Validating an Automated Outcomes Surveillance Application Using Data from a Terminated Randomized, Controlled Trial

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Background

FDA medical product recalls in recent years have highlighted limitations present in the current adverse event reporting system. Population level data, such as a mandatory cardiac device registry, allow for substantially different and complementary types of data analysis to current systems. However, prospective monitoring methodologies for these types of data are not well described.

In this study, we evaluated the performance of SPC and BUS methodologies to detect elevated event rates in a randomized, controlled trial that was terminated by a DSMB given elevated adverse event rates in the intervention arm.

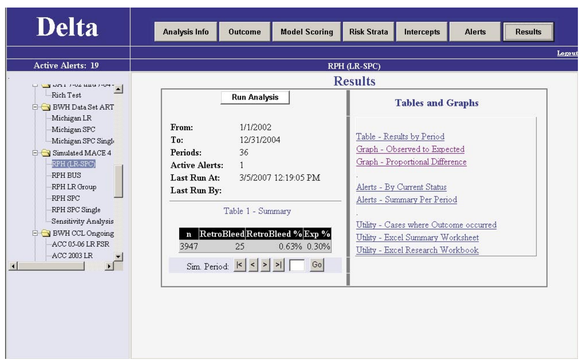

Figure 1: DELTA Results Screen Providing an Example of Layout and LR-SPC Summary Options

Methods

A Time in Myocardial Infarction (TIMI) trial evaluated whether an oral glycoprotein IIb/IIIa inhibitor would reduce the recurrence of cardiovascular events among patients with acute coronary syndromes after standard medical therapy.[1] A total of 10,288 patients were recruited into a control arm and two intervention arms (different dosing but otherwise identical to 30 days). The trial was stopped early by the DSMB for an increase in the 30 day mortality noted in one of the intervention arms.

The intervention arm in which the DSMB stopped the trial for was evaluated in DELTA using the control arm as the baseline or comparison event rate. Such a comparison can be considered unbiased because of the randomized, controlled trial design and provides an excellent basis for alerting for different rates between SPC and BUS.

SPC, LR-SPC (logistic regression risk-adjusted SPC) and BUS methodologies in DELTA are described in detail elsewhere.[2] These methods were evaluated in a monthly simulated prospective manner using 95% confidence interval thresholds and compared to the Fisher's exact test method.

Figure 2: Cumulative Event Rates & Alerting Boundaries for Statistical Process Control (SPC) Method

Results

The DSMB Fisher's exact analysis revealed significant elevations in the intervention arm from months 7 to 14, when the trial was terminated. SPC, shown in Figure 1, alerted in the same manner (7 to 14), and LR-SPC alerted from month 8 to 14. BUS did not alert in any month.

1 Cannon CP, McCabe CH, Wilcox RG, et al. Oral glycoprotein IIb/IIIa inhibition with orbofiban in patients with unstable coronary syndromes (OPUS-TIMI 16) trial. Circulation. Jul 11 2000;102(2):149-156.
2 Matheny ME, Ohno-Machado L, Resnic FS. Monitoring device safety in interventional cardiology. J Am Med Inform Assoc. Mar-Apr 2006;13(2):180-187.

Discussion

This preliminary evaluation showed that the SPC and LR-SPC performed acceptably well in comparison to standard trial monitoring methodology, but BUS did not fire during the evaluation. The increased specificity and decreased sensitivity apparent using BUS may not be desirable for monitoring experimental therapies. The optimal methods to monitor adverse events may vary by setting and require further study.