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Superfluous Medical Studies Called Into Question

By David Brown
Washington Post Staff Writer
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In medical research, nobody is convinced by a single experiment.

A finding has to be reproducible to be believable. Only if different scientists in different places do the same study and get the same outcomes can physicians have confidence the finding is actually true. Only then is it ready to be put into clinical practice.

Nevertheless, one of medicine's most overlooked problems is the fact that some questions keep being asked over and over. Repeated tests of the same diagnostic study or treatment are a waste -- of time and money, and of volunteers' trust and self-sacrifice. Unnecessary clinical trials may also cost lives.

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All this is leading some experts to ask a new question: "What part of 'yes' don't doctors understand?"

Two papers dramatically illustrated this problem last year and may have helped nudge the medical establishment toward doing something about it.

One article examined 18 years of research on aprotinin, a drug used to reduce bleeding during heart surgery. The other looked at studies on the relationship between a baby's sleeping position and sudden infant death syndrome. Both concluded that research on these subjects went on long after the answers were known -- namely, that aprotinin worked and that babies sleeping on their backs were less likely to die of SIDS.

The odyssey of aprotinin, which is derived from the lung tissue of cows, was recounted in the journal Clinical Trials.

Dean Fergusson and his colleagues at the Ottawa Health Research Institute found 64 randomized, controlled trials -- the most authoritative type of study -- on the use of aprotinin in heart surgery. They were done in half a dozen countries over 18 years, starting in 1987.

Two-thirds were little more than variations on each other. And nearly all showed the same thing: Patients who received aprotinin during surgery bled less. They had only one-third the chance of needing a blood transfusion of patients who did not get the drug.

What was surprising was that this advantage was clear by June 1992, after the 12th of the 64 studies. If researchers after that time had familiarized themselves with previous studies -- and especially if they had analyzed summaries of those studies, called "meta-analyses" -- they might not have considered it necessary to run their own.

But it appears that very few of them studied closely what had been published previously about aprotinin. On average each new paper listed only one-fifth of the previous studies in its references. Only two research teams mentioned the two published "overviews" of aprotinin research, one from 1994 and the other from 1997. Both of them demonstrated the unquestionable advantage of giving the drug.

In all 64 studies, the patients were randomly assigned to get aprotinin or a placebo. In general, mortality did not differ between the two groups. But some of the patients receiving a placebo had bleeding and needed transfusions that they might have

avoided had they been given aprotinin.

Being given a placebo long after aprotinin's value had been proved probably did not cost lives. The same cannot be said of medicine's failure to pay attention to studies of infant sleep position.

Last April, in the International Journal of Epidemiology, Ruth Gilbert of the Institute of Child Health in London examined 40 studies of SIDS and sleep position going back to 1965.

Gilbert found that if researchers had pooled the results of the oldest studies and analyzed them, they might have gotten a big hint by 1970 that putting babies to sleep on their stomachs raised the risk of SIDS. Instead, that observation did not become convincing until the late 1980s.

Researchers now know that sleeping on the stomach raises the risk of SIDS sevenfold. That realization led to "Back to Sleep" campaigns in Britain in 1991 and in the United States in 1994.

Between 1970 and the unveiling of that advice, 11,000 British infants -- who might have survived if sleeping on the back had been the norm -- died of SIDS. In the United States, Europe and Australia, "at least 50,000 excess deaths were attributable to harmful health advice," Gilbert and her colleagues wrote.

The problem is evident even in research on the highest-profile diseases.

In 1992, Joseph Lau, then at the Department of Veterans Affairs hospital in Boston and now at Tufts University, published a paper that has become a classic in epidemiology. He examined 33 clinical trials of streptokinase, a drug that dissolves clots in the coronary arteries of people having heart attacks.

The trials were conducted from 1959 to 1988. Lau conducted a "cumulative meta-analysis" of the results. This is done by adding each trial's patients and their outcomes to all the preceding ones. The result was a running scorecard of streptokinase's performance.

Lau determined that by the end of the eighth trial in 1973, the evidence was clear that heart attack patients who got streptokinase had 25 percent lower death rates than those who did not. That conclusion, and the percentage, did not budge while 34,542 more patients were enrolled in 25 more trials of streptokinase over the next 15 years.

There are lots of reasons this kind of thing happens.

In many of the aprotinin studies, the researchers tested the drug in subgroups of patients or altered variables to see if outcomes changed. The drug is very expensive, so they tried different doses. Sometimes they added it to the blood in the heart-lung machine; sometimes they injected it directly into the patient. Some studies examined not only aprotinin's effects on bleeding, but also on the function of artery bypasses to restore blood flow to the heart muscle.

Additionally, surgical culture and practices differ somewhat from country to country, and apparently surgeons in some nations felt they needed to study the drug themselves before adopting its use.

Even given these justifications, however, there was much repetition. Two studies of aprotinin's effects on patients taking aspirin were published in 1994, another in 1998, and another in 2000. All showed the same thing: Aprotinin worked for those patients, too.

The reason for the plethora of SIDS studies was different. The evidence that stomach-sleeping was hazardous arose from observational studies, which are inherently less authoritative than controlled trials where people are randomly assigned to do one thing or another. It takes more observational studies to persuade doctors to change something as important as advice to new parents.

The number of unnecessary studies that occur is an open question.

Nobody requires that medical scientists review previous research to make sure the question they are asking has not already been answered. This may change, though.

The Lancet, a British journal, announced last summer that it will require that authors submitting papers show they performed a meta-analysis of previous research or consulted an existing one.

"In 10 years we are going to look back on this time, and we won't believe this wasn't done as a matter of course," said Steven N. Goodman, a physician and biostatistician at Johns Hopkins University who edits Clinical Trials.

The current state of affairs, in his opinion, is indefensible.

When a patient volunteers for a randomized clinical trial, he or she strikes an implicit bargain with the researcher. The patient may benefit, but even if he does not, others will. That is because the study will produce new knowledge. But if the question is already settled, then the patient's sacrifice and altruism are for naught.

"In the ethical world, two things need to be considered -- harms and wrongs," Goodman said. "People in unnecessary trials are sometimes harmed, but I would say they are always wronged. And in the world of clinical research, wrongs are almost worse than harms."