

# Monitoring the Pediatric Clinical Trials Enterprise

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A series of policies and laws coupled with improved awareness of the importance of evidence to inform practice have led to a significant increase in the number of pediatric clinical trials. In a report in this month's *Pediatrics*, Cho and colleagues<sup>1</sup> raise a host of important questions.

Cho et al used ClinicalTrials.gov to examine the landscape of nonvaccine pediatric trials with an enrollment >1000. Unsurprisingly, they found an imperfect relationship between burden of disease and number of clinical trials. They also found that the vast majority of investigators were from high-income countries as opposed to low- or middle-income countries. The majority of trials in their sample were funded by nonprofit and public organizations. As best they could ascertain, less than two-thirds of completed trials were published within 12 months of completion. Most investigators were from high-income countries.

The analysis is focused on large trials with an emphasis on whether the trials assessed mortality as an outcome. Although diseases with a high mortality might best be addressed by large trials, many diseases of children are nonfatal or chronic diseases with a low mortality where other primary outcome measures may be more appropriate.

Although this analysis has a number of limitations, including the imperfect representation of non-US trials in ClinicalTrials.gov, it is important to

recognize the value of monitoring the trial landscape using registry data. Without ClinicalTrials.gov it would be difficult or impossible to review the broad clinical trials enterprise (CTE). Multiple analyses<sup>2,3</sup> of the overall trial enterprise using ClinicalTrials.gov have pointed to trends in the CTE. The good news is that almost all trials are registered before enrollment starts, as required by law for applicable trials including a US site. Additionally, many trials are well designed, answer the intended question that is appropriately prioritized, and publicly and transparently report results. However, there remain too many other trials that are not well designed, lack adequate statistical power, or address redundant or unimportant questions. A significant number of trials do not reach completion, and many completed trials fail to report their results in a timely manner, even when legally required to do so.

These trends pertain to trials in children as well as in adults. Of course, there are many specific issues to be addressed in trials involving children. Because children cannot give consent to participate, trials may be more difficult to conduct and may be more expensive. Children of different ages and stages of development have distinctly different health issues, and the design of medical products, including sizing of devices and dosing and methods of administration of drugs, are heterogeneous.

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Cho et al chose to focus on nonvaccine large trials and to exclude cluster randomized controlled trials from their analysis. Although these decisions are sensible from one perspective, it would be useful to see the full view of trial designs. For example, cluster randomized controlled trials may be the more efficient design for studying certain infectious diseases or nutrition-based conditions that account for much pediatric death and disability in low- or middle-income countries.

Other conditions of interest that are not addressed by this analysis are now the focus of important policy considerations. For example, pregnancy can be a high-risk situation that is understudied. In addition, studies of rare genetic diseases are important yet challenging; single-arm studies are common<sup>4</sup> and trials are labor intensive, complicated, and often judged to be infeasible.

Improvement in the ability of low-income countries to conduct large trials for high burden diseases would take an unprecedented level of funding, international

collaboration, and positive views of interventional, randomized trials. At a time when the world is seriously considering rebuilding infrastructure after the pandemic, an adequate infrastructure for clinical trials should be a focus. Just as we need roads, bridges, and broadband Internet, we need a clinical trials infrastructure that can produce needed answers about how to prevent, diagnose, and treat both the leading causes of death and disability and the many less-common causes of disability and poor quality of life in children and adults.

Without clear goals for the optimal CTE, however, it will be difficult to assess current effort, make the case for greater investment and changes in the structure, and monitor the impact of whatever changes or investments are made. We should continuously reassess our goals, change policies to attempt to achieve those goals, measure, and iterate to refine policies, structures, and operations until we reach the desired state. It is not beyond the reach of our combined human and technological talent to assure

parents and their children that we can have high quality evidence about every disease, driven by transparency and purposeful optimization of effort to answer the questions that are most important to improve health outcomes and quality of life.

#### ABBREVIATION

CTE: clinical trials enterprise

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