Studying the post-COVID-19 condition: research challenges, strategies, and importance of Core Outcome Set development

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Abstract

Background: A substantial portion of people with COVID-19 subsequently experience lasting symptoms including fatigue, shortness of breath, and neurological complaints such as cognitive dysfunction many months after acute infection. Emerging evidence suggests that this condition, commonly referred to as long COVID but also known as post-acute sequelae of SARS-CoV-2 infection (PASC) or post-COVID-19 condition, could become a significant global health burden.

Main text: While the number of studies investigating the post-COVID-19 condition is increasing, there is no agreement on how this new disease should be defined and diagnosed in clinical practice and what relevant outcomes to measure. There is an urgent need to optimise and standardise outcome measures for this important patient group both for clinical services and for research and to allow comparing and pooling of data.

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Conclusions: A Core Outcome Set for post-COVID-19 condition should be developed in the shortest time frame possible, for improvement in data quality, harmonisation, and comparability between different geographical locations. We call for a global initiative, involving all relevant partners, including, but not limited to, healthcare professionals, researchers, methodologists, patients, and caregivers. We urge coordinated actions aiming to develop a Core Outcome Set (COS) for post-COVID-19 condition in both the adult and paediatric populations.

Keywords: COVID-19, COVID-19 sequelae, Long COVID, Post-acute sequelae of SARS-CoV-2 infection, PASC, Post-COVID-19 condition, Outcomes, Core Outcome Set

Background
The coronavirus disease 2019 (COVID-19) pandemic has necessitated rapid responses from healthcare systems and research networks globally. Although a large amount of comprehensive data on acute symptoms and clinical management has been collected and analysed, there are currently no established clinical definition or Core Outcome Sets (COS). Indeed, even the terminology of the condition is debated with variable terms and definitions for the post-COVID-19 condition including long COVID, “long haulers”, post-acute sequelae of SARS-CoV-2 infection (PASC), or post-COVID-19 condition, the term used by the World Health Organization (WHO). With over 217 million confirmed COVID-19 cases globally [1], post-COVID-19 condition risks affecting millions of people worldwide, making it an urgent research priority [2]. Although wide-scale vaccination may eventually lead to a decline in the number of COVID-19 cases, with cases rising worldwide, the pandemic is far from over. There is an urgent need for consensus on critically important core outcomes to be measured in post-COVID-19 condition. Establishing a COS will ensure that critically important outcomes are measured and reported in a consistent manner in research and practice settings. The consistent use of the most important outcomes across studies and clinical practice is essential to compare and collate the research findings with translation into clinical recommendations for patient care.

In this manuscript, we discuss the existing data known about post-COVID-19 condition research following WHO’s systematic approach to identifying research gaps [3] with the principal purpose of suggesting and outlining the implementation of a COS for the post-COVID-19 condition (i) to allow for the assessment of outcomes which are of the greatest relevance and importance to stakeholders and relevant target populations including patients, families, clinicians, researchers, health systems, public health policymakers, industry, and funding organisations; (ii) to improve the consistency and quality of data collection; and (iii) to build a foundation for data sharing for pooled analysis for meta-analysis and comparison of results across studies and global regions.

Given the current immediate need for an accepted post-COVID-19 condition COS, the development of a COS for the post-COVID-19 condition could act as a guide over the next few years until more is known and/or review or reassessment is indicated.

Post-COVID condition health consequences
Recent editorials [4–6] and National Institutes of Health (NIH) [7] and WHO [8] sponsored conferences have drawn attention to an increasing number of people experiencing health consequences following the acute phase of SARS-CoV-2 infection and are calling for research into the risk factors, clinical features, diagnosis, management, and outcomes. Increasing funding opportunities have subsequently followed [9, 10]. It is important to note that most data regarding post-COVID-19 condition have been generated prior to the condition definition announcement. Thus, earlier studies may not fit the proposed definition criteria. Post-COVID-19 condition extends beyond the cardio-respiratory system to affect most other bodily systems both anatomically and physiologically [11]. Although causes of post-COVID-19 condition are unclear, persistent immune activation may be involved [12]. Risk factors for different syndromes of post-acute SARS-CoV-2 sequelae have not been characterised, but it has been hypothesised that several post-COVID-19 condition phenotypes may exist, although pathophysiology, management, and outcomes are currently unknown.

Long-term health consequences of COVID-19 remain unknown, but reports suggest that prolonged symptom duration and limitations in functioning are common among hospitalised as well as non-hospitalised adults [13, 14] and children [15, 16]. The spectrum of long-lasting symptoms is wide and varies from mild discomfort to severe adverse effects on physical, cognitive, and psychosocial health [17], with important wider implications on functioning, including employment and school attendance.

Multiple studies from different countries found that many individuals experienced persistent symptoms 6 months after COVID-19, with fatigue or muscle weakness, sleep difficulties, and anxiety or depression among the most common sequelae [13, 14, 18]. A recent study
suggests that although most COVID-19 survivors recover both physically and functionally a year after acute infection, some still experience problems with mobility, pain or discomfort, and anxiety or depression compared with non-COVID-19 controls [19]. The data emerging from the controlled studies are in agreement with the earlier reports. A recent analysis of the data from over 250,000 electronic health records demonstrated that more than one in three individuals had one or more features of post-COVID-19 condition recorded between 3 and 6 months after a diagnosis of COVID-19, which was significantly higher when compared with individuals with influenza [20–24]. Disease severity, female sex, and younger age were associated with a higher risk of post-COVID-19 condition development.

Yet, it is unknown whether persistent symptoms and associated abnormalities will fully resolve or whether some may leave life-long dysfunction. It is also worth noting that investigations into the post-COVID-19 condition can be difficult, with high loss to follow-up, frequent use of unvalidated measurement instruments, lack of inclusion of controls during the pandemic, and censoring of data (e.g. for death) not always fully considered in published studies. Differential diagnosis can be challenging with specific symptoms attributed to post-COVID-19 condition being a sign of an ongoing problem (e.g. dysautonomia in people reporting heart rate variability) [25].

Investigation of potential post-COVID-19 condition treatment options is still in its early days. Approaches mainly focus on rehabilitation and symptomatic management. Some experts suggest that antibodies and T cells able to recognise SARS-CoV-2 induced by vaccine “may help the immune system to stop the virus during its first few replications before it can establish hidden reservoirs in the body” [26]; however, the evidence regarding the effectiveness of SARS-CoV-2 vaccines in post-COVID-19 condition treatment is somehow conflicting [27, 28]. One of the major obstacles in the development of intervention strategies for post-COVID-19 condition is the lack of agreed outcomes to be assessed in clinical trials.

The pandemic and subsequent mitigation strategies have also had a substantial impact on the psychosocial well-being of the general population worldwide, with many people experiencing anxiety and depression, due to isolation, economic instability, job insecurity, sickness/death of infected family members, COVID-19-related stigma, lack of trust in government agencies, and constant media attention focused on the pandemic threats [29]. Disruption of care for those with pre-existing conditions has also had a large impact. For example, according to the WHO Pulse survey on continuity of essential health services during the COVID-19 pandemic [30], 45% of countries still reported disruptions to services for mental, neurological, and substance use disorders in the first quarter of 2021. On a similar scale, rehabilitation services disruptions continue to be reported by 53% (of 89 countries).

In addition, indirect impacts of COVID-19 on mental health [31], psychosocial, and neurological sequelae have been reported in adults following COVID-19 [32], and many patients are facing a variety of consequences including fatigue, shortness of breath, and cognitive dysfunction as well as reduced quality of life [18] with an impact on everyday functioning, even months following acute infection [19].

With millions of people affected by COVID-19, even a small percentage developing the 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 [5]. A recent study has reported that previously hospitalised patients with COVID-19 had increased rates of multiorgan dysfunction compared with the general population [33].

Terminology and clinical definitions

With many unresolved issues regarding this condition, the inclusion of patients’ perspectives has become increasingly important to the development of a COS. Importantly, there is currently no agreement on a clinical definition and which outcomes should be measured and how they should be measured. WHO has recently completed a Delphi consensus to finalise a clinical case definition of post-COVID-19 condition as described below [34]. This official WHO definition was published recently and is formulated as the following: “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 and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, and cognitive dysfunction, but also others and generally have an impact on everyday functioning. Symptoms may be new onset following the initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time” [35].

Other organisations have also proposed interim definitions such as the United Kingdom National Institute for Health and Care Excellence (NICE) who suggest an interim definition of post-COVID-19 syndrome as “signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks, and are not explained by alternative diagnoses” [36]. Due to the scarcity and high degree of heterogeneity of existing studies, the definition may change with the emergence of new evidence, but diversity in diagnostic criteria, methodology, and outcomes measured may
slow down the progress. There is a need for terminology harmonisation, and consensus between major public health and government research organisations and professional bodies should be reached for the benefit and convenience of clinicians, researchers, and most importantly patients. With the growing evidence on COVID-19 consequences, there is a risk that the number of different terms used for the post-COVID-19 condition will increase further with increasing phenotyping of this condition.

Core Outcome Set definition and relevance
Outcomes are measured in clinical research or practice to help evaluate relevant associations, safety and efficacy, risk factors, and effectiveness of interventions [37]. The lack of agreed upon outcomes and associated measurement instruments may complicate the evidence synthesis due to the inability to pool data in meta-analyses [38], resulting in a heterogeneous, incomplete, and low-quality evidence base and a barrier to clinical guideline development and policymaking. A COS comprises a minimum list of outcomes recommended for assessment in all studies, clinical practice setting, or both, for a specific condition and is necessary to harmonise research outputs and increase their comparability, quality, and generalisability to ensure their relevance to all interested partners. The failure to consider the views of patients and their families in selecting outcomes may result in less relevant outcome measures being evaluated, while the most important outcomes may be missed.

Core Outcome Sets for COVID-19 and post-COVID-19 condition
A number of COVID-19-related COS are registered at the Core Outcome Measures in Effectiveness Trials (COMET) Initiative web-registry of planned, ongoing, and completed COS studies [39]. These initiatives provide clinicians, researchers, and policymakers with important information on the relevant aspects of COVID-19 and allow for the generation of harmonised high-quality data. Notably, COVID-19 COS development projects were undertaken in a rapid fashion, in contrast with the usual COS development process which typically takes several years.

Although none of the available COVID-19-related COS projects is solely dedicated to the post-COVID-19 condition, some include outcomes for “rehabilitation period”, “longer term impacts”, and “recovery” outcomes [40, 41]. Despite a well-established and standardised approach to COS development, which is generally guided by the COMET Handbook, the development of COS for the post-COVID-19 condition may be a complex task given the diversity and multisystem nature of infection sequelae [33]. COS previously developed for other conditions, which may be relevant for people recovering from COVID-19, should be considered a potential option for certain groups of individuals (e.g. acute respiratory failure/acute respiratory distress syndrome survivors after hospital discharge) [42]. We reviewed studies; assessed in the living systematic review of long COVID [43], data from the clinical trial registries, and available case report forms; and outlined outcomes previously measured in long COVID studies (Table 1).

Considerations and limitations within vulnerable populations
The development of a COS in vulnerable populations such as people with disabilities/comorbidities, undergoing complex treatment (e.g. chemotherapy or transplantation), elderly, racial and ethnic minority groups, pregnant women, and children have special challenges that merit additional considerations. These challenges revolve not just around the constellation of symptoms but also the right time for the assessment and the individual on whom these are assessed. For a pregnant woman who was infected in the first trimester and recovered fully before delivery, any adverse birth outcome, such as preterm birth, stillbirth, or pregnancy complication (e.g. preeclampsia or gestational diabetes), may or may not be part of the post-COVID-19 condition [44]. Whether the congenital anomalies in the neonate or any neonatal complication following maternal COVID-19 can be defined as a potential post-COVID-19 condition for the neonate or infant requires consideration. It is particularly important to differentiate an adverse birth outcome that could be attributed to maternal COVID-19 from one that would have occurred otherwise due to other risk factors, irrespective of maternal COVID-19 status. This is similar to ruling out other aetiologies within the general population (non-pregnant adults).

Considerations and limitations within low-middle income settings
There are multiple implications to the COVID-19 pandemic on low- and middle-income countries (LMICs) including lack of available healthcare resources to meet the needs of the local population, not only with COVID-19 infection, but for other acute and chronic conditions as well [45]. Another anticipated challenge for LMICs is the recognition of the post-COVID-19 condition. Post-acute care of physical, cognitive, and mental health disabilities may go under-recognised, especially in low-resource contexts in which all efforts are focused on containing COVID-19 dissemination and providing an appropriate care for severely ill patients. This may impact research on the post-COVID-19 condition as well as identification and management in LMICs.
| Outcome area     | Outcome domain (per COMET taxonomy)                                       | Outcome                                                                                                                                 |
|------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Death            | All-cause mortality                                                       | Sustained prothrombotic changes                                                                                                      |
|                  |                                                                            | Anaemia                                                                                                                                |
|                  |                                                                            | Thrombocytopenia                                                                                                                        |
|                  |                                                                            | Neutrophil to lymphocyte ratio changes                                                                                                 |
|                  |                                                                            | Changes in inflammatory markers                                                                                                        |
|                  |                                                                            | Changes in serum creatine kinase (CK)                                                                                                  |
|                  |                                                                            | Changes in lactate dehydrogenase (LDH)                                                                                                 |
| Physiological/   |                                                                            | Changes in glutamic-pyruvic transaminase (GPT)                                                                                           |
| clinical         |                                                                            | Electrolytes changes                                                                                                                     |
| 3. Cardiac outcomes |                                                                            | Angina pectoris                                                                                                                         |
|                  |                                                                            | Acute coronary disease                                                                                                                  |
|                  |                                                                            | Heart rhythm issues                                                                                                                      |
|                  |                                                                            | Heart failure                                                                                                                           |
|                  |                                                                            | Palpitations                                                                                                                            |
|                  |                                                                            | Chest tightness                                                                                                                          |
|                  |                                                                            | Newly diagnosed hypertension                                                                                                            |
|                  |                                                                            | Myocardial fibrosis                                                                                                                      |
|                  |                                                                            | Myo- or pericarditis                                                                                                                     |
|                  |                                                                            | Changes in cardiovascular fitness                                                                                                       |
|                  |                                                                            | Signal variations in the electrocardiogram (ECG)                                                                                         |
|                  |                                                                            | High blood pressure                                                                                                                     |
| 4. Endocrine outcomes |                                                                            | Diabetes mellitus                                                                                                                        |
|                  |                                                                            | Worsening control of existing diabetes (T1/T2)                                                                                           |
|                  |                                                                            | Diabetic ketoacidosis                                                                                                                    |
|                  |                                                                            | Hyperlipidaemia                                                                                                                          |
|                  |                                                                            | Subacute thyroiditis                                                                                                                     |
|                  |                                                                            | Hyperthyroidism                                                                                                                          |
|                  |                                                                            | Hypothalamic-pituitary-adrenal axis suppression                                                                                           |
| 5. Ear and labyrinth outcomes |                                                                            | Tinnitus                                                                                                                               |
|                  |                                                                            | Hearing problems                                                                                                                         |
| 6. Eye outcomes  |                                                                            | Visual disturbance                                                                                                                      |
|                  |                                                                            | Red eyes/eye irritation                                                                                                                  |
|                  |                                                                            | Conjunctivitis                                                                                                                           |
|                  |                                                                            | Dry eye disease                                                                                                                          |
|                  |                                                                            | Sicca syndrome                                                                                                                          |
| 7. Gastrointestinal outcomes |                                                                            | Nausea or vomiting                                                                                                                       |
|                  |                                                                            | Diarrhoea                                                                                                                               |
|                  |                                                                            | Gastritis                                                                                                                               |
|                  |                                                                            | Dyspepsia                                                                                                                               |
|                  |                                                                            | Gastro-oesophageal reflux disease (GORD)                                                                                                 |
|                  |                                                                            | Dysphagia                                                                                                                               |
|                  |                                                                            | Bloody stool                                                                                                                            |
### Table 1 The long list of outcomes used in post-COVID-19 condition studies (Continued)

| Outcome area | Outcome domain (per COMET taxonomy) | Outcome |
|--------------|-------------------------------------|---------|
| 8. General outcomes | Enrichment of opportunistic organisms and depletion of beneficial commensals | Fatigue |
| | Post-infectious irritable bowel syndrome | Fever |
| | Constipation | Malaise |
| | New daytime sweating | Weakness |
| | New night sweats | Unspecified pain |
| | Flushing | Sleep disorder |
| | Loss of appetite | Chest pain |
| | Hair loss | Breathlessness |
| | Unspecified pain | Sleep apnea |
| | New daytime sweating | Voice change |
| | New night sweats | Abdominal pain |
| | Flushing | Faints |
| | Loss of appetite | Limb oedema |
| | Hair loss | Dry mouth |
| | Unspecified pain | Dental issues |

| 9. Hepatobiliary outcomes | Chronic liver disease | Liver function test changes |
| 10. Immune system outcomes | Hyperinflammatory state-induced SARS-CoV-2 | Post-MIS-C: coronary artery aneurysm, neurologic (headache, encephalopathy, stroke and seizure) complications |

| 11. Infection and infestation outcomes | Prolonged viral faecal shedding | Tuberculosis |
| 12. Metabolism and nutrition outcomes | Unintentional weight loss | Unintentional weight gain |
| | | New-onset bone demineralisation |
| | | Unintentional change in body constitution |

| 13. Musculoskeletal and connective tissue outcomes | Myalgia | Arthralgia |
| | Limb pain—upper or lower | Muscle atrophy |
| | Changes in neuromuscular performance during resistance exercise | Dorsal/low back pain |

| 14. Outcomes relating to neoplasms: benign, malignant, and unspecified (including cysts and polyps) | Worsening of pre-existing cancer/neoplasm |
| 15. Nervous system outcomes | Dizziness |
| Outcome area | Outcome domain (per COMET taxonomy) | Outcome |
|--------------|--------------------------------------|---------|
|              |                                      | Headache |
|              |                                      | Stroke   |
|              |                                      | Autonomic dysfunction |
|              |                                      | Tremors   |
|              |                                      | Seizures   |
|              |                                      | Taste disturbance |
|              |                                      | Smell disturbance |
|              |                                      | Bradykinesia |
|              |                                      | Dysmetria |
|              |                                      | Speech difficulty/dysarthria |
|              |                                      | Numbness   |
|              |                                      | Guillain-Barré syndrome |
|              |                                      | Abnormal reflex status |
|              |                                      | Trigeminal neuralgia |
|              |                                      | Neuralgia/neuropathy |
|              |                                      | Frontal release signs |
|              |                                      | Parkinsonism |
|              |                                      | Problems with balance |
|              |                                      | Encephalitis |
|              |                                      | Brain physiology changes |
|              |                                      | Restless legs |
|              |                                      | Abnormal muscle tone |
| 16. Renal and urinary outcomes |                                      | New-onset bladder incontinence |
|              |                                      | Acute kidney injury |
|              |                                      | Chronic kidney disease |
|              |                                      | Urinary tract infections |
|              |                                      | Problems passing urine |
|              |                                      | Microhaematuria |
|              |                                      | Renal function tests change |
|              |                                      | COVID-19-associated nephropathy (COVAN) |
| 17. Reproductive system and breast outcomes |                                      | Dysmenorrhea |
|              |                                      | Erectile dysfunction |
|              |                                      | Semen/sperm changes |
|              |                                      | Infertility |
| 18. Psychiatric outcomes |                                      | Depression |
|              |                                      | Anxiety |
|              |                                      | Post-traumatic stress disorder (PTSD) |
|              |                                      | Acute stress disorder |
|              |                                      | Mood change |
|              |                                      | Obsessive-Compulsive Disorder (OCD) |
|              |                                      | Behaviour change |
|              |                                      | Thoughts of self-harm/suicide |
|              |                                      | Risk to self and/or others |
| Outcome area | Outcome domain (per COMET taxonomy) | Outcome |
|--------------|-------------------------------------|---------|
| 19. Respiratory, thoracic, and mediastinal outcomes | | Psychosis |
| | | Traumatic bereavement |
| | | Substance abuse |
| | | Smoking habit |
| | | Hallucinations |
| | | Sore throat |
| | | Sneezing |
| | | New-onset Chronic obstructive pulmonary disease (COPD) |
| | | Excessive sputum expectoration |
| | | Nasal congestion |
| | | Catarrh |
| | | Wheezing |
| | | Cough |
| | | Lung fibrosis |
| | | Pleurisy |
| | | Pleural effusion |
| | | Pain on breathing |
| | | Pulmonary function abnormalities |
| | | Hypoxaemia |
| | | Respiratory failure |
| | | Respiratory disease |
| | | Bronchiectasis |
| | | Asthma |
| 20. Skin and subcutaneous tissue outcomes | | Ulcers |
| | | Skin rash |
| 21. Vascular outcomes | | Thromboembolism |
| | | Venous thrombosis |
| | | Pulmonary and systemic vascular disease |
| 22. Congenital, familial, and genetic outcomes | | |
| 23. Pregnancy and puerperium and perinatal outcomes, including breastfeeding and weaning | | |
| Life impact | 24. Physical functioning | Post-exertional malaise |
| | | Impaired mobility |
| | | Walking/gait abnormality |
| | | Problems with usual activities |
| | 25. Social functioning | COVID-related relationship issues |
| | 26. Role functioning | Functioning |
| | | Work/occupational function changes |
| | 27. Emotional functioning/well-being | Demoralisation symptoms |
| | | Coping issues |
| | | Low mood |
| | | Burnout |
| | | Perceived stigma/discrimination |
| | | Worry about infecting others |
Current definitions for the assessment of specific outcomes involve advanced laboratory and imaging techniques which require resources and skills. Such skills and resources may not be readily available in resource-limited settings. An inclusive approach should be taken while compiling the COS, by including alternate definitions and methods of measurement which may be acceptable for low-middle income settings. Extraordinary care must be taken to strike a balance between accuracy of the assessment and feasibility across the globe. The development of a COS for post-COVID-19 condition should account for cultural and social differences and restrictions in access and resources. Clinicians, researchers, and patient representatives from LMICs should be engaged in the COS development process to ensure global representability and future applicability of the COS.

**Limitations to existing research**

Although attention to the problem of the post-COVID-19 condition is increasing, there are still many unanswered questions and important limitations impacting research quality and understanding of COVID-19 sequelae.

We outline these as well as potential mitigation strategies following a systematic approach [3] or defining

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Table 1 The long list of outcomes used in post-COVID-19 condition studies (Continued)

| Outcome area | Outcome domain (per COMET taxonomy) | Outcome |
|-------------|-------------------------------------|---------|
| 28. Cognitive functioning | | Worry about invasion of privacy |
| | | Need for accurate information from the government |
| | | Fear of no full recovery |
| | | Confusion |
| | | Concentration impairment |
| | | Memory impairment |
| 29. Global quality of life | | Reduced quality of life |
| | | Reduction in health-related quality of life scores |
| 30. Perceived health status | | Illness perceptions |
| 31. Delivery of care | | Lack of information/uncertain prognosis |
| | | Difficulty accessing and navigating services |
| | | Difficulty being taken seriously/achieving a diagnosis |
| | | Variation in standards (e.g. inconsistent criteria for seeing, investigating, and referring patients) |
| | | Variable quality of the therapeutic relationship |
| 32. Personal circumstances | | Self-care ability |
| | | COVID-related life issues such as debt, unemployment, and family relationships |
| | | Personal finances difficulties |
| Resource use | 33. Economic | Health economic |
| 34. Hospital | | Post-intensive care syndrome |
| 35. Need for further intervention | | Hospital readmission |
| | | Further healthcare contact |
| | | Lung transplantation |
| | | Oxygen dependence |
| | | RRT requirement |
| | | Need for regular medical check-ups after discharge |
| | | Need for psychiatric service |
| Adverse events | 36. Societal/carer burden | Care dependency |
| | | Carer burden |
| | 37. Adverse events/effects | Vaccination adverse effects |
| | | Adverse effects of prednisolone |
research priorities through planning, implementation, publishing, and evaluation phases in Table 2. The table was drafted by DM and critically appraised and approved by all the authors. Post-COVID-19 condition still has no consensus definition, well-defined clinical phenotypes, or clearly explained underlying physiological mechanisms. WHO has highlighted “three Rs” related to post-COVID-19 condition—recognition, research, and rehabilitation, and initiated working groups aiming to provide a post-COVID-19 condition clinical definition [46] and outline plausible explanations of the physiological mechanisms as well as proposed an interim clinical case definition through a multi-disciplinary, gender-based, international Delphi consensus [34].

The number of studies assessing post-COVID-19 condition is increasing, generating a large amount of data, where validity remains unknown. There is a large variability in reporting and quantification of post-COVID-19 condition symptoms among the studies. It is important to note that not only symptom presence is essential, but symptom duration and severity also merit consideration. The lack of pre-morbid data for comparison is one of the major limitations of post-COVID-19 condition research. Any abnormalities found are normally attributed to post-COVID-19 condition assuming that the patient did not have asymptomatic abnormal testing before infection.

Few international initiatives have created instruments for data collection. The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) has developed follow-up protocols and surveys for adults and children to assess the prevalence and risk factors for long-term physical and psychosocial health consequences following COVID-19 diagnosis. A post-COVID-19 condition case report form has been designed by the WHO to report standardised clinical data from individuals after hospital discharge or after the acute illness to examine the medium- and long-term consequences of COVID-19. Although these instruments assist harmonised data collection, an increasing number of tools

### Table 2 Existing limitations of post-COVID-19 condition research and potential mitigation strategies

| Issue                                                                 | Potential mitigation strategies |
|----------------------------------------------------------------------|--------------------------------|
| 1. The definition of the post-COVID-19 condition.                    | A few initiatives were launched, including a WHO working group aiming to provide a clinical case definition of the post-COVID-19 condition. |
| 2. Pathophysiological mechanisms still lacking.                      | A WHO working group has been set up to outline plausible hypotheses regarding the underlying immunological and physiological mechanisms of post-COVID condition. Multinational studies aimed to dissect the underlying mechanisms of the post-COVID-19 condition should be launched by multilateral organisations and universities. |
| 3. Rapidly emerging data.                                            | Core Outcome Set (COS) should be developed keeping the balance between speed and quality. Acute COVID-19 COS initiatives [41] may be used as an example of efficient management and rapid development. Involving principle investigators from ongoing studies to investigate the possible additional sources of data and allow for the dissemination of the COS upon development. |
| 4. Target population and scope:                                      | Despite the focus of COVID-19 research on adults, all age and severity (during acute phase) groups (including asymptomatic individuals) should be included (approaches to patient routing differ within and between the countries and criteria for hospital admission vary). It is imperative to develop COS for children and their carers as the post-COVID-19 condition may potentially have a detrimental life-long effect on child health. A single COS aiming at clinical as well as research settings may be developed. |
| ● Hospitalised cohorts may be potentially different to those studies investigating non-hospitalised patients. | Ongoing systematic reviews may assist with the development of a list of candidate outcomes for the evaluation as part of a Core Outcome Set. Patient engagement should drive the agenda to ensure that patient-important outcomes are captured. This can be achieved by survey/Delphi process and consensus meetings. Post-COVID-19 condition COS development is a priority. |
| ● Criteria for hospitalisation vary substantially within hospitals and countries (i.e. hospitalised patients are different). | Measurement instruments used in the studies should be systematically reviewed and assessed for validity/truth, discrimination ability, and feasibility. |
| ● The need for a separate Post-COVID-19 condition COS development for children has not been established. | |
| 5. What to measure?                                                  | |
| ● There is a need to define which data should be assessed in the trials and in clinical practice. | |
| 6. How to measure the Post-COVID-19 condition?                       | |
| ● Existing "validated" tools (e.g. quality of life instruments) have not been validated in COVID-19, and study participants are often asked about their experience pre-COVID retrospectively, which may lead to selection and recall bias. | |
| ● New measurement instruments may need to be developed if no adequate instruments exist for prioritised Core Outcome Domains. | |
from reputable organisations may result in data heterogeneity with different centres prioritising different instruments.

There are few ongoing initiatives tackling the problem of data heterogeneity by systematically reviewing available evidence in the live format [43], which may inform COS initiatives and assist with the long list of outcome development. However, systematic reviews will not address the problem of instrument validity. Assessment of the validity may take a long time, and meanwhile, a COS should be developed.

A significant gap and limitation within post-COVID-19 condition research exist within paediatric and adolescent development considering that life-long consequences may exist [47]. Outcomes of interest in children and adolescents may be very different to the adult population, and COS for this age group should be specifically developed engaging the children and adolescents themselves, as well as their parents and carers.

Conclusions
This manuscript was written by a multidisciplinary (allergists, critical care specialists, ENT specialists, infectionists, immunologists, neurologists, psychiatrists, paediatricians, pulmonologists, specialists in global and public health experts, epidemiologists, methodologists, rehabilitation specialists, and people with lived experience of post-COVID-19 condition), gender-balanced, international group of experts, including members of the ISARIC Consortium, US Centers for Disease Control and Prevention (CDC), experts involved in the WHO post-COVID condition clinical characterisation group, leads of international COVID-19 cohorts, members of Core Outcome Measures for post-COVID-19 condition/long COVID initiative and patient representatives, to outline the unmet needs and justification for Core Outcome Set development for the post-COVID-19 condition which may become a major public health burden. Previous research in various medical fields has demonstrated the importance and usefulness of COS in both research and clinical practice. There is a need to rapidly develop a COS for the post-COVID-19 condition which will allow for the improvement in data quality, harmonisation, and comparability between different geographical locations. The joint initiative requires input from all relevant partners, including, but not limited to, healthcare professionals, researchers, methodologists, patients, and carers. We urge local and international funding agencies to provide support for coordinated actions aiming to develop COS for post-COVID-19 condition in adults and children.

Abbreviations
CDC: US Centers for Disease Control and Prevention; COMET: Core Outcome Measures in Effectiveness Trials Initiative; COS: Core Outcome Set; COVID-19: Coronavirus disease 2019; ISARIC: International Severe Acute Respiratory and Emerging Infection Consortium; LMICs: Low- and middle-income countries; NICE: National Institute for Health and Care Excellence; NIH: National Institutes of Health; PASC: Post-acute sequelae of SARS-CoV-2 infection; SARS-CoV-2: Severe acute respiratory syndrome-related coronavirus 2; WHO: World Health Organization.
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