Protecting Children Through Research

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Given the relative lack of pediatric clinical trials and the common pediatric use of untested or underinvestigated interventions in care, stakeholders increasingly recognize a need to bolster the trial-informed evidence base both in the United States and abroad. This need is particularly acute in the setting of drug trials. However, despite recent improvements in pediatric participation, children continue to be underrepresented. As explored in the article by Pathma Joseph and colleagues[1] in this month's issue of *Pediatrics*, the problem has multiple causes and trials often fail to include any children or those who might benefit most from treatment. Building on the data presented by Joseph et al,[1] we suggest that, although care must be taken to protect children, the best way to bolster outcomes and protect children is through research, not from research.

Frequently, drugs that are available for adults are not formulated and authorized for children. Medications available for treatment of the >3 million HIV-infected children worldwide are a telling example. Of the 6 regimens recommended for first-line treatment in adults with HIV in the United States, 4 are not currently licensed for use in children <12 years old or weighing <35 kg. The other 2 are not recommended for children <2 years of age. Although effective treatments exist for pediatric HIV, the drugs with pediatric formulations and available dosing standards are less effective and/or less well tolerated than the newer drugs recommended for adults.[2] Data in children are lacking. Although doctors caring for children living with HIV have some well-studied treatment options, lack of research often makes off-label pediatric drug use necessary for other indications. More than one-third of all pediatric prescriptions are for off-label uses.[3] Neonatal and pediatric doses for off-label pharmaceuticals are frequently extrapolated from adult studies, failing to account for the unique physiology of young children.[4] Medicines that lack pediatric labeling have a threefold greater odds of being implicated in hospital-based pediatric adverse drug reactions than drugs with pediatric labeling.[5] In young children, off-label drug use is particularly likely to have inconclusive or no evidence supporting effectiveness.[6] Especially concerning, later experience with commonly used but untested drugs sometimes demonstrates harm.[7,8]

As opposed to clinical trials, for which informed consent processes ensure that parents of enrolling children are made aware of risks and benefits, a minority of health care providers inform parents of potential safety concerns when prescribing unlicensed/off-label drugs for children in routine clinical practice.[9] As a result, parental awareness of off-label prescribing is low, with a recent survey showing that fewer than one-third of parents were aware of off-label drug use in children.[10] Parents who have limited knowledge of how common off-label use is in general pediatric practice are more likely to refuse to include their children in studies.[11]

Joseph and colleagues[1] explore challenges of conducting pediatric trials through a multinational study of researchers', regulators', and sponsors'

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views. A strength is the purposeful sampling of respondents from both low-, middle- and high-income countries. Although participants acknowledged that changes in the regulatory environment have enabled more trials in children, they stressed that inequities still abound. In particular, research agendas should be aligned with global child health care needs through increased international collaborations. Collaborations between US institutions and international bodies are sometimes stymied by differences in cultural and ethical standards. What may protect a child in one cultural context could disadvantage a vulnerable child in another. For example, although US-based institutional review boards typically require that consent for a minor's participation in a study be granted only by a biological parent or legal guardian, guardianship in some international settings is determined outside of formal legal systems, leaving nobody authorized to consent if US regulatory standards are applied.[12]

Although challenges remain,[13] certain resources may help to accelerate research on the safety and efficacy of medication for children. Pediatric clinical research networks, groups of medical practices affiliated to systematically examine and improve care,[14] may provide knowledge and infrastructure to support clinical trials. According to a recent review, 70 pediatric clinical research networks have been formed in the United States and abroad, including both primary care and subspecialty settings.[15] The examination of secondary data, increasingly available through the growing number of electronic health records, also may help to identify patterns of medication use and side effects to guide care and help direct clinical trials where they are most needed.[16]

Ultimately, the ethical principle of justice[17] demands that individuals, groups, and communities should not be unfairly excluded from the potential benefits of research participation. As the article by Joseph et al[1] and this commentary assert, overprotection of children may be as harmful as underprotection. Concerted effort across nations is needed to ensure that children are protected through clinical trials addressing their unique needs.

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