

the potential to rapidly investigate the drug exposure and safety experience within large, well-defined and diverse populations.

ACKNOWLEDGEMENTS

We are indebted to the statistical programmers at each of the sites for their work in extracting the study data and testing the programming algorithms, to Kimberly Lane and the HMORN CERT Data Coordinating Center for their help in overseeing the study and Meredith Chace for editing and data checking. This study was funded by a grant from AHRQ (2U18HS010391) supporting the HMO Research Network Centers for Education and Research on Therapeutics (CERT).

REFERENCES

1. Committee on the Assessment of the US Drug Safety System. *The Future of Drug Safety: Promoting and Protecting the Health of the Public*. Institute of Medicine of the National Academies: Washington D.C., 2006.
2. Wysowski DK, Swartz L. Adverse drug event surveillance and drug withdrawals in the United States, 1969–2002: the importance of reporting suspected reactions. *Arch Intern Med* 2005; **165**(12): 1363–1369.
3. Piazza-Hepp TD, Kennedy DL. Reporting of adverse events to MedWatch. *Am J Health Syst Pharm* 1995; **52**(13): 1436–1439.
4. Brewer T, Colditz GA. Postmarketing surveillance and adverse drug reactions: current perspectives and future needs. *JAMA* 1999; **281**(9): 824–829.
5. Davis RL, Kolczak M, Lewis E, et al. Active surveillance of vaccine safety: a system to detect early signs of adverse events. *Epidemiology* 2005; **16**(3): 336–341.
6. Lieu TA, Kulldorff M, Davis RL, et al. Real-time vaccine safety surveillance for the early detection of adverse events. *Medical Care*. 2007; **45**(10):S89–S95.
7. Platt RAS, Davis RL, Destefano F, et al. Pharmacovigilance in the HMO Research Network. In *Pharmacovigilance*, Ronald D, Mann EBA (eds). New York, Wiley: 2002; 582.
8. Clark JA, Klinecicz SL, Stang PE. Spontaneous adverse event signaling methods: classification and use with healthcare treatment products. *Epidemiol Rev* 2001; **23**(2): 191–210.
9. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol* 2003; **158**(9): 915–920.
10. McMahon AD, Evans JM, McGilchrist MM, McDevitt DG, MacDonald TM. Drug exposure risk windows and unexposed comparator groups for cohort studies in pharmacoepidemiology. *Pharmacoepidemiol Drug Saf* 1998; **7**(4): 275–280.
11. van Staa TP, Abenhaim L, Leufkens H. A study of the effects of exposure misclassification due to the time-window design in pharmacoepidemiologic studies. *J Clin Epidemiol* 1994; **47**(2): 183–189.
12. Spiegelhalter D, Grigg O, Kinsman R, Treasure T. Risk-adjusted sequential probability ratio tests: applications to Bristol, Shipman and adult cardiac surgery. *Int J Qual Health Care* 2003; **15**(1): 7–13.
13. Wald A. Sequential tests of statistical hypotheses. *Ann Math Stat* 1945; **16**: 177–186.
14. Wald A. *Sequential Analysis*. Wiley: New York 1947.
15. Kulldorff M, Davis RL, Kolczak M, Lewis E, Lieu TA, Platt R. *A maximized sequential probability ratio test for drug and vaccine safety surveillance*. Working paper, Department of Ambulatory Care and Prevention. 2007; available at www.dac-p.org/faculty_kulldorff.html
16. Tata LJ, Fortun PJ, Hubbard RB, et al. Does concurrent prescription of selective serotonin reuptake inhibitors and non-steroidal anti-inflammatory drugs substantially increase the risk of upper gastrointestinal bleeding? *Aliment Pharmacol Ther* 2005; **22**(3): 175–181.
17. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. *Stat Med* 2006; **25**(10): 1768–1797.