Validating an Automated Outcomes Surveillance Application Using Data from a Terminated Randomized, Controlled Trial (OPUS [TIMI-16])
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Abstract
We sought to validate an automated outcomes surveillance system (DELTA) using OPUS (TIMI-16), a multi-center randomized, controlled trial that was stopped early due to elevated mortality in one of the two intervention arms. Methodologies that were incorporated into the application (Statistical Process Control [SPC] and Bayesian Updating Statistics [BUS]) were compared with standard Data Safety Monitoring Board (DSMB) protocols.

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.

Methods
OPUS 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. 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 (described elsewhere) in DELTA were evaluated in a monthly simulated prospective manner using 95% confidence interval thresholds and compared to the Fisher’s exact test 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.

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.