Q&A

Questions for Lisa Croen: How to design children's studies

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It has been a sobering two years for studies on children at a national scale. Ambitious projects that follow children from birth to adulthood can be the best way to identify environmental factors that affect health. In practice, however, they can be extremely tricky to carry out.

In December 2014, Francis Collins, director of the U.S. National Institutes of Health (NIH), **canceled** the **National Children's Study** after a five-year pilot effort, saying the study was proving to be unfeasible. Last month, the U.K. government **nixed a similar study** in that country eight months after its launch. The U.K. researchers had planned to enroll 60,000 pregnant women in all, and 16,000 of them by July 2016. As of September 2015, however, they had just 249.

Both studies were staggeringly expensive. The challenges of recruiting enough participants also seemed insurmountable.

Despite these hurdles, these types of long-term studies are worth doing because they collect information 'prospectively,' as children grow up, and can accurately capture the trajectory of a condition. The more practical, but less rigorous, alternative is to look back at people's medical records to find factors that might have contributed to their condition.

Lisa Croen, director of the Autism Research Program at Kaiser Permanente, has designed both types of studies. She has access to thousands of medical records through Kaiser Permanente, a managed healthcare provider in California. But she is also an investigator for the Early Autism Risk Longitudinal Investigation (**EARLI**) — a multisite project launched in 2009 and funded in part by the NIH — that aims to start out with 1,200 pregnant women who have one child with autism. Researchers then plan to follow each child's development until he or she turns 3.

We asked Croen how researchers can design and conduct large, long-term studies and avoid the pitfalls.

Spectrum: **Why do you think these long-term national studies are failing?**

Lisa Croen: They're very challenging to do. If you're enrolling women during pregnancy, you have to find them. Researchers used to recruit participants by mail, but mail is becoming something that fewer people pay attention to. The same goes for email. With the sheer volume that people receive, it's easy to delete something you don't recognize without even reading it.

It's really difficult to engage people in research studies. Even in studies that are targeted and you have an interested population, such as families with autism, it's still very difficult to engage them in long-term studies because they have a lot of other priorities in their lives. Researchers ask a lot from study participants, and it's hard for people to find time for that.

I was kind of amazed when I looked at the response rate for the U.K. study that was just canceled. Their numbers were so low compared with the number that they had projected. It's distressing on the one hand, but unsurprising on the other.

S: Are there ways to address these recruiting challenges?

LC: In the EARLI study, we recruit women during pregnancy, but we only invite those who already have a child with autism. These families are very invested in knowing what's going to happen with their second child and doing everything they can to have the **optimal outcome** for that new baby.

We're also piggybacking on women's clinical visits. We've built a pregnancy cohort here in Kaiser Permanente Northern California with 20,000 pregnant women enrolled already. We present women with the opportunity to join the study during their first prenatal care appointment, when they can agree to donate a blood sample. We collect the samples during routine clinic appointments, one in the first trimester and one in the second trimester, so they don't have to go anywhere special. They are already having blood taken and the consent is for three extra tubes of blood. Participation does not require an extra needle stick.

I also think it makes all the difference that they're being invited to participate in the context of their clinical care. It's not just some random invitation for research that comes from someone they don't know and don't recognize.

This approach has worked quite well for us: We've had a nearly 20 percent response rate with very little effort. The women also agree to complete a survey and provide access to their medical records. Maybe 30 to 40 percent end up completing the survey. Once the kids are born and grow up, we will be able to go back and look for links between any diagnoses they receive and these specimens.

S: Should researchers be moving away from long-term prospective studies?

LC: As much as possible, we need to take advantage of the existing data from families. We can use information such as people's medical records or blood specimens that they're already giving for clinical purposes.

But data collected for clinical purposes is not going to have everything you're interested in for research purposes. For example, the Kaiser pregnancy blood samples are not given after fasting. I have colleagues who do gestational diabetes work and, for what they measure, they need a fasting sample. So this kind of resource can't accommodate everything.

Collecting data prospectively is still far superior to looking at existing data. It's a real balance, and I don't know what the answer is.

S: Are there any efforts that take this balance into account?

LC: One way that people are trying to address it is a new U.S. effort called **ECHO** that will replace the National Children's Study. The researchers involved in ECHO are proposing to pool data from existing longitudinal studies. This approach has a lot of logistical challenges because the selection criteria and the type of data collected vary across the studies.

So the question becomes whether it’s really possible to harmonize the information across these studies to come up with a big sample size. This might be possible for some basic things, but I think more specific questions about environmental exposures will be difficult to answer.