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ON THE MIDWAY

AN ENEMY IN OUR MIDST



Photo by Dan Dry



CHILDREN IN MEDICAL RESEARCH: HAS THE PENDULUM SWUNG TOO FAR?

by *Lainie Friedman Ross, MD, PhD*

In the past decade, U.S. medical research policy has shifted to a “Children First” philosophy. This is in sharp contrast to the “Children Last” policy implemented after World War II, which held that adults should be enrolled as research subjects before children, because children are vulnerable and need additional protection. Articulated in the late 1970s in the Belmont Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, this philosophy became accepted in research practice.

However, the protection had a drawback: Health issues unique to children were understudied and underfunded. By the late 1960s, Harry Shirkey, MD, a prominent pediatrician, was already advocating greater participation of children, arguing they would become “therapeutic orphans” without pediatric drug investigation. By 1995, his fears were confirmed

when the American Academy of Pediatrics stated that more than 80 percent of drugs prescribed to children had never been tested on them.

By the late 1990s, the research pendulum had swung to emphasize the need for research involving children. The National Institutes of Health, the U.S. Food and Drug Administration and the U.S. Congress set policies encouraging involvement of children earlier in the process. Although the changes increased the participation of children, it is not clear they achieved their goals: to advance pediatric knowledge and to promote pediatric health care. In fact, in some cases, superfluous studies are being conducted and are exposing children to unnecessary risks.

Consider asthma research: In the United States alone, asthma affects about 5 million children, although evidence suggests a significant number of children with asthma remain undiagnosed. Among U.S. children under 15, asthma accounts for more than 5 million outpatient visits, almost a million emergency department visits, about 166,000 hospitalizations and 200 deaths annually. It is a serious disease.

In 1998, asthma was estimated to cost \$12.7 billion in the United States.

Prescriptions accounted for about 25 percent of the cost. Two main classes of drug therapy are anti-inflammatory medication and smooth-muscle airway relaxants. Anti-inflammatory medications are recommended as daily prophylaxis for all asthmatic children except those with the most modest disease. Since the 1980s, inhaled corticosteroids (ICS) have become the anti-inflammatory medication of choice. Not surprisingly, many companies want to capture part of the market and have developed such medications.

European literature reporting the efficacy and safety of different ICS treatments is five to 10 years ahead of that in the United States, and many of these drugs were approved for use in Europe before the FDA approved them. To garner FDA approval, pharmaceutical companies often had to repeat studies already done abroad.

Colleagues and I identified 70 clinical asthma trials performed in the United States between Jan. 1, 1998, and Dec. 30, 2001, that included at least some pediatric subjects. Sixty-six of these studies documented partial (3) or complete (63) pharmaceutical funding, suggesting that most of these studies were being done for FDA purposes. Forty-five of the 70 studies were done as placebo-controlled trials,

meaning that the experimental ICS was compared to a “dummy pill” in contrast to a clinical trial that compared one anti-inflammatory medication with another. While placebo-controlled trials may be scientifically neater, they unfortunately expose children with asthma to an increased risk of a potentially life-threatening asthma attack.

Our analysis found that subjects in placebo-controlled trials were more likely to have an acute exacerbation of asthma than subjects in equivalency trials. It also found that subjects in the placebo arm did worse than their peers who received the experimental drug. This was not a surprise to the researchers, one of whom commented in her study, “Asthma symptoms would be expected to worsen in the placebo group during the treatment period because these patients were dependent on inhaled steroids but were not allowed treatment with inhaled steroids while in the study.”

So rather than accept European clinical asthma trials that documented the benefits of the various ICS medications, U.S. policy exposed many children to unnecessary risks. Had the FDA permitted companies to include high-caliber European studies in their applications, these risks could have been avoided.

The new U.S. policies further expose children to additional risks because they have led to an increase in the number of children enrolled in adult trials. In fact, 52 of the 70 asthma studies enrolled children and adult subjects; only 18 enrolled children exclusively. The purpose of expanding the research to include children should be to enhance the well-being of the individual child or to promote knowledge about children as a class. As such, one would assume that any trial that enrolled children would have as one of its goals an assessment of the drug’s safety and efficacy on children. Unfortunately, only eight of these studies differentiated between adult and pediatric

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subjects at baseline, and only one performed subset analyses to determine if the treatment responses in children were the same or different than the responses in adults, or whether adverse events and withdrawals occurred more often in pediatric subjects or in adults. That is, the children helped the researchers achieve accrual goals more quickly, but the research results did not advance pediatric knowledge. Given that many of these studies were placebo-controlled, subjects were not ensured benefit either.

In response to two studies published in *Journal of the American Medical Association* in 2001, I wrote a letter to the editor asking why children were included if not enough subjects were enrolled to make useful subset analyses. One investigator agreed that “studies involving children must balance the generalizability of results against the risk of participation.” Another responded that “neither trial was designed specifically to evaluate if the response of children or adolescents differed from adults; rather patient selection was based on criteria that would permit the results to be generalized to the patient populations for which these medications were approved by the U.S. Food and Drug Administration and routinely prescribed.”

The second author was following the letter but not the spirit of the new policies that require the inclusion of children. Had I been able to respond, I would have asked the second researcher to provide moral justification for enrolling children if there were no plans to analyze the pediatric data separately. While it helped the researchers achieve enrollment criteria more quickly, including children in these studies was unethical because it placed some at risk without plans to benefit either individual

children or the class of children generally.

Children are a vulnerable population and need additional protection. This means that we should maintain a “Children Last” philosophy with two caveats. First, “Children Last” does not mean children should be ignored. I support pediatric research when the research is promising and can be done only in children.

Second, “Children Last” should be a presumption, but exceptions should be permitted. For example, exceptions are desirable if the condition is life-threatening and no therapy exists. This holds for emerging infectious diseases like avian flu. But it requires that if children are enrolled, there must be a plan to enroll enough to perform subset analyses in order to benefit children as a class.

Current policies to promote pediatric participation in clinical trials are too focused on access. Even worse, they are not necessarily being implemented in a way that promotes either the advancement of the individual child’s health or the advancement of pediatric medicine more generally. The shift from a focus on protection to a focus on access has exposed children to significant and unnecessary risks. The pendulum has swung too far.

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