Equity in research: a global consensus statement on the urgency of including children in long COVID clinical trials

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Efforts are urgently needed to intentionally address this inequity in long COVID research to include children early in clinical trial design. https://bit.ly/3RMGmYz

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Long COVID, a post-acute infection syndrome triggered by SARS-CoV-2, is now recognised as a major cause of disability worldwide [1], affecting both children and adults. The World Health Organization (WHO) defines long COVID in children as: "new onset of symptoms impacting everyday functioning that last at least 2 months, occurring within 3 months of probable or confirmed acute SARS-CoV-2 infection" [2]. While elegantly designed clinical trials have been established to identify effective treatments for long COVID, children are notably excluded. We propose that inclusion of children in long COVID clinical trials is justified, and unwarranted age-related exclusion criteria for current clinical trial designs impose unintentional and unnecessary barriers to treatment for children with long COVID.

In contrast to acute COVID-19, where age is the greatest risk factor for morbidity and mortality [3], population reports suggest that the severity and range of post-COVID symptoms are generally similar between affected adults and children/adolescents [4]. While adults are more likely to be diagnosed with long COVID, detailed assessments show that following SARS-CoV-2 infection, children are at increased risk of developing fatigue, cognitive dysfunction, difficulty sleeping, and numerous other symptoms of long COVID, beyond the impact of pandemic-related social isolation, remote learning, and stress [5]. Additionally, children with long COVID, similar to adults, suffer from postural orthostatic tachycardia syndrome (POTS) [6], impaired exercise tolerance as assessed by cardiopulmonary exercise testing [7], and autonomic cardiac dysfunction [8]. These reports highlight the multisystemic, persistent and disruptive clinical manifestations of long COVID that children experience, mirroring disease reported in adults.

Global estimates project that over 60 million adults have developed new-onset long COVID [8]. In the USA alone, large studies suggest nearly 6 million children are living with long COVID [9], highlighting that children are not spared from this post-COVID condition. Importantly, changes in the health of children during these crucial developmental and educational stages of life can have significant, lasting impact individually and on society [10]. A study surveying large cohorts of children from March 2022 to December 2023 found that there was a 7.7 increased odds ratio of school loss in children with prior SARS-CoV-2 infection [5], underscoring the considerable disruption caused in the post-infectious period. Further, rates of autoimmune disease, thyroid disease and diabetes mellitus are all increased in the post-infectious period in children, mirroring post-infectious health risks in adults [11]. Thus, it is essential that efforts to improve the clinical care and outcomes of individuals affected with long COVID include children, so as to not prolong the medical and societal impact of long COVID in these developing children.

Current pathomechanistic hypotheses of long COVID do not suggest any age-related differences in pathology outside of organ injury directly related to severe acute infection. Indeed, one hypothesis suggests that following SARS-CoV-2 infection, viral reservoirs can persist in both children and adults, and long COVID is associated with Spike antigenaemia and correlating hyperinflammation [12]. SARS-CoV-2 RNA and/or antigen has been seen in the gastrointestinal tract, lymphoid tissue and brain tissue of both children and adults, months to years after acute infection, suggesting persistent viral reservoirs across all ages [13]. Clinical trials have been developed to target these viral reservoirs, using existing antivirals such as nirmatrelvir/ritonavir, remdesivir and others [14], albeit with negative results to date [15]. Despite nirmatrelvir/ritonavir being approved for acute infection from age 12 years, none of the existing long COVID clinical trials include children. Although the safety and pharmacokinetics of extended courses of nirmatrelvir/ritonavir have not yet been specifically studied in this age group, the vast majority of approved drugs use dosing that is equivalent in adults and adolescents, and pharmacokinetic assessments including allometric scaling have been proposed to avoid unnecessary dedicated clinical trials in adolescents [16]. Alternatively, if a proposed therapy does not yet have safety data in either adults or children, a staggered approach could be considered, whereby pharmacokinetics are measured in the first cohort of adults. Then, allometric scaling of adult pharmacokinetic data would predict adolescent drug clearance to allow enrolment of children 12 years and older, rather than requiring a delayed, designated trial for these older children. Thus, mechanisms exist to expedite inclusion of children in emerging clinical trials for long COVID.

Furthermore, inflammatory profiles of long COVID are similar across children and adults. Spike antigenaemia can be detected in circulation of children with long COVID, and dysregulated inflammatory responses with neutrophil activation, contraction of naïve and switched B cell compartment with increased regulatory T lymphocytes [17], increased inflammatory cytokine profiles [18], and circulating fibrin amyloid microclots [19]. While complete immunoprofiling of children with long COVID has not yet been directly compared to adults with long COVID, no evidence exists to suggest differences in the underlying mechanism of disease. Clinical trials are underway or being developed to target immune dysregulation in long COVID. Example therapies include intravenous immunoglobulin, monoclonal antibodies, kinase and tumour necrosis factor-α inhibitors. Many of these therapies have already been approved for paediatric indications, thus, again, safety and tolerability are not primary considerations of these studies and children could be safely included in these clinical trial designs. In addition, while the developing immune system matures over time, the immune system in adults is not so distinct from that of an adolescent to warrant separate, delayed clinical trials. Moreover, children lack confounding, inflammatory co-morbidities that can be seen in ageing adults, making them ideal candidates for studying long COVID and other post-viral syndromes. Therefore, rationale exists for inclusion of children in clinical trials repurposing immunomodulators to target immune dysregulation in long COVID. In these trials targeting inflammatory responses, when safety profiles have already been established in children, inclusion of children needs to be mandated.

Additional considerations in trial design are end-point assessments for efficacy. Because no biomarkers exist, many clinical trials depend on patient-reported outcomes (PROs). Several PROs exist that have been adapted and validated in the paediatric population and therefore can be readily implemented across all age ranges. A few examples include the Pediatric Quality of Life Inventory [20], which can be used to assess fatigue in young children through to adulthood. Further efforts are needed to define specific long COVID symptom assessments across paediatric and adult cohorts. Additional outcomes, such as changes in POTS criteria, are also impacted by age. However, these outcomes can readily be evaluated within a larger population, as compared to individual treatment response, or within a paediatric subgroup analysis. A core outcome set for paediatric long COVID has already been proposed through a rigorous Delphi process [21].

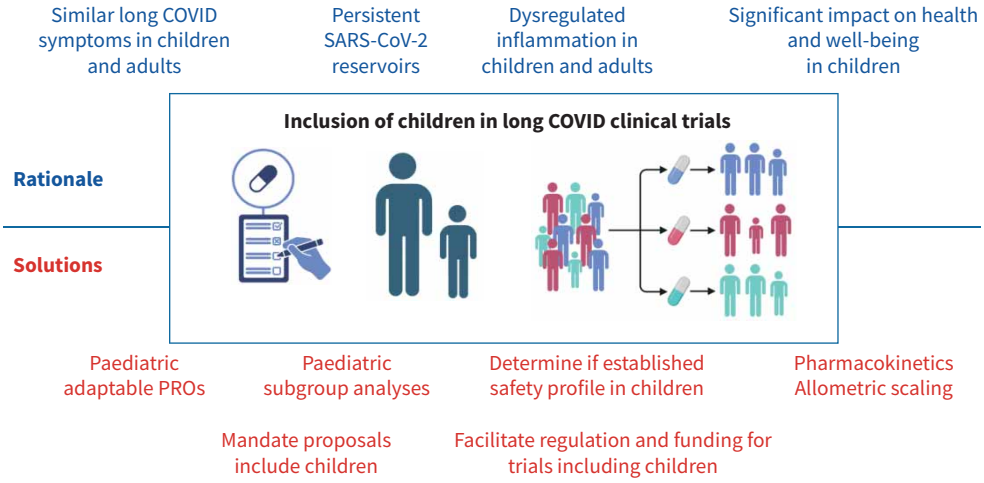

FIGURE 1 Overview of rationale behind and strategies for including children in long COVID clinical trials. PRO: patient-reported outcome. Figure created using Biorender.

Additionally, we urge paediatric providers and parents of children with long COVID to be involved in study design to allow prioritisation and determine meaningful outcome measurements.

Importantly, the families of children with long COVID are desperate for treatments. Some children have been ill for more than 4 years, a significant proportion of their childhood. Countless families report that their previously active and social child can no longer attend school or socialise with peers. Meanwhile, reports highlight that long COVID negatively impacts longevity and cardiovascular health [22]; families do not want to wait for secondary clinical trials and age-imposed delays. Without a cure for long COVID, and with unknown long-term effects and societal costs, delaying access to clinical advances exacerbates the frustration and hopelessness in these families.

In summary, children should be included in ongoing and future clinical trials for long COVID (figure 1). Age-related protections and regulations must be incorporated, including obtaining institutional review board/research ethics approval along with paediatric assent and parental consent prior to including children in clinical trials. We urge clinicians and researchers to amend existing protocols and design future protocols to include children in clinical trial design in order to avoid unnecessary delays and harm for children with long COVID. We also urge a clear statement from the WHO prioritising and facilitating the regulation and funding for clinical trials inclusive of children with long COVID.

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