A. Research Proposal *(7 pages)*

TITLE: Improving the safety of implantable medical devices

AIM: The aim of this research is to apply novel methods to existing data sources to enhance early identification and communication of potential safety issues associated with medical devices, thereby building a more efficient and pro-active post-market surveillance system.

BACKGROUND

Medical devices provide significant health benefits but also have the potential to cause harm. Some recent examples include the withdrawal of ASR metal-on-metal hip replacements due to unacceptably high revision rates (2010), implantable cardiac defibrillator leads that fractured and caused inappropriate shocks (2011), textured breast implants that caused a rare cancer (2019), and transvaginal mesh that caused chronic pain, bleeding and suffering (2019). However, these withdrawals occurred after the products had been on the market for up to 15 years (1-4). One of the reasons for this lag is the paucity, poor quality and in some instances absence of premarket clinical safety studies for implantable medical devices (5). A further significant issue associated with medical device withdrawal, is what can be done for persons who already have the device implanted. For example, reoperating to remove the device is itself associated with significant risks, including the risk of death. Better methods for *early identification and communication of potential safety issues* would contribute significantly to improving patient outcomes and avoiding unnecessary harm. Building a more efficient post-market surveillance system of devices is critical so that action can be taken promptly to control and minimise harm when safety issues emerge.

Building a pro-active post-market surveillance system

An essential part of a post-market surveillance system is the detection and verification of emerging safety signals. The definitions of a signal in this context differ. One, which we adopt, is that a signal is reported information of an adverse event with a potential relationship to a product that deserves further attention (6). Adverse events related to medical devices can produce health effects in the form of clinical signs (e.g. bleeding), symptoms (e.g. pain), conditions (e.g. depression) and health impacts (e.g. device revision or death). We will apply novel methods based on machine learning techniques and Natural Language Processing (NLP) together with methods used in pharmacovigilance to extract and combine information from different types of existing data sources, thus triangulating information from multiple sources, to improve and accelerate detection and verification of safety signals. Furthermore, we will develop innovative interactive visualisation tools to facilitate early and effective communication of potential safety signals to stakeholders.

Detecting emerging safety signals in spontaneous reports data

The Therapeutic Goods Administration (TGA) is responsible for regulating medical devices in Australia. One of the mechanisms by which the TGA currently monitors medical devices is through spontaneous adverse event reports received from manufacturers, consumers, and health professionals. The reported adverse events are made public in the Australian Database of Adverse Event Notifications (DAEN). While the spontaneous reports may provide early warning of potential signals**,** *the reports contain large amounts of unstructured free text which must be manually reviewed to identify and triage the safety issues*. The identification of safety signals from the reports relies heavily on deciphering the content of the unstructured data. This creates particular difficulties for identification of potential adverse events and product relationship as it is possible for the report to focus on the device failures per se (e.g. broken leads, flat battery), the physical consequence of device failure (e.g. haemorrhage), or the symptoms of failure (e.g. pain). This is further complicated by different stakeholders providing different types of reports. As evident in our pilot study of the DAEN data (7), reports made directly by patients differed significantly from manufacturer reports,

with patients tending to focus on symptoms and manufacturers tending to focus on device malfunction. The connection between the event (e.g. pain development) and the device implantation may be distant, creating further difficulties in establishing associations with the adverse events. Further, classic causality assessments that are appropriate to medicines such as rechallenge and temporality, are more difficult to apply or not applicable at all to devices. It is for these reasons that new methods such as machine learning and NLP are required to identify safety signals in spontaneous report data.

Investigating safety signals in health claims data

While spontaneous reports of adverse events such as those in the DAEN can be used to generate hypotheses about potential safety issues, drawbacks include problems with underreporting, lack of exposure time and lack of standardised coding. Health claims data, on the other hand, are suitable for hypothesis testing because they contain patient level comparator data i.e. patients who have not experienced adverse events or been exposed to the device under investigation. Claims data are comprehensive and have been used extensively in the investigation of adverse events associated with use of medicines. Medical devices, however, differ from medicines in several respects: the exposure to the device is continuous; discontinuing is difficult and may be associated with harm; there is often a long latency until adverse effects appear; designs vary between devices of the same class; the device may be assembled from many components, each with different risk profiles; and specific information about the implanted device may not be available. Methods used in pharmacoepidemiology employed for post-market surveillance of medical devices are evolving and it is not known which of the methods can successfully be adapted to post-market surveillance of medical devices (8). The research team has piloted study designs in an administrative claims database demonstrating that it is feasible to use health claims data for this purpose (2, 9-11). Our proposed project will significantly advance critical research in this area.

RESEARCH PLAN

The research objectives are to use novel methods, including NLP, machine learning techniques, and Bayesian and other methods from pharmacovigilance (e.g. disproportionality, sequential probability ratio) to:

1. Detect and classify safety signals in spontaneous report databases;
2. Verify potential safety signals in a health claims database;
3. Extract and combine information from different analytical approaches and data sources to inform the development of an effective post-market surveillance system;
4. Design and develop visualisation tools to communicate emerging safety signals to consumers, regulatory bodies, and other stakeholders.

Case study – synthetic mesh

Synthetic, implantable mesh provides an ideal case study for this project. Implantable mesh has been widely used across multiple body sites including treatment of pelvic organ prolapse, stress urinary incontinence, hernia repair, and breast reconstruction. Side effects often have a long latency, and a major concern is when native tissue grows into the mesh with potential for the mesh to abrade the native tissue. The *safety of synthetic mesh in surgical procedures has become an issue of national and international concern* due to patient and clinician self-report of significant harm, including long term pain, serious clinical events such as bowel obstruction, and significant effects on mental health (4, 12, 13). Despite this, more than 30,000 urogynaecological procedures and 100,000 hernia procedures are performed each year in Australia (14). Further evidence is required to determine its safety, particularly for hernia repair and urinary incontinence. While synthetic mesh will be the class of devices we examine first, other medical devices including cardiac devices and stents will follow.

Detect and classify potential safety issues in spontaneous reports data (objective 1)

Data sources: Two publicly available medical device spontaneous reports databases will be used, one containing reports specific to the Australian market, the other being the largest spontaneous report database in the world. This will ensure that we have sufficient data for machine learning techniques. In both databases it is mandatory for manufacturers to report adverse events that may have led to a death, serious illness or injury, but adverse event reporting is voluntary for consumers and health professionals. The first database is the **Australian Database of Adverse Event Notification (DAEN)**. In 2017, more than 5,300 adverse events were reported, with most from sponsors of medical devices (85%). The remaining reports were from doctors, nurses and allied health professionals (11%), and consumers (4%) (15). Information on reported adverse events is made public in the searchable DAEN and it is updated monthly. The second database is the United States based **Manufacturer and User Facility Device Experience (MAUDE),** which is updated weekly and has over 4 million medical device reports submitted to the Food and Drug Administration (FDA) since 1991 (16). Data from MAUDE from 2005 to 2020 will be downloaded and prepared for analysis by following a previously developed user guide (16) ensuring effective use of the data. The user guide will be adapted to the data (2012-2020) available from DAEN.

Methods: We will screen both spontaneous reports databases for safety signals. By building a labelled dataset of known events from DAEN, we will use supervised machine learning techniques to classify new reports as containing adverse events or not. We will start with explainable machine learning methods such as naïve Bayes classifiers that are well-adapted to text data as a proof-of-concept, and to elucidate potential search terms indicating negative consequences. The use of training and test sets will allow us to compare a range of techniques of differing levels of explainability and to evaluate their performance.

Searching spontaneous reports databases requires the use of relevant search terms. The choice of terms changes success rates considerably (17, 18). Therefore, NLP techniques such as text mining and emotion detection will be used. Emotion detection is an NLP technique encompassing sentiment analysis that uses emotion lexicons (e.g. Linguistic Inquiry and Word Count (LIWC) and National Research Council (NRC)) to characterise and quantify the emotional content of reports, and thereby classify levels of harm into serious or otherwise (10). These features will then be used to improve our supervised machine learning techniques for identifying events in the data.

Techniques such as topic modelling can also be used here, particularly recent methods such as network topic modelling (19) which has shown improvements over traditional methods like latent Dirichlet allocation (LDA) to do feature engineering. We have recently developed methods for streamlined classification and prediction using topic modelling (20) in other contexts which will be deployed to improve predictions by accounting for common groupings of words or topics across documents.

Custom dictionaries tailored to medical reports will also be used to improve the effectiveness of sentiment analysis in health research (21). Since the spontaneous reports are expected to contain negative sentiment, this will be used as a way to remove any bias from the use of dictionary-based words in a medical context. For example, in our study of DAEN reports (7), words such as "patient" and "experienced" were used as a neutral noun and verb, rather than positive adjectives in the standard dictionary. We will investigate techniques such as "word shift" graphs (22) to diagnose and visualise such issues, and then adjust the underlying sentiment dictionaries to account for this lack of context. The "hedonometer" approach of CI Mitchell and colleagues presents a natural framework for this form of dictionary-based

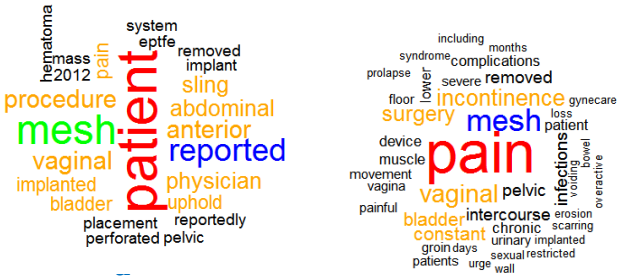

Figure 1 Word clouds from a sample of DAEN reports of gynaecological mesh submitted by (a) device sponsors and (b) health practitioners and consumers.

sentiment analysis, and has previously been adapted for measuring public health characteristics through unstructured social media text data (23). Word shift analysis may also determine the difference in language and sentiment in the reports submitted by device sponsors, health practitioners and consumers. The difference is illustrated in Figure 1 by the world clouds produced from a sample of 36 publicly available DAEN reports 2011-2017.
Following the detection of potential safety signals in the spontaneous reports, the next step will be to improve and automate the extraction of any potential adverse events from the unstructured free text. Such methods are inherently unsupervised in nature and rely on the ability to cluster similar reports based on the text contained within. Recent methods for event detection which we have developed in the context of social media (24) use a novel approach to cluster documents based on both semantic and temporal similarity at once, and are likely to be applicable in this context as well. Indeed, related approaches have been deployed in the health space to detect adverse drug reactions from spontaneous reports (25). By incorporating temporal information into the vector representation of reports we will extract more useful information to detect otherwise undetectable events from the data. Finally, we will investigate word embedding-based approaches (26) to extract correlated groups of words that are associated with adverse events.
In addition to NLP techniques, we will use statistical algorithms for active surveillance as suitable models for medical devices which have recently been reviewed (8). The R software package 'mdsstat' (27) facilitates testing of the MAUDE database using common signal detection methods derived from both quality control (such as cumulative and Shewhart x-bar Control Charts) or pharmacoepidemiology (disproportionality analysis, proportional odds ratios and Bayesian Confidence Propagation Neural Networks). Adapting this software to the DAEN database will be investigated. Chung et al. (8) recommend using disproportionality analysis for active surveillance of medical devices if a suitable 'gold standard' comparator device can be identified and this approach will be investigated as a priority. The identified potential safety issues will be reviewed manually using clinical knowledge and a framework proposed by Clark et al. (6) to assess the potential relationship between the adverse event and the device.

Verify potential signals in a health claims database (objective 2)
Data source: For hypothesis testing of potential safety issues, **the Department of Veterans' Affairs (DVA) health claims database** will be used. The DVA dataset contains comprehensive linked data on all prescription medicines, medical devices, and hospitalisations since 2005 which have been subsidised by the DVA. Full costings of private hospital admissions are available which enables devices to be tracked at the patient and product level. The database has a current treatment population of about 230,000 people with a median age of 82 years and is updated monthly. The DVA dataset is the only dataset available in Australia that includes links between hospital admissions and other data sources such as medical devices, pharmaceuticals, and Medicare services.
Study design: Retrospective cohort studies will be conducted across the period 2005 to 2020 using DVA data. Outcomes investigated will include potential adverse events identified from the spontaneous reports databases, as well as from a literature search and clinical knowledge (28-30). For the case study using synthetic mesh, two study cohorts will be created consisting of patients who had (1) urogynaecological procedures and (2) hernia repair. Billing (the Australian Government's Prosthesis List) and procedure codes (Australian Classification of Health Interventions) will be used to classify the mesh products and the procedure location and type. Whether the procedures involved a mesh product (exposure) will be determined by using unique billing codes for individual devices. Health effects that will be investigated, comparing mesh and non-mesh procedures, include (1) rates and risks of hospitalisations for adverse events, re-operations and death; and (2) use of medicines; e.g. analgesic medicine as a proxy for pain.
Methods: The primary analysis method will be survival analysis of time from first surgery to adverse event, which can account for implantation time which does not change during follow-up.

An active comparator, new user study design, will be explored to reduce confounding by indication (31), with the comparator group being patients who had surgery without the use of mesh. We will investigate the adaption of methods to control for confounders, and emulate randomised controlled trials for causal inference to medical devices, such as propensity score methods, target trials, and doubly robust targeted maximum likelihood estimators (32). Clustering techniques including latent class analysis, Bayesian networks, or trajectory analysis will be used to identify groups with similar characteristics, such as the type of mesh, which may distinguish between those who have experienced harm and those who have not or identify worse performing devices.

Sample size calculation: The DVA database captures an older population. We estimate that there are approximately 150,000 hernia procedures captured in the data, while the number of urogenital procedures is less due to the relatively high age of the women in the data. In a previous study we (11) found that in the DVA database there were N=3129 women who had gynaecological mesh implanted between 1 July 2005 and 31 December 2016. Assuming a control group of the same size, a significance level of 0.05 and power of 0.8, this sample size allows detection of an absolute difference in the proportion of adverse events of 0.071 i.e. an absolute difference in proportions of adverse events between the two groups of 7.1%.

Extract and combine information from different analytical approaches and data sources (objective 3)

Potential safety issues detected in the spontaneous reports data will be verified in the DVA data and vice versa. Results from both approaches will be compared with known safety issues from mesh products withdrawn by the TGA. Since problems with mesh have already been identified and some devices withdrawn from the market, we can calibrate our approach by comparing safety signals identified using our approach with known adverse events. The two approaches will be evaluated with respect to how, when integrated in an iterative process, they can inform the building of a post-market surveillance system for mesh implants (Figure 2). For example, it is anticipated that the spontaneous reports will first be screened for adverse events using NLP. The adverse events will then be analysed using survival analysis in the DVA data. Next, the best performing device identified using cluster analysis in the DVA data could be used as the 'gold standard' comparator in disproportionality analysis in the spontaneous reports. We will investigate how the approach can be applied to other classes of medical devices including cardiac devices and stents. Other sources of spontaneous report data on adverse effect of medical devices will also be considered for suitability to NLP in the evaluation, e.g. Twitter, Google trend and Reddit.

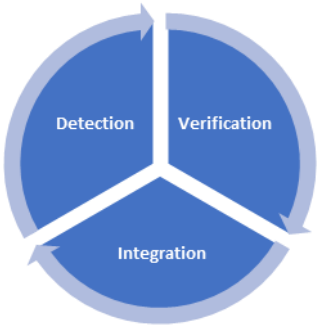

Figure 2 Process for signal identification in a post-market surveillance system

Design and develop visualisation tools (objective 4)

As part of a communication strategy we will develop interactive visualisation tools informed by the outcomes and in consultation with end-users. For example, we will deliver a dashboard of indicators based on analysis of the text of reports and which will be aimed at consumers, clinicians, regulators or manufacturers. Word clouds of frequent words (such as Figure 1) in spontaneous reports are simple communication tools that are accessible to consumers. CI Mitchell and colleagues have recently developed an online dashboard to visualise patients' experiences with COVID-19 through time series of topics and sentiment extracted from social media text data on a daily basis (33) (see Figure 3 below). By comparing trends in topic proportions over time with those for sentiment proportions, they identified two clear clusters of positive and negative emotions associated with the evolution of early and late symptoms, potentially signalling emerging mental health issues related to COVID-19. We will develop this tool further to provide a real-time display of changes in language expressed in spontaneous reports relating to adverse events and medical devices.

Other possible indicators include a time series of spontaneous reports, either in total or classified by the level of harm, submitted for a particular device. Visualisation of results from disproportionality analysis or statistical process control may be useful for regulators and manufacturers. We will develop the dashboard in R, with the aim to release a package such that other researchers may use the tool for their own analysis and visualisations (e.g. using Shiny Applications).

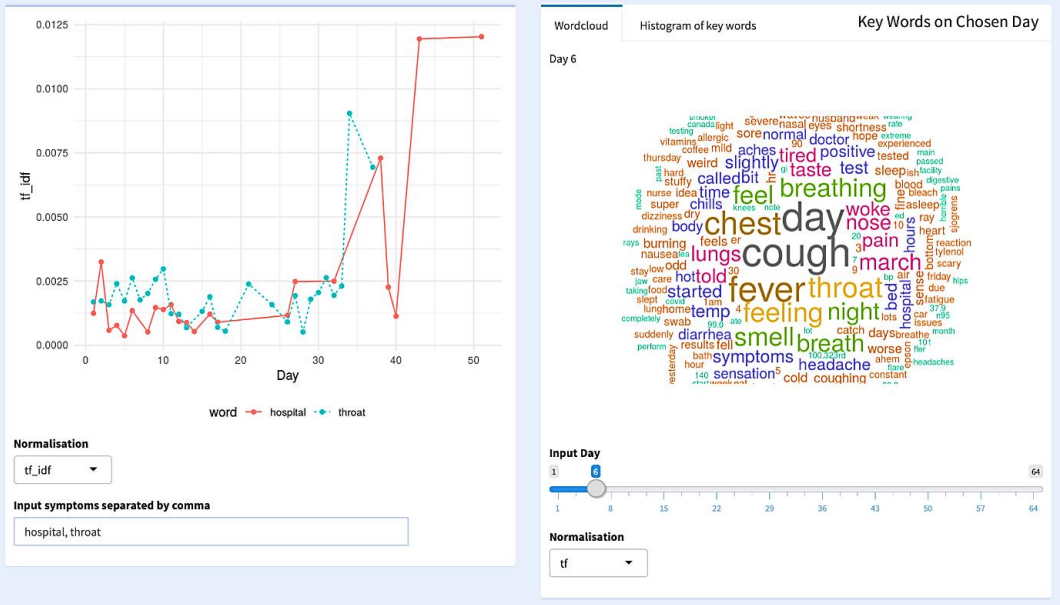

Figure 3 Interactive visualisation of patients' experiences with COVID-19 (33)

Ethical considerations: The study uses de-identified secondary data and is classified as low risk. Ethics approval will be sought from the University of South Australia and the DVA's Human Research Ethics Committees.

Community involvement and/or plans to transfer knowledge to stakeholders or into practice: An advisory committee will be formed to provide advice, mitigate risk, support the project and disseminate findings. Representatives from the Consumers Health Forum, the TGA, the Australian Commission on Safety and Quality in Health Care, The Royal Australian and New Zealand College of Obstetricians and Gynaecologists, the Royal Australasian College of Surgeons, industry and others as appropriate, will be invited to meet bi-yearly. CI Gillam and AIs Roughead and Pratt have an established working relationship with the TGA, the regulatory body in Australia. They have conducted studies on medical devices on request from the TGA (adverse effects in metal-on-metal hip replacements and safety of MRI in patients with pacemakers) and the TGA has been involved in the work of the NHMRC Medicines and Devices Surveillance CRE. Through our well-established contacts, the TGA will be kept informed of the progress throughout the project and consulted where appropriate. The visualisation tools, which will be developed in consultation with end-users, will form a platform for knowledge translation to consumers, regulatory bodies, and other stakeholders.

OUTCOMES AND SIGNIFICANCE

When safety issues with medical devices are not identified early patients suffer unnecessary harm. By applying novel methods to different existing data sources, we will enhance the quality and timeliness of detection and verification of potential safety issues. Our creation of interactive visualisation tools will facilitate early and effective communication of safety issues to stakeholders. The strengths of the study include the reiterative triangulation of information from different data sources and methods and the integration of the team's specialist expertise in mathematics, statistics, pharmacoepidemiology, clinical medicine, medical devices and public health. The approach will build multidisciplinary capacity in medical device surveillance. The research will result in better mechanisms for early identification and communication of potential medical device safety signals, thereby improving patient outcomes and avoiding unnecessary harm.

IDENTIFIED RISKS

Risk	Initial rating	Mitigation	Residual rating
Unable to access data or use data for analyses	High	Use publicly available data (DAEN and MAUDE). The DVA has provided agreement for applications which involve use of their data for medical device surveillance to AI Roughead. Use published guidelines to prepare the MAUDE data and apply these to DAEN. Establish data management plan.	Low
Spontaneous report and DVA data not suitable for identification of safety signals	High	The team has piloted NLP on DAEN data, showing that it is feasible (7). We have extensive experience in use of DVA data for analysing health outcomes. Our previous analysis of the DVA data has demonstrated fit for purpose for medical device adverse events evaluation (2, 9, 10).	Low
Methods not suitable for identification of signals	High	Use a variety of different approaches, so there is flexibility to identify the best performing methods for our purpose. Draw on CIs and AIs extensive and diverse skillset to adapt existing methods.	Low
Issues with development of visualisation tools	Extreme	Use CI Mitchell's extensive expertise with development of similar tools (22, 33). Employ a visualisation tool specialist. Examine use of other sources of data (Twitter, Reddit). Consult advisory committee, ensuring relevance for stakeholders. Establish intellectual property registers.	Medium
Misclassification of adverse events	Moderate	Use CIs clinical expertise to verify classification of identified safety issues and consult with advisory committee. Consult with CIs and AIs wide network of clinical experts.	Low
Lack of computer power	Moderate	This has been mitigated but if more capacity is needed the relevant departments at the University of Adelaide and the University of South Australia will be approached.	Low
Lack of skilled personnel	Moderate	Use existing staff at the QUMPRC with expertise in NLP, machine learning and pharmacoepidemiological methods.	Low
Identification of unanticipated risks	Moderate	Establish a risk management plan, characterising risk identification, source, impact, mitigation, likelihood and consequence for identified risks.	Low

TIMELINE

The project will take place over 3 years. The timing of key activities is outlined below. Year 1 will involve data preparation and adaption of methods, year 2 will focus on conducting analyses, combing approaches and designing visualisation tools. In year 3 findings will be disseminated.

Year	**2021**				**2022**				**2023**			
Quarter	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Ethics approval	▪											
Advisory committee meetings	▪		▪		▪		▪		▪		▪	
Develop study protocol and analysis plan	▪											
Prepare spontaneous report data for analysis		▪	▪									
Analyse spontaneous report data, evaluate findings			▪	▪	▪	▪	▪					
Conduct cohort study, evaluate findings			▪	▪	▪	▪	▪					
Integrate information, evaluate approaches					▪	▪	▪	▪	▪	▪		
Design and develop visualisation tools						▪	▪	▪	▪	▪		
Disseminate findings (conferences, publications)										▪	▪	▪

B. References *(2 pages)*

1. Hauser RG, Maisel WH, Friedman PA, Kallinen LM, Mugglin AS, Kumar K, et al. Longevity of Sprint Fidelis implantable cardioverter-defibrillator leads and risk factors for failure: implications for patient management. Circulation. 2011;123(4):358-63.
2. Gillam MH, Pratt NL, Inacio MC, Roughead EE, Shakib S, Nicholls SJ, et al. Heart failure after conventional metal-on-metal hip replacements. Acta Orthop. 2017;88(1):2-9.
3. Loch-Wilkinson A, Beath KJ, Magnusson MR, Cooter R, Shaw K, French J, et al. Breast Implant-Associated Anaplastic Large Cell Lymphoma in Australia: A Longitudinal Study of Implant and Other Related Risk Factors. Aesthet Surg J. 2019.
4. Welk B, Reid J, Kelly E, Wu YM. Association of Transvaginal Mesh Complications With the Risk of New-Onset Depression or Self-harm in Women With a Midurethral Sling. JAMA surgery. 2019.
5. Zheng SY, Dhruva SS, Redberg RF. Characteristics of Clinical Studies Used for US Food and Drug Administration Approval of High-Risk Medical Device Supplements. Jama. 2017;318(7):619-25.
6. Clark JA, Klincewicz SL, Stang PE. Spontaneous Adverse Event Signaling Methods: Classification and Use with Health Care Treatment Products. Epidemiologic Reviews. 2001;23(2):191-210.
7. Kelly L, Gillam M, Pratt N, Roughead L. Signal detection in spontaneous adverse events reports of medical devices: Commercial in confidence report to the Therapeutic Goods Adminstration. The Quality Use of Medicines and Pharmacy Research Centre; 2018.
8. Chung G, Etter K, Yoo A. Medical device active surveillance of spontaneous reports: A literature review of signal detection methods. Pharmacoepidemiol Drug Saf. 2020;29(4):369-79.
9. Gillam MH, Pratt NL, Inacio MCS, Shakib S, Sanders P, Lau DH, et al. Rehospitalizations for complications and mortality following pacemaker implantation: A retrospective cohort study in an older population. Clin Cardiol. 2018;41(11):1480-6.
10. Gillam MH, Inacio MCS, Pratt NL, Shakib S, Roughead EE. Magnetic Resonance Imaging in People With Cardiac Implantable Electronic Devices: A Population Based Cohort Study. Heart, lung & circulation. 2018;27(6):748-51.
11. Gillam MH, Kerr M, Pratt NL, Lim R, Roughead EE. Mesh use in urogynaecological procedures between 2005 and 2016: An Australian cohort study. Aust N Z J Obstet Gynaecol. 2019;59(1):105-9.
12. Franneby U, Sandblom G, Nordin P, Nyren O, Gunnarsson U. Risk factors for long-term pain after hernia surgery. Ann Surg. 2006;244(2):212-9.
13. Cunningham HB, Weis JJ, Taveras LR, Huerta S. Mesh migration following abdominal hernia repair: a comprehensive review. Hernia. 2019;23(2):235-43.
14. Australian Institute of Health and Welfare (AIHW). Procedures data cubes [Available from: https://www.aihw.gov.au/reports/hospitals/procedures-data-cubes/contents/data-cubes#.
15. Craig A, O'Meley P, Carter P. The Need for Greater Reporting of Medical Device Incidents. EMJ Innov. 2019;3(1):56-63.
16. Ensign LG, Cohen KB. A Primer to the Structure, Content and Linkage of the FDA's Manufacturer and User Facility Device Experience (MAUDE) Files. EGEMS (Wash DC). 2017;5(1):12.
17. Kavanagh KT, Kraman SS, Kavanagh SP. An Analysis of the FDA MAUDE Database and the Search for Cobalt Toxicity in Class 3 Johnson & Johnson/DePuy Metal-on-Metal Hip Implants. J Patient Saf. 2018;14(4):e89-e96.
18. Yao B, Kang H, Wang J, Zhou S, Gong Y. Exploring Health Information Technology Events from FDA MAUDE Database. Stud Health Technol Inform. 2018;250:187-91.

19. Gerlach M, Peixoto TP, Altmann EG. A network approach to topic models. Sci Adv. 2018;4(7):eaaq1360.
20. Glenny V, Tuke J, Bean N, Mitchell L, editors. A framework for streamlined statistical prediction using topic models. Joint SIGHUM Workshop on Computational Linguistics for Cultural Heritage, Social Sciences, Humanities and Literature (LaTeCH-CLfL `19); 2019 2019.
21. Denecke K, Deng Y. Sentiment analysis in medical settings: New opportunities and challenges. Artif Intell Med. 2015;64(1):17-27.
22. Mitchell L, Frank MR, Harris KD, Dodds PS, Danforth CM. The geography of happiness: connecting twitter sentiment and expression, demographics, and objective characteristics of place. PLoS One. 2013;8(5):e64417.
23. Alajajian SE, Williams JR, Reagan AJ, Alajajian SC, Frank MR, Mitchell L, et al. The Lexicocalorimeter: Gauging public health through caloric input and output on social media. PLoS One. 2017;12(2):e0168893.
24. Mathews P, Gray C, Mitchell L, Nguyen GT, Bean Ng. SMERC: Social media event response clustering using textual and temporal information. 2018 IEEE International Conference on Big Data (Big Data). 2018:3695-700.
25. Gattepaille L. Using the WHO database of spontaneous reports to build joint vector representations of drugs and adverse drugs reactions, a promising avenue for pharmacovigilance. 2019 IEEE International Conference on Healthcare Informatics (ICHI). 2019:1-6.
26. Sulieman L, Gilmore D, French C, Cronin RM, Jackson GP, Russell M, et al. Classifying patient portal messages using Convolutional Neural Networks. J Biomed Inform. 2017;74:59-70.
27. Chung G, Xu Z, Bottine S, Ahmed I, Ihrie J. R Package 'mdsstat'. R package version 0.3.0 ed2019.
28. Lockhart K, Dunn D, Teo S, Ng JY, Dhillon M, Teo E, et al. Mesh versus non-mesh for inguinal and femoral hernia repair. Cochrane Database Syst Rev. 2018;9:CD011517.
29. Morling JR, McAllister DA, Agur W, Fischbacher CM, Glazener CM, Guerrero K, et al. Adverse events after first, single, mesh and non-mesh surgical procedures for stress urinary incontinence and pelvic organ prolapse in Scotland, 1997-2016: a population-based cohort study. Lancet. 2017;389(10069):629-40.
30. Kokotovic D, Bisgaard T, Helgstrand F. Long-term Recurrence and Complications Associated With Elective Incisional Hernia Repair. Jama. 2016;316(15):1575-82.
31. Lund JL, Richardson DB, Sturmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. Curr Epidemiol Rep. 2015;2(4):221-8.
32. Lendle SD, Fireman B, van der Laan MJ. Targeted maximum likelihood estimation in safety analysis. J Clin Epidemiol. 2013;66(8 Suppl):S91-8.
33. Murray C, Mitchell L, Tuke J, Mackay M. Symptom extraction from the narratives of personal experiences with COVID-19 on Reddit. arXiv preprint arXiv:200510454 (2020). 2020.
34. Lenzer J, reporters I. Medical device industry: international investigation exposes lax regulation. BMJ. 2018;363:k4997.

C. Innovation and Creativity statement *(1 page)*

This project will be the first in Australia to combine information from an Australian spontaneous report database (DAEN) and a health claims database (DVA data) to enhance early identification and communication of potential safety issues associated with medical devices, thereby building a more efficient and pro-active post-market surveillance system.

We propose a **new application of existing approaches** to post-market surveillance of medical devices both with respect to methods and to the use of existing data sources. The use of NLP and machine learning techniques on DAEN, backed up by concurrent analyses of the MAUDE database, is an **innovative approach to post-market surveillance** that will have a significant impact nationally and internationally on how information embedded in spontaneous reports is extracted and processed. The approach will have a substantial impact through the rapid identification of safety issues associated with mesh and to medical devices in general, providing information that is currently not available and which will **drive the establishment of a more efficient post-market surveillance system for medical devices**. The system has the potential to be expanded by linking other data sources, e.g. registry data and electronic health records as well as data from social media (Twitter, Reddit).

Our proposed approach is novel in that it adapts existing pharmacoepidemiological techniques, including study design and methods, to the study of medical device adverse events and post-market surveillance. The new application of pharmacoepidemiological approaches to medical device surveillance will have a significant impact on how health claims data are analysed for adverse events associated with medical devices.

Machine learning is a rapidly developing field and the techniques we have proposed are new to post-market surveillance of medical devices. In the Natural Language Processing domain, dealing with clinical text is one of the foremost challenges, due to the unique terminologies and ontologies, and non-standard document structures, and domain expertise is required. This project presents an ideal opportunity to make significant advances in this field, through the unique combination of researchers across medicine, statistics, bioinformatics, and Natural Language Processing. We will be **developing a new technology, in the form of interactive visualisation tools based on the spontaneous reports data, which has the potential to enhance communication and transparency of medical device issues** and will likely translate into policy through enhanced regulatory decision making. Furthermore, by enabling online visualisation of safety information the tools have the potential to improve the rate of reporting of adverse events by the public. Currently less than 5% of reports in Australia come from the public.

The DVA data are unique in Australia in that they include detailed information on the medical devices in patient level data linked to hospitalisation and medicines. The data are therefore well suited to evaluate adverse events associated with medical devices, which is currently not possible in any other databases in Australia. However, if the Unique Device Identifier system (UDI) is introduced in Australia information about medical devices received by individual patients will become available in other databases and the findings from our research will provide important firsthand knowledge on how to best utilise this system. Furthermore, because the UDI has been introduced in other countries such as the United States, our findings will have international relevance.

The research has significant potential to **result in changes in current policy and processes** through collaboration with the TGA. The results of this project will be communicated to the TGA and will support the TGA's commitment to continually monitoring the safety and effectiveness of medical devices and to manage any risks associated with specific products. The evidence gained from this research about synthetic mesh, when expanded to other medical devices, would **represent a breakthrough in post-market surveillance of implantable medical devices.**

D. Significance statement *(1 page)*

Our study advances research to improve the safety of medical devices. While post-market surveillance of adverse events associated with medicines is well-developed, post-market surveillance of medical devices is lagging in research and development. This despite widespread and continuing emergence of safety issues causing serious adverse events, injuries and death as reported by the International Investigative Consortium of Journalists (IICJ) who published the Implant Files in 2018 (34). By researching how novel methods can be applied to existing data sources to identify safety issues early, our proposal will address an area of critical importance and inform the national and international efforts to improve post-market surveillance of medical devices.

Our study's outcomes will improve the understanding of adverse event identification in available data sources. With an increase in the amount of health care data, robust methods for extracting and analysing the large amount of information contained in different data sources are of critical importance to health services and public health generally. The knowledge generated from our research on application of novel methods to different data sources will guide practice and have significant implications for this area.
The research promises to produce evidence of adverse events associated with synthetic mesh at a population level. This will impact policy and practice by informing decision making on risk benefit of the use of synthetic mesh for the TGA, health service providers, and clinicians.
By developing expertise in junior researchers in investigating medical device safety in spontaneous reports and health claims data, the research will build capacity in medical device surveillance, a field where there currently is a shortage of expertise in Australia.

Our study will impact on how potential safety issues are communicated. We will develop interactive visualisation tools, such as dashboards, that can be adapted to, and be developed in collaboration with the intended end-users, including consumers, regulators, clinicians, industry and researchers. For example, by interactively visualising sentiments in spontaneous reports data, the dashboard will provide a platform for early detection and monitoring of potential safety issues in the data enabling patients to check on their device, or regulators to initiate further investigations. The visualisation tools will ensure that the knowledge generated from our research will be translated to stakeholders.

Publications. Each element of the research will be published in quality peer reviewed journals to ensure wide national and international dissemination and impact of the findings. We will produce a least 7 journal articles throughout this project:

1. Findings from applying NLP and machine learning techniques to spontaneous reports data to detect and classify potential safety issues associated with synthetic mesh.
2. Evaluation of NLP and machine learning approach to analyse spontaneous reports data.
3. Evaluation of methods and adverse events associated with synthetic mesh in DVA data.
4. Improving post-market surveillance of synthetic mesh by integrating information from spontaneous reports data and health claims data.
5. Review of how to adopt our findings to other medical devices and build a model for signal detection and verification in a post-market surveillance system.
6. Development of visualisation tools to communicate potential safety issues in a timely manner to consumers, regulatory bodies and other stakeholders.
7. Development of a software R package for visualisation tools (Shiny Apps).

Additional outputs: A workshop on how to use machine learning techniques and NLP for medical devices surveillance will be developed, aimed at analysts, regulators, and industry, which will ensure further dissemination, collaboration and capacity building.

E. Capability statement *(1 page)*

With expertise and training in medical device safety and adverse events, biostatistics, applied mathematics, data science, health informatics, pharmacoepidemiology, public health, clinical medicine and research translation, the team has the capabilities and content knowledge to address all aspects of the research and execute the project. **CI Gillam,** a leading expert in medical device epidemiology, has the necessary cross disciplinary capabilities in clinical medicine, biostatistics, and public health to lead the project. She has successfully led several research projects on medical device safety conducted at the NHMRC funded Medicines and Devices Surveillance Centre of Research Excellence (CRE), including projects relating to systemic toxicity with metal hip replacements, adverse events in pacemaker recipients, transvaginal mesh utilization, and safety of MRI scanning in pacemaker patients (2, 9-11). As a member of the Advisory Committee on Medical Devices she has provided expert advice to the TGA and has conducted consultancy work on the safety of medical devices. She has access to an extensive network of national and international experts in clinical medicine, public health, medical device epidemiology and biostatistics who can be consulted where appropriate. **CI Kelly**, a senior statistician, has extensive experience working with linked data and the DVA database, and with a range of methods used in pharmacoepidemiology and medical device surveillance, as well as machine learning techniques. She will provide in-depth knowledge of statistical methods employed in the project and oversee the analysis of the DVA data. **CI Mitchell** will bring to the team considerable expertise in text mining, sentiment analysis, NLP techniques and prediction from textual data. As an expert in the use of machine learning techniques to extract information from unstructured text and to develop visualisation tools, he will ensure that the state-of-the-art techniques are utilised and provide supervision and mentorship in implementation of the techniques. **CI Lim**, with clinical experience in urogynaecological research and devices as well as research translation, will together with **CI Gillam** provide assessment of adverse events associated with use of synthetic mesh and other medical devices, ensuring that the outcomes are relevant for stakeholders. **CI Stanford**, a health informatics expert with experience from medical device industry will oversee the data management of the spontaneous report databases, development of statistical methods and as an expert in use of R will have a role in all aspects of the project.

The CIs will be supported by **AI Roughead** who is an international leader in the field of pharmacoepidemiology and **AI Pratt** who has significant expertise in statistical methods in signal detection in medicine and medical devices. **CIs Gillam, Kelly** and **Lim** and **AIs Roughead** and **Pratt** have worked collaboratively in the Medicines and Devices Surveillance CRE from 2012 to 2018. The research team has worked extensively with the DVA dataset, and access to the DVA data will be sought through **AI Roughead's** established connections with the DVA. The project sits within the Quality Use of Medicines and Pharmacy Research Centre (QURMPC) at the University of South Australia which conducts research with a focus on improving the safety of medicines and medical devices in the Australian community. It has multidisciplinary staff skilled in biostatistics, epidemiology, research translation, pharmacoepidemiology, data linkage and health policy who are available to provide exceptional support throughout the project. Computationally intensive tasks will be performed on the University of Adelaide's Phoenix supercomputer facility that includes 3802 CPU's, 15TB memory, approximately 300TB high performance storage and approximately 700TB research data storage which will be enough for the proposed project. The CIs will be supported by junior post-graduate researchers which will ensure capacity building and successful delivery of the project outcomes. The advisory committee consisting of key stakeholders including consumers, clinicians, industry and the TGA will ensure end-user consultation and involvement in all aspects of the project.

F. Indigenous Research Excellence Criteria (if applicable) *(2 pages)*

N/A

G. Cancer Australia PdCCRS (if applicable) *(1 page)*

N/A