that the "radiation problem is very severe" and predicted it will be hard to overcome. But Goldin says both robots and humans ultimately will be needed for Mars exploration.

The working group has been asked to set near- and long-term goals for the kinds of technology and research infrastructure needed. A self-described "cheerleader" for the program, Baltimore says that the venture "is a real opportunity for thinking in novel ways about programs that cut across two agencies. ... Interdisciplinary science is on everyone's tongue. Today, it's a reality."

–ANDREW LAWLER

PSYCHIATRY

Are Placebo-Controlled Drug Trials Ethical?

HOUSTON—The psychiatric research community is increasingly polarized by a seemingly simple question: Is it ethical to use placebos in drug trials? Specifically, can you give some of your patients a dummy pill, if it means suspending their regular medication and possibly worsening their symptoms? Critics argue that doing so makes patients suffer unnecessarily and may drive some to suicide. But the Food and Drug Administration (FDA) has insisted that placebo-controlled trials are the only scientifically sound way to test the efficacy of most psychiatric drugs. Drug companies say they have no choice but to comply, and most researchers have gone along—some of them reluctantly.

> **"If the patient was your son or your mother, would you withdraw active treatment?"**
>
> —Karin Michels

Now, the FDA has two large meta-analyses to defend its policy. Both show that being in a placebo group does not increase the risk of suicide. But those studies—the most definitive to date—seem unlikely to quell the controversy. At a meeting* earlier this month where one of the studies was presented, critics lashed out again at placebo-controlled trials, calling them "unethical" and "immoral." Karin Michels, a clinical epidemiologist from Harvard University, asked: "If the patient was your son or your mother, would you withdraw active treatment from them for the sake of science?"

Instead of using fake pills, critics argue that new psychiatric drugs should be compared to one of the many drugs already on the market. Nobody would even consider using placebos for such treatable diseases as cancer and AIDS, Michels pointed out, adding that the practice violates the Declaration of Helsinki. Worse still, some psychiatric patients sign up for such trials without fully understanding what they're getting into, said Harold Vanderpool of the University of Texas (UT) Medical Branch in Galveston. For these reasons, Institutional Review Boards (IRBs), the panels at universities and hospitals that scrutinize trials for human risks, are increasingly loath to approve the use of placebos in psychiatric trials, says Paula Knudson, who administers an IRB at UT Houston.

But FDA maintains that psychiatric drugs—and some others, such as antihypertensives—are a special case because their effects are notoriously hard to prove. It's common in these trials for 30% to 50% of the patients in the placebo group to improve, thanks to a phenomenon called the placebo effect, while those on the real drug improve just a bit more. Indeed, even already-approved drugs regularly fail to beat placebos in later trials. If all FDA demanded was that a new drug perform as well as an old one, it would have no way of knowing how much of that improvement was caused by the placebo effect, officials say.

Because the placebo effect is so fickle, and nobody knows how to reduce it, FDA usually recommends that psychiatric drugs be tested in three-armed trials, in which a new drug is compared to a placebo and an existing treatment. If both drugs fail to beat the placebo, the whole trial is written off as a failure. Some people may be worse off from getting a placebo instead of an approved treatment, admits Thomas Laughren, team leader of FDA's Psychiatric Drug Products Group, but that's an acceptable risk as long as patients' lives are not at stake.

Laughren believes they are not. He and his colleagues conducted a meta-analysis of every recent trial submitted to FDA to win approval for eight new antidepressants (including blockbusters such as Prozac and Zoloft) and four antipsychotic drugs. More than 42,000 patients took part in these trials. In the antidepressant trials, 0.02% of the patients in the placebo group committed suicide during the trial, compared with 0.10% in the experimental drug groups and 0.13% in the groups that received an older drug. Laughren cautioned that those results must still be corrected for the amount of time patients spent in the trial, but he was confident that won't significantly alter the outcome. Trials with schizophrenic patients showed similar results. And the outcomes also match those from a smaller study led by psychiatrist Arif Khan from the Northwest Clinical Research Center in Bellevue, Washington, who looked at FDA data from seven antidepressant trials that together enrolled almost 20,000 people. The study, published in the April *Archives of General Psychiatry*, also failed to see an increased suicide risk.

But the critics are unimpressed. The Khan paper, for instance, is accompanied by six commentaries—three of them arguing that the study doesn't justify the use of placebo controls. Suicide is just one risk psychiatric patients face, says Michels. "Shouldn't we also think of the quality of life of the people we're withholding the active treatment from?" she asks. And Vera Hassner Sharav, president and founder of a New York City lobby group called Citizens for Responsible Care and Research, adds that suicide rates in all trial groups may have been increased; simply enrolling in a study that includes a placebo arm causes great stress and anxiety in some patients, she says. Michels and Hassner Sharav argue that trials that compare two active drugs could produce statistically relevant outcomes if they had more patients, time, and money.

Despite the arguments, participants at the Houston meeting did find common ground. Only patients fully capable of making a sound decision should be enrolled in trials, and they should be informed as fully as possible. Researchers can also reduce risks by screening out patients likely to harm themselves or others and by making sure there's a friend or family member on standby. IRBs should be especially vigilant, says Knudson. Her own panel has sometimes required that severely depressed or psychotic patients be hospitalized for the first 3 weeks of a trial to make sure they're okay. Pharmaceutical companies and researchers don't necessarily like these restrictions, she concedes, but they do provide a safeguard.

–MARTIN ENSERINK

PALEONTOLOGY

Revealing a Dinosaur's Heart of Stone

In the fall of 1998, Andrew Kuzmitz, a physician in Ashland, Oregon, invited seven cardiologists to a local hospital to view a computerized tomography (CT) scan. The experts all agreed on what they were seeing: two large, oval chambers or ventricles, divided by a septum. "Every one of them said, 'It's a heart,' " says Kuzmitz. But this was no ordinary heart: It belonged to a 66-million-year-old dinosaur. "As soon as I put the scan

* Placebo in mental health research: Science, ethics and the law, UT Houston, 7 to 8 April.