Changes to high-risk medical devices often supported by low-quality research

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Clinical trials that test changes in the design or use of high-risk medical devices are often poorly designed, and can rely on inadequate or potentially biased data, according to a new study by researchers at the

UC San Francisco and Yale School of Medicine.

In the study, published August 15, 2017 in *JAMA*, the authors reviewed clinical trials supporting U.S. Food and Drug Administration (FDA) approval of changes to high-risk devices over the last decade. They found that fewer than half of these studies were randomized, blinded, or controlled - the "gold standards" for clinical trials of drugs.

The FDA defines high-risk devices as those that "that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury."

The consequences of poor testing of medical devices can be severe several of the devices investigated in the clinical trials analyzed in the new paper had been recalled for safety or efficacy issues.

"There's a lot of pressure on the FDA to speed things up, to let innovative or life-changing treatments go to market," said Rita Redberg, MD, MSc, a professor of medicine at UCSF and the study's senior author, "but you don't know if they're innovative or life-changing until you've done a careful study. These were short studies, with low-quality data, and little follow-up after approval."

The paper is published alongside another from researchers at the London School of Economics and Harvard Medical School that notes similar problems in accelerated approval paths for pharmaceuticals. In an accompanying editorial, former FDA Commissioner Robert Califf MD, MACC, calling for continued discussion and reform of both approval processes.

Investigation found brief studies, incomplete data

To mitigate the potential hazards of high-risk medical devices, the FDA requires that these devices undergo rigorous initial clinical testing, known as premarket approval (PMA), before they are sold, a process that Redberg and her collaborators have been studying for years.

In a 2009 study, her research team found that, more often than not, clinical studies to support PMA lacked blinding, randomization, or proper controls. That study was a wake-up call for device regulators. "We got a ton of emails from people thanking us for exposing this important issue that nobody was talking about," said Redberg.

But the original PMA is seldom the whole story. As device makers update their devices - modifying the design or providing for different uses than the original purpose - they must submit "supplements" to the FDA for approval.

"Many devices can have hundreds of different supplements attached to them," said Sarah Zheng, MD, a resident physician in psychiatry at UCSF, and a co-lead author on the paper. "So we wanted to check the quality of evidence supporting these important changes as well."

Redberg and Zheng were joined in the research by co-lead author Sanket S. Dhruva, MD, who received his MD from UCSF in 2009, completed his residency in Internal medicine in 2009, and is now a Robert Wood Johnson Foundation Clinical Scholar at Yale School of Medicine.

There are many paths to supplement approval, and only one, the so-called panel track, requires clinical data, so the team investigated the rigor of 78 panel track supplement approvals, supported by 83 studies. The studies supporting supplements, they found, suffered the same problems as the PMA studies.

As with PMA studies, most supplement trials weren't blinded,

randomized, or controlled. But in nearly a quarter of the supplement studies, the analysis procedures were changed after the study began, and many failed to present data from all the participants, potentially biasing the studies' results. Most studies lasted less than six months, and many presented incomplete data on age and sex, making it harder for physicians to evaluate the risk of a device in particular patients.

"Physicians and patients need to be aware of how little we actually know about these devices," said Zheng. "If patients need to have the device removed because it isn't functioning properly, that can be very risky and expensive."

Little recourse if devices harm patients

The investigation takes on particular significance because patients who are harmed by FDA-approved devices have few legal options. In 2008, the U.S. Supreme Court ruled in Riegel v. Medtronic, Inc. that FDA approval protects manufacturers from lawsuits over devices' safety or efficacy; this principle is likely to hold even if approval is based on a study that did not follow best practices. "If the FDA approved it, that's that," said Redberg.

In order to improve post-approval procedures, the FDA has discussed standardizing data on medical device failures, leveraging electronic medical records and assigning a unique ID to each device to make it easy for doctors to report device failures or safety threats. "The FDA says they want to do more work on post-approval, but nothing's in place yet," said Redberg. "Even when they do ask for a post-approval study, it's often not completed or done at all."

"I think there has to be more public and congressional calls to have reasonable assurance of safety and effectiveness before devices are approved," said Redberg said. "Until then, all we know is that a lot of

devices on the market haven't been shown to be safe or effective."

More information: *JAMA* (2017). jamanetwork.com/journals/jama/… .1001/jama.2017.9414

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