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Phase IV Studies Ethics & Scientific Issues IOM Report Released

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By Karen Gilden

Post-marketing (or Phase IV) studies are routinely cited as the fastest growing drug research phase. Phase IV studies are initiated after the FDA has approved a product for the open market. In late August 2012, the New England Journal of Medicine (NEJM) published an article[1] commenting on the May 2012 Institute of Medicine report entitled "**Ethical and Scientific Issues in Studying the Safety of Approved Drugs[2].**" In the wake of several high-profile controversies surrounding post-approved drugs (including Vioxx®, Avandia® and Fen-Phen) the FDA requested the Institute of Medicine convene a committee to evaluate five specific questions involved in conducting studies of approved drugs. Briefly, these questions were:

1. What are the ethical and informed consent issues to be addressed when designing randomized clinical trials (RCTs) to evaluate safety risks?
2. What are the strengths and weaknesses of various research approaches (including observational studies, patient registries, meta-analysis and RCTs) to generating evidence about safety issues?
3. What are the speed, cost and value implications to follow-up studies that investigate pre-approval or post-marketing concerns?
4. Under what circumstances should head-to-head RCTs for safety be required?
5. How should FDA factor in different types of safety evidence in considering various regulatory actions?

While both the IOM Report and the NEJM article address these scientific and public health and welfare issues, the implications for larger cancer programs rests with the role Phase IV studies play in their program's overall clinical research portfolio and research initiative goals. Issues could include what percentage of available trials are Phases I, II, III and IV; understanding the stronger regulatory role which the local Institutional Review Board may be charged with vis-à-vis Phase IV informed consent; and pharmaceutical industry pressures to surface how much money they pay individual physicians to enroll patients into Phase IV studies.

Various purposes are often assigned to Phase IV studies, including significant market-based or commercial (sales) objectives. From a science perspective, these post-marketing trials are used to determine the safety and efficacy of a drug across a broader population (than earlier phase trials). Phase IV research studies how a drug works in the real world. Post-marketing studies can investigate side effects, establish the incidence of adverse reactions and determine the drug's effects over long-term administration or with a broader segmented population base.

Patient safety issues, as well as public and medical professionals' pressure to validate a benefit-to-risk ratio for new drugs, is shifting the pharmaceutical industry's post-marketing studies away from primarily business goals. Increasingly, Phase IV studies deal with:

- Regulated post-approval monitoring that identifies drug safety and efficacy issues when thousands of patients are prescribed and take the drug;
- Quantifying the risk-benefit ratio;
- Monitoring health outcomes and cost of care; as well as,
- Measuring patient compliance, adherence to dosing schedules and preference for specific medications.

Phase IV studies come with historical baggage. Often post-marketing studies were primarily product marketing efforts, referred to pejoratively as "seed" studies. David Kessler, MD and former head of the FDA, commented on such trials, stating, "*Some company-sponsored trials of approved drugs appear to serve little or no scientific purpose. Because, they are, in fact, thinly veiled attempts to entice doctors to prescribe a new drug being marketed by the company, they are often referred to as 'seeding trials.' Features that distinguish such trials from scientifically rigorous studies include the use of a design that does not support the stated research goals, the recruitment of investigators not because they are experts or leading researchers but because they are frequent prescribers of competing products in the same therapeutic class, disproportionately high payments given to 'investigators' for their work (although the only work may be to write prescriptions for the drug), sponsorship of the studies by the company's sales and marketing division rather than its research departments, minimal requirements for data, and the collection of data that are of little or no value to the company.*"[3]

All community oncologists, regardless of their discipline or specialty, and all experienced cancer program administrators are aware of the continued under-recruitment of patients to research studies. Efforts to improve enrollment in industry trials, though much more tightly regulated now than in the past, nevertheless can include sponsors offering financial and other incentives to investigators. Some recruitment practices may undermine the informed consent process, a foundational premise to ethical human research. Patients and human subjects' rights are part of the ethical challenge all cancer program participants face. The IOM Report and subsequent discussion articles like the Mello, et al. NEJM manuscript should prove helpful to cancer program leaders as they seek to understand the emerging recommendations for Phase IV studies and how these recommendations may influence their local cancer program's research initiatives.

You can read the IOM report by accessing http://books.nap.edu. The NEJM article is available (free) at www.nejm.org.

[i] Mello, MM, et al. Ethical considerations in studying drug safety – The Institute of Medicine Report. N Engl J Med 2012: 367:959-964

[2] National Research Council Ethical and Scientific issues in Studying the Safety of Approved Drugs. National Academies Press. May 1, 2012.

[3] Kessler, DA, MD. et al. Therapeutic-Class wars – Drug promotion in a competitive marketplace. N Engl J Med M 1994; 331: 1350-1353.