensus for exclusion of an outcome from the COS was defined as ≤50% of the respondents, in each stakeholder group, rating the outcome 7-9 (critically important).

Consensus meeting

An online interactive consensus meeting was held using the Zoom platform. The meeting was conducted in English and chaired by an experienced independent facilitator. Participants completing both rounds of the Delphi survey were eligible to participate and were asked to express their interest during the online Delphi process. These expressions of interest were considered to help assure distribution of attendees across the stakeholder groups and

international representation. There were 27 voting participants who agreed to take part. There were only five health care professionals or researchers with post COVID-19 condition who agreed to take part; this was not sufficiently large for consensus-related voting as a separate stakeholder group so they were asked to select which of the other two groups they would be most appropriate to join; one joined the health care professionals or researchers group, and four joined the patient group. These final two stakeholder groups had the following composition: 12 Patients (7 UK, 1 Ireland, 1 Greece, 1 Belgian, 1 Spain, 1 USA), 15 health care professionals/researchers (2 USA, 2 India, 1 UK, 1 Russia, 1 Chile, 1 Switzerland, 1 Belgium, 1 Brazil, 1 Norway, 1 Canada, 1 Sweden, 1 Nigeria, 1 Ghana). Prior to attending the meeting, participants received background information and a copy of their own ratings from the Delphi survey and a summary of outcomes that would be discussed at the meeting. People with lived experience and their carers were also invited to attend a pre-meeting, led by the COMET Patient and Public Coordinator, where they were provided with further information about the purpose of COS, what to expect at the consensus meeting and had the opportunity to ask questions.

The consensus meeting was structured using results from the second Delphi round based on the outcomes which had reached the pre-defined definition of consensus "in" and consensus "out". Outcomes where at least one stakeholder group, but not all, had reached the definition of consensus "in" were prioritised for discussion. Outcomes where 65% or more, but less than 80% of participants in each stakeholder group rated the outcome 7-9 were also included for discussion. All arguments in favour of inclusion of the outcome were invited first, followed by arguments against. After discussion participants were invited to confidentially rate the outcome again, using the 1-9 scale. Stakeholder groups rated outcomes separately and the same criteria for inclusion were applied i.e. 80% or more participants in each stakeholder group rating the outcome 7-9, "critically important".

Statistical analysis

Free text comments were translated from the French, Russian, Spanish and Chinese surveys into English and collated and reviewed by the group. We used descriptive statistics for the scores for each outcome across the three stakeholder groups. It was agreed a priori that only participants who rated at least 50% of outcomes would be included in the analysis. The data analysis process from Round 1 was repeated for Round 2. Graphs displaying the distribution of ratings for each outcome, stratified by stakeholder group, were produced using R (version 4.0.2) [7].

Attrition bias between Delphi rounds 1 and 2 was assessed by calculating the mean overall Round 1 score for each participant. The distribution of the mean Round 1 scores for participants who completed both Rounds 1 and 2 was compared to the mean scores for participants completing Round 1 only and displayed graphically, stratified by stakeholder group.

Results

Identification of outcomes

Review of the existing evidence (i.e., living systematic review, clinical trial protocols and additional papers, including a major patient-led survey [5]) resulted in 268 studies and/or trials, eligible for inclusion that reported a total of 200 individual outcomes.

The final list of outcomes (Table S4) that was rated in the first round of Delphi included 24 outcomes grouped under four domains (mortality n=1, life impact n = 5, physiological/clinical n=16, resource use n=2). The order in which each outcome was presented to participants in the online Delphi process was randomised by domain.

Online Delphi Consensus Process

The first round of the Delphi took place between 5 August and 13 September 2021, with a total of 1535 participants from 71 countries participating. Of these 1533 participants invited to the second Delphi round, 75% (1148/1535) from 59 countries rated 50% or more of the outcomes. Demographic characteristics and responses, by stakeholder group and country of residence, are presented in Table 1. The detailed list of participants is presented in the table S5.

Response rates in the second round (compared to Round 1 participation) were: 71% for 'people with post COVID-19 condition and family members/caregivers', 80% for 'healthcare professionals and researchers without post COVID-19 condition' and 75% for 'healthcare professionals and researchers with post COVID-19 condition'. In assessing attrition bias (Table S6) the average scores of participants completing Round 1 only were similar to the average scores of those completing both rounds of the Delphi process (Table S7).

Table 1. Participant characteristics

	Round 1	**Round 2**
	***n* = 1535**	***n* = 1148**
Stakeholder group, *n (%)*		
People with post COVID-19 condition and family members/caregivers	810 (53)	579 (50)
Healthcare professionals and researchers with post COVID-19 condition	169 (11)	126 (11)
Healthcare professionals and researchers without post COVID-19 condition	556 (36)	443 (39)
Gender, *n (%)*		

Male	392 (26)	301 (26)
Female	1135 (74)	841 (73)
Non-binary, other or no answer	6 (<1)	4 (<1)
Other	1 (<1)	1 (<1)
Prefer not to answer	1 (<1)	1 (<1)
Age group, *n (%)*		
18-29	89 (6)	57 (5)
30-39	404 (26)	299 (26)
40-49	565 (37)	423 (37)
50-59	343 (22)	262 (23)
60-69	119 (8)	94 (8)
70-79	15 (1)	13 (1)
Geographical areas, *n (%)**		
Asia	95 (6)	60 (5)
Africa	31 (2)	21 (2)
Australasia	29 (2)	24 (2)
Europe	1015 (66)	763 (66)
North America	287 (19)	226 (20)
South America	77 (5)	53 (5)
Ethnicity, *n*		

White	975 (64)	753 (66)
South Asian	68 (4)	47 (4)
Hispanic/Latino/Spanish	350 (23)	246 (21)
East Asian/Pacific Islander	43 (3)	33 (3)
Indigenous peoples	4 (<1)	4 (<1)
Black	25 (2)	16 (1)
Middle Eastern/North African	12 (1)	10 (1)
Other	58 (4)	39 (3)

*One participant in each survey did not specify their location.

At the end of the first round of Delphi, 10 of the 24 outcomes reached consensus for inclusion in the COS. Eight outcomes represented 'physiological/clinical outcomes' domain (fatigue or exhaustion; pain; cardiovascular functioning, symptoms, and conditions; respiratory functioning, symptoms, and conditions; nervous system functioning, symptoms, and conditions; cognitive functioning, symptoms, and conditions; mental functioning, symptoms, and conditions; post-exertion symptoms) and two 'life impact outcomes' domain (work/occupational and study changes; physical functioning, symptoms, and conditions) (Table S8).

A total of 520 free text responses suggesting additional outcomes were received, with two additional outcomes identified for the second Delphi round: "eye symptoms and conditions", reported in 13 responses and "muscle and joint symptoms and conditions", reported in six.

Delphi Round 2 was conducted between 1 October and 5 November 2021, with participants rating 26 outcomes with 10 meeting criteria for "consensus in" and 5 for "consensus out". For five outcomes at least one, but not all, stakeholder groups rated it as "consensus in": survival, sleep related functioning, symptoms and conditions, muscle and joint symptoms and conditions, satisfaction with life or personal enjoyment, and healthcare resource utilisation. These were considered at the subsequent consensus meeting. Six outcomes did not reach the required cut-off for inclusion within all three groups. However, two of these outcomes "social role- functioning and relationship problems" and "family carer burden" were rated 7-9 by 65% or more in each of the groups and were considered at the consensus meeting.

Consensus meeting

Thirty participants were invited to the consensus meeting, of whom 27 attended ('people with post COVID-19 condition and family members/caregivers' (n=8); 'healthcare professionals and researchers with post COVID-19 condition' (n=5); 'healthcare professionals and researchers without post COVID-19 condition' (n = 14).

Due to the limited number of attendees from the 'healthcare professionals and researchers with post COVID-19 condition' group for consensus voting at the meeting, these five participants self-selected allocation into one of the other two groups: 'people with post COVID-19 condition and family members/caregivers' and 'healthcare professionals and researchers'. The voting participants of the consensus meeting are described in table S9.

The seven outcomes were discussed in the following order: survival; sleep functioning, symptoms and conditions; muscle and joint functioning, symptoms and conditions; satisfaction with life; social role-functioning and relationships problems; family/carer burden; healthcare resource utilisation. After discussion and voting only one outcome, 'survival,' met the predefined criteria for consensus and was added to the COS (**Box 1**).

Box 1. Consensus core outcomes:

Physiological/clinical outcomes

1. Cardiovascular functioning, symptoms and conditions
2. Fatigue or Exhaustion
3. Pain
4. Nervous system functioning, symptoms and conditions
5. Cognitive functioning, symptoms and conditions
6. Mental functioning, symptoms and conditions
7. Respiratory functioning, symptoms and conditions
8. Post-exertion symptoms

Life impact outcomes

9. Physical functioning, symptoms and conditions
10. Work/occupational and study changes

Survival

11. Survival

Outcome from the previous COS

12. Recovery*

*Outcome was added 'a-priori' as a part of previously published COS on COVID-19 [8]

A full report of the consensus meeting is provided in **Supplementary material**.

Discussion

We report on a large, rigorous international consensus study of 1535 participants from 71 countries (including 53% people with lived experience and their carers) to develop a core outcome set for post COVID-19 condition, for use in clinical research and practice. A two-round online international modified Delphi process (presented in 5 languages) followed by an interactive, facilitated online consensus meeting was conducted with very good participation and retention across all three stakeholder groups ('people with post COVID-19 condition and family members/caregivers', 'healthcare professionals and researchers without post COVID-19 condition' and 'healthcare professionals and researchers with post COVID-19 condition'). Eleven outcomes achieved the a priori criteria consensus for inclusion in the COS focusing on: fatigue or exhaustion; pain; post-exertion symptoms; work/occupational and study changes; survival; and "functioning, symptoms and conditions" for each of the following outcomes: cardiovascular, respiratory, nervous system, cognition, mental and physical. It was also agreed that 'recovery' outcome should be added as a part of previously published COS on COVID-19 [8].

A COS is defined as an agreed-upon minimum set of outcomes that should be measured and reported in all studies in a specific field, highlighting critical outcomes that matter most to relevant stakeholders. A COS does not prohibit researchers from including other outcomes but provides a minimum recommendation of the outcomes to be measured and reported in every study in the field. The "gold standard" approach to COS development has been outlined by the Core Outcome Measures in Effectiveness Trials (COMET) Initiative.

Consensus regarding outcome importance is often conducted using a modified Delphi process with a group of relevant stakeholders, including researchers, healthcare professionals, methodologists and patient representatives. In this project, patient/caregiver involvement was ensured throughout the entire COS development. The consensus process included stakeholders from 71 countries across six continents, under the ISARIC umbrella, in collaboration with the COMET initiative and the WHO to increase generalisability and worldwide applicability of this project's findings.

Complexity and multidimensionality of post COVID-19 condition is reflected in multiple studies, reporting the involvement of many different organ systems. It has been hypothesised that different post COVID-19 condition phenotypes may exist, although exact causes, management and outcomes are unknown. The WHO definition of post COVID-19 condition includes the most prevalent symptoms, such as fatigue, shortness of breath, cognitive dysfunction that generally have an impact on everyday functioning. Fluctuating or relapsing symptoms are also commonly reported. As reflected in the WHO definition, people with post COVID-19 condition can have other symptoms. Eight of the eleven outcomes in this COS are within the physiological/clinical outcome domain and cover all of the most prevalent symptoms reported in existing research. The developed COS is complementary to the WHO definition as both are aiming at harmonisation. The definition provides a standardised term for post COVID-19 condition, while the COS identifies the minimum outcomes that should be measured in all research studies and clinical practice.

There was a general agreement across stakeholder groups for most outcomes. One difference occurred with the "muscle and joint symptoms and conditions" outcome, with 92% of 'people

with post COVID-19 condition and family members/caregivers' scoring this outcome as critical, while only 25% of 'healthcare professionals and researchers' voting this outcome as critical, reflecting distinct stakeholders' perspectives. Although "muscle and joint symptoms and conditions" did not meet an a priori consensus criteria for inclusion in the COS this result shows high importance of this outcome among people with post COVID-19 condition, which should be considered by researchers and clinicians. We would like to underscore that absence of a particular outcome in the COS does not mean that this outcome is not important. Importance of "muscle and joint symptoms and conditions" was acknowledged by both stakeholder groups (100% of 'people with post COVID-19 condition and family members/caregivers' and 92% of 'healthcare professionals and researchers' rated this outcome as 'important' or 'critical'), however, it is not critical enough to be recommended for inclusion in the COS to be measured in every study.

This COS project focused on adults. Children and young people also may develop post COVID-19 condition, although data are still emerging. The necessity of COS development for children with post COVID-19 condition has been previously highlighted and the need for COS in this population was raised during the consensus meeting. Although this study excludes the paediatric population we acknowledge the importance of COS development for this age group [9].

With millions of people affected by COVID-19, even a small percentage developing post COVID-19 condition will result in a detrimental effect on society and public health, with many people in need of long-term follow-up, management and support [10]. There is a growing need for patients' and their carers' voices to be heard. COS development is an urgent priority as such research markedly expands. This project is aiming to ensure that research is directed towards evaluating outcomes of critical importance for people suffering from post COVID-19 condition. The COS presented in this manuscript is the result of the consensus from clinicians, researchers, and people with lived experience and their carers, which is important to relevant stakeholder groups, including research funders and policymakers to help advance the field via improving harmonisation and comparability.

A consensus-based COS for post COVID-19 condition was developed and included the following outcomes: fatigue or exhaustion; pain; post-exertion symptoms; work/occupational and study changes; survival; and "functioning, symptoms and conditions" for each of the following outcomes: cardiovascular, respiratory, nervous system, cognition, mental and physical. 'Recovery' was added a-priori as a part of previously published COS on COVID-19 [8]. Although twelve domains is a very large number for a regular COS it is understandable and expected for a new conditions such as post COVID-19 condition and can bring harmonisation in early stage of research. Once the condition is better understood the COS may be revised and the number of domains may be reduced to guarantee higher feasibility. Future research will establish which measurement instruments are the most appropriate to measure the core outcomes.

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