Limiting the problem of missing data urged for clinical trials

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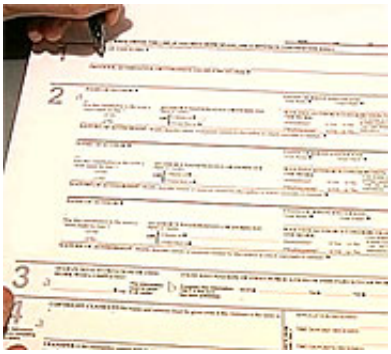

Missing data compromise inferences from clinical trials, and due to the problematic nature of compensation with analysis methods, the importance of avoiding missing data in clinical trials is paramount, according to a special report published in the Oct. 4 issue of the *New England Journal of Medicine*.

(HealthDay)—Data missing from clinical trials can undermine the credibility of those trials, and little attention has been focused on this issue until recently, experts say.

Even regulatory guidelines that direct how clinical trials should be run offer little advice on dealing with missing information, according to a new report from an expert panel commissioned by the National Research Council.

And, while statisticians may be able to control for the missing data, they

can end up making "assumptions about what the outcomes would've been, and when you're doing a phase 3 clinical trial [that could lead to a drug's regulatory approval or denial], people don't want to make assumptions. They want to assure balance, which argues for trying to limit the amount of missing data," said the panel chairman, Rod Little, a biostatistics professor at the University of Michigan School of Public Health in Ann Arbor.

Another panel member, Kay Dickersin, who directs the Center for Clinical Trials and the U.S. Cochrane Center at the John's Hopkins Bloomberg School of Public Health in Baltimore, agreed. "When data are missing from clinical trials, the findings become questionable or of no use. Why are the data missing? Is it because the people with data missing all got better? All got worse? We don't know why the data are missing, and so we cannot even guesstimate what the true findings of the study would be would be if no data were missing," Dickersin said. "The main point is that it is far better to prevent missing data than to try to 'fix' the problem in the analysis," she added.

Findings from the panel are published as a special report in the Oct. 4 issue of the *New England Journal of Medicine*.

In May, a study published in the *Journal of the American Medical Association* also took clinical trials to task, finding that many are small and of poor quality. That study found that cancer treatment trials often failed to follow the highest standards.

To address the potential problems stemming from missing data in clinical trials, the U.S. Food and Drug Administration requested that the National Research Council convene an expert panel in 2008. The current report focuses primarily on phase 3 clinical trials assessing the safety and efficacy of drugs, biologic products and some medical devices.

Missing data was defined by the panel as information that would have been meaningful to the results of the trial.

The panel found that a major cause of missing data is participants who stop taking their assigned treatment because it's not working, the side effects are troubling or the drug regimen is too inconvenient.

But the panel suggested that researchers should continue to gather follow-up information on them anyway.

"People have the right to discontinue any treatment, but often people don't follow-up. The panel is making the point that in a lot of situations, it's useful to get that information," said Little.

Dickersin said another issue is missing data even when follow-up visits were kept. "Sometimes patients may attend their follow-up visits, but not answer all the questions they were asked. So if, for example, some people in a study about pain fail to fill in their diaries about daily pain, then we may not know that pain relief is only for a short time with the test drug when long-term pain relief is what patients are seeking," she said.

The panelists outlined a number of steps that could be taken to limit the amount of missing data in clinical trials. They include:

- Conducting a brief run-in period in which all participants are assigned an active drug to see who can tolerate it.
- Allowing the use of rescue medications as part of the treatment regimen, so these drugs are accounted for in the analysis.
- Targeting a group that doesn't have enough current treatment options, because they have more incentive to stay in the trial.
- Shortening the follow-up period.

The panel also recommended changes in the statistical analysis of missing data at the end of the study. Little said some of the current methods used may be too simplistic.

The bottom line, he said, is that "we want to make the best possible decisions about which drugs are effective and safe."

Dickersin added, "Study participants are making an incredibly important contribution to current and future health care by participating in clinical trials. They can contribute to the impact of the findings by ensuring that they follow the protocol as asked.
"And, even when they have to change treatments or stop the treatment to which they were assigned—say, because of side effects—they still can help the study's success by returning for visits and completing all study forms and questionnaires," she added.

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