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1 **Core Outcome Set for Research and Clinical Practice in Post COVID-19**  
2 **Condition (Long COVID) in Adults: An International Delphi Consensus**  
3 **Study ‘PC-COS’**

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51 **Disclaimer:** The findings and conclusions in this report are those of the authors and do not  
52 necessarily represent the official position of the International Severe Acute Respiratory and  
53 Emerging Infection Consortium, and the World Health Organisation.

54 **Contributions:** DM and TN conceived the idea for the study. PW led the methodological  
55 team. DM, TN, PW and DMN designed the study protocol and were responsible for the day to  
56 day running of the project. NSe, CP, AK and JC undertook the literature review, identified  
57 outcomes and categorised them for inclusion in the online Delphi survey. NSe coordinated the  
58 data revision process. NH, SLG and NSe developed the online Delphi surveys and contributed  
59 to the day to day management of the project. DM, TN, WDG, NSc, JP, PO, CA, AT, JS, DMN  
60 and PW participated in the project methodology discussions throughout the duration of the  
61 project. SLG and NH undertook the data analysis and organised the consensus meeting. JP  
62 coordinated the translation of study materials and smooth communication with the WHO.  
63 JVD provided the lead for WHO administrative aspects of the study. FS and AA provided  
64 invaluable people with lived experience perspectives throughout the study. DM drafted the  
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68  
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80 Harmonising Outcome Measures for Eczema (HOME) initiative and Co-Chair Hand Eczema  
81 Core Outcome Set (HECOS) initiative. JP was employed by WHO in the Case Management  
82 team, HQ, WHE at the time of the manuscript writing. He is also a chair of the e-Learning  
83 committee and member of the Council at the European Society of Intensive Care Medicine.  
84 JVD is the lead of the clinical management response pillar for COVID-19 and in that capacity  
85 convene the WHO Clinical Characterization and Management Research working group. The  
86 Post COVID-19 COS steering committee was a sub working group of this bigger group. PRW  
87 reports that she received funding from the UK National Institute for Health Research (NIHR).  
88 She is also a chair of the Core Outcome Measures in Effectiveness Trials (COMET)  
89 Management Group. Other authors declare that they have no competing interests.

90  
91

92 **Summary**

93

94 Currently, no agreement exists on which health outcomes should be measured in post COVID-  
95 19 condition. To address this, a rigorous multi-step modified Delphi consensus study was  
96 conducted, which included a comprehensive literature review and grouping of outcomes in  
97 post COVID-19 condition that informed a two-round online modified Delphi process followed  
98 by an online consensus meeting to finalise the core outcome set (COS). 1535 participants from  
99 71 countries, representing six continents, were involved, with 1148 participating in both Delphi  
100 rounds. Eleven outcomes met consensus for the COS: fatigue; pain; post-exertion symptoms;  
101 work/occupational and study changes; survival; and “functioning, symptoms and conditions”  
102 for each of the following outcomes: cardiovascular, respiratory, nervous system, cognition,  
103 mental and physical. A ‘Recovery’ outcome was added a-priori due to being part of a previously  
104 published COS on COVID-19. This international consensus-based COS provides a framework  
105 for assessing post COVID-19 condition in global clinical research and practice settings.  
106

107 **Key messages**

108

109 **Rationale and approach**

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

121 **Findings**

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

127 **Future Directions and Implications**

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

136

137

## 138 **Introduction**

139

140 Coronavirus disease 2019 (COVID-19) may have a wide variety of consequences, including  
141 persistence of symptoms for many months after the acute phase. Different names have been  
142 suggested for this phenomenon, including the most widely used term Long COVID, as well as  
143 Post-Acute Sequelae of SARS-CoV-2 infection (PASC), and/or post-COVID syndrome. The  
144 prevalence of COVID-19 sequelae substantially varies between the studies with some authors  
145 reporting over a half of individuals having persistent symptoms 6 months after recovery from  
146 acute SARS-CoV-2 infection and many still having complaints after 12 months <sup>1,2</sup>

147

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

156

157 With a rapid increase in the number of studies investigating post COVID-19 condition, there  
158 are many different outcomes evaluated. Such heterogeneity is a common problem across  
159 medical research hampering the ability to compare and contrast research, and conduct meta-  
160 analyses to inform evidence-based decision making e.g. regarding effective treatments. A  
161 classic example comes from schizophrenia research where over a 60 year period, 2194  
162 different scales were used to study the effectiveness of various interventions <sup>4</sup> with this  
163 heterogeneity prohibiting meaningful comparisons and meta-analyses of studies. In order to  
164 assist with data standardisation and ensure that the most important outcomes are consistently  
165 assessed, the Core Outcome Set (COS) concept is increasingly being recognised <sup>5</sup>.

166

167 To address this issue and help ensure that critical outcomes are consistently assessed, Core  
168 Outcome Sets (COS) have been developed in different fields. A COS is defined as “an agreed  
169 standardised collection of outcomes which should be measured and reported, as a minimum,  
170 in all [clinical] trials for a specific clinical area”<sup>6</sup>. COS are also suitable for use in other types  
171 of research and clinical practice<sup>5</sup>. A COS is an agreed-upon minimum set of outcomes that  
172 should be measured and reported in all studies in a specific field, highlighting a consensus of  
173 outcomes that matter most to people with lived experience, their families, researchers,  
174 healthcare professionals, funders and other relevant stakeholders. A COS does not prohibit  
175 researchers from including other outcomes but provides a recommendation of the minimum  
176 set of outcomes to measured and reported in every study in the field. The “gold standard”  
177 approach to COS development has been outlined by the Core Outcome Measures in  
178 Effectiveness Trials (COMET) framework and consists of two steps: (a) “what to measure?”,  
179 and (b) “how to measure?” <sup>7,8</sup>. Consensus regarding outcome importance and instrument  
180 validity and applicability is normally reached within a large group of various stakeholders,  
181 including but not limited to researchers, healthcare professionals, methodologists, public  
182 health experts, people with lived experience representatives.

183

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

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

194  
195 There is an urgent need to develop a COS for post COVID-19 condition to ensure that critically  
196 important outcomes are measured and reported in a consistent manner. Herein, we report on  
197 the development of a COS for post COVID-19 condition in adults for use in clinical research  
198 and practice.

199

## 200 **Methods**

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

210

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

217

218 The study protocol has been developed a priori. The project was registered  
219 (<https://www.comet-initiative.org/Studies/Details/1847>) with funding by the National  
220 Institute for Health Research (NIHR) (Grant COV-LT2-0072) supporting the second stage of  
221 the process. Ethical approval for the study was given by the UK Health Research Authority and  
222 by the South West - Cornwall & Plymouth Research Ethics Committee (REC number  
223 21/SW/0109).

224

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

228

## 229 **Developing a list of outcomes**

230

231 An extensive list of outcomes, informing the COS consensus process, was created using data  
232 from a living systematic review <sup>2</sup>, clinical trial protocols and additional studies, including a  
233 survey led by people with lived experience <sup>11</sup>, and a list of additional references suggested by

234 experts involved (see appendix p 3). The search strategy used in the living systematic review  
235 was restricted to publications and protocols written in English and is presented elsewhere <sup>2</sup>.  
236 Selected studies published beyond the systematic review search period (till 17 March 2021), as  
237 well as other systematic reviews, narrative reviews and opinion papers were also reviewed (see  
238 appendix p 3). Research protocol data were extracted from two clinical trials registries, the  
239 National Library of Medicine’s Clinical Trials.gov and International Clinical Trials Registry  
240 Platform (ICTRP), and reviewed by one of four independent reviewers (NSe, AK, CP, JC). All  
241 reported outcomes were extracted verbatim.

242  
243 Unique outcomes from the list were classified using an existing taxonomy by Dodd *et al* (see  
244 appendix p 16)<sup>12</sup>, with iterative review and discussion by the methodology group, ‘core group’  
245 and the project steering committee to generate a list of outcomes presented in Round 1 of the  
246 modified Delphi consensus process. The final list of outcomes was approved by the  
247 International Steering Committee.

248

### 249 **Stakeholder groups**

250

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

257

### 258 **Modified Delphi Consensus Process**

259

260 The consensus process involved a two-round online modified Delphi process in which  
261 participants were asked to rate each outcome using the Grading of Recommendations  
262 Assessment, Development and Evaluation (GRADE) scale <sup>13</sup>, a 9-point scale that is commonly  
263 divided into 3 categories for COS projects: Not Important (1 – 3), Important but Not Critical  
264 (4 – 6), and Critical (7 – 9). An option of “unable to rate” was also provided together with the  
265 ability to add text-based comments for each outcome.

266

267 The Delphi and all participant information materials were available in English, Chinese,  
268 Russian, French and Spanish. The Delphi survey was delivered using DelphiManager software  
269 (<http://www.comet-initiative.org/delphimanager>). For the details of the Delphi consensus  
270 process see appendix p 55.

271

### 272 **Definition of consensus on outcome inclusion/exclusion**

273

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

276

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

279

280

281

## 282 **Consensus meeting**

283 An online interactive consensus meeting was held using the Zoom platform. The meeting was  
284 conducted in English and chaired by an experienced independent facilitator.

285 The consensus meeting was structured using results from the second Delphi round based on  
286 the outcomes which had reached the pre-defined definition of consensus “in” and consensus  
287 “out”. Outcomes where at least one stakeholder group, but not all, had reached the definition  
288 of consensus “in” were prioritised for discussion. Outcomes where 50% or more, but less than  
289 80% of participants in each stakeholder group rated the outcome 7-9 were also included for  
290 discussion. All arguments in favour of inclusion of the outcome were invited first, followed by  
291 arguments against. After discussion participants were invited to confidentially rate the  
292 outcome again, using the 1-9 scale. Stakeholder groups rated outcomes separately and the  
293 same criteria for inclusion were applied i.e. 80% or more participants in each stakeholder  
294 group rating the outcome 7-9, “critically important”. For the details of consensus meeting see  
295 appendix p 55.

296

## 297 **Statistical analysis**

298 Free text comments were translated from the French, Russian, Spanish and Chinese surveys  
299 into English and collated and reviewed by the group. We used descriptive statistics for the  
300 scores for each outcome across the three stakeholder groups. It was agreed a priori that only  
301 participants who rated at least 50% of outcomes would be included in the analysis. The data  
302 analysis process from Round 1 was repeated for Round 2. Graphs displaying the distribution  
303 of ratings for each outcome, stratified by stakeholder group, were produced using R (version  
304 4.0.2) <sup>14</sup>.

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

310

## 311 **Results**

### 312 **Identification of outcomes**

313

314 Review of the existing evidence (i.e., living systematic review, clinical trial protocols and  
315 additional papers, including a major survey led by people with lived experience <sup>11</sup>) resulted in  
316 259 studies and/or trials, eligible for inclusion that reported a total of 200 individual  
317 outcomes.

318

319 The final list of outcomes (see appendix p 26) that was rated in the first round of Delphi  
320 included 24 outcomes grouped under four domains (mortality n=1, life impact n = 5,  
321 physiological/clinical n=16, resource use n=2). The order in which each outcome was  
322 presented to participants in the online Delphi process was randomised by domain.

323

### 324 **Online Delphi Consensus Process**

325

326 The first round of the Delphi took place between 5 August and 13 September 2021, with a total  
327 of 1535 participants from 71 countries participating. Of these 1533 participants invited to the  
328 second Delphi round, 75% (1148/1535) from 59 countries rated 50% or more of the outcomes.

329 Demographic characteristics and responses, by stakeholder group and country of residence,  
 330 are presented in Table 1. The detailed list of participants is presented in appendix p 29.

331

332 Response rates in the second round (compared to Round 1 participation) were: 71% for ‘people  
 333 with post COVID-19 condition and family members/caregivers’, 80% for ‘healthcare  
 334 professionals and researchers without post COVID-19 condition’ and 75% for ‘healthcare  
 335 professionals and researchers with post COVID-19 condition’. In assessing attrition bias (see  
 336 appendix p 36) the average scores of participants completing Round 1 only were similar to the  
 337 average scores of those completing both rounds of the Delphi process (see appendix p 37).

338

339

340 **Table 1. Participant characteristics**

341

	<b>Round 1</b>	<b>Round 2</b>
	<b><i>n</i> = 1535</b>	<b><i>n</i> = 1148</b>
<b>Stakeholder group, <i>n</i> (%)</b>		
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)
<b>Gender, <i>n</i> (%)</b>		
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)
<b>Age group, <i>n</i> (%)</b>		
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)

343 At the end of the first round of Delphi, 10 of the 24 outcomes reached consensus for inclusion  
344 in the COS. Eight outcomes represented ‘physiological/clinical outcomes’ domain (fatigue or  
345 exhaustion; pain; cardiovascular functioning, symptoms, and conditions; respiratory  
346 functioning, symptoms, and conditions; nervous system functioning, symptoms, and  
347 conditions; cognitive functioning, symptoms, and conditions; mental functioning, symptoms,  
348 and conditions; post-exertion symptoms) and two ‘life impact outcomes’ domain  
349 (work/occupational and study changes; physical functioning, symptoms, and conditions) (see  
350 appendix p 39).

351  
352 A total of 520 free text responses suggesting additional outcomes were received, with two  
353 additional outcomes identified for the second Delphi round: “eye symptoms and conditions”,  
354 reported in 13 responses and “muscle and joint symptoms and conditions”, reported in six.

355  
356 Delphi Round 2 was conducted between 1 October and 5 November 2021, with participants  
357 rating 26 outcomes with 10 meeting criteria for “consensus in” and 5 for “consensus out”. For  
358 five outcomes at least one, but not all, stakeholder groups rated it as “consensus in”: survival,  
359 sleep related functioning, symptoms and conditions, muscle and joint symptoms and  
360 conditions, satisfaction with life or personal enjoyment, and healthcare resource utilisation.  
361 These were considered at the subsequent consensus meeting. Six outcomes did not reach the  
362 required cut-off for inclusion within all three groups. However, two of these outcomes “social  
363 role- functioning and relationship problems” and “family carer burden” were rated 7-9 by 65%  
364 or more in each of the groups and were considered at the consensus meeting.

### 365 366 **Consensus meeting**

367  
368 Thirty participants were invited to the consensus meeting, of whom 27 attended (‘people with  
369 post COVID-19 condition and family members/caregivers’ (n=8); ‘healthcare professionals  
370 and researchers with post COVID-19 condition’ (n=5); ‘healthcare professionals and  
371 researchers without post COVID-19 condition’ (n = 14).

372  
373 Due to the limited number of attendees from the ‘healthcare professionals and researchers  
374 with post COVID-19 condition’ group for consensus voting at the meeting, these five  
375 participants self-selected allocation into one of the other two groups: ‘people with post COVID-  
376 19 condition and family members/caregivers’ and ‘healthcare professionals and researchers’.  
377 The voting participants of the consensus meeting are described in appendix p 48.

378  
379 The seven outcomes were discussed in the following order: survival; sleep functioning,  
380 symptoms and conditions; muscle and joint functioning, symptoms and conditions;  
381 satisfaction with life; social role-functioning and relationships problems; family/carer burden;  
382 healthcare resource utilisation. After discussion and voting only one outcome, ‘survival,’ met  
383 the predefined criteria for consensus and was added to the COS (**Box 1**).

384  
385  
386  
387  
388  
389  
390

391 Box 1. Consensus core outcomes:  
392

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\*

393 \*Outcome was added 'a-priori' as a part of previously published COS on COVID-19 <sup>15</sup>

394

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

396

## 397 Discussion

398

399 We report on a large, rigorous international consensus study of 1535 participants from 71  
400 countries (including 53% people with lived experience and their carers) to develop a core  
401 outcome set for post COVID-19 condition, for use in clinical research and practice. A two-  
402 round online international modified Delphi process (presented in 5 languages) followed by an  
403 interactive, facilitated online consensus meeting was conducted with very good participation  
404 and retention across all three stakeholder groups ('people with post COVID-19 condition and  
405 family members/caregivers', 'healthcare professionals and researchers without post COVID-  
406 19 condition' and 'healthcare professionals and researchers with post COVID-19 condition').  
407 Eleven outcomes achieved the a priori criteria consensus for inclusion in the COS focusing on:  
408 fatigue or exhaustion; pain; post-exertion symptoms; work/occupational and study changes;  
409 survival; and "functioning, symptoms and conditions" for each of the following outcomes:  
410 cardiovascular, respiratory, nervous system, cognition, mental and physical. It was also agreed  
411 that 'recovery' outcome should be added as a part of previously published COS on COVID-19  
412 <sup>15</sup>.

413

414 A COS is defined as an agreed-upon minimum set of outcomes that should be measured and  
415 reported in all studies in a specific field, highlighting critical outcomes that matter most to  
416 relevant stakeholders. A COS does not prohibit researchers from including other outcomes but  
417 provides a minimum recommendation of the outcomes to be measured and reported in every

418 study in the field. The “gold standard” approach to COS development has been outlined by the  
419 Core Outcome Measures in Effectiveness Trials (COMET) Initiative.

420 Previous studies on post COVID-19 condition have focused on outcomes which were  
421 considered important by investigators but may not be of the same level of importance to those  
422 who live with the condition. In Europe <sup>16</sup> and the United States (US) <sup>17</sup> there has been major  
423 financial investment in Long COVID research, with \$1.2 billion allocated in the US alone.  
424 Hence, COS development is an urgent priority as such research continues to expand. Existing  
425 international research, predominantly focused on the more acute stage of covid-19, have been  
426 completed, with recommendations for core outcomes and associated measures, including a  
427 novel 1-item longer term measure of recovery, following an international survey with over  
428 9,000 respondents from 111 countries, including nearly 800 people with suspected or  
429 confirmed COVID-19 and their family members and over 3,500 members of the general public  
430 <sup>15,18</sup>. The COMET Initiative brought COS developers together to agree a ‘meta-COS’ for acute  
431 covid <sup>19</sup> to ensure accessibility and harmonisation of the available sets. In addition to this 1-  
432 item novel recovery measure, the development of a COS for Long COVID can build upon  
433 previous successful initiatives that may have relevance. For example, core outcome measures  
434 developed for clinical research in survivors of acute respiratory failure and acute respiratory  
435 distress syndrome are relevant to studies of survivors of critical COVID-19 disease  
436 ([www.improveLTO.com](http://www.improveLTO.com)) <sup>20</sup>.

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

444  
445 Complexity and multidimensionality of post COVID-19 condition is reflected in multiple  
446 studies, reporting the involvement of many different organ systems. It has been hypothesised  
447 that different post COVID-19 condition phenotypes may exist, although exact causes,  
448 management and outcomes are unknown. The WHO definition of post COVID-19 condition  
449 includes the most prevalent symptoms, such as fatigue, shortness of breath, and cognitive  
450 dysfunction that generally have an impact on everyday functioning. Fluctuating or relapsing  
451 symptoms are also commonly reported. As reflected in the WHO definition, people with post  
452 COVID-19 condition can have other symptoms. Eight of the eleven outcomes in this COS are  
453 within the physiological/clinical outcome domain and cover all of the most prevalent  
454 symptoms reported in existing research. The developed COS is complementary to the WHO  
455 definition as both are aiming at harmonisation. The definition provides a standardised term  
456 for post COVID-19 condition, while the COS identifies the minimum outcomes that should be  
457 measured in all research studies and clinical practice.

458  
459 There was a general agreement across stakeholder groups for most outcomes. One difference  
460 occurred with the “muscle and joint symptoms and conditions” outcome, with 92% of ‘people  
461 with post COVID-19 condition and family members/caregivers’ scoring this outcome as  
462 critical, while only 25% of ‘healthcare professionals and researchers’ voting this outcome as  
463 critical, reflecting distinct stakeholders’ perspectives. Although “muscle and joint symptoms

464 and conditions” did not meet an a priori consensus criteria for inclusion in the COS this result  
465 shows high importance of this outcome among people with post COVID-19 condition, which  
466 should be considered by researchers and clinicians. We would like to underscore that absence  
467 of a particular outcome in the COS does not mean that this outcome is not important.  
468 Importance of “muscle and joint symptoms and conditions” was acknowledged by both  
469 stakeholder groups (100% of ‘people with post COVID-19 condition and family  
470 members/caregivers’ and 92% of ‘healthcare professionals and researchers’ rated this  
471 outcome as ‘important’ or ‘critical’), however, it is not critical enough to be recommended for  
472 inclusion in the COS to be measured in every study.

473

474 Our study has several limitations. First, although a very broad range of individuals residing in  
475 different geographical locations were involved in the Delphi consensus process, more than a  
476 half of the participants were white, and the majority of the respondents were residing in the  
477 United Kingdom, United States of America or Spain. Male participants were under-  
478 represented in the Delphi process. Both disbalances may potentially result in a lack of external  
479 validity/generalisability Second, only a small number of Delphi participants were involved at  
480 the consensus meeting and their views may not be representative of everyone's opinion on the  
481 matter. This is an accepted and common limitation of all the studies assembled using Delphi  
482 methodology. Third, the number of individuals within the ‘healthcare professionals and  
483 researchers with post COVID-19 condition’ group was insufficient to allocate them into a  
484 separate group for the consensus meeting. However, this is highly unlikely to impact the  
485 outcome of the Delphi process. Fourth, due to the importance to public health and research in  
486 the field, it was necessary to expedite the COS development process and data regarding  
487 chronicity, time from diagnosis, and socioeconomic status of the participants has not been  
488 collected, which may be associated with the selection bias. However, detailed information  
489 collection on study participants is very uncommon in Delphi research. As per the WHO post  
490 covid condition definition "post-COVID-19 condition occurs in individuals with a history of  
491 probable or confirmed SARS-CoV-2 infection". Thus both, individuals with laboratory-  
492 confirmed and suspected COVID-19 were invited and some individuals may not have had  
493 COVID-19 although they thought they had <sup>21</sup>. It should also be acknowledged that this COS  
494 project is focused on adults. Children and young people also may develop post COVID-19  
495 condition, although data are still emerging. The necessity of COS development for children  
496 with post COVID-19 condition has been previously highlighted and the need for COS in this  
497 population was raised during the consensus meeting. Although this study excludes the  
498 paediatric population we acknowledge the importance of COS development for this age group  
499 <sup>22</sup>.

500

501 With millions of people affected by COVID-19, even a small percentage developing post  
502 COVID-19 condition will result in a detrimental effect on society and public health, with many  
503 people in need of long-term follow-up, management and support <sup>23</sup>. There is a growing need  
504 for people with lived experience and their carers' voices to be heard. COS development is an  
505 urgent priority as such research markedly expands. This project is aiming to ensure that  
506 research is directed towards evaluating outcomes of critical importance for people suffering  
507 from post COVID-19 condition. The COS presented in this manuscript is the result of the  
508 consensus from clinicians, researchers, and people with lived experience and their carers,  
509 which is important to relevant stakeholder groups, including research funders and  
510 policymakers to help advance the field via improving harmonisation and comparability.

511

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

528

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

540

541 In conclusion, a consensus-based COS for post COVID-19 condition was developed and  
542 included the following outcomes: fatigue or exhaustion; pain; post-exertion symptoms;  
543 work/occupational and study changes; survival; and "functioning, symptoms and conditions"  
544 for each of the following outcomes: cardiovascular, respiratory, nervous system, cognition,  
545 mental and physical. 'Recovery' was added a-priori as a part of previously published COS on  
546 COVID-19 <sup>15</sup>. Although twelve domains is a very large number for a regular COS it is  
547 understandable and expected for a new conditions such as post COVID-19 condition and can  
548 bring harmonisation in early stages of research. Once the condition is better understood the  
549 COS may be revised and the number of domains may be reduced to guarantee higher  
550 feasibility. Future research will establish which measurement instruments are the most  
551 appropriate to measure the core outcomes. Future steps for the development of this COS will  
552 be to determine which measurement instruments best measure these outcomes.

553

554 **Search strategy and selection criteria**

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

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582  
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585

586

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