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

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Contributions: DM conceived the idea for the study. DM led the methodological team and supervised the research team work throughout the project. DM, TN, PRW, DMN and NSe designed the study protocol. DM, TN, PRW, and DMN carried out the methodological discussions at the start of the project. DM, NSe and AC were responsible for the day-to-day running of the project. AM, ND, AA, LX, PB, PR, KA undertook the literature review, identified outcome measures and outcome measurement instruments and categorised them for inclusion in the online Delphi survey and expert Delphi survey. NSe and AC coordinated the data revision process. NSe and AC developed the online Delphi surveys and contributed to the day-to-day management of the project. NSe, AC, AM, ND were responsible for setting up the Delphi Manager. DM, NSe, AC, AM, ND were responsible for communication with stakeholders. NSe, AC, AM, ND prepared the instructions and materials for Delphi process participants. NSe, AM, ND were involved in the process of setting up and updating the website. DM, NSe, AC, AM, ND, AA, LX organised the 'What to measure' Consensus meeting. DM, NSe, AC, AM were responsible for instrument cards design and contents. DM, AC, NSe, AM, AA, LX organised the 'How to measure' Consensus meeting. DM, AC, NSe, DB, CB and SV participated in the project methodology discussions throughout the duration of the project. NN undertook the data analysis. NSe and AC organised the consensus meeting and consensus workshop. KK, NSc and JVD led the WHO administrative aspects of the study. SM provided and coordinated invaluable perspectives of people with lived experience throughout the study into its design and implementation. DM, NSe and AC drafted the manuscript; all authors reviewed and approved the final manuscript.

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Summary

The COVID-19 pandemic substantially impacted different age groups, with children and young people (CYP) not exempted. Many have experienced enduring health consequences. Presently, there is no consensus on the health outcomes to assess in CYP with post COVID-19 condition. Furthermore, it is unclear which measurement instruments are appropriate for use in research and clinical management of CYP with post-COVID-19. To address these unmet needs, we conducted a consensus study, aiming to develop a core outcome set (COS) and an associated core outcome measurement set (COMS) for evaluating post-COVID-19 condition in CYP. Our methodology comprised of two phases. In phase 1 (to create a COS), we performed an extensive literature review and categorisation of outcomes, and prioritised those outcomes in a two-round online modified Delphi process followed by a consensus meeting. In phase 2 (to create the COMS), we performed another modified Delphi consensus process to evaluate measurement instruments for previously defined "core outcomes" from phase 1, followed by an online consensus workshop to finalise recommendations regarding the most appropriate instruments for each core outcome. In phase 1, 214 participants from 37 countries participated, with 154 (72%) contributing to both Delphi rounds. The subsequent online consensus meeting resulted in a final COS which encompassed seven critical outcomes: fatigue; post-exertion symptoms; work/occupational and study changes; as well as functional changes, symptoms, and conditions relating to cardiovascular, neuro-cognitive, gastrointestinal, and physical outcomes. In phase 2, 11 international experts were involved in a modified Delphi process, selecting measurement instruments for a subsequent online consensus workshop where 30 voting participants discussed and independently scored the selected instruments. As a result of this consensus process, four instruments met a priori consensus criteria for inclusion: 'PedsQL multidimensional Fatigue scale' for 'fatigue'; 'PedsQL Gastrointestinal symptom scales' for 'gastrointestinal'; 'PedsQL Cognitive Functioning Scale' for 'Neuro-cognitive' and 'EQ5D family' for ‘physical functioning’. Despite proposing outcome measurement instruments for the remaining three core outcomes ('cardiovascular', 'post-exertional malaise', 'work/occupational and study changes'), a consensus was not achieved. Our international, consensus-based initiative presents a robust framework for evaluating post-COVID-19 condition in CYP in research and clinical practice via a rigorously defined COS and associated COMS. It will aid in the uniform measurement and reporting of relevant health outcomes worldwide.

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Introduction

While the majority of people infected with SARS-CoV-2 recover quickly, a significant number experience ongoing or relapsing symptoms for a prolonged period of time. Most research on post COVID-19 condition has focused on adults, with a much smaller number of paediatric studies. The prevalence of signs/symptoms after COVID-19 in children and young people (CYP) remains largely unknown due to heterogeneous terminology across the studies, but a recent systematic review estimated prevalence of symptoms one month after infection to be up to 25% [1]. Estimation of post COVID-19 condition prevalence is somehow difficult due to heterogeneity in terminology used and methodology applied [2]. A large multinational study estimated that around three percent of individuals under 20 years old with symptomatic SARS-CoV-2 infections had persistent fatigue, cognitive, and respiratory symptom clusters upon recovery from the acute infection [3,4], while reassuring data from the recent UK Office for National Statistics suggests that the incidence of post COVID-19 condition is now less than one percent [5]. Some studies estimated cumulative incidence of persistent symptoms following SARS-CoV-2 infection between 24% and 58% of CYP [6].

A diversity of outcomes is being evaluated in research on post COVID-19 condition in CYP. This heterogeneity hinders the ability to compare findings and conduct meta-analyses to inform evidence-based decisions. There is also a risk that ongoing or future interventional trials will not address some critically important outcomes as some outcomes important in one group may not be important in another or vice versa. These issues highlight the need for core outcome set (COS) development, to ensure that important outcomes are not missed in research or clinical practice on post COVID-19 condition in CYP [7]. COS are useful in various medical fields and can improve data quality, harmonisation, and comparability between different studies and clinical practices [8,9]. A COS is a universally agreed-upon, harmonised set of outcomes that, at a minimum, should be measured and reported in every clinical trial within a specific medical area. These sets are also developed in other types of research and clinical practice. They represent a consensus on the most critical outcomes for people with lived experience, their families, researchers, health professionals and other key stakeholders. The "gold standard" approach to COS development has been outlined by the Core Outcome Measures in Effectiveness Trials (COMET) framework and consists of two steps: (a) "what to measure?", and (b) "how to measure?" Once the COS is developed, the most appropriate outcome measurement instruments for assessing the "core outcomes" should be defined to provide practical measurement instruments for researchers and practitioners [9].

In 2021, an international group of experts defined the COS domains recommended to be used in all future research and clinical care for adults with post COVID-19 condition [10] and the second phase of this project defined the Core Outcome Measurement Set (COMS) in 2022 [11]. However, adults and CYP have distinct physiological and developmental characteristics, which may result in different presentations and long-term implications of post COVID-19 condition. Hence, it is crucial to have a tailored COS and COMS specifically designed for CYP to accurately capture and address these nuances as COS/COMS potentially may be required for different groups of paediatric population. To this end, we conducted an international study to develop a COS and COMS for post COVID-19 condition in CYP for use in clinical research and practice.

Methods

First phase (COS development)

The development of the COS involved three stages: (1) reviewing the outcomes reported in studies on post COVID-19 condition in CYP to develop a list of outcomes for stakeholder consideration; (2) a two-round online modified Delphi consensus process to rate the importance of the outcomes for the COS; (3) an online interactive consensus meeting to review and agree upon the final COS. The study protocol was developed a priori, and the project was registered (https://www.comet-initiative.org/Studies/Details/1847). Ethical approval for the study was obtained from the Sechenov University Ethics Committee on 20.01.2022 (protocol number 01-22).

The intended COS was developed for CYP below 18 years old, to be applied to post COVID-19 condition in clinical research and practice settings. The terms post COVID-19 condition and Long COVID were used interchangeably throughout the process.

Study group and participants

An international and multidisciplinary group of experts, including CYP with post COVID-19 experience and their caregivers, conducted a project under the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) umbrella. The Core Outcome Measures in Effectiveness Trials (COMET) Initiative and the World Health Organization (WHO) collaborated with this project.

Participants were categorised into three distinct stakeholder groups: (a) CYP with post COVID-19 condition and their carers; (b) health professionals working with CYP with post COVID-19 condition; and (c) researchers studying post COVID-19 condition in CYP. For health professionals and researchers, prerequisites for participation included experience in treating CYP with post COVID-19 condition and conducting research in CYP with post COVID-19 condition, respectively. More details can be found in the appendix 5, p 4.

Developing a list of outcomes

The COS consensus process was informed by a comprehensive search of Medline, Embase, and the WHO COVID-19 Research Database (from inception until December 29, 2021). An additional search was performed on June 1, 2023, prior to consensus meeting, to screen for more recent evidence. The search was limited to English-language publications and protocols. The detailed search strategy can be found in the appendix 1, pp 5-9.

Data from research protocols were extracted from two clinical trials registries, Clinical Trials.gov and the International Clinical Trials Registry Platform, and reviewed by the reviewers (NS, AC, AM, ND, AA, LX, PB, PR, KA), with two reviewers extracting the data from each record independently. We classified unique outcomes from the list into domains (appendix 1, pp 27-82) using an existing taxonomy by Dodd and colleagues [12].

Delphi process and definitions

We conducted a two-round online modified Delphi consensus process [9]. In the first round, survey participants anonymously rated each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) scale [13], which is a nine-point scale commonly divided into three categories for COS projects: not important (1-3), important but not critical (4-6), and critically important (7-9). Each outcome had an "unable to rate" option and an option to add text-based comments. More details can be found in the appendix 5, p 4.

In the second round of the Delphi process, participants were shown their original rating from the first round alongside overall ratings of each of the three stakeholder groups for each outcome. They were then asked to rate each outcome again using the same scale.

Consensus for inclusion of an outcome in the COS was defined a priori as 80% or more of participants in each stakeholder group rating the outcome as critically important . Consensus for exclusion of an outcome from the COS was defined as 50% or less of respondents in each stakeholder group rating the outcome as critically important . Outcomes that did not meet these criteria were discussed at the consensus meeting.

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

initiative.org/delphimanager). Further details of the Delphi consensus process are included in appendix 1, pp 80-106.

Consensus meeting

We conducted an interactive online consensus meeting via Zoom, extending invitations to individuals with firsthand experience and their caregivers. The consensus meeting was conducted in English under the guidance of an experienced independent facilitator. The meeting was organised around the results from the second round of the Delphi.

The agenda prioritised outcomes that met the inclusion consensus by at least one stakeholder group, despite not being agreed upon by all. Additionally, outcomes deemed 'critically important' by at least 50% (but not more than 80%) of the participants in each stakeholder group were also selected for discussion.

Each of three stakeholder groups assessed outcomes independently, utilising the aforementioned threshold for defining inclusion — i.e., an outcome rated as critically important by 80% or more participants in all stakeholder groups. For further details regarding the consensus meeting process, please refer to appendix 2.

Data analysis

Descriptive statistics were used to show the overall scores of each stakeholder group for the three GRADE categories for all outcomes considered at each stage, to determine whether they met the predefined criteria for inclusion or exclusion.

Similarly to the PC-COS adult project [10], we agreed a priori that only responses from Delphi participants who rated at least 50% of outcomes would be included in the analysis. Free-text comments were translated into English from the French, Russian, Spanish, and Chinese surveys and collated and reviewed by the core group. Bar plots displaying the distribution of ratings for each outcome, faceted by stakeholder group, were produced using R (version 4.2.1) and shown to participants in the second Delphi round.

Second phase (Outcome measurement instruments consensus)

Literature review of outcome measurement instruments

The core group reviewed all measurement instruments that emerged from our literature search. More details can be found in the appendix 5, p 4.
Given that the measurement properties of non-COVID specific instruments had not been assessed in a post COVID-19 population, assessment of the measurement properties of these instruments was not undertaken [11].
For all instruments, feasibility-related data (e.g. time, cost, language/translations) were considered by the experts and presented at consensus meeting to the participants. It was decided a priori that instruments requiring trained personnel, additional software, clinical facilities, or not pertaining to "core outcomes" would be excluded to ensure applicability of COMS across different settings. The instruments needed to be available for use even in “low resource areas” and not require in person assessment or medical equipment.

Expert Delphi Consensus

The core group refined a comprehensive list of instruments derived from systematic literature and clinical trials review. Instruments requiring trained personnel, additional software, clinical facilities, or not pertaining to "core outcomes" were excluded.

A group of independent international experts, with extensive experience in post COVID-19 condition research and/or clinical practice, anonymously reviewed these instruments over two rounds. They provided feedback in excel spreadsheets on each instrument and suggested potential additions, which were assessed for feasibility and applicability by the core group. Approved new instruments were presented in the second round for further review. In the second round, each expert received a list of instruments accompanied by anonymised expert feedback from the first round. After reviewing the comments from the first round, they had the opportunity to modify their initial selection or retain it. Each expert indicated their preference for each instrument's inclusion in the consensus workshop.

Instruments that garnered "include" or "maybe" responses from more than 50% of the experts were forwarded to the online consensus meeting. We prepared “instrument cards”, modified for the purposes of the project from the previous studies (https://www.improvelto.com/instruments/), for each outcome, collating a summary table of instruments selected for discussion. These were shared with the consensus workshop participants beforehand.

Consensus workshop

Upon obtaining expert review results, we convened at an online consensus workshop to discuss the shortlisted instruments. The consensus meeting was conducted in English and the study lead (DM) acted as a facilitator without voting rights.

Instruments selected as a result of ‘expert review’ as per criteria outlined above were discussed at the meeting. Consensus for an instrument to be included was defined as 70% or more participants from a total number of voting participants. If participants did not cast a vote on a given instrument, not less than 70% of voting participants were required to consider the vote valid.

Results

Literature review

We conducted a review of available studies and trial protocols on post COVID-19 condition in CYP. This review found 212 studies and protocols that met the inclusion criteria, as detailed in appendix 1, pp 10-27. These studies and protocols reported a total of 1097 outcomes, as detailed in appendix 1, pp 27-79.

The outcomes were classified and reviewed iteratively by the core group and project steering committee. After discussion, the steering committee approved 25 outcomes (appendix 1, pp 80-82) for consideration in the first round of the Delphi process. These 25 outcomes were categorised into four domains: survival (one outcome); physiological or clinical (17 outcomes); life impact (five outcomes); and resource use (two outcomes). Figure 1 summarises the steps taken in the development of the COS and COMS.

First phase (Core Outcome Set development)

Delphi process

The first round of the online Delphi process was conducted from November 23 to December 24, 2022. A total of 228 individuals registered to participate in the study, and 214 participants (94%) from 37 countries completed the first round, which required them to rate 50% or more of the 25 outcomes. Of these participants, 154 (72%) from 31 countries participated in the second round of the Delphi process and rated 50% or more of the outcomes in this subsequent round. Demographic characteristics of the participants for each Delphi round are presented in Table 1. Further details about the Delphi participants can be found in appendix 1 (pp. 83-90).

Upon completion of the first round of the Delphi process, the participant ratings indicated that the COS should include three of the 25 outcomes, while four outcomes should be excluded, and consensus criteria for 18 outcomes were not met. Table 2 and appendix 1, pp. 90-94 provide further details.

The core group reviewed 72 submitted free-text responses related to additional outcomes, with no new outcomes added in the second Delphi round. Four participants suggested adding “recurrent infections" as a new outcome. This suggestion was discussed within the core group with a decision made for not including it due to the lack of evidence for post-COVID immune deficiency in children, the complexity of the outcome, and the difficulty in differentiating it from infections stemming from other aetiologies. There was also overlap with some of the outcomes already present as a part of the Delphi process, and core group highlighted practical challenges in monitoring and documenting such infections.

The second Delphi round occurred from February 19 to March 31, 2023, during which 154 participants assessed the 25 outcomes. Subsequently, four outcomes met criteria for inclusion, with three in the physiological or clinical domain and one in the life impact domain. Eight outcomes were excluded. Thirteen other outcomes received mixed ratings across the stakeholder groups, which led to their discussion at a subsequent consensus meeting.

Consensus meeting

The consensus meeting was conducted online on April 28, 2023. For feasibility purposes voting participants were divided into two stakeholder groups: (a) CYP with post COVID-19 condition and their carers (n=11); (b) health professionals working with CYP with post COVID-19 condition and researchers studying post COVID-19 condition in CYP (n=12). Detailed descriptions of the participants who attended the consensus meeting can be found in appendix 2 (pp. 3-4).

Upon ratification of outcomes that were voted “in” and “out” upon the Delphi process the thirteen outcomes were discussed in the following order: survival; post-exertion symptoms; mental/psychological functioning, symptoms, and conditions; respiratory functioning, symptoms, and conditions; pain; sleep-related functioning, symptoms, and conditions; gastrointestinal functioning, symptoms, and conditions; muscle and joint symptoms and conditions; work/occupational and study changes; satisfaction with life or personal enjoyment; social role-functioning and relationships problems; healthcare resource utilisation; family/carer burden.

After discussions and subsequent voting, three additional outcomes met the predefined consensus definition for inclusion. These included “post-exertion symptoms” with 100% (11 out of 11) of the CYP with post COVID-19 condition and their carers and 84% (10 out of 12) of the health-care professionals and researchers rated it as critically important, based on the GRADE rating of 7–9; “gastrointestinal functioning; symptoms; and conditions” with 100% (11 out of 11) and 84% (10 out of 12) as well as “work/occupational and study changes” rate as critical by 100% (11 out of 11) and 91% (11 out of 12) participants respectively. Consequently, three outcomes were incorporated into the COS, joining the four previously agreed-upon outcomes. This brought the total number of outcomes in the COS to seven. The results derived from both the Delphi process and the consensus meeting can be accessed in appendix 1, pp. 90-106.A report of the consensus meeting is available in appendix 2.

Second phase (Core Outcome Measurement Set development)

Literature review of outcome measurement instruments

A comprehensive literature review found 1762 instruments used across post COVID-19 condition studies and trial protocols. Following removal of duplicates and mapping of identified instruments to the core outcomes, the number was reduced to 225. An independent assessment of these instruments by the core group, taking into account a priori defined criteria, further reduced the list to 30. In addition to these, the study group identified five relevant PROMIS instruments, bringing the total to 35 outcome measurement instruments. These instruments,

detailed in appendix 3, pp. 6-16, were mapped to seven "core outcomes" described above. The COS development steps are summarised in Figure 1.

Expert Delphi

A group of eleven international experts anonymously reviewed instruments provided by the study team over two Delphi rounds. Round 1 ran from June 8 to June 21, 2023, with all the experts completing this round. All the experts were invited to participate in round two. Round 2 ran from July 3 to July 13, 2023; with all the experts providing their feedback and scoring. Further details of experts involved in the Delphi process are detailed in appendix 3, pp. 16-17.

Of the instruments reviewed in round 1, 18 out of 35 instruments met pre-specified criteria for inclusion for discussion at consensus workshop. A single instrument (stomach reflux symptom by Visual Analog Score) was excluded by the core group due to the non-specific nature of this VAS. All other instruments from round 1 were taken forward to round 2. Additional potential instruments were assessed for feasibility and applicability by the core group. 15 approved new instruments were presented in the second round for further review, including one instrument that was specific to the post COVID-19 condition in adults which is currently in the process of validation for CYP. A total of 49 instruments were reviewed in round 2 and 20 of them met pre-specified criteria for inclusion for discussion at consensus workshop. The WHO Disability Assessment Schedule (WHODAS 2.0) Children and Youth 36-Item Version instrument was found upon the pre-meeting literature search update and included for discussion at the consensus workshop.

Consensus workshop

Ahead of the consensus workshop, materials were circulated to all individuals invited to the meeting. The online consensus workshop was held on July 31, 2023, with 46 individuals participating in this three and a half-hour session. This attendance included six study team members, nine observers, and 30 voting participants (eight carers of CYP with post COVID-19 condition; and 22 health professionals and researchers with expertise in post COVID-19 condition in CYP, mirroring the approach taken for the first phase of the project and previous process of COS development for the adult population [10,11]). Details of those who participated in the consensus workshop can be found in appendix 4, pp. 2-3.

At the start of the online workshop, participants were briefed about the process and a priori defined criteria for consensus. Participants were reminded that multiple instruments could be chosen or voted 'in' within a domain. Voting on each instrument was independent. The subsequent outcomes and measurement instruments discussed were: Cardiovascular functioning, symptoms, and conditions (PedsQL Cardiac Module; Symptom Burden Questionnaire for Long COVID (Circulation scale) and Malmo POTS score (MAPS)); Gastrointestinal functioning, symptoms, and conditions (PedsQL Gastrointestinal Symptoms Scales; Questionnaire on Pediatric Gastrointestinal Symptoms (QPGS) and Symptom Burden Questionnaire for Long COVID (Stomach and Digestion Scale)); Neurocognitive functioning, symptoms, and conditions (PROMIS Pediatric Cognitive Function - Short Form 7a; PedsQL Cognitive Functioning Scale and Symptom Burden Questionnaire for Long COVID (Memory, Thinking & Communication scale, movement scale, muscles and joints, pain scales)); Fatigue (Chalder fatigue questionnaire; PROMIS Paediatric Fatigue; PedsQL Multidimensional Fatigue Scale and Symptom Burden Questionnaire for Long COVID (Fatigue scale)); Post-exertion symptoms (CDC symptom inventory for CFS; PEM items from DePaul Symptom Questionnaire and Symptom Burden Questionnaire for Long COVID (Fatigue scale)); and Physical functioning, symptoms, and conditions (EQ5DY instrument; PROMIS Physical Activity and Symptom Burden Questionnaire for Long COVID (Impact on Daily Life Scale)); Work occupational and study changes (Symptom Burden Questionnaire for Long COVID (Impact on Daily Life Scale) and WHO DAS 2 Children and Youth 36-Item Version).

Following discussion and voting, 'PedsQL multidimensional Fatigue scale' instrument for 'fatigue' with 26/26 (100%) of consensus meeting participants voting 'Yes' for inclusion so it was added to the COMS; 'PedsQL Gastrointestinal symptom scales' for 'gastrointestinal' 23/26 (88%); 'PedsQL Cognitive Functioning Scale' for 'Neuro-cognitive' with 21/25 (84%) and 'EQ5D family' for physical functioning 24/25 (96%), respectively. Overall, four measurement instruments were selected for inclusion into COMS (see Table 3 and Figure 2).

Consensus was not achieved for recommending measurement instruments for the remaining three core outcomes. Table 3 indicates the voting results and reasons for exclusion for the instruments discussed at the meeting but not reaching consensus. Detailed consensus workshop report is available in the appendix 4.

Discussion

This manuscript presents the findings of a large, rigorous international consensus study aimed at developing a COS and a COMS for post COVID-19 condition that are intended for use in CYP in research and clinical practice settings. Seven outcomes achieved the predefined consensus definition for inclusion in the COS: fatigue; post-exertion symptoms; work, occupational and study changes; as well as functional changes, symptoms, and conditions relating to cardiovascular, neuro-cognitive, gastrointestinal, and physical outcomes. Agreement regarding the most appropriate instruments to be used was reached for four outcomes: these were the EQ5D family (for physical functioning) and the fatigue, gastrointestinal symptoms and cognitive functioning scales of the PedsQL. The consensus process reduced the number of potential instruments for measuring the seven core outcomes from over 200, despite no single measurement instrument reaching consensus for the remaining three outcomes.

Through our consensus process, we identified seven critical outcomes to be incorporated in both research and clinical practice, ensuring that the most salient aspects of the condition are consistently and effectively addressed. Five of the seven consensus-based outcomes in this COS are in the physiological or clinical outcomes domain and cover many of the frequently reported symptoms in CYP. While the WHO clinical case definition of post COVID-19 condition in CYP [14] offers a consistent clinical terminology, the COS delineates the essential outcomes that ought to be assessed in every study and clinical setting.

Across stakeholder groups, there was a broad consensus on the significance of most outcomes. Two outcomes, namely 'sleep-related functioning, symptoms, and conditions' and 'pain', narrowly missed the predefined threshold. A notable divergence in perspectives emerged regarding the 'family/carer burden' outcome. CYP with post COVID-19 condition and their carers deemed this outcome as critically important. In contrast, only 34% of health-care professionals and researchers viewed it with the same level of importance. Despite not meeting the criteria for inclusion in the COS, the significance of this outcome was recognised by both groups, with 100% of CYP and caregivers and 84% of health-care professionals and researchers rating it as either important or critically important (appendix 2). The emphasis placed on these outcomes suggests that they warrant consideration in research and clinical settings. It is important to note that COS is a necessary minimum that should always be measured but do not preclude from measuring other outcomes.

It is also worth noting that a small number of "CYP with Long COVID and their family and carers" acknowledged the critical importance of 'mental' outcome assessment, with concerns of stigmatisation being raised. Many parents shared their experience of being troubled and hesitant to discuss mental problems of their child with healthcare providers, as the symptoms in a child are often attributed to mental health challenges/issues. This is in contrast to the COS for post COVID-19 condition in adults, which includes this outcome [10]. All health professionals/researchers considered this outcome important with 7/12 (59%) feeling that it is critical. Mental health-related symptoms are common, and it is understandable to suffer effects on emotional wellbeing due to

having an illness such as post COVID-19 condition as it has a direct effect on an individual's life. Concerns of stigmatisation should not stand in the way of being able to assess the child or young person holistically and hence provide necessary support. Health professionals and researchers need to approach this delicate topic with care, while carers of CYP with post COVID-19 condition should not see attempt to assess mental health as lack of trust to their concerns about their child.

Overall, the paediatric COS seems to focus more on functional and symptomatic outcomes directly relevant to CYP'sdaily lives, such as school and physical activities, while the adult COS encompasses a broader range of health aspects, including respiratory, mental health and survival, which are important for all age groups, but more pertinent to the adult population. These differences underscore the unique health impacts and assessment needs of these two age groups in post-COVID-19 condition research.

The PedsQL and EQ5D families of instruments offer multiple age-specific versions [15,16]. These versions contain questions pertinent to a child's development, and they have been translated into various languages and are used across different medical disciplines.

Consensus regarding measurement instruments was not achieved for three outcomes. There were several potential reasons for this. Firstly, post COVID-19 condition is a recently discovered condition and the mechanistic understanding in CYP is still in its infancy. This heterogeneity can influence instrument preference, and the unique considerations of the paediatric population such as specific needs for different age groups or inability to appropriately articulate their complaints in younger children, introduce added complexity. Secondly, past experiences with various instruments may have introduced implicit bias, thereby influencing participant scoring. At least one of these measurement instruments can be potentially considered for each core outcome although they should be used with caution taking into account workshop participants feedback (appendix 4, pp. 4, 7, 10).

Our study has some limitations. Firstly, while the Delphi consensus process for the COS incorporated individuals from diverse geographical locations, the majority were white, and were resident in the UK and the United States. The Delphi process also saw an underrepresentation of male participants, which is a common problem in survey/Delphi research, and particularly related to CYP, and has previously been acknowledged [18,19]. Both imbalances could potentially result in a lack of external validity or generalisability. Although the Delphi has been conducted in multiple languages some widely used languages (e.g. Hindi and Arabic) were missing. These demographic imbalances might challenge the external validity of our findings. Long COVID disproportionately impacts underprivileged groups, with potential rural vs. urban disparities in healthcare access and quality. This might influence the utilisation rating among family and carers, who form a significant portion of participants. Treatment for Long COVID can be costlier, hitting lower-income individuals and LMIC populations harder [20]. Secondly, a consensus meeting during the first phase of the project included only a limited subset of Delphi participants, whose perspectives might not encompass the full spectrum of views on the subject. However, this limitation is an inherent component in the Delphi methodology. It is also important to note that the meeting did not overturn the “in”/ “out” results from the Delphi, and it allowed discussion of those not reaching consensus previously. Thirdly, given the pressing public health implications of COS development, we expedited our study. Consequently, we did not gather data on chronicity, time since diagnosis, and participants' socioeconomic status. A similar approach was previously employed for the adult COS development. Yet, it is worth noting that comprehensive data collection on Delphi participants is not standard practice. In line with the WHO's definition, our study included individuals with both confirmed and probable SARS-CoV-2 infections. However, it is possible that some with a "probable" diagnosis might not have had the infection. Lastly, in the second phase of the project, aiming at outcome measurement instrument selection, the Delphi process has been conducted without involvement of CYP with post COVID-19 condition and their carers. Instead, an international panel of experts conducted a Delphi process. This approach aimed to expedite the consensus process and reduce the potential burden on participants, drawing insights from a similar process conducted for adults. This has been mitigated in

part by involvement of carers of CYP with post COVID-19 condition at the final consensus workshop. Another limitation is absence of COSMIN methodology for selecting instruments implementation in the COMS development, as measurement properties of non-COVID-19-specific instruments had not been assessed in a post-COVID-19 population.

While the incidence of new acute SARS-CoV-2 cases has seen a decline, it is imperative to address the lingering legacy of post COVID-19 condition, particularly due to its prolonged persistence. With the acute cases becoming less frequent, there is a potential risk of the broader community adopting an 'out of sight, out of mind' perspective. However, it is crucial to highlight the substantial absolute number of CYP globally who are grappling with Long COVID. The long-term implications of this condition on their growth, maturation, and overall development underscore the need to recognise post COVID-19 condition not merely as a transient concern but rather as a chronic health issue. This rigorous international consensus study has successfully delineated a COS and a COMS tailored for post COVID-19 condition in CYP. While the consensus provides clarity in a nascent and multifaceted field, it also underscores the need for continued exploration, especially for outcomes where consensus remains elusive. As we navigate the complexities of post COVID-19 conditions in CYP, this consensus serves as a guidance for both research endeavours and clinical practices towards a more unified and informed approach (Box 1). The outcomes of this study may also be useful not only within its immediate context but also as a model for future pandemic situations. We believe that the generalisable knowledge derived from this COMS exercise can significantly benefit the broader academic and medical communities in the future challenges.

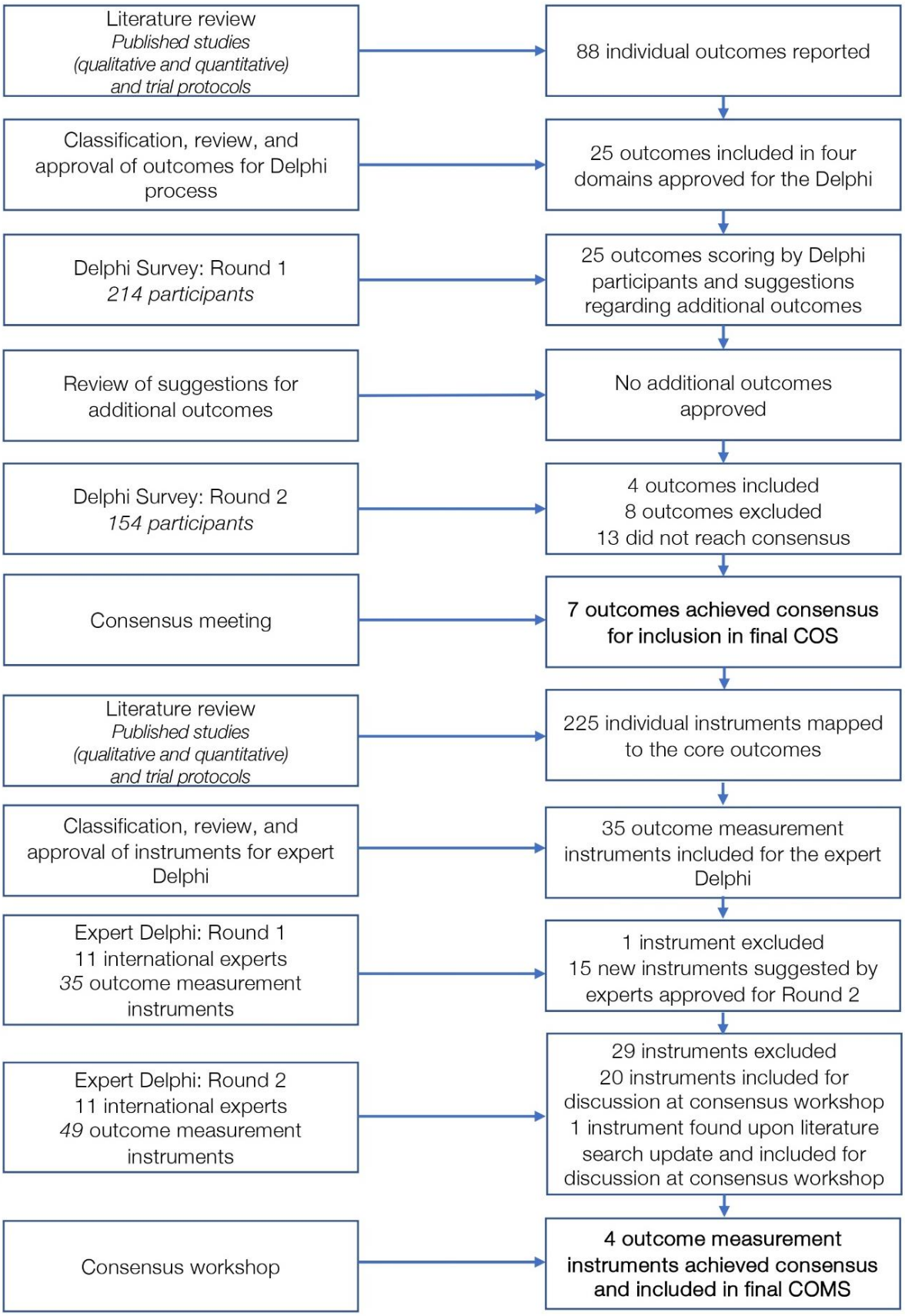

Figure 1. Overview of the COS and COMS development process.

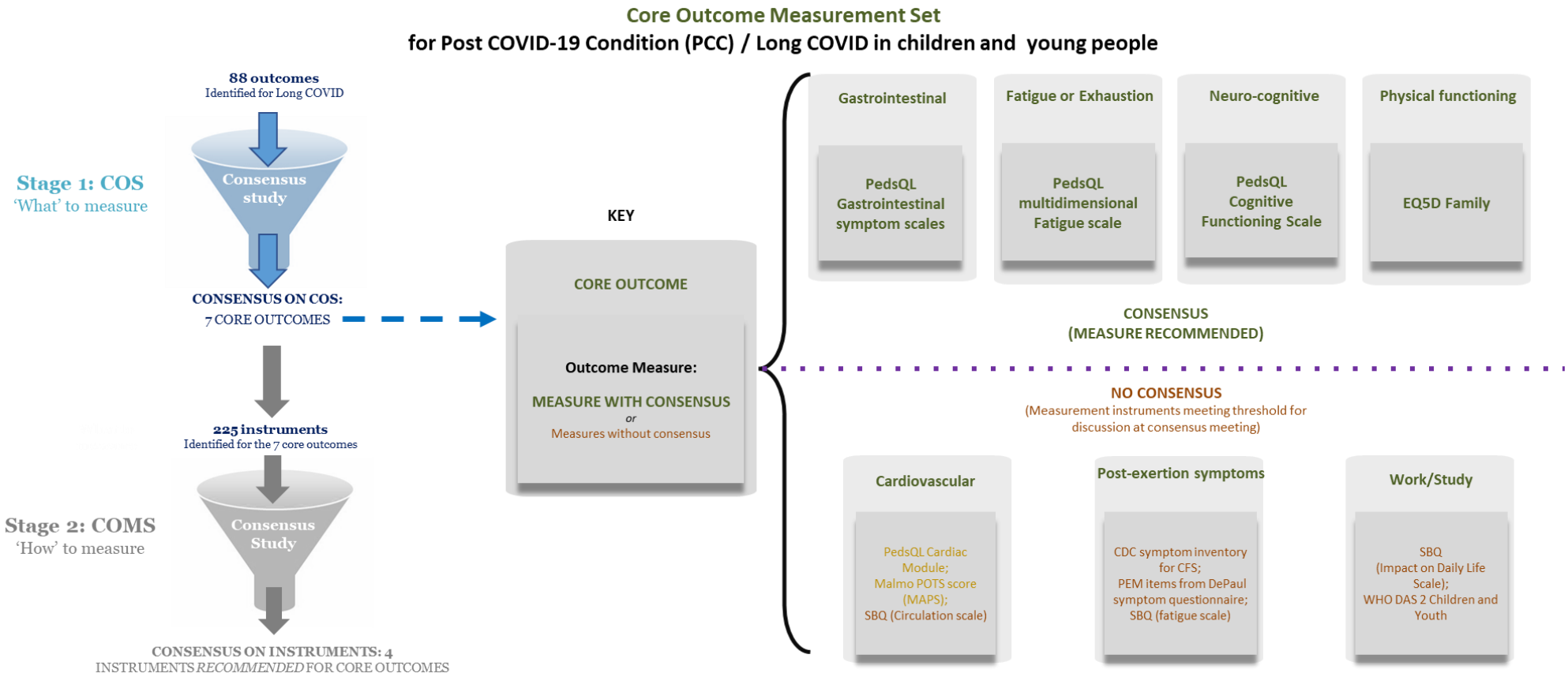

Figure 2. Core Outcome Measurement Set for post-COVID-19 condition in children and young people.

Green colour indicates core outcomes and instruments reaching consensus for use in relation to a particular outcome; Yellow colour indicates instruments not reaching consensus, with more than a half of consensus meeting participants voting for this instrument prioritisation; Red colour indicates instruments not reaching consensus, with less than a half of consensus meeting participants voting for this instrument prioritisation.

Table 1. Core Outcome Set (COS) Delphi participants demographics.

	Delphi Round 1 (*n* = 214)	Delphi Round 2 (*n* = 154)
Stakeholder group, *n (%)*		
Children and young people (≤18 years old) who have experience of living with post-COVID-19 condition (also known as Long COVID)	26 (12)	21 (14)
Family and carers of children and young people (≤18 years old) with Long COVID	115 (54)	76 (49)
Health professionals who have experience treating children and young people (≤18 years old) with Long COVID	37 (17)	32 (21)
Researchers studying Long COVID in children and young people (≤18 years old)	36 (17)	25 (16)
Other	*Participants reclassified after R1 review and analysed within appropriate groups*	
Gender, *n (%)*		
Male	47 (22)	34 (22)
Female	166 (78)	119 (77)
Non-binary	1 (<1)	1 (<1)
Other	0 (0)	0 (0)
Prefer not to answer	0 (0)	0 (0)
Age group, *n (%)*		
2-11	6 (3)	3 (2)
12-18	21 (10)	19 (12)
18-39	40 (19)	33 (21)
40-59	139 (65)	94 (61)
60-79	8 (4)	5 (3)
Geographical area, *n (%)*		
Asia	8 (4)	6 (4)
Africa	1 (<1)	1 (<1)
Australasia	11 (5)	8 (5)
Europe	163 (76)	120 (78)
North America	24 (11)	13 (8)
Central America	1 (<1)	0 (0)
South America	6 (3)	6 (4)
Ethnicity, *n (%)*		
White	180 (84)	130 (84)
South Asian	5 (2)	4 (3)
Hispanic/Latino/Spanish	8 (4)	6 (4)
East Asian/Pacific Islander	4 (2)	1 (<1)
Indigenous peoples	0 (0)	0 (0)
Black	1 (<1)	1 (<1)
Middle Eastern/North African	6 (3)	5 (3)
Other	10 (5)	7 (5)
Not all percentages add up to 100% owing to rounding		

Table 2. Summary of Delphi and consensus meeting voting on outcomes stratified by domains.

	Delphi Round 1	Delphi Round 2	Consensus meeting
Mortality/survival			
Survival	No consensus	No consensus: for discussion	Exclude
Physiological/clinical			
Cardiovascular functioning; symptoms; and conditions	No consensus	Include in the COS	N/A
Endocrine and metabolic functioning; symptoms; and conditions	No consensus	Exclude	N/A
Hearing-related functioning; symptoms; and conditions	Exclude	Exclude	N/A
Gastrointestinal functioning; symptoms; and conditions	No consensus	No consensus: for discussion	Include in the COS
Pain	No consensus	No consensus: for discussion	Exclude
Fatigue or Exhaustion	Include	Include in the COS	N/A
Sleep-related functioning; symptoms; and conditions	No consensus	No consensus: for discussion	Exclude
Muscle and joint symptoms and conditions	No consensus	No consensus: for discussion	Exclude
Taste- and/or smell-related functioning; symptoms; and conditions	Exclude	Exclude	N/A
Neuro-cognitive system functioning; symptoms; and conditions	Include	Include in the COS	N/A
Mental / Psychological functioning; symptoms; and conditions	No consensus	No consensus: for discussion	Exclude
Kidney and urinary-related functioning; symptoms; and conditions	No consensus	Exclude	N/A
Respiratory functioning; symptoms; and conditions	No consensus	No consensus: for discussion	Exclude
Skin; hair; dental and/or nail-related functioning; symptoms; and conditions	Exclude	Exclude	N/A
Post-exertion symptoms	No consensus	No consensus: for discussion	Include in the COS
Vision-related functioning; symptoms; and conditions	No consensus	Exclude	N/A
Fever/body temperature changes	No consensus	Exclude	N/A
Life impact			
Satisfaction with life; or personal enjoyment	No consensus	No consensus: for discussion	Exclude
Physical functioning; symptoms; and conditions	Include	Include in the COS	N/A

Social role-functioning and relationships problems	No consensus	No consensus: for discussion	Exclude
Work/occupational and study changes	No consensus	No consensus: for discussion	Include in the COS
Stigma	Exclude	Exclude	N/A
Resource use			
Healthcare resource utilisation	No consensus	No consensus: for discussion	Exclude
Family/carer burden	No consensus	No consensus: for discussion	Exclude

All outcomes from Delphi round 1 were included in round 2, regardless of ratings in round 1.
N/A = not applicable (outcomes were included in the COS after 2 rounds of Delphi).

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15 **Table 3. Consensus workshop voting results for outcome measurement instruments.**

COS outcome	Outcome Measure	N (%) participants voting to INCLUDE in consensus meeting	Result
Cardiovascular functioning, symptoms and conditions	PedsQL Cardiac Module	16/28 (57)	Not included in the COMS
	Symptom Burden Questionnaire for Long COVID (Circulation scale)	7/27 (25)	Not included in the COMS
	Malmo POTS score (MAPS)	18/27 (64)	Not included in the COMS
Gastrointestinal functioning, symptoms, and conditions	PedsQL Gastrointestinal Symptoms Scales	23/26 (88)	Included in the COMS
	Questionnaire on Pediatric Gastrointestinal Symptoms (QPGS)	2/26 (8)	Not included in the COMS
	Symptom Burden Questionnaire for Long COVID (Stomach and Digestion Scale)	6/26 (23)	Not included in the COMS
Fatigue or Exhaustion	Chalder fatigue questionnaire	3/26 (12)	Not included in the COMS
	PROMIS Paediatric Fatigue	3/26 (12)	Not included in the COMS
	PedsQL Multidimensional Fatigue Scale	26/26 (100)	Included in the COMS
	Symptom Burden Questionnaire for Long COVID (Fatigue scale)	3/26 (12)	Not included in the COMS
Post-exertion symptoms	CDC symptom inventory for CFS	5/26 (19)	Not included in the COMS
	PEM items from DePaul Symptom Questionnaire	10/26 (38)	Not included in the COMS
	Symptom Burden Questionnaire for Long COVID (Fatigue scale)	6/26 (23)	Not included in the COMS

Neuro-cognitive system functioning, symptoms, and conditions	PROMIS Pediatric Cognitive Function - Short Form 7a	9/24 (36)	Not included in the COMS
	PedsQL Cognitive Functioning Scale	21/25 (84)	Included in the COMS
	Symptom Burden Questionnaire for Long COVID (Memory, Thinking & Communication scale, movement scale, muscles and joints, pain scales)	4/24 (16)	Not included in the COMS
Physical functioning, symptoms, and conditions	EQ5DY instrument	24/25 (96)	Included in the COMS
	PROMIS Physical Activity	2/25 (8)	Not included in the COMS
	Symptom Burden Questionnaire for Long COVID (Impact on Daily Life Scale)	3/25 (12)	Not included in the COMS
Work/occupational and study changes	Symptom Burden Questionnaire for Long COVID (Impact on Daily Life Scale)	5/22 (23)	Not included in the COMS
	WHO DAS 2 Children and Youth 36-Item Version	7/23 (30)	Not included in the COMS

Box 1: Key messages

Rationale and approach

- In children and young people, the post COVID-19 condition, also known as Long COVID is associated with a range of persistent symptoms following infection with SARS-CoV-2.
- Research on post COVID-19 condition varies in outcomes studied. A consensus on a minimum set of essential outcomes, referred to as Core Outcome Set (COS) is needed for better data comparison in children and young people.
- There is also an urgent need for decisions to be made on which measurement instruments are the most appropriate for assessing these core outcomes, in order to develop a Core Outcome Measurement Set (COMS), to optimise data comparability and synthesis.
- To develop the COS, we conducted a study that included a literature review, a two-round online Delphi process with over 214 participants from 37 countries, with over half of them being parents of children with post COVID-19 condition and children and young people, and an online consensus meeting. The Delphi process included rating 25 different outcomes.
- For the development of COMS, we then performed an expert online modified Delphi process and an online consensus workshop to discuss and then vote anonymously on measurement instruments.

Findings

- In the field of paediatric care, it is recommended that the following outcomes to be consistently measured in research and clinical practice when assessing post COVID-19 condition: fatigue; post-exertion symptoms; alterations in studies, work, or occupational activities; as well as functional changes, symptoms, and conditions relating to cardiovascular, neuro-cognitive, gastrointestinal, and physical health.
- Instruments for measurement of fatigue, gastrointestinal, neuro-cognitive outcomes and physical functioning were recommended for use in research and clinical practice for children and young people with post COVID-

19 condition. For the three other core outcomes, the most favoured measurement instruments identified from this consensus procedure have been documented, even though no individual measurement instrument met a priori criteria for consensus.

Future Directions and Implications

- To enhance our understanding of post COVID-19 condition in children, there is a need for further standardisation of clinical and research practices using the identified core outcomes and associated measurement instruments.

- Future research should focus on refining and validating the measurement instruments that were favoured but did not achieve consensus among participants.

- Incorporating the lived experiences and perspectives of children and young people affected by post COVID-19 condition as well as their carers is crucial for future research, including instrument development and improvements to patient care.

- Agreed measurement instruments should be considered in future work and insights from this research should guide policymakers in creating initiatives that address the effects of post-COVID-19 condition on children and young people in both healthcare and research environments.

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