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Serious adverse events rare in healthy volunteers participating in Phase I drug trials

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Many people believe that phase I trials with healthy volunteers are very risky and because they pose risks with no benefits, unethical. But how risky are such trials? Less than 1% of 11,000 healthy volunteers who participated in 394 phase I trials for new drugs experienced serious complications, according to a new meta-analysis of participants in non-cancer, phase I medication trials. In addition, none of the volunteers died or suffered persistent disabilities linked to the experimental drugs. In the largest study of its kind, researchers found only 34 (0.31%) healthy volunteers with serious adverse events, which are defined by the FDA as those that result in death; are life-threatening; require or prolong in-patient hospitalization; or cause a disability, congenital anomaly or birth defect. And half of these serious adverse events, such as Dengue fever or those affecting the volunteers taking a placebo, were not linked to the phase I experimental drugs or study procedures. Despite the fact that more than 100,000 healthy people annually participate in non-oncology phase I studies worldwide, there is little systematic research quantifying their risks. However, this study, led by researchers at the Perelman School of Medicine at the University of Pennsylvania and published in *The BMJ*, found the risks to be very low.

"The findings provide good support for the general safety of phase I trials," said lead author Ezekiel J. Emanuel, MD, PhD, chair of the department of Medical Ethics and Health Policy at Penn. "Some have claimed that these trials pose high risks of harm to participants. But these findings show such claims to be essentially without empirical validity." Overall, there were three serious adverse events for every

1,000 participants, with several occurring in subjects receiving placebos and others judged unrelated to the study drug or a study procedure.

The meta-analysis examined 394 non-cancer, phase I studies comprising 11,028 healthy, compensated, voluntary participants (4,620 unique individuals, some of whom participated in more than one study) conducted between September 2004 and March 2011 at Pfizer Inc.'s three worldwide dedicated phase I testing sites in Belgium, Singapore and the United States. In phase I trials, researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

The investigators found that 63.7% of participants experienced a combined total of 24,643 adverse events, and the other 36.3% experienced no adverse events of any kind. Nearly a quarter (24.1%) of all adverse events were judged to be unrelated to the study drug, and the vast majority (84.6%) of adverse events were classified as mild, 14.4% as moderate, and 1% as severe. The "mild" classification means that symptoms did not interfere with usual functioning while a severe adverse event interferes significantly with a subject's basic daily functioning; for example, a broken finger. The most common adverse events were headache (12.2%), drowsiness (9.8%), diarrhea (6.9%), nausea (5.9%), dizziness/lightheadedness (5.4%), and vomiting (2%).

Examples of serious adverse events include chest pain, blurred vision, elevated enzyme levels, and abdominal pain and cramping. Of the 34 serious adverse events, 11 were related to the study drug and seven to study procedures, while 16 were unrelated to a study drug or procedure, including four that occurred in participants receiving a placebo. With a total of 143 (36%) studies involving placebo, 10.3% of all adverse events (2,528) occurred in participants receiving placebo. Nearly 20% of the adverse events occurred on the first day of the study. These have been hypothesized as being linked to changes in behavior required to take part

in a study, such as withdrawing from smoking and drinking alcohol or caffeinated beverages, rather than from the study drug.

"Some may question the reliability of these data because the adverse events were determined and classified by investigators from the pharmaceutical company," Emanuel said. "But this is unlikely. for several reasons. First, over 24,000 adverse events were reported. Second, the informed consent documents given to participants encourage them at multiple places to report changes in health 'however minor.' Third, it is not in the interest of the pharmaceutical company to minimize recording of adverse events since determinations must be made about whether to conduct additional expensive clinical studies. Finally, salaries or bonuses for phase I researchers at Pfizer do not depend upon the outcomes of phase I studies, so there is no financial incentive to 'cheat.'"

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