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JAMA Article Looks at Data-Sharing in Clinical Trials for Heart Disease

Discussion of When and How to Share Data, and When to Suspend a Study Authored by Dr. Jeffrey Borer of NewYork-Presbyterian/Weill Cornell

NEW YORK (April 9, 2008) — How and when to share clinical trial data for heart studies — including when to suspend a study — is vitally important to physician-scientists and regulators as an increasing number clinical trials evaluate new treatments. This issue is explored in the April 9 Journal of the American Medical Association (JAMA) in a commentary article authored by Dr. Jeffrey S. Borer of NewYork-Presbyterian Hospital/Weill Cornell Medical Center and Drs. David J. Gordon and Nancy L. Geller — both of the National Heart, Lung and Blood Institute (NHLBI).

Treatment decisions are based on findings from scientific studies called clinical trials that can sometimes involve many thousands of patients. Several of these studies — such as those involving the drugs Avandia, Vytorin and, earlier, Vioxx — have been the subject of recent controversies in the media.

Increasingly clinical trials are monitored by independent, external groups called Data and Safety Monitoring Committees (DSMCs), charged with protecting the safety of trial participants and preserving trial integrity and credibility. These committees are the only groups that can know results of blinded trials (trials in which participants and investigators are not aware of treatment assignments) while the trials are ongoing. The proper function of DSMCs is subject to discussion and debate. The JAMA article addresses one aspect of this debate.

“Several situations exist in which it is reasonable and appropriate for the DSMC to share interim data from a blinded trial with operational study personnel and sponsors. These situations might include the need for ‘mid-course corrections,’ when the number of outcome events — like deaths and heart attacks — is substantially lower in the untreated group than was expected in a trial to reduce such problems,” says Dr. Jeffrey S. Borer, article co-author and director of Cardiovascular Pathophysiology and co-director of The Howard Gilman Institute for Valvular Heart Diseases at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, and the Gladys and Roland Harriman Professor of Cardiovascular Medicine at Weill Cornell Medical College.

“If this happens,” Dr. Borer continues, “the total number of patients slated to participate in the trial may be inadequate to test the therapy’s effectiveness. In this case, the DSMC might notify the sponsor and suggest an increase in the number of subjects to be recruited into the study. However, the DSMC would not tell the sponsor the number of events that had occurred in each treatment group.”

While sharing some data would be reasonable and appropriate in several other situations, Dr. Borer stresses that “the DSMC should share patient treatment assignments related to interim outcome/event data with the sponsor in only one situation — when recommending premature termination of the study.”

Reasons the DSMCs recommend termination include:

- The committee perceives a rising toll of adverse events that appears to outweigh any possible benefit from the treatment.
- No evidence of benefit is apparent and statistical analysis suggests that continuation is highly unlikely to produce such benefit (called “futility analysis”).

- Evidence of benefit is so overwhelming and important (example: reduction in death rate) and risks sufficiently low, that the benefit/risk relation is highly likely to be maintained if the trial continued to its planned conclusion. It would be unethical to withhold the good treatment, not only from all trial participants, but also from other members of society who might benefit. According to the authors, this decision must be undertaken with great caution because of the well-known variability of results over time, even in large trials.

The article notes that while there are differences in data-sharing procedures between industry-sponsored and government-sponsored trials, all sponsors "own" their data, and can demand unblinded information even if this is considered unwise by the DSMC.

The authors recommend that before doing so, the sponsor should consider the long-term consequences of such action, which can affect regulatory acceptability, future analyses and publication of the data.

"In such settings, if the DSMC is concerned that trial credibility or validity will be compromised by the release of interim data, there are few avenues open to the committee except formal protest or resignation," says Dr. Borer, since no legally constituted regulatory body has provided relevant guidance or regulation to deal with the issue of interim data release.

The authors note that discussion and debate will continue regarding the appropriate sharing of interim data as society increasingly depends on clinical trials for advancing medical treatments.

The article is based on presentations by the authors and subsequent discussion held during the Ninth Cardiovascular Clinical Trialists (CVCT) Workshop in Paris, France, in 2006.

The Howard Gilman Institute for Valvular Heart Diseases at Weill Cornell Medical College helps cardiologists, cardiothoracic surgeons and other physicians take advantage of the most current concepts in the evaluation and treatment of heart valve diseases, and provides state-of-the-art patient care. The Institute's co-directors, Dr. Jeffrey S. Borer and Dr. O. Wayne Isom, are leaders in their fields and direct a team of clinical cardiologists, surgeons and research scientists who are at the cutting-edge of this emerging public health concern. For more information, visit **www.gilmanheartvalve.org**.

NewYork-Presbyterian Hospital/Weill Cornell Medical Center

NewYork-Presbyterian Hospital/Weill Cornell Medical Center, located in New York City, is one of the leading academic medical centers in the world, comprising the teaching hospital NewYork-Presbyterian and Weill Cornell Medical College, the medical school of Cornell University. NewYork-Presbyterian/Weill Cornell provides state-of-the-art inpatient, ambulatory and preventive care in all areas of medicine, and is committed to excellence in patient care, education, research and community service. Weill Cornell physician-scientists have been responsible for many medical advances — from the development of the Pap test for cervical cancer to the synthesis of penicillin, the first successful embryo-biopsy pregnancy and birth in the U.S., the first clinical trial for gene therapy for Parkinson's disease, the first indication of bone marrow's critical role in tumor growth, and, most recently, the world's first successful use of deep brain stimulation to treat a minimally-conscious brain-injured patient. NewYork-Presbyterian, which is ranked sixth on the U.S.News & World Report list of top hospitals, also comprises NewYork-Presbyterian Hospital/Columbia University Medical Center, Morgan Stanley Children's Hospital of NewYork-Presbyterian, NewYork-Presbyterian Hospital/Westchester Division and NewYork-Presbyterian Hospital/The Allen Pavilion. Weill Cornell Medical College is the first U.S. medical college to offer a medical degree overseas and maintains a strong

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