

WHO update: post COVID-19 condition Clinical case definition and update on clinical activities

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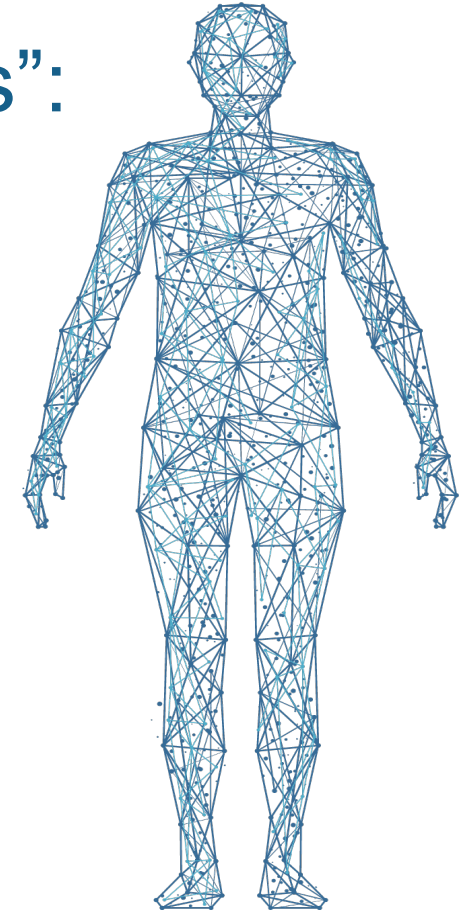
6 October 2021, 13:35–13:45 CET Salle C, WHO HQ

Advance our understanding of post COVID-19 condition

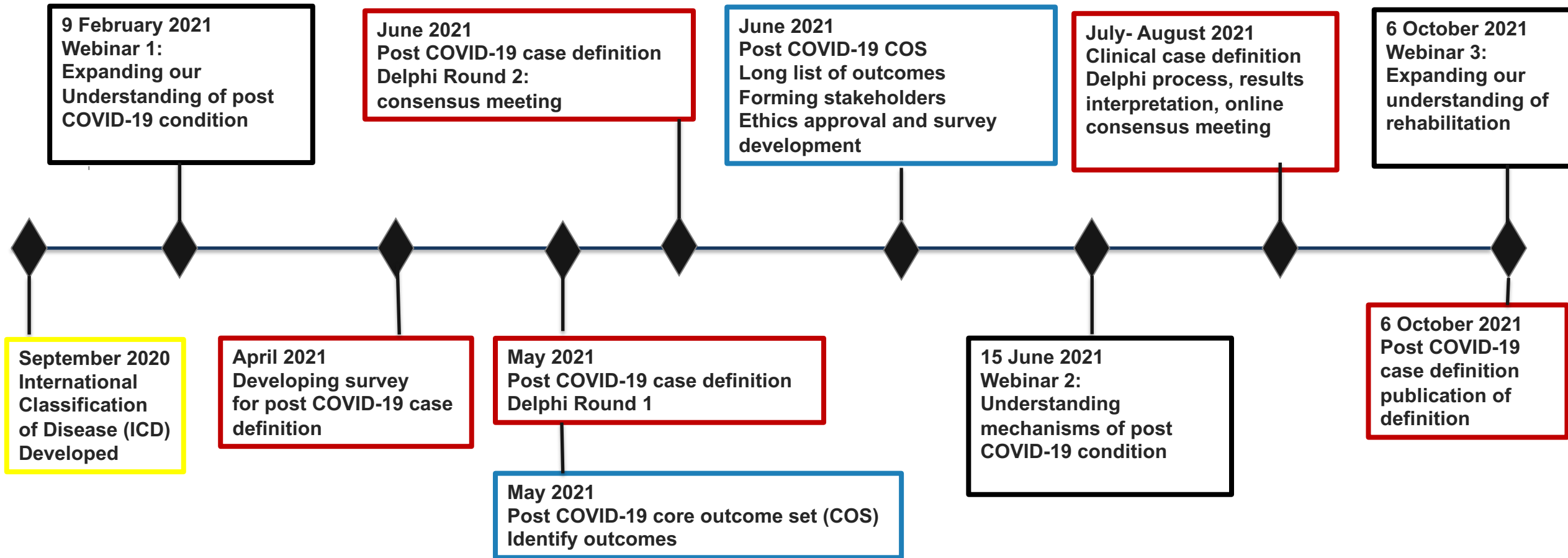
A series of three seminars on the WHO's three "Rs":

1. Recognition and burden
2. Research
3. **Rehabilitation**

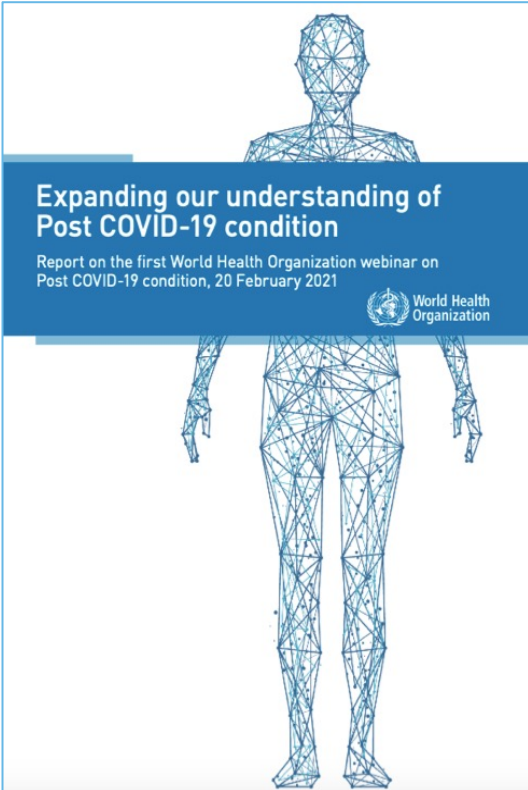
“Without established mechanisms, no COVID-19 new treatments”



Post COVID-19 condition: milestones and timelines



Webinar 1: Recognition and burden (9 February 2021)



- **Aim: Recognition and burden**
- 14 speakers and a **peak of 623 attendees**
 - Presentations describing cohorts from around the globe
 - 3 working groups discussed clinical descriptors, laboratory diagnostics and research priorities
- **Launch of the post COVID-19 condition CRF**

Summary: It has become apparent that not all patients experiencing COVID-19 have full symptom resolution, and some patients report the emergence of new symptoms over time.

Variations may represent heterogenous expressions of disease determined by host biology/genetics and/or distinct disease processes. However, differences might be also explained by the use of different methods for diagnostic approach and accuracy of symptom detection.

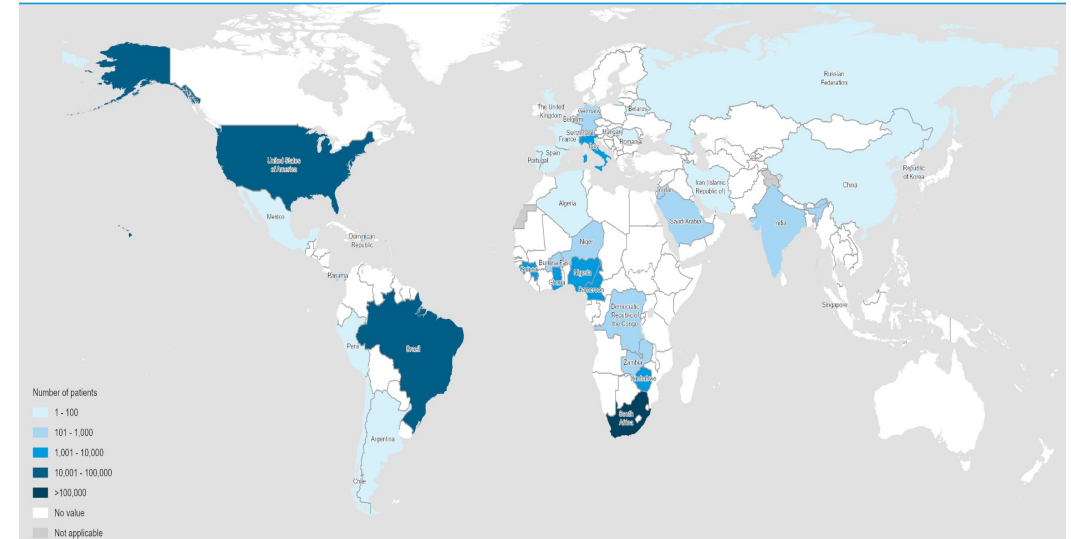
<https://www.who.int/teams/health-care-readiness-clinical-unit/covid-19/data-platform/>

<https://www.who.int/publications/i/item/9789240025035>

WHO Global Clinical Platform for COVID-19

- Uses **anonymized, individual-level data** from **hospitalized patients** with COVID-19
- Generates global, regional, country reports that can inform national responses and evidence-based guidelines on clinical management of COVID-19.
- **CRF 4: Describe mid- and long- term sequelae** of patients discharged from hospitals or managed at home

Global COVID-19 Clinical Data Platform: Country Contributors
(as of 12/08/2021)




N=481,681

Patient-level data on hospitalized COVID-19 patients (As of September 1, 2021)

Modules of Post COVID-19 Condition CRF

Post COVID-19 Condition CRF

- Designed to build upon the Core CRF

 **World Health Organization**

**WHO Global Clinical Platform for COVID-19
Case Report Form (CRF) for COVID-19 sequelae ("Post COVID-19 CRF")**

The WHO has established a Global Clinical Platform¹ of COVID-19 and invites all Member States and health facilities to report anonymised patient-level clinical information to the WHO platform using standardized Case Report Forms (CRF):

- Core CRF captures clinical information on individuals hospitalized for COVID-19
- Core-P CRF has information on pregnant women hospitalized for COVID-19
- MIS-CRIF has information related to multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19
- Post COVID-19 CRF, designed to build upon the Core CRF and assess the medium- and long-term sequelae of COVID-19

The Post COVID-19 CRF includes 3 modules:

- Module 1** includes background, demographic and clinical information related to the acute episode of COVID-19.
- Module 2** includes questions pertaining to the post-acute illness period to help identify patients who require further clinical evaluation.
- Module 3** includes medical assessment and results of examinations, tests, or diagnoses made during the follow up visit. Based on results, patients should be referred for clinical care or rehabilitation as per national protocols.

The Post COVID-19 CRF is intended to serve as: (i) A clinical tool that can be used by Member States to document the mid- and long-term sequelae of COVID-19. Uniformity in the follow up of patients will ensure that mid- and long-term clinical and rehabilitation needs are identified, and patients are provided the care they need; (ii) WHO is not necessarily recommending the comprehensive testing described in the CRF for all individuals; clinician judgement is required to select the test needed for clinical care. This CRF is a tool for gathering standardized information regarding post COVID-19 sequelae through the WHO Global Clinical Platform. Such data collation and its analysis would improve national and global knowledge of the consequences of COVID-19, inform further public health responses and prepare for large investigational studies.

Criteria for completion of Post COVID-19 CRF: Variables' data dictionary available on the WHO website¹ support data entry. The CRF can be administered either as part of routine follow up or at a specific time point to any patient in the post-acute phase of COVID-19, regardless of hospitalization. While it is suggested to prioritize the completion of the CRF for patients who were hospitalized for a severe or critical episode of COVID-19, the CRF should be administered, where possible, also to patients who suffered from COVID-19, including those with mild or moderate illness, and who received care either at home or in a hospital setting.

Time-points for administration: The form can be completed any time during follow up after an acute episode of COVID-19. However, to support standardization and data comparability, it should preferably be completed 4 to 8 weeks after hospital discharge from the acute ward or after acute illness, and every 6 months thereafter. However, in case of persistent symptoms/signs at 4-8 weeks after hospital discharge or after acute illness, it is recommended to complete the CRF at 3-month intervals, for as long as needed (see figure below).

Mode of administration: Module 1-2: face-to-face administration and completion by a health care worker is preferred. However, when this is not possible, the form can be either self-administered, or completed remotely (online or through telephone) by the caregiver. For children, the form should be completed by the primary caregiver (preferred) or by the legal guardian.

Module 3: face-to-face administration and completion by a health care worker.

Module 1 needs to be completed only once during the first follow up visit, while Modules 2 and 3 should be completed at every follow up visit.

General guidance: Please contact COVID_ClinPlatform@who.int if you need assistance with data entry, if you have any query on the CRF, and to let us know that you are using the forms.

For individuals who were hospitalized with suspected or confirmed diagnosis of COVID-19:

From hospital discharge

Post COVID CRF: module 1, 2, 3

4-8 weeks

4-5 months

7-8 months

13-14 months

For individuals who were not hospitalized with suspected or confirmed diagnosis of COVID-19:

From acute illness of COVID-19

Post COVID CRF: module 1, 2, 3

4-8 weeks

4-5 months

7-8 months

13-14 months

If symptoms/signs do not persist: follow up visit at 4-8 weeks, and every 6 months thereafter, if possible.

¹ <https://www.who.int/teams/health-care-readiness-clinical-unit/covid-19/data-platform>

POST COVID-19 CASE REPORT FORM published 9 February 2021, revised 15 2021
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WHO reference number: WHO/2019-nCoV/Post_COVID-19_CRF/2021.1

MODULE 1 Acute COVID-19 episode

Retrospective information

- Demographics
- Diagnostic/other tests
- Co-morbidities
- Medications
- Complications/Co-infections
- Clinical Management (therapeutics + supportive care)
- Pregnancy Status upon Admission

MODULE 2 Follow-up

Physician Encounter

- Reinfection
- Vaccination status
- Occupation
- Functional status
- Signs and symptoms since acute episode

MODULE 3 Follow-up

Clinical examinations, laboratory tests and diagnosis

- Neurological exam
- Radiographic exam
- Blood tests
- Other clinical tests and scales
- New diagnosis of illness/complication received

Webinar 2: Research (15 June 2021)

Understanding mechanisms of post COVID-19 condition

Considered at least seven potential causes (likely multifactorial)

1. Inflammatory/hyperinflammatory state
2. Immune dysregulation/autoimmune
3. Coagulation/vasculopathy
4. Direct viral toxicity/viral persistence
5. Autonomic dysfunction
6. Endocrine/metabolic
7. Maladaptation of the ACE-2 pathway



<https://www.who.int/news-room/events/detail/2021/06/15/default-calendar/expanding-our-understanding-of-post-covid-19-condition-webinar-2>

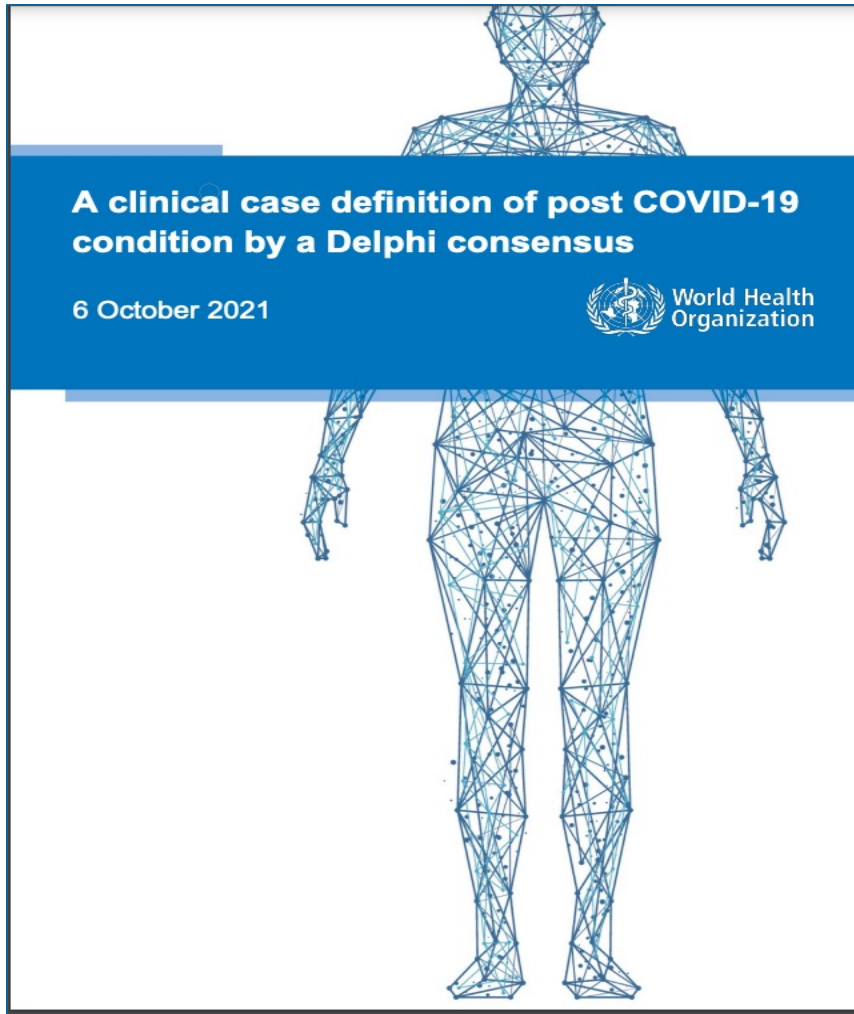
Post COVID-19 condition case definition by Delphi consensus

WHO's post COVID-19 condition case definition as of October 2021

Post COVID-19 condition 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, that cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others which 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.

* A separate definition may be applicable for children

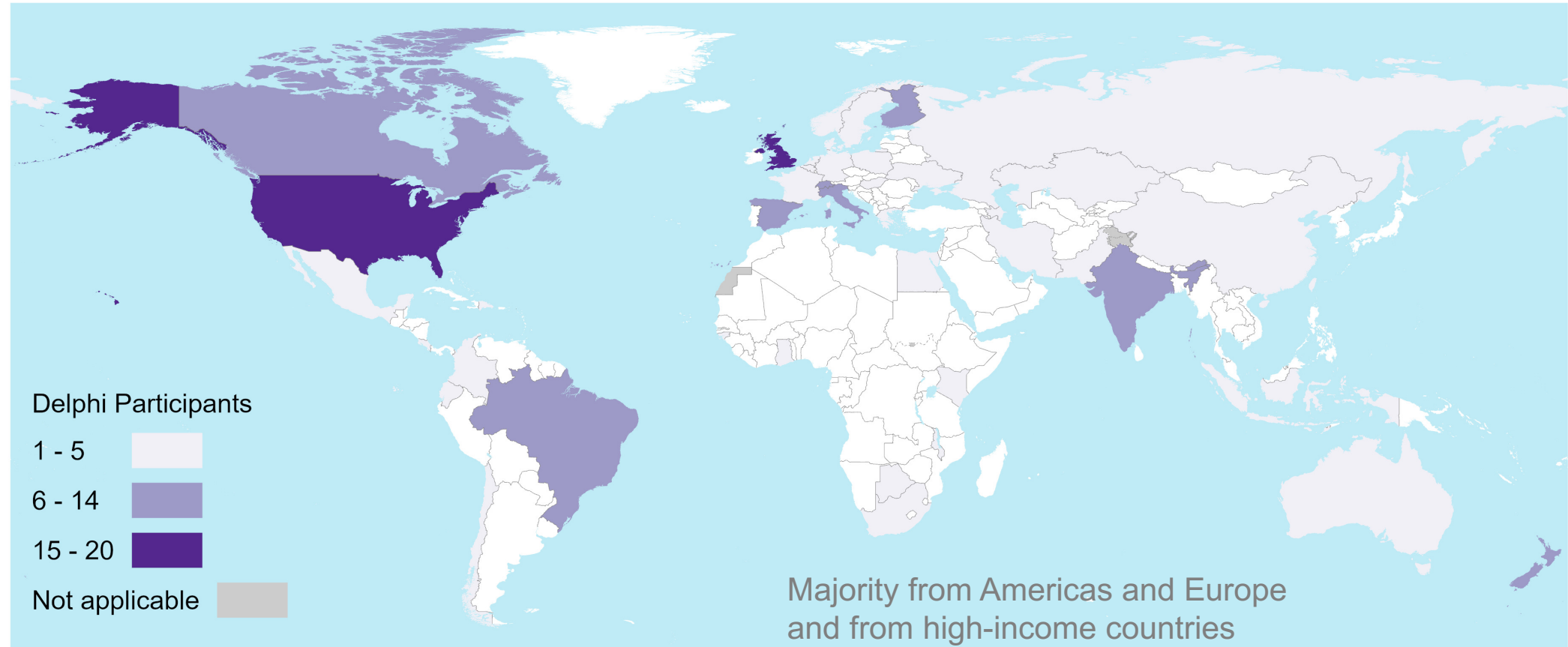
Post COVID-19 condition by a two-round Delphi consensus methodology



The full case definition report developed between May – June 2021 can be found on the WHO website:

<https://apps.who.int/iris/bitstream/handle/10665/345824/WHO-2019-nCoV-Post-COVID-19-condition-Clinical-case-definition-2021.1-eng.pdf>

Participants represented 44 countries in every WHO region



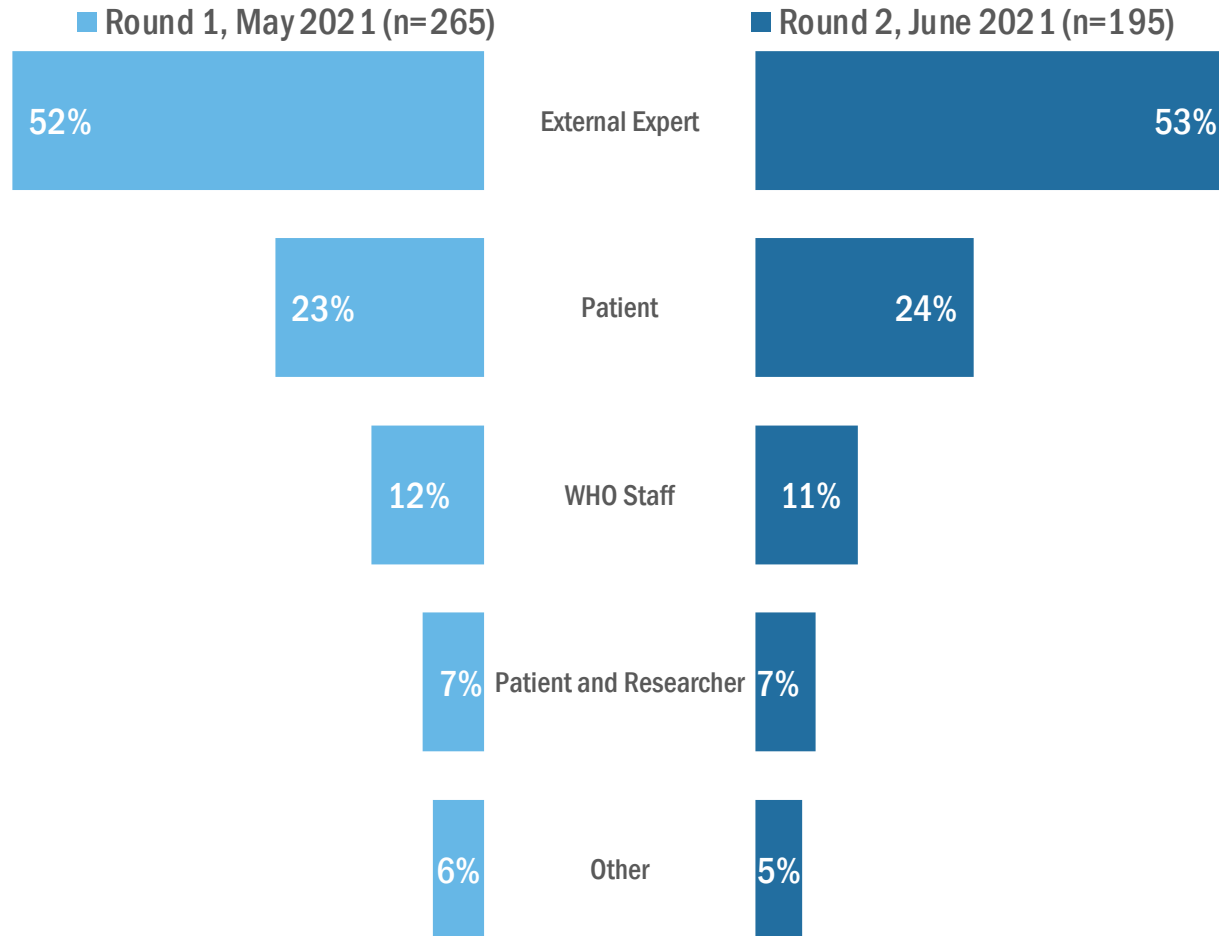
The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: WHO, Delphi Manager
Map Production: WHO Health Emergencies Programme



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No difference in the backgrounds of participants in Rounds 1 and 2



Approximately 40% female
in Rounds 1 and 2

A final total of 12 domains were included in the definition

1. History of SARS-CoV-2 infection
2. SARS-CoV-2 laboratory confirmation
3. Minimum time period from onset of symptoms (or from date of positive test for asymptomatic): 3 months
4. Minimum duration of symptoms at least 2 months
5. Symptoms and/or impairments: cognitive dysfunction, fatigue, shortness of breath, others
6. Minimum number of symptoms
7. Clustering of symptoms
8. Time-course nature of symptoms: (fluctuating, increasing, new onset, persistent, relapsing)
9. Sequelae of well-described complications of COVID-19 (stroke, heart attack, etc.)
10. Symptoms cannot be explained by an alternative diagnosis
11. Application of definition to different populations: Include separate definition for children, others
12. Impact on everyday functioning

Post COVID-19 condition Core outcome set

Post COVID-19 condition Core Outcome Study set

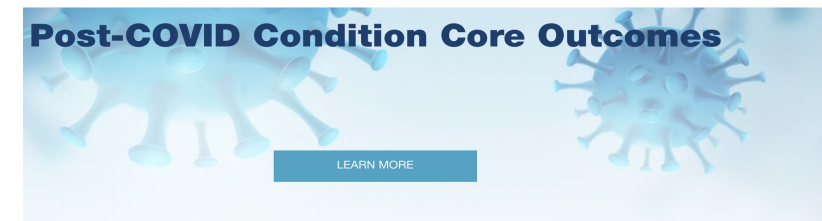
Aim: To rapidly develop a standardized core outcome set (COS) for global use in post COVID-19 condition (PCC) trials, other research and clinical settings

Methods: Optimal (COMET) methods

Input from international stakeholders: Patients with PCC, researchers, clinicians, caregivers and COS methodologists

Design: Delphi studies +/- consensus meetings

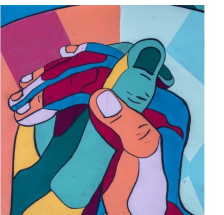
- Stage 1: “What” to measure – complete in November 2021
- Stage 2: “How” to measure – complete ASAP in 2022



PC-COS Project

The Coronavirus disease 2019 (COVID-19) pandemic has necessitated rapid responses from healthcare systems and research networks all over the world. The post-COVID-19 condition, also known as Long-COVID-19 is becoming an important target for research and clinical practice. With an increasing number of studies assessing sequelae of COVID-19, there is a need for a standardised evaluation and reporting of outcomes.

PC-COS project is an international consensus study to develop a standardised set of outcomes – a 'core outcome set' (COS) – to be used by all future trials examining outcomes and clinical practice in people with the post-COVID condition.



Post COVID-19 COS: Stage 1 “What” to measure

Methodology: working group selected 24 outcomes for rating in 1st round of Delphi study available in English, Spanish, French, Russian and Chinese languages

Survival	Cognitive functioning, symptoms and conditions	Fatigue or exhaustion
Cardiovascular functioning, symptoms, conditions	Mental functioning, symptoms and conditions	Social role functioning and relationship problems
Endocrine and metabolic functioning, symptoms, and conditions	Taste- and/or smell-related functioning symptoms and conditions	Work/occupational changes and study
Hearing-related functioning, symptoms and conditions	Kidney and urinary-related functioning, symptoms and conditions	Stigma
Gastrointestinal functioning, symptoms and conditions	Reproductive and sexual functioning, symptoms and conditions	Satisfaction with life or personal employment
Pain	Respiratory functioning symptoms and conditions	Health care resource utilization
Sleep-related functioning, symptoms, and conditions	Skin, hair, and/or nail-related functioning symptoms and conditions	Family/carer burden
Nervous system functioning, symptoms and conditions	Physical functioning symptoms and conditions	Post-exertion symptoms

Post COVID-19 COS: Stage 1 “What” to measure

1530 participants from 70 countries

- 25 European (66% participants)
- 19 Asian (6%)
- 12 South American (5%)
- 10 African (2%)
- 3 North American (19%)
- 2 Australian (2%)

3 key stakeholder groups

1. Professionals (researchers and/or clinicians with PCC expertise)
2. Professionals with PCC
3. People with PCC (family and caregivers)

2 new outcomes (suggested by > 1% of participants) added for 2nd round, launched 1 October 2021

Webinar 3: Expanding our understanding on rehabilitation

Over 3000 participants registered for today's webinar

Objectives:

1. Introduction to rehabilitation for post COVID-19 condition
2. Interventions for rehabilitation for post COVID-19 condition
3. Models of rehabilitation Care for post COVID-19 condition

Acknowledgements

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Silvia Bertagnolio

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Vanessa Cramond

Wouter De Groute

Bridget Griffith

Krutika Kuppalli

Marta Lado

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++ interpreters and IT support team at the WHO