

Long COVID in children: Core Outcome Set is urgently needed

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A rapidly increasing number of studies around the world are investigating the frequency, characteristics and risk factors of long COVID, also known as post-COVID-19 condition, in adults ¹ and children and young people ², with some aiming to evaluate its mechanisms and treatment interventions. However, multiple methodological limitations have been highlighted, including a lack of harmonisation in terminology and definitions ^{1,3}, and absence of agreed research and clinical outcomes to be assessed.

The Core Outcome Set (COS) concept was proposed and implemented across disciplines in order to ensure that the most critical and relevant research outcomes are reported, to facilitate data harmonisation and collaborative analysis ⁴. A COS is an agreed-upon minimum set of outcomes that should be measured and reported in all studies in a specific field. The consensus on the outcomes is normally reached with involvement of all relevant stakeholders, including, people with lived experience and their families, researchers, and healthcare professionals. A paper in The Lancet Respiratory Medicine (ref) outlines a long-awaited list of COS agreed by stakeholders as critical to assess in research and clinical settings of long COVID in adults. Increasing data shows an urgent need for development of COS for Long COVID in children and young people ⁵ to ensure that domains or outcomes of specific importance to younger generation affected by long Covid are not missed.

Research into long Covid in children and young people is lagging behind adults ¹. The cause for the lack of attention to children and young people may partly be due to the early pandemic data indicating that CYP infected with SARS-CoV-2 were mainly asymptomatic or suffering from mild symptoms. Later data shows that long Covid can affect CYP and adults following mild Covid-19. The prevalence of long COVID in children and young people remains unclear and published literature suggests that between 4 and 66% can be affected, depending on the outcome definition and methods applied ⁶. A group of experts formulated some of the unmet needs in long COVID research and potential impact on CYP and society a year ago ⁵. Most are still relevant a year later, due to a lack of inclusion of CYP in long Covid research. The International Paediatric Post-COVID-condition in Children Collaboration (IP4C), a large group of researchers, paediatricians, health care workers and CYP with lived experience of long Covid and their family members held a meeting focused on identifying the top research priorities for paediatric long COVID in December 2021. These included development of an international, 'living' long Covid guideline to facilitate equity in access to diagnostics and care and reduce risk of non-evidence-based treatments; development of international collaboration in research programmes and evidence exchange aiming at timely translation of new evidence into guidelines; COS and a universal clinical case definition development.

Although COMET recommendations on the methodological process of COS development is similar for different age groups ⁷, there are some challenges to keep in mind pertinent to CYP (Table). People with lived experience are normally involved in the COS development process,

however, recent research ⁸ demonstrated that only one in ten of paediatric COS developed for other conditions, had direct input from CYP. Most of the initiatives instead engaged parents or carers as proxy for CYP. It is unclear which methods of CYP involvement are the most appropriate and result in the most robust results. This is especially challenging in an international setting with language barriers and CYP from different age groups innovative methods using visual approaches might be required. Outcomes of critical importance may vary among CYP depending on their age. Developmental aspects may be of higher importance in early age, while social engagement, participation in education, sport and other activities may be more critical in older CYP. An age-adjusted modular COS for CYPs may need to be considered, at the same time, development of a single COS would facilitate harmonisation and for a better comparability between CYP of different ages. If a single COS for CYP is developed, the selection of measurement instruments should be age appropriate. There is also a challenge to deliver a high-quality COS under time pressure, keeping the balance between the time to deliver and methodological rigor.

Although long COVID prevalence in CYP may be lower than in adult populations, the impact on physical and psychological health may be life-long. This will not only create increasing demands on health services but will have wider socio-economic impact for the children affected. It may adversely affect career opportunities and earnings, productivity, economics as well as social activities and relationships and longevity. Previous COS initiatives across the fields and conditions have demonstrated that without appropriate COS development there is a risk to overlook certain domains or outcomes of importance to patients. Further, heterogeneous domains or outcomes measured using a large number of different instruments, thereby impairing comparability and effective synthesis of results. It is imperative to rapidly initiate projects aiming to develop COS and associated measurement and data harmonisation tools in long COVID in CYP, to provide stakeholders with appropriate tools for urgently needed studies to improve long term Covid-19 outcomes in children and young people globally.

Table. Main reasons/challenges in developing Core Outcome Set for children with long COVID.

Reasons:

- Setting-up minimal requirements for the outcomes assessed in research and clinical settings
- Transparent and agreed selection of outcomes to be used in intervention trials
- Harmonisation of data collection
- Improvement of the data quality and potential for meta-analyses
- Better opportunities for the guideline development

Challenges:

- Keeping balance between the time of development and high methodological standards
- Involvement of children and young people in the Delphi consensus process
- Language barriers may result in lack of participation from some geographical locations
- Biased selection of relevant stakeholders (e.g. dominance of patient group representatives)
- Potential need in development of different COS for different age groups
- Absence of age-appropriate instruments for some outcomes
- Inability to reach a consensus on COS

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