VICTORIAN CENTRE FOR BIOSTATISTICS

ViCBiostat

Victorian Centre for Biostatistics

Seminar

Friday 28th March 2014
9.30am to 10.30am
Lecture Theatre, Level 5
Alfred Centre
99 Commercial Road, Prahran

Drug Safety and Vioxx® Controversy

Dr KyungMann Kim

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Recently there has been a number of drug safety concerns involving, for example, cyclooxygenase-2 (COX2) inhibitors such as Vioxx® (rofecoxib) and Celebrex® (celecoxib). These both are non-steroidal anti-inflammatory drugs selectively inhibiting cyclooxygenase-2, an enzyme responsible for inflammation and pain, and were approved by the US Food and Drug Administration in December 1998 for treatment of osteoarthritis and rheumatoid arthritis and May 1999 for treatment of osteoarthritis, acute pain and dysmenorrhea, respectively. The US National Cancer Institute launched the **A**denoma **P**revention with **C**elecoxib (APC) trial in November 1999, and shortly afterwards Merck launched the **A**denomatous **P**olyp **PR**evention **O**n **V**ioxx (APPROVe) trial in February 2000. A regularly scheduled review of the interim safety data from the APPROVe trial by its external safety monitoring board led to a voluntary withdrawal of Vioxx® on 30 September 2004, followed by early termination of the APC trial due to safety concern on 17 December 2004 by the NCI. In this review I will provide the general background on the drug safety issues and illustrate the challenges, with post-marketing trials of COX2 inhibitors as an example. More specifically, I will review the development of Vioxx®, the events leading up to its voluntary withdrawal by Merck, subsequent publications about cardiovascular adverse events for the APPROVe and APC trials, and surrounding controversy, with liability litigations in the background. I will attempt to draw lessons in terms of clinical trials design, conduct, monitoring, analysis and publication. In particular, I will highlight the controversy surrounding the analysis of cardiovascular events and the interpretation of emerging difference in the Kaplan-Meier estimates from the APPROVe trial.

Dr KyungMann Kim is a graduate of the University of Wisconsin-Madison with a degree in Statistics, Dr.Kim was Assistant and Associate Professor of Biostatistics at Harvard School of Public Health and Dana-Farber Cancer Institute, Associate Professor of Biostatistics at the University of Michigan School of Public Health, and Visiting Associate Professor of Ophthalmology at Johns Hopkins University. He has sat on advisory panels and data monitoring committees for both the United States National Institutes of Health, Department of Veterans Affairs, Department of

Defense, and the Environmental Protection Agency and for biopharmaceutical and device industry, in addition to service to the American Statistical Association, the Society for Clinical trials, the International Biometric Society, and the International Society for Clinical Biostatistics. He was inducted as a Fellow of the Society for Clinical Trials in 2012 for his contributions to the advancement of clinical trials through methodologic development; trial coordination, conduct and leadership, and service to the society. He is also an elected Fellow of the American Association for the Advancement of Science (2012) as well as of the American Statistical Association (2005). His area of statistical research includes sequential methods and interim analysis, clustered data analysis including analysis of panel count data, and methods for clinical trials, and his collaborative research has been primarily in clinical and translational cancer research.

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