Report

Signal detection of spontaneous medical device reports over time accounting for multiple comparisons

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Table of contents

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# 1. Abstract

Objective

Materials and Methods

Results

Discussion

Conclusion

# 2. Introduction

Adverse events from implantable medical devices are commonly reported to regulatory bodies in the form of unstructured free-text in spontaneous reports. Detecting safety signals from the reports for post-market surveillance can be challenging. Spontaneous reports of adverse events may be submitted by manufacturers, clinicians and consumers to the Database of Adverse Event Notifications (DAEN), maintained by the Australian Therapeutic Goods Administration (TGA) in the form of unstructured free text. Pelvic (urogynaecological) mesh was used to treat women for pelvic organ prolapse and stress urinary incontinence. While the device provided benefits to some women, others experienced serious complications.

The pelvic mesh was removed from market in …

There is still ongoing heath, financial and legal fallout from the device’s use [Dec 22](https://www.abc.net.au/news/2022-12-04/mesh-implant-class-action-shine-lawyers-payout-dispute/101728850)

[talk about standard signal detection in structure databases]

[has there been any NLP of free-text in adverse events/safety monitoring?]

The aim of this study was to develop an in-principle, end-to-end pipeline to complement traditional signal detection of disproportionately higher reporting rates of adverse events, using a historical true-positive pelvic mesh, to utilise information currently not used to screen for medical device safety issues to:

1. classify the DAEN reports into topics, based on the free-text descriptions of the adverse events, using natural language processing (NLP)
2. implement best-in-class, repeated looks over time signal detection algorithms on NLP process data
3. report time to signal findings for the true-positive pelvic mesh safety for generalisation and feasibility
4. compare the screening detection timings to more widespread concerns

# 3. Methods

The DAEN was searched for reports on pelvic and hernia mesh from 2012-2017. Topic modelling, a Natural Language Processing technique, was used to profile the unstructured text into mixtures of clinically relevant topics. A report was considered to contain a particular topic if the probability it contains words relating to the topic, P(topic = | document), was over a certain threshold, which was varied in the analysis.

Disproportionality analysis was used to detect potential signals from the most frequent clinical topic from pelvic mesh, with hernia mesh and other devices used as comparators. Measures are based on a contingency table for the number of adverse events with and without the most frequent topic in the device of interest and the comparator. Testing was performed on the DAEN at quarterly intervals, if new data were accumulated in the interval, over the study period, commencing in 2012.

## 3.1 Data aquisition

The data is thanks to [curtis-murray](https://github.com/curtis-murray) at his [MedicalDevicesNLP](https://github.com/curtis-murray/MedicalDevicesNLP) repo

* Natural language processing of the TGA spontaneous reports of medical device database (DAEN)
* Each record has an estimate of P(topic == "pain" | Level, Doc) using hierarchical stochastic block modelling (hSBM)
* P(topic == "pain" | Level, Doc) estimates for each record are roughly interpreted as the proportion of the NLP analysed free text that is considered as using/describing words related to pain

And example record and processing values (description limited to 150 characters):

| ReportID | Report date | Class | Device | P(‘pain’|doc) | ARTG no. | Event | Source | Event type | Description |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 37537 | 2015-02-06 | other\_device | Class IIa | 0.029 | 137859 | Injury | Industry | Mechanical | Patient admitted for routine SFA angioplasty. The physician had completed the procedure without incident and had withdrawn the balloon catheter fro… |
| 36797 | 2015-08-27 | other\_mesh | Class III | 0.020 | 219240 | Injury | Industry | Material | 3 weeks post-op, patient contacted the surgeon saying that the wound was opening, and she could see the implant. The patient sent photos, and there… |
| 40917 | 2016-04-24 | pelvic\_mesh | Class IIb | 0.538 | 92718 | Injury | Consumer | Other | Have had pelvic pain, pain with sex incontinence with bowel and bladder, cannot sit, walk, stand on feet for extended time. |
| 45432 | 2017-03-29 | hernia\_mesh | Class IIb | 0.214 | 98833 | Injury | Consumer | Other | Atrium mesh implanted in my abdomen. Severe right sided abdominal pain ongoing. Also had further surgery to repair hernia due to reoccurrence of he… |
| 44402 | 2017-12-01 | other\_device | Class III | 0.000 | 149128 | No Injury | Other | Other | Sponsor distributed a Customer Letter dated 20th December 2016 announcing the immediate discontinuation of their CE-marked Umbilical Vessel Cathete… |
| 45624 | 2017-12-04 | other\_device | Class 1 | 0.000 | 121950 | No Injury | Health Professional | Mechanical | Operating table started tilting patient on its own during procedure. Emergency stop button pressed - table stopped briefly and began to tilt patien… |
| 45265 | 2017-12-18 | other\_device | Class IIb | 0.250 | 177101 | Injury | Industry | Other | Pain, possible rupture and swelling around prosthesis. |

## 3.2 Analysis data

Signal detection of disproportionate adverse events (AEs) will often have tabulated count data accumulated over time. The data at time point can be summarised as below:

|  | AE(s) | AE(s) |
| --- | --- | --- |
| Target exposure |  |  |
| Comparator exposure |  |  |

where

* AE(s) is the set of AEs (or singular AE) of interest,
* AE(s) is the complementary set to the AEs of interest,
* *Target exposure* is the medical device(s) of interest,
* *Comparator exposure* is the medical devices to which the *Target exposure* is being compared, and
* , , and (all ) are the respective counts of AEs recorded up until (i.e., cumulative) time .

In the motivating example of the pelvic mesh device, the contingency table can be written more specifically as

|  | Pain AEs | Not pain AEs |
| --- | --- | --- |
| Pelvic mesh |  |  |
| Comparator exposure |  |  |

where

* *AEs pain* is the count of AEs that contain “pain” themes greater or equal to some pre-specified threshold as estimated by the hSBM (that is, ), and
* *Comparator exposure* can be any relevant set of medical devices to compare the pelvic mesh to (e.g., hernia mesh or all other mesh devices or all other devices).

## 3.3 Signal detection over time

We will consider the three signal detection statistics below:

* Proportional reporting ratio (PRR),
* Bayesian Confidence Propagation Neural Network Information Component (BCPNN IC with MCMC CIs), and
* the maxSPRT statistic

As signal detection is being undertaken repeatedly as data are being accumulated, alpha spending needs to be considered. The below table classifies the aforementioned signal detection methods by their null hypothesis as well as whether they control for the family-wise error rate (FWER)

| Null hypothesis | non-FWER version | FWER version |
| --- | --- | --- |
| Ratio of pain AEs to all AEs in target and comparator groups has a ratio of 1 | PRR | binary, group sequential maxSPRT |
| Independence of pain AEs and target group (based on marginal counts) | IC | IC with -spending scheme |

We will demonstrate how the group sequential binary maxSPRT, as described in previous work, is equivalent to a FWER-controlled PRR method of signal detection.

Methods used included the Bayesian Confidence Propagation Neural Network (BCPNN) and the maximised Sequential Probability Ratio Test (maxSPRT) which accounted for multiple testing through alpha spending. The BCPNN was used with and without adjusting for multiple testing. The test statistic for BCPNN is the information criterion (IC) which represents the log2 of the ratio of observed to expected adverse events (0 under the null hypothesis of no association between the topic and pelvic mesh).

maxSPRT was developed for near continuous sequential monitoring (called “group sequential” when monitored at discrete time points or after set accumulatios of events), maintaining the correct overall alpha level. The test statistic is based on the maximized (log-)likelihood ratio statistic which uses the observed and expected (under the null hypothesis) reporting ratio assuming binomial adverse event accumulation. The critical value of the likelihood ratio statistic is determined by the 100(1-α)% quantile of possible likelihood ratio statistics from binomial adverse event counts under the null hypothesis over the entire group sequential follow-up.

### 3.3.1 Proportional reporting ratio (PRR)

The PRR estimate is calculated

In the context of signal detection, an elevated proportional reporting ratio is of concern. Therefore the one-sided hypothesis test (proportional reporting of the target is less than the comparator) is used and is not rejected until

at the level where is the quantile of the standard normal distribution. The above threshold is equivalent to the lower bound of the approximate % confidence interval for a standard two-sided hypothesis test.

### 3.3.2 Bayesian Confidence Propagation Neural Network (BCPNN) Information Component (IC)

The Information Component (IC) statistic is an estimate of the observed-to-expected ratio of the number of target exposure AEs of interest on the log-scale under independence between the target exposure and AEs of interest based on information theory [(Bate et al., 1998)](https://doi.org/10.1007/s002280050466)

where denotes the marginal probability of an observed count for the target exposure, denotes the marginal probability of an observed count for the AE of interest, and denotes the joint probability.

The BCPNN IC of [Noren et al. (2006)](https://doi.org/10.1002/sim.2473) uses a Bayesian inference based *maximum a posteriori* (m.a.p.) central estimate of the IC,

where , and are the (assumed constant over time) underlying probabilities of the multinomial-distributed observed events , and , respectively ( corresponding to the count also included). The underlying probabilities are modelled using Dirichlet priors resulting in a Dirichlet posterior distribution. The one-sided null hypothesis of the joint probability target exposure and AEs of interest is equal or less than the marginal products () can be rejected when the quantile of the Markov Chain Monte Carlo (MCMC) empirical distribution is greater than 0. Similarly to the rejection rule for the PRR, this threshold corresponds to the lower bound of the % equal-tailed credible region in a two-sided hypothesis test.

### 3.3.3 maxSPRT

[Kulldorff et al. (2011)](https://doi.org/10.1080/07474946.2011.539924) outlined that the relative risk (RR) at a given point-in-time for accumulated binary data (that is, “success”/“failure” events or AE of interest or not) of a target group relative to a comparator has the maximum likelihood estimate of

where

* is the ratio of the total AEs for the comparator to the total AEs for the target,
* is the count of target exposure AEs in ,
* is the count of all AEs in (target and comparator exposure), and
* is therefore the count of comparator exposure AEs in .

In the context of our data, the values , and are the quantities , and , respectively, at time .

Therefore the RR maximum likelihood estimate at time can be re-written

which is the PRR estimate at time as before.

The (maximised) log-likelihood ratio statistic of (equivalently, ) can be determined calculated as

The maxSPRT test is considered significant when is greater than the pre-computed critical value which is the % percentile of the values generated under the null hypothesis for group sequential looks at the data . The CV can either be computed exactly or by MCMC to approximate the LLR distribution when

## 3.4 Analysis choices

* Threshold choose
* How many “looks”
* how to choose alpha spending
* sample size limitations for maxsprt - not an issue now can use MCMC method of EmpiricalCalibration

# 4. Results

Pelvic mesh had the highest proportion of reports including the word “pain”, followed by other and hernia mesh (Figure 1).

|  |
| --- |
| Frequency of pain topic in pelvic, hernia and other mesh and other devices. |

The cumulative number of pain topics in pelvic mesh increased sharply in Q4 2014 compared with the previous quarter. The table shows the cumulative table each quarter up to 2015-Q1 with hernia mesh as the comparator (and pain topic threshold of 0.05).

Cumulative quarterly AE counts of pelvic mesh ( is pain topic count) compared to hernia mesh ( is pain topic count) using a pain topic threshold of 0.05.

| Quarter |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 2013-Q3 | 1 | 4 | 12 | 1 | 10 |
| 2013-Q4 | 2 | 6 | 14 | 1 | 10 |
| 2014-Q1 | 3 | 6 | 14 | 1 | 11 |
| 2014-Q2 | 4 | 7 | 15 | 1 | 14 |
| 2014-Q3 | 5 | 9 | 17 | 3 | 21 |
| 2014-Q4 | 6 | 26 | 19 | 4 | 27 |
| 2015-Q1 | 7 | 27 | 19 | 4 | 28 |
| 2015-Q2 | 8 | 27 | 19 | 4 | 28 |
| 2015-Q3 | 9 | 27 | 20 | 4 | 28 |
| 2015-Q4 | 10 | 27 | 20 | 6 | 28 |
| 2016-Q1 | 11 | 30 | 21 | 6 | 28 |
| 2016-Q2 | 12 | 34 | 21 | 6 | 28 |
| 2016-Q3 | 13 | 34 | 21 | 7 | 33 |
| 2016-Q4 | 14 | 36 | 23 | 7 | 33 |
| 2017-Q1 | 15 | 45 | 23 | 8 | 34 |
| 2017-Q2 | 16 | 58 | 24 | 8 | 37 |
| 2017-Q3 | 17 | 68 | 24 | 8 | 38 |
| 2017-Q4 | 18 | 77 | 25 | 8 | 38 |

Words associated with “pain” comprised the most frequent clinical topic for pelvic mesh Optimal threshold for P(topic = “pain”| document) pain topics in pelvic mesh for earliest detection from maxSPRT and multiple adjusted BCPNN, depending on comparator (Figure 2):

* Hernia mesh < 0.09
* Other mesh 0.06 – 0.08
* All other devices: Unstable for thresholds > 0.06

Combining results, the best threshold is 0.06 Earliest time period when signal was detected with and without adjustment for multiple testing and maxSPRT by year, with hernia mesh as a comparator:

|  |  |
| --- | --- |
| BCPNN | August 2014 |
| BCPNN with adjustment for multiple testing | December 2014 |
| maxSPRT | December 2014 |

|  |
| --- |
| Test statistic values over time. |

|  |
| --- |
| Time when methods reached critical values for signal detection. |

# 5. Conclusion

Urogynaecological mesh was withdrawn from the Australian market in 2018, while our retrospective analysis with a 0.06 threshold detected signals between August – December 2014. We have demonstrated the potential of using topic modelling in spontaneous reports for signal detection in post-market surveillance.

# 6. Session information

format(Sys.time(), '%d %b %Y')

[1] "25 Sep 2023"

sessionInfo()

R version 4.2.2 (2022-10-31 ucrt)  
Platform: x86\_64-w64-mingw32/x64 (64-bit)  
Running under: Windows 10 x64 (build 19045)  
  
Matrix products: default  
  
locale:  
[1] LC\_COLLATE=English\_Australia.utf8 LC\_CTYPE=English\_Australia.utf8   
[3] LC\_MONETARY=English\_Australia.utf8 LC\_NUMERIC=C   
[5] LC\_TIME=English\_Australia.utf8   
  
attached base packages:  
[1] stats graphics grDevices utils datasets methods base   
  
other attached packages:  
 [1] arrow\_11.0.0.2 gsDesign\_3.4.0 knitr\_1.42 ggrepel\_0.9.3   
 [5] ggthemes\_4.2.4 ggplot2\_3.4.1 stringr\_1.5.0 lubridate\_1.9.2  
 [9] forcats\_1.0.0 tidyr\_1.3.0 dplyr\_1.1.2 readr\_2.1.4   
  
loaded via a namespace (and not attached):  
 [1] Rcpp\_1.0.10 pillar\_1.9.0 compiler\_4.2.2 tools\_4.2.2   
 [5] bit\_4.0.5 digest\_0.6.31 jsonlite\_1.8.4 evaluate\_0.20   
 [9] lifecycle\_1.0.3 tibble\_3.2.1 gtable\_0.3.1 timechange\_0.2.0   
[13] pkgconfig\_2.0.3 rlang\_1.1.1 cli\_3.6.0 rstudioapi\_0.14   
[17] yaml\_2.3.7 xfun\_0.37 fastmap\_1.1.1 withr\_2.5.0   
[21] systemfonts\_1.0.4 generics\_0.1.3 vctrs\_0.6.3 hms\_1.1.2   
[25] bit64\_4.0.5 grid\_4.2.2 tidyselect\_1.2.0 glue\_1.6.2   
[29] R6\_2.5.1 textshaping\_0.3.6 fansi\_1.0.4 rmarkdown\_2.20   
[33] farver\_2.1.1 tzdb\_0.3.0 purrr\_1.0.1 magrittr\_2.0.3   
[37] scales\_1.2.1 ellipsis\_0.3.2 htmltools\_0.5.6 assertthat\_0.2.1   
[41] xtable\_1.8-4 colorspace\_2.1-0 ragg\_1.2.5 labeling\_0.4.2   
[45] utf8\_1.2.3 stringi\_1.7.12 munsell\_0.5.0