Core Outcome Set for Research and Clinical Practice in Post COVID-19 Condition (Long COVID) in Adults: 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 people with lived experience perspectives throughout the study. DM drafted the manuscript; all authors reviewed and approved the final manuscript.

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Summary

Currently, no agreement exists on which health outcomes should be measured in post COVID-19 condition. To address this, a rigorous multi-step modified Delphi consensus study was conducted, which included a comprehensive literature review and grouping of outcomes in post COVID-19 condition that informed a two-round online modified Delphi process followed by an online consensus meeting to finalise the core outcome set (COS). 1535 participants from 71 countries, representing six continents, were involved, with 1148 participating in both Delphi rounds. Eleven outcomes met consensus for the COS: fatigue; 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. A 'Recovery' outcome was added a-priori due to being part of a previously published COS on COVID-19. This international consensus-based COS provides a framework for assessing post COVID-19 condition in global clinical research and practice settings.

Key messages

Rationale and approach

- Post COVID-19 Condition (Long COVID) encompasses a very wide variety of sequalae that can persist for many months after infection with SARS-CoV-2.
- Research and clinical care focused on post COVID-19 condition have substantial heterogeneity in the outcomes evaluated. There is a need for consensus on a minimum set of critical outcomes ("Core Outcome Set" [COS]) to be measured in post COVID-19 condition, to optimize comparison and synthesis of data.
- We sought to develop a COS for post COVID-19 condition in adults for use in clinical research and practice worldwide via a consensus study that included a literature review, two-round online Delphi process (with 1535 participants, including 53% people with lived experience and their carers, from 71 countries, rating 26 different outcomes), and an online consensus meeting.

Findings

- Twelve outcomes reached consensus for the COS and should be measured in clinical research and practice for post COVID-19 condition: fatigue; pain; post-exertion symptoms; work/occupational and study changes; survival; "functioning, symptoms and conditions" for each of the following outcomes: cardiovascular, respiratory, nervous system, cognition, mental and physical; recovery.

Future Directions and Implications

- An important next step is achieving consensus on a minimum set of measurement instruments for this COS, balancing their validity and feasibility for use in global clinical research and practice, with continued inclusion of perspectives from people with lived experience, their carers, clinicians, and researchers.
- The use and reporting of this COS for adults with post COVID-19 condition is an important step to optimize and accelerate research, especially the development of evidence-based treatments, and to ensure consistent evaluation of these important outcomes in clinical settings.

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 the most widely used term Long COVID, as well as Post-Acute Sequelae of SARS-CoV-2 infection (PASC), and/or post-COVID syndrome. The prevalence of COVID-19 sequelae substantially varies between the studies with some authors reporting over a half of individuals having persistent symptoms 6 months after recovery from acute SARS-CoV-2 infection and many still having complaints after 12 months [1,2]

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."[3]

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. A classic example comes from schizophrenia research where over a 60 year period, 2194 different scales were used to study the effectiveness of various interventions [4] with this heterogeneity prohibiting meaningful comparisons and meta-analyses of studies. In order to assist with data standardisation and ensure that the most important outcomes are consistently assessed, the Core Outcome Set (COS) concept is increasingly being recognised [5].

To address this issue and help ensure that critical outcomes are consistently assessed, Core Outcome Sets (COS) have been developed in different fields. 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"[6]. COS are also suitable for use in other types of research and clinical practice[5]. A COS is an agreed-upon minimum set of outcomes that should be measured and reported in all studies in a specific field, highlighting a consensus of outcomes that matter most to people with lived experience, their families, researchers, healthcare professionals, funders and other relevant stakeholders. A COS does not prohibit researchers from including other outcomes but provides a recommendation of the minimum set of outcomes to 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) framework and consists of two steps: (a) "what to measure?", and (b) "how to measure?" [7,8]. Consensus regarding outcome importance and instrument validity and applicability is normally reached within a large group of various stakeholders, including but not limited to researchers, healthcare professionals, methodologists, public health experts, people with lived experience representatives.

Involvement of people with lived experience is critical, and it has been previously demonstrated that their outcomes might differ from outcomes selected by researchers or

clinicians. For example, as a part of Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) people with Rheumatoid Arthritis identified the importance of fatigue [9]. This unexpected suggestion made a significant impact at future OMERACT activities and fatigue has been subsequently included as a core outcome measure in clinical trials of rheumatoid arthritis management. OMERACT activities also demonstrated that further development and implementation of COS in rheumatoid arthritis resulted in the COS uptake rate increase over time, reaching 77%, providing evidence that consistency in outcomes measured across the studies can be improved and appropriate outcomes assessment can be achieved [10].

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 to 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. All steps of the study process are presented in figure 1.

The study protocol has been developed a priori. The project was registered (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 [2], clinical trial protocols and additional studies, including a survey led by people with lived experience [11], and a list of additional references suggested by

experts involved (see appendix p 3). The search strategy used in the living systematic review was restricted to publications and protocols written in English and is presented elsewhere [2]. 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 (see appendix p 3). 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* (see appendix p 16)[12], 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 [13], 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). For the details of the Delphi consensus process see appendix p 55.

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.

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 50% 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". For the details of consensus meeting see appendix p 55.

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) [14].

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 survey led by people with lived experience [11]) resulted in 259 studies and/or trials, eligible for inclusion that reported a total of 200 individual outcomes.

The final list of outcomes (see appendix p 26) 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 appendix p 29.

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 (see appendix p 36) the average scores of participants completing Round 1 only were similar to the average scores of those completing both rounds of the Delphi process (see appendix p 37).

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) (see appendix p 39).

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 appendix p 48.

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 [15]

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 [15].

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.

Previous studies on post COVID-19 condition have focused on outcomes which were considered important by investigators but may not be of the same level of importance to those who live with the condition. In Europe [16] and the United States (US) [17] there has been major financial investment in Long COVID research, with $1.2 billion allocated in the US alone. Hence, COS development is an urgent priority as such research continues to expand. Existing international research, predominantly focused on the more acute stage of covid-19, have been completed, with recommendations for core outcomes and associated measures, including a novel 1-item longer term measure of recovery, following an international survey with over 9,000 respondents from 111 countries, including nearly 800 people with suspected or confirmed COVID-19 and their family members and over 3,500 members of the general public [15,18]. The COMET Initiative brought COS developers together to agree a 'meta-COS' for acute covid [19] to ensure accessibility and harmonisation of the available sets. In addition to this 1-item novel recovery measure, the development of a COS for Long COVID can build upon previous successful initiatives that may have relevance. For example, core outcome measures developed for clinical research in survivors of acute respiratory failure and acute respiratory distress syndrome are relevant to studies of survivors of critical COVID-19 disease (www.improveLTO.com) [20].

Consensus regarding outcome importance is often conducted using a modified Delphi process with a group of relevant stakeholders, including researchers, healthcare professionals, methodologists and people with lived experience representatives. In this project, people with lived experience and 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, and 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.

Our study has several limitations. First, although a very broad range of individuals residing in different geographical locations were involved in the Delphi consensus process, more than a half of the participants were white, and the majority of the respondents were residing in the United Kingdom, United States of America or Spain. Male participants were under-represented in the Delphi process. Both disbalances may potentially result in a lack of external validity/generalisability Second, only a small number of Delphi participants were involved at the consensus meeting and their views may not be representative of everyone's opinion on the matter. This is an accepted and common limitation of all the studies assembled using Delphi methodology. Third, the number of individuals within the 'healthcare professionals and researchers with post COVID-19 condition' group was insufficient to allocate them into a separate group for the consensus meeting. However, this is highly unlikely to impact the outcome of the Delphi process. Fourth, due to the importance to public health and research in the field, it was necessary to expedite the COS development process and data regarding chronicity, time from diagnosis, and socioeconomic status of the participants has not been collected, which may be associated with the selection bias. However, detailed information collection on study participants is very uncommon in Delphi research. As per the WHO post covid condition definition "post-COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection". Thus both, individuals with laboratory-confirmed and suspected COVID-19 were invited and some individuals may not have had COVID-19 although they thought they had [21]. It should also be acknowledged that this COS project is 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 [22].

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 [23]. There is a growing need for people with lived experience 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.

Future challenges regarding this post COVID-19 condition COS should be mentioned. Importantly, implementation and uptake of COS varies across clinical conditions [24]. Known barriers to uptake of COS include lack of validated measurement instruments, lack of key stakeholder groups' involvement in COS development, and lack of awareness of the COS [24]. To help mitigate such issues, our project was undertaken in collaboration with major organisations, such as ISARIC, COMET and the WHO, to ensure wide dissemination of the study results and applicability of the COS across different geographical areas. Moreover, this project team has been actively engaging with additional large initiatives and investigators in the field to seek input and share study results. Finally, recommendations for dissemination provided by prior COS stakeholders are being followed to further assist with this aim [25]. The optimal time points for the outcome assessment is yet to be estimated and although a minimum set of time points require harmonisation (eg 3, 6 and 12 months) additional time points should be considered to develop a better understanding of post COVID-19 condition patterns changes over time. It is preferred for the first follow-up to happen not earlier than three months after the acute event so COVID-19 consequences are assessed in light of the WHO developed post COVID-19 condition definition.

Finally, future directions also include achieving consensus on measurement instruments for each outcome in the COS which is needed to achieve greater consistency and comparability for research in the field. This important objective will be achieved once a second phase of the project is completed, that will continue to consider perspectives from clinicians, people with lived experience, their carers and researchers, along with added considerations of balancing the validity and feasibility of relevant potential measurement instruments within the global research and clinical setting. Moreover, with millions of children and young people experiencing SARS-CoV-2 infection, potential lifelong adverse effects may have detrimental consequences to the individuals and result in substantial burden to healthcare services [26]. A COS for post COVID-19 condition in children and young people is urgently needed to ensure harmonisation of international clinical research and practice [12,22].

In conclusion, 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 [15]. 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 stages 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. Future steps for the development of this COS will be to determine which measurement instruments best measure these outcomes.

Search strategy and selection criteria

We used the data from a living systematic review [2], clinical trial protocols and additional studies, including research led by people with lived experience and a list of additional references suggested by the experts involved in the study (see appendix p 3). The following databases were used in the living systematic review: Medline and CINAHL (EBSCO), Global Health (Ovid), WHO Global Research Database on COVID-19 and LitCovid. The search time frame was limited to 1 January 2020 to 17 March 2021. Additional search was performed at Google Scholar on 17 March 2021, screening the first 500 titles. We manually reviewed selected studies published beyond the systematic review search period, as well as other systematic reviews, narrative reviews and opinion papers and relevant references cited in the articles found.

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