

# Medical Research: The Who, What, When, Where and Why of It

In companion articles, two writers share their perspectives on medical research participation. Lauren Gerstmann reports on the history of medical research and the evolution of its safety practices, and she describes the various kinds of studies and their benefits. Terri Cerda focuses on the future of medical research, outlines practicalities to consider before you volunteer and describes current studies you may want to investigate.

## The Evolution of Medical Research

By Lauren Gerstmann, MPH

**Y**ou're already being poked and prodded by the doctor on a regular basis, so why would you choose to be poked and prodded more as part of a medical research study? In addition to increasing medical knowledge and helping to improve clinical practice, participation in medical research can offer you personal benefit. Medical research, particularly clinical trials, can offer you access to a medical device or drug years before it is commercially available. And, as your health will be closely monitored during your participation, it can offer you a way to obtain medical care for little or no charge without the involvement of your insurance company. But, there are risks involved. Historically, inadequate care was taken to minimize these risks. Government and local oversight has greatly improved the ethics of medical research, but it is still up to you to decide if the potential benefits of your participation justify your involvement.

### Early History of Medical Research

Experimental research first began toward the end of the 18th century. Methods were crude but effective, although there was no oversight of the ethical implications of research. For example, Edward Jenner (1749–1823) is known for developing the first smallpox vaccination. His work eventually led to almost total eradication of smallpox in the developed world, but his methods were incredibly risky as he first tested unproven smallpox vaccines on his son and neighborhood children.

At the beginning of the 20th century, the average age at death was 45 years. People were dying at young ages in

large part from infectious diseases such as measles, mumps, rubella (illnesses we vaccinate against today). By the beginning of the 21st century, the average age at death had increased to 78 years.<sup>1</sup> Vaccinations were discovered through experimental research and, along with increased sanitation, are widely considered responsible for increasing the average age at death by more than 30 years.

Unfortunately, ethical practices lagged way behind the increasing sophistication of research protocols.

### Developing Ethical Practices

In the mid-1900s, the public became aware of the darker side of unregulated experimentation when 23 physicians under the Nazi regime went on trial at Nuremberg for experimenting on prisoners. The legal judgment resulted in, among other things, 10 mandated standards to which physicians must conform for the ethical conduct of research. These points are known as the Nuremberg Code.

Although the code was internationally respected, it was not adopted in the United States because it was widely assumed that U.S. research was conducted with a higher standard. Although this was generally true, there were exceptions, including the Tuskegee Public Health Service Syphilis Study, conducted between 1932 and 1972. The study was designed to study the treatment and natural history of syphilis in African-American men. The study subjects did not give informed consent, and, when other researchers confirmed that penicillin could effectively cure syphilis and it became a standard ➤

<sup>1</sup> Staff Background Paper: The Promise and the Challenge of Aging Research, the President's Council on Bioethics, December 2002, <http://www.bioethics.gov/background/agingresearch.html>.

treatment in 1947, information about the treatment and the drug itself were withheld from subjects.

In 1964, the World Medical Association reinterpreted the Nuremberg Code as the Declaration of Helsinki. Research journals worldwide required that any research published must be in accordance with the ethical precepts set forward in the declaration. As American researchers became more involved with the ethics of research, Congress authorized a National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research to identify the basic ethical principles that underlie the conduct of human research. The commission developed the Belmont Report, setting forth the idea that all medical research should follow three principles:

- Respect for persons, which specifies that subjects must give informed consent to participate
- Beneficence, which specifies that research should have social and/or scientific value
- Justice, which specifies that research subjects should be chosen fairly

The Belmont code remains the standard that researchers follow today. At a national level, it is interpreted by the National Institutes of Health (through the Office for Human Research Protections) and by the Federal Drug Administration. At the local level, all research must be conducted under the guidance of an Institutional Review Board (IRB), a multidisciplinary, objective group that reviews all studies to make sure that they are conducted ethically, legally and within the spirit of the Belmont Report.

When IRBs evaluate a research study, they spend a significant amount of time evaluating the risk-to-benefit ratio. In other words, they determine whether the potential benefit to subjects is worth any risk that the subjects might incur to their health or privacy. Scientists use several different study methods, and some are inherently riskier than others. But generally, the riskier a study is, the more potential for immediate, measurable benefits. If a study is being conducted at multiple locations, a Safety and Data Monitoring Committee will oversee the study at all of its locations, and will make reports to each local IRB, allowing each to evaluate the safety of the overall study.

## Observational Studies

Some studies are simply observational. In other words, scientists observe behavior or collect questionnaire data, but do not change their subjects' behavior in any way. These types of studies were used to investigate whether fluoridating the drinking supply caused excess cancers. Observational studies are the least risky studies, involving some risk to privacy but no risk to health. But, while they describe behaviors, it is very difficult to draw any conclusions from an observational study. For instance, there is a well-known study that concludes there is a relationship between fluoridation and cancer.<sup>2</sup> But, when the National Health Service examined this along with 50 other observational studies in 1991, they concluded that other factors (such as smoking patterns and changes in occupational exposures) may have caused these cancers.<sup>3</sup> Despite the fact that cancers increased when fluoride was introduced into the drinking water, observational studies alone can suggest, but cannot prove, that the fluoride caused the increase in cancer. If there are birds flying in the sky every time a pedestrian is hit by a car, we cannot conclude that the birds are causing the accidents. Correlation does not always equal causation.

## Randomized Studies

The most effective research will cause a change in treatment or behavior and will measure the effect of that change. For us to be sure that the effect we are measuring is due to the change we have implemented, we need to factor out any confounding information. For example, if we are measuring the effect of a nicotine patch on smoking cessation, we need to be sure that any decreases in smoking are due to the patch that subjects are wearing, rather than to a confounding doctor visit where subjects receive smoking cessation counseling.

Scientists do this by designing randomized studies. In other words, subjects are assigned to a treatment or a non-treatment (placebo or control) group by chance. People who are being treated are compared to people who are not being treated. The study should be large enough that the two groups are similar in almost every way, including age, gender and race/ethnicity. At the end of the study, the two groups are compared, and any new changes between them can be explained by the study.

For example, a group of researchers set out to evaluate whether aspirin could help prevent the recurrence of

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<sup>2</sup> Yiamouyiannis, J.A. and Burke, Dean. "Fluoridation and Cancer: Age Dependence of Cancer Mortality Related to Artificial Fluoridation." *Fluoride*, Vol. 10 #3 (102-123) 1977.

<sup>3</sup> Public Health Service, Department of Health and Human Resources, Review of Fluoride Benefits and Risks, Report of the Ad Hoc Subcommittee of the Committee to Coordinate Environmental Health and Related Programs, February 1991 <http://www.health.gov/environment/Reviewoffluoride/>.

colon polyps (benign growths with the potential to progress to cancer). They studied more than 1,000 people who had polyps and randomly assigned them to a low dose of aspirin, a high dose of aspirin or a placebo. Statisticians evaluated all three groups to make sure that there were no other significant differences between them. At the conclusion of the study, the researchers were able to determine that low-dose aspirin can play a role in preventing colon polyps from recurring.<sup>4</sup>

### Kinds of Prevention

Research studies are defined in terms of primary, secondary and tertiary prevention. Primary prevention is anything done to prevent negative health outcomes in the general population. For example, diabetes screening and counseling at a public health fair is primary prevention (although it is not a research study). Secondary prevention is targeted at high-risk groups. Providing colonoscopies to people with a family history of colon cancer is secondary prevention. If you take it a step further, and design a randomized clinical trial to determine whether aspirin will prevent colon cancer in this high-risk group, you are working on a secondary prevention clinical trial.

Tertiary prevention is not what we typically think of as prevention at all. It is the clinical term for treating a condition someone already has. Chemotherapy is a tertiary prevention for cancer. The preferred method for research in tertiary prevention is a randomized clinical trial, but these trials need to be conducted very carefully in order to minimize risks to the participants. There are several ways to do this. A trial of a new medication to treat heart disease might use an established medication as the control (rather than using a placebo control) so that no subjects have to take the risk of going completely off medication. The medication in a new AIDS trial, if proven very effective, might be offered to all enrolled subjects (including those who were taking the placebo) after the study is over.

### Weighing the Decision

Because of the ethical guidelines now in place for medical research, every patient who participates in medical research is a volunteer, and should be treated fairly and with respect. When you make the decision to participate, you need to determine your own comfortable risk-to-benefit ratio. Generally, primary prevention studies are the least risky but they will offer the least personal gain. Secondary prevention studies generally carry low-to-moderate risk, and may prevent some individuals from getting a disease. But, the main benefit of a secondary

prevention trial is to help at-risk groups learn more about disease and/or disability prevention. As with participation in any medical research trial, be sure to discuss your participation with your doctor in order to determine that it is reasonably safe for you. It is also important to keep in mind that you always have the right to withdraw your participation in the research study without jeopardizing your care by your physician or at your physician's institution.

Tertiary studies are the riskiest, but can also offer you the most immediate or significant results. For example, tertiary studies have been used to determine the safest and most effective doses of immune globulin therapy, and also to determine the least painful methods of immune globulin administration. But, these types of studies expose you to the most risk: risk of side effects and risk that the drug or device will not work. You need to carefully evaluate whether the potential benefits are worth it.

Read on to learn more about the decision to participate in medical research.

## Medical Research: The Decision to Participate

By Terri Cerda

Choosing to take part in medical research is a very important and very personal decision. Before deciding to participate, it is crucial that you learn as much as possible about the study you are considering. Ask questions and become well-informed. Discuss it with family, physicians and research staff. You should have enough information to feel confident when you make your decision—whether or not you enroll.

**The following is a list of questions to consider as part of your decision-making process.**

1. What is the purpose of the study?
2. Who is conducting the study?
3. Why do researchers believe the experimental drug or treatment will be helpful or effective?
4. Has the medication or treatment been tested before? If so, what was the outcome?
5. What kinds of tests, medications or experimental treatments will be used to gain information?
6. What are the possible risks, side effects and benefits and how do they compare with the possible risks, side effects and benefits of my current treatment? ➤

<sup>4</sup> Baron, J, et al. A randomized trial of aspirin to prevent colorectal adenomas, *New England Journal of Medicine*, Volume 348:891-899, March 2003.

7. How might the research affect my life?
8. How long will the study last?
9. Will hospitalization be required?
10. Who will pay for the experimental treatment? If there is a cost to me, will my insurance cover it?
11. What type of long-term follow-up will be required?
12. Will I be reimbursed for my expenses?
13. How will I know if it is working and will the research results be given to me?
14. If the treatment is proven effective, will I be offered access to it when the study is complete?
15. Can I drop out of the study?
16. Will researchers work with my physicians?
17. What if I am harmed?
18. Will I be paid for participation?
19. Who can I call if I have problems or concerns?
20. How will my privacy be protected? Can anyone find out that I am participating in the research study and can anyone access my medical information?

If you do not understand or are unclear about the answers to any of your questions, do not hesitate to ask for clarification. It is a good idea to have a family member or friend with you when you are asking questions, so you can compare notes about what you heard. Even better, take a tape recorder so, if you are given permission to record any conversations, you can thoughtfully review the information you gather when considering your decision.

### Primary Immune Deficiency Studies

According to Katherine Groden, research coordinator at the National Institutes of Health (NIH) in Bethesda, Md., researchers face many challenges in finding volunteer participants for clinical research. Because primary immune deficiency diseases (PIDDs), particularly common variable immune disease (CVID), are considered rare, with a limited patient population, it is difficult to identify individuals to take part in PIDD studies. Additionally, the criteria for participation are often narrow and specific, further complicating the recruitment of patients who qualify for the study. In fact, the NIH and other organizations recruiting for research purposes are limited in their ability to contact patients and must rely heavily on referrals from physicians. Nonetheless, patients are recruited, although sometimes slowly, and many quickly recognize the benefits of participating.

Cyn and Drew Olivera of Southern California have learned firsthand the importance of medical research participation.

At age 2, their son, Drew, was diagnosed with X-linked agammaglobulinemia (XLA). After taking part in an XLA research study at St. Jude's Children's Research Hospital this past year, they learned that Drew has an extremely rare PIDD called mu heavy chain defect.

The Oliveras cited their ability to access specialists not otherwise available to them and their wish to help others as their reasons to enroll Drew, now 6, in the research program. Despite all the blood tests, a bone marrow aspiration and X-rays Drew underwent during the course of the study, the Oliveras have no second thoughts about their decision. They report no adverse or negative experiences. As a result of their participation, Drew will be closely monitored, returning to St. Jude's every six months for follow-up. Drew sees the entire experience as an exciting opportunity to travel.

"We need to be a resource for each other. There may be just one unique thing about Drew that gives insight for many others and their fight to gain information [about primary immune deficiencies]," states Cyn Olivera. The Oliveras have participated in one other research program, administered by Dr. Robert Roberts at UCLA Children's Hospital, Department of Allergy and Immunology. In the future, they plan to enroll in other studies that relate to Drew's disorder and satisfy their desire to help others, but only after weighing the risks versus the benefits. "We look at the bigger picture; it's not just us dealing with this disorder."

Over the years, advances made in the knowledge base regarding PIDD have been greatly enhanced through research since the identification of "hypogammaglobulinemia" by O.C. Bruton in 1952.<sup>1</sup> Many researchers and immunologists readily admit there is still a great deal to learn about the more than 120 disorders classified as primary immune deficiency diseases. The number of identified disorders is sure to grow. There remain unanswered questions concerning the role of genetics in these disorders and adequate and appropriate ways to treat or prevent them in the future. Finding answers depends on the ability of researchers to gain the participation of individuals seeking change and improvement in the ways PIDD is diagnosed, treated and prevented.

If you ultimately decide to participate in medical research, you have likely determined that the potential benefits outweigh the potential risks. Your decision also represents, whether conscious or not, a commitment to help other patients who will benefit from the knowledge derived from the research. ■

<sup>1</sup> Martin, NH: Recognition of Hypogammaglobulinaemia Syndrome. In Hypogammaglobulinaemia in the United Kingdom. Edited by MRC Working Party on hypogammaglobulinaemia. London: Her Majesty's Stationary Office; 1971:1-3