Epidemiology applied to the regulations of medical devices in Australia

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The Australian National University.

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Declaration

I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at ANU or any other educational institution, except where due acknowledgement is made in the thesis. Any contribution made to the research by others is explicitly acknowledged in the thesis. I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation or linguistic expression is acknowledged.

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Acknowledgments

This is the toughest part of writing the thesis as there are so many people to acknowledge. But I'll do my best to not leave anyone out.

To start with, I would like to thank the Australian Government Department of Health and Aged Care and the National Centre for Epidemiology and Population Health at the Australian National University for funding and providing the Master of Philosophy (MPhil) in Applied Epidemiology (MAE) program. It is an inspiring initiative and a source of hope. I would not be at this stage if it wasn't for the encouragement of Adriana Platona to go a step further in my career and Professor Martyn Kirk who was the first person from the program I got in contact with.

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Finally, I would like to dedicate this thesis to my family (including those who are far, far away). First of all, in loving memory of my mother who left this world while I was starting with my MAE projects. Secondly to my closest ones: my children, Isabella and Luca. I hope that you forgive me for the time I had to trade in order to complete my MAE. I'll promise I will make it up to both of you. And, last but not least, to the love of my life: my wife Diana. Tough years, but I am so glad that we went through them together.

Thesis abstract

This thesis presents the results of research projects I completed to meet the competency requirements of the Master of Philosophy (Applied Epidemiology) at the Australian National University. I completed these projects while based at the Therapeutic Goods Administration (TGA) in Canberra, working in the Devices Clinical Section from February 2018 to February 2022.

A major MAE requirement is the response to an acute public health threat (usually an outbreak investigation). In April 2018, I was commissioned to provide clinical advice and aid in the investigation of a cluster of cases of intraocular lens opacification (IOLO) in Australia detected during routine vigilance activities directed by the post-market section of the medical devices branch. I participated in all the aspects of the subsequent investigation, which aimed to identify a causative factor to the outbreak and take consequent regulatory action. For the purpose of the investigation, I decided to implement a novel approach by applying the 10 steps of disease outbreak investigation to a non transmissible event. By the end of the 3-year period analysed, 13 cases of IOLO were reported to the TGA. The adverse event notification rate in Australia (141.3 per million) was 7 times higher than the worldwide figure (17.1 per million). Even though it was not possible to determine the root cause of the events, the initial hypotheses were ruled out: a medical device manufacturing related issue and a different pattern of reporting of adverse events by the Australian ophthalmologic community. As a consequence of the investigation, a change in the instructions for use (IFU) of the affected model of the intraocular lens was put in place to inform the users of the devices about this rare but critical adverse event.

Furthermore, I evaluated the current recall data collection in Australia by the TGA and proposed the implementation of a surveillance system with the aim of monitoring and detecting signals related to different recall actions in Australia. Attributes from the CDC guidelines for evaluating surveillance systems were used to frame the collection and analysis of information from several sources. For instance, I conducted interviews with key stakeholders, reviewed workflows and varied documentation, and used my own experience at giving clinical advice as a Medical Officer during the process of recall actions. Although a single database manages most of the process of a recall action, the main finding of this research was that the current structure in place for managing and capturing the data from a recall by the TGA is complex and includes several different databases and IT systems. After considering the analysis carried out during the project, a new system was proposed to improve the existing rudimentary data analysis and provide a framework to gather evidence which will assist in dealing more efficiently with recalls for medical devices and implement prompt regulatory actions. Key recommendations included the implementation of an analytic tool for data analysis,

improvement of the current online applications and reports by the sponsors of the faulty medical devices and proposing an international standard for recall reporting.

My final core project merged the data analysis and the epidemiological study competency. The aim of this project was to create a predictive model for identifying problematic hip prostheses earlier in their lifecycle. For that purpose, I conducted initially a retrospective data analysis after linking two public health databases: the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) database, which captures revisions as primary outcome, and the internal adverse event database held by the TGA through the Incident Reporting and Investigation Scheme (IRIS). Currently, the AOANJRR identifies outliers in its annual reports which are prostheses with a higher than anticipated rate of revision (HTARR). After linking the data collected by the TGA from 2008 to 2020 specifically for hip prostheses incidents, I tested different variables within the internal dataset in order to predict the hip prostheses which were identified as problematic in the 2018 AOANJRR Annual report. Unfortunately, I was not successful in creating that tool. The inability to precisely predict the outcome at the individual hip product level using adverse event data was probably related to poor quality of the reporting of adverse events and underreporting of the incidents to the TGA. Despite of this, some keywords have the potential to correlate to prostheses with HTAAR and could be useful after improving adverse event reporting to the regulator.

In this thesis, I present my MAE journey, demonstrate my fulfillment of the requirements for the MAE program and the contribution my work has delivered to strengthen the regulation of medical devices in Australia.

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Abbreviations and acronyms

ANU	Australian National University
AOA	Australian Orthopaedic Association
AOANJRR	Australian Orthopaedic Association National Joint Replacement Registry
ARTG	Australian Register of Therapeutic Goods
ASA	American Society of Anaesthesiologists
ASR	Articular Surface Replacement
BIA-ALCL	Breast Implant Associated-Anaplastic Large Cell Lymphoma
BMI	Body Mass Index
CAPA	Corrective And Preventive Action
CDC	Centers for Disease Control and Prevention
CHO	Chief Health Officers
CMO	Chief Medical Officer
DCS	Devices Clinical Section
DIR	Device Incident Report
DMEK	Descemet's Membrane Endothelial Keratoplasty
DSEK	Descemet-Stripping Endothelial Keratoplasty
EMA	European Medicines Agency
ESL	English as a Second Language
FDA	Food and Drug Administration
GMDN	Global Medical Device Nomenclature
HHE	Health Hazard Evaluation
HTARR	Higher Than Anticipated Rate of Revision
ICD	Implantable Cardioverter Defibrillator
IFU	Instructions For Use

IMDRF	International Medical Device Regulators Forum
IOL	Intraocular Lens
IOLO	Intraocular Lens Opacification
IQR	Interquartile range
IRIS	Incident Reporting and Investigation Scheme
MAE	Master of Philosophy (MPhil) in Applied Epidemiology
MHRA	Medicines and Healthcare Products Regulatory Agency
MQB	Manufacturing Quality Branch
MRI	Magnetic Resonance Imaging
NCEPH	National Centre for Epidemiology and Population Health
NPV	Negative Predictive Value
PHAA	Public Health Association Australia
PIL	Patient Information Leaflet
PMMA	Polymethyl methacrylate
PPV	Positive Predictive Value
PRO	Patient-Reported Outcome
PROM	Patient-Reported Outcome Measure
PSAB	Pharmacovigilance and Special Access Branch
QMS	Quality Management System
RAMP	Recalls and Medicine Problems
RANZCO	Royal Australian and New Zealand College of Ophthalmologists
SARA	System for Australian Recall Actions
SOP	Standard Operating Procedures
TGA	Therapeutics Goods Administration

THR	Total Hip Replacement
UDI	Unique Device Identification
URPTG	Uniform Recalls Procedures for Therapeutic Goods
WHO	World Health Organization
WI	Work Instruction

Chapter One: Field placement overview and MAE competencies

“Cada loco con su tema.”

Saying in Spanish

Literal translation: “Each crazy person with his/her theme.”

Contents

Overview of MAE field placement

Introduction

For my Master of Philosophy in Applied Epidemiology ("MAE") field placement, I was based at the Devices Clinical Section (DCS) of the Therapeutic Goods Administration (TGA), located in Canberra Australia. This was a unique opportunity as before starting the MAE program, I was already working as a Medical Officer within DCS.

In this chapter, I provide a brief outline of my field placement, describe my experiences as being a scholar of the MAE program, and summarise the different projects which were completed to demonstrate a range of competencies relevant to the applied epidemiology field.

Summary of field placement and public health experience

The TGA is part of the Australian Government Department of Health and Aged Care and is responsible for protecting the health and safety of the community by regulating therapeutic goods including prescription medicines, vaccines, sunscreens, vitamins and minerals, medical devices, blood and blood products as per mandate of the *Therapeutic Goods Act 1989*.

TGA's vision is for "better health and wellbeing for all Australians through regulatory excellence". To accomplish that purpose, the TGA safeguards and enhances the health of the Australian community through effective and timely regulation of therapeutic goods and is responsible for regulating the supply, import, export, manufacturing and advertising of therapeutic goods.

DCS is a service provider to internal stakeholders, with our principal service being the provision of clinical assessment and medical advice across all aspects of the devices regulatory program. As being placed specifically in the DCS, the main goal was to develop all my projects dealing with medical devices.

Since I joined the TGA in 2016, I have been being exposed to varied public health experiences with the particularity of approaching them through the prism of regulation of medical devices. I have been very fortunate working across the pre-market assessment of devices and post-market tasks including recalls. During these years at the TGA, I have come across certain activities which could be perceived as similar to some of the competencies of the MAE program such as teaching sessions, presentations at conferences, writing a communication for a lay audience or performing literature searches. Those activities and previous experiences made my path through the MAE more straightforward.

As I was already working for the TGA, no adaptation to the field placement was necessary. Even though contributing to the core functions of the section and business as usual activities was the real

challenge due to the fast pace and amount of work of the section. Availability of time was always the critical point when trying to balance the priorities of my work with the section with the projects of the MAE.

Despite the difficulties, I had the opportunity to apply field epidemiology skills I was acquiring during the course blocks and projects to my day-to-day job.

Background to medical devices regulation in general

Medical devices play a growing role in the care of millions of patients worldwide (1). Devices for diseases ranging from heart failure to diabetes improve patient outcomes and may ease disease management (2, 3). The term "medical device" includes a broad category of products ranging from therapeutic goods with local applications, such as tissue cutting, bandages, or propping open clogged arteries, to highly sophisticated heart valves, ventilators or defibrillators. Because these devices vary widely in type and are highly essential for patients' care, their manufacture, distribution, and sale must be regulated to ensure their quality, safety, and performance. Medical devices are used for the diagnosis, monitoring and treatment of virtually every disease or condition and therefore, have become a necessary and critical component in health-care delivery. There is a vast array of devices in circulation, with estimations around 500 000 medical devices worldwide available to healthcare providers and patients (4). But this is a highly innovative field, being the wide array of medical equipment, gadgets, and complex machinery that are used across clinical settings ranging from small community care clinics to large super-specialty hospitals just evidence of an ever-growing role of medical devices in the delivery of health care. A good example of this growth and novelty is the use of robotics in different high-risk, high-precision surgeries today (5).

In Australia, the medical devices are regulated by the TGA. Before being launched in the Australian market the medical devices must be included in a database called the Australian Register of Therapeutic Goods (ARTG). In Australia, medical devices are classified into following classes; class I, class I- supplied sterile, class I- incorporating a measuring device, class IIa, class IIb and class III. Class I poses a minimum risk whereas class III belongs to the highest risk. There is a distinct classification system for In vitro diagnostic medical devices (IVDs).

A manufacturer has to prove that both the device and manufacturing process used to make the device adhere to the requirement of the therapeutic good legislation under conformity assessment of medical devices. The certificate granted by the regulatory body proving that a manufacturer has been assessed and has the proper system in place to manufacture the device is known as conformity assessment evidence. As part of this process, the manufacturer has to demonstrate compliance with

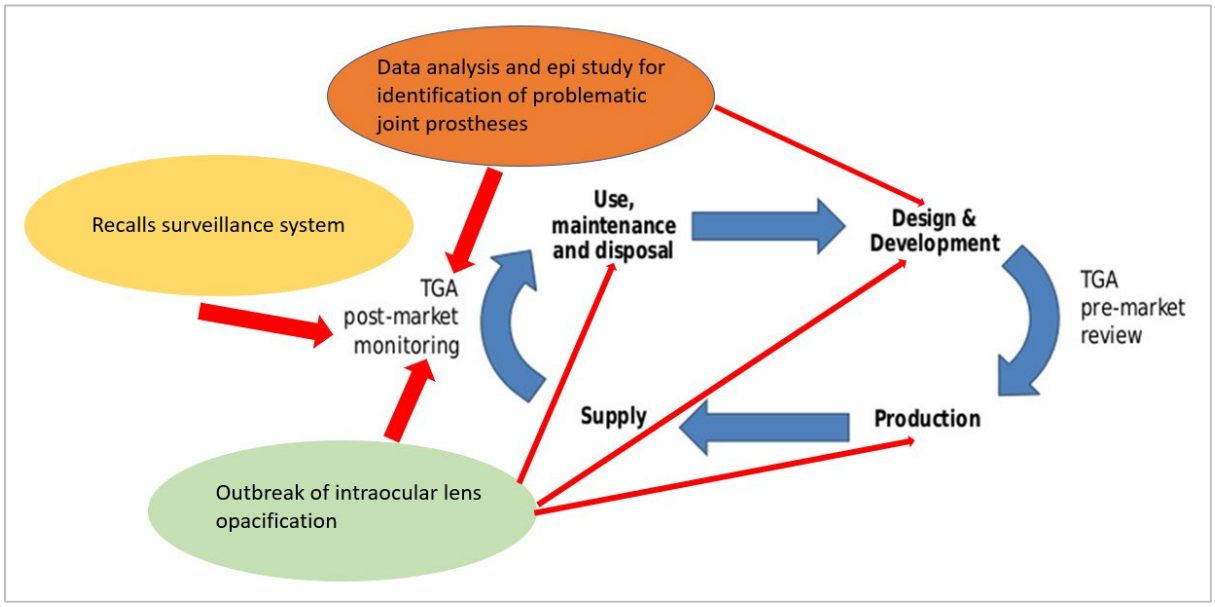
the Essential Principles which are the pillars of the system. After this pre-market approval process, a sponsor will be able to supply the product in Australia. In the Australian market, the sponsor refers to the person who either imports, or arranges the importation of, the goods into Australia or the person who, in Australia, manufactures the goods, or arranges for another person to manufacture the goods, for supply (whether in Australia or elsewhere). In relation to the recall of therapeutic goods, the sponsor also includes the person to whom the goods are on, or cancelled or suspended from the ARTG; or supplying exempt goods; or illegally supplying goods or manufacturing goods.

As part of the life cycle of the device, post-market vigilance and monitoring is also part of TGA's role. This includes different activities such as evaluation of adverse events reporting, review of products currently in the market and overview of recall actions.

Reflections on my MAE journey

Through my core projects and the lessons learnt through the MAE, I acquired a comprehensive overview of how assimilating field epidemiology principles into the TGA is a good idea. When starting to slow down the pace after five hectic, fully packed and intense academic years, it is good to step back and analyse my results in perspective. Regulation of therapeutic goods, and in particular medical devices is extremely complex and full of uncertainties. My specific experience through the program demonstrated the usefulness of field epi at certain points during the life cycle of a medical device (see Figure 1), but the possibilities are endless.

Figure 1. Targets of my projects throughout the life cycle of a medical device



Furthermore, technique and methods, which have been demonstrated to work and resolve problems in field epidemiology, are applicable to different areas of the work that we do a the TGA. The epidemiological knowledge acquired through the program has motivated me more and combined my passion of these two worlds which never should be separated.

The major difficulties and roadblocks encountered during my experience in the MAE program were:

a. COVID-19: even though my master projects were not directly related to the course of the propagation of the virus around the world, priorities at my workplace changed to adapt to the fluid requirements of the pandemic. My contribution to that area has been limited to giving clinical advice regarding devices which could be used to diagnose or treat coronavirus. In the meantime, lockdowns, isolations and quarantines were part of our daily life. Everyone has been impacted and this thesis cannot be the exception.
b. Full time vs Part time: although I initiated as a full-time student, it became evident at about the middle of program that priorities were more related to the day-to-day work in DCS and depending on the priorities I had to place my MAE project in stand-by until the completion of a specific task.

The major recurrent themes I identified during this long and exciting journey were:

a. Collaboration: is key to achieve the objectives of the MAE. Without the support of supervisors, colleagues and a multitude of internal and external stakeholders, it would be impossible to complete the program. The MAE is not an exception to the rule that to achieve your goals you have to accept the help of others.
b. Adaptability and resilience: the MAE program must adapt constantly to changes in circumstances of the environment and have the capacity to recover from the difficulties. If you persevere, you will reach the finish line.

In summary, the program is a tremendous opportunity to acquire specific training in epidemiology combined with practical on-the-job learning and networking possibilities.

Summary of core program requirements

I completed the following requirements for the qualification of Master of Philosophy (Applied Epidemiology).

Competency / **Chapter**	Chapter Two Outbreak	Chapter Three Surveillance	Chapter Four Data analysis & Epi study	Chapter Five Teaching
Investigate an acute public health problem	✓			
Design or evaluate a surveillance system		✓		
Analysis of a public health dataset			✓	
Design and conduct an epidemiological study			✓	
Literature Review	✓	✓	✓	
Conference abstract and presentation	✓		✓	
Peer-reviewed publication (draft)	✓			
Report to a non-scientific audience	✓			
Group teaching & evaluation				✓
Lessons from the field				✓

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Chapter 2: An applied field epidemiology approach to the investigation of opacification of intraocular lenses

Advanced draft of paper for publication

“A otro perro con ese hueso.”

Saying in Spanish

Literal translation: “To another dog with that bone.”

Contents

Preface

Routine cataract surgery is a common procedure with good results for the patient. The surgeon will ideally implant an intraocular lens (IOL) in the capsular bag to correct the refractive error secondary to the removal of the natural lens in the eye (aphakic IOL). A second type, more commonly known as phakic IOL is placed inside the eye without removing the natural lens (1, 2).

There are different ways to classify intraocular lenses according to materials, optics, haptics, designs and refraction index (3). The production and manufacturing of the lenses has evolved with the years and new designs and materials (including acrylic and silicone) are used nowadays (4, 5). Despite of these advancements, adverse events could be related to faults in the device. These faults could have minimal impact if detected before implantation such as mislabelling or cracks in the IOL. Others, although rare, could be significant as can impede the vision such as the case which is the subject of this report: IOL opacification (IOLO) (6-8).

Patient safety is recognised as a global health priority by the World Health Organization (WHO) and is addressed through continuous improvement processes, based on learning from errors and adverse events or complications (9). Patient safety aims to prevent and reduce risks and harm to patients. An adverse event such as IOLO has a critical patient safety impact with devastating consequences on quality of life, such that it constitutes an important public health threat. There are few studies on this specific complication (6).

One of the earliest reports of IOLO dates to 1991 when Milauskas reported brown discoloration and central haze in silicone IOLs (10). It is interesting to note that even though the introduction of foldable acrylic IOLs goes back to the 1980s after improvements in material chemistry, reports on surface precipitates on other lens material such as hydrogel (hydrophilic) IOLs only began to emerge as a problem in the early 2000s (11-13). If the opacification affects an area of the IOL which is not directly in the visual axis of the patient, probably the patient will be asymptomatic. When the opacification affects the visual axis, then the symptoms can be severe though with a dramatic loss of vision. Furthermore, opacification can present during implantation due to improper manipulation of the device, but most of the cases have a delayed onset. Even though the opacification can be resolved by exchanging the IOL, this additional procedure carry its own risks.

This series of cases relates to late onset (several months to years after surgery) of deposits at least partly of calcium and phosphate, also described in the literature as calcification. It is worth noting that calcium and phosphate are present in sufficient quantity within the normal eye for it to drop out of the aqueous humour and attach to the IOL.

My role

In April 2018, I was initially approach by one of the teams of the Devices Post-market and Vigilance Section to provide clinical advice and help in the initial stages of a device incident report investigation. The trigger for this investigation was a cluster of reports of intraocular lens opacification related to a certain brand.

I was given the opportunity to be involved in all the aspects of the investigation and led the response to this outbreak. I ended up conducting the following tasks as part of this project:

- Developed the research proposal;
- Cleaned and analysed the dataset using Microsoft Excel;
- Conducted a literature review;
- Liaised with the supplier of the device to request further information; and
- Proposed regulatory actions.

As part of the dissemination strategies of the findings of this investigation, I prepared this advanced draft of a paper for publication in a national peer-reviewed journal (Clinical and Experimental Ophthalmology, the official journal of the Royal Australian and New Zealand College of Ophthalmologists (RANZCO)). Additionally, I presented two posters: the first one during the 51st Annual Scientific Congress of RANZCO, and the second one at the Communicable Diseases Control Conference organised by the Public Health Association Australia (PHAA), both events took place in November 2019 (Appendices 1 and 2). I was also fortunate to have been invited to present at the celebration of the World Epi Day organised by National Centre for Epidemiology & Population Health Research School of Population Health in September 2021 (Appendix 3).

Lessons learnt

This project was my first encounter with field epidemiology at my placement. Even though it was a great opportunity to start applying the concepts learnt through the course block, it was particularly challenging as it did not evolve as routine infectious outbreaks do: it had a different (slow) pace as the cases presented several months or years after the devices were implanted. Although IOLO can present a few days after lens implantation, the timeframes for the investigation of IOLO have a longer lag period for the usual definition of an acute disease (sudden onset, sharp rise, short course). This fact was a significant challenge during my investigation.

Even though adapting an infectious diseases method to a non-transmissible pathology has been done in the past, adapting it further to the constraints of the regulatory environment was like giving that extra step which could change your investigative path in unexpected ways. It was exploring an unchartered territory (which can actually be really fun!).

I have to admit that matching the steps of an outbreak investigation to the steps of the routine TGA processes was demanding, especially when I had to handle missing or sub-quality data or wait for months to see a change in the pattern of the outbreak due to the frequency of cases and the relatively long lag period for presentation. Another obstacle was the impossibility of applying all the recommended investigative steps as not all of them were easily applicable to this particular scenario. But being resilient and flexible was the key to solve this hurdle. At the end of the project, I had that nice sensation of fulfilment or accomplishment because I was able to follow a clear set of steps (like a lighthouse in the middle of the mist). I learnt that conducting an investigation has to observe certain rules and integrate a systematic process if you want consistent results.

The particular circumstances of this project required adaptation of typical approaches to outbreak investigation. For example, using a standard case-control approach for investigation of the outbreak was ruled out as obtaining appropriate controls would be problematic due to availability of the databases to the investigator. From the regulator perspective, access to patient data, including risk factors and confounders, was not possible.

I had to discover how to best collaborate with the supplier of the product to gather accurate information on time and at regular intervals in order to do an adequate follow-up. Writing formal letters requesting information (with all the legal background attached), sending emails and having phone conversations was an essential part of the learning curve. As a regulator needs to build strong relationships with its stakeholders, this is a crucial skill within my placement and certainly I will be looking to continue using this competence in the near future.

Public health impact

IOLO is one of those “orphan” conditions: it does not get as much attention as other more common complications after IOL implantation. Nevertheless, its consequences can be devastating for the patient if severe and will require a surgical intervention to fix it.

Despite the causal factors for this outbreak were not determined, it was important to rule out faults in the manufacturing processes that could eventually affect specific batches of the product. This was accomplished by reviewing manufacturer’s processes and study results. Another difficulty was dealing with underreporting of adverse events, which makes complicated sometimes to extract solid conclusions.

In investigating a medical device adverse event, a systematic approach is required to better understand an often complex causality. A structured approach is required, beginning with analysis of the device in its clinical context aiming to uncover any possible wider causes (14). Some of the

proposed perspectives consider different elements such as device, clinical team, patient, and infrastructure or focus on methods of failure mode (of the device) analysis developed initially for technical purposes (15, 16). These approaches to classification and analysis are useful for manufacturers and users of the devices and can be seen as complementary to the methods proposed in this project. They do not consider the role of the regulator, however. Those approaches concentrate more on a particular adverse event, coding and investigating its roots, but the information accessed by the regulator could differ in certain aspects and is examined to determine if taking regulatory action is justified.

In this investigation, I applied a novel approach to the routine reviews carried out for medical devices adverse events: a systematic approach based on the Centers for Disease Control and Prevention (CDC) 10 steps of disease outbreak investigation. For me, this path made a huge difference to the course of the investigation and brought "the certainty among the uncertainties". Even though this approach was initially developed for infectious diseases, it has applicability in non-transmissible pathologies. Undertaking a novel approach to handle it by integrating the infectious disease outbreak investigation steps ensures that all the evidence will be gathered systematically and any regulatory action will be based on the best information available. This methodology was proven to be applicable and it can be used in similar medical devices investigations. Furthermore, from the regulator's perspective, it is necessary for medical device investigations to start with adequate planning and provide a systematic but flexible "big picture" overview before applying any hierarchical approach to classify causes. For instance, as part of this adaptative approach, some of the 10 steps were not pertinent, varied in terms of timelines or were not bound to a restrictive order.

Basing the investigation in the 10 steps process provided a framework for this project which allowed adaptation of the steps to fit specific challenges. For example, without impacting adversely in the outcome, timelines for certain actions overlapped with others or specific steps were not fulfilled after considering the availability of information. Another advantage of the proposed methodology is that it relies on the consideration of a wide range of possible causes for adverse event reported, such as operator related, infrastructure, clinical and patient factors. The need to consider different variables directly impacts on a well-informed and evidence-based regulatory action which could affect large parts of the population. In this particular case, two main hypotheses were generated and refined according to the information available, including the descriptive analysis.

The introduction of further information in the Instructions for Use (IFU) is a risk mitigating measure which helps the clinician implanting this type of devices provide an informed consent to the patients with a clearer risk determination.

Considering the current legal requirement of Patient Information Leaflets (PILs) for implantable devices, I took the opportunity to draft a new format of communication for a non-technical audience. This was an identified opportunity to provide more easily accessible messaging about IOLO (Appendix 4).

Acknowledgments

Many thanks to the collaboration of the post-market team which were always there to respond to my queries. Also want to mention the supplier of the product in Australia as they were always approachable and keen to cooperate with the request for information and discuss avenues to mitigate the risks to the Australian patients.

Cover page

i. **Category of the manuscript:** Original Article – Clinical Science

ii. **Title of the paper:** An applied field epidemiology approach to the investigation of opacification of intraocular lenses

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vi. **Short running title:** Opacification of intraocular lenses

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Abstract

Importance and background: Intraocular lens opacification is a rare complication after cataract surgery. However, it constitutes an important adverse event which can significantly reduce the vision of affected patients, necessitating explantation or exchange of the medical device.

Design: We report a novel application of field epidemiology to investigate an "outbreak" of intraocular lens opacification cases that occurred in Australia, detected by the vigilance system of the Therapeutic Goods Administration, between August 2016 and September 2020.

Methods: Descriptive case series which explores the applicability of the standard 10 steps of disease outbreak investigation within the regulatory environment of medical devices.

Results: During a period of 3 years, 13 cases of intraocular lens opacification were reported to the TGA. The adverse event notification rate in Australia (141.3 per million) was 7 times higher than the worldwide figure (17.1 per million). The manufacturer of the device conducted additional investigations in the material and the manufacturing processes. No root cause has been identified to date. No new cases have been identified since September 2020.

Conclusions and relevance: It is important to understand the difficulties and roadblocks in applying the methods to investigate infectious diseases outbreaks to medical devices. There are several limitations in the data available from adverse events reports related to IOLs, but by following a consistent method for investigation, a clearer perspective of the problem can be made, and the likelihood of understanding a medical device "outbreak" directly affecting the ophthalmological community is increased.

Key words

Intraocular lens, Opacification, Investigation, Applied Epidemiology

Introduction

An intraocular lens (IOL) is a lens implanted in the eye to treat large refractive errors (17). The first IOL was implanted by Sir Harold Riley on 29 November 1949 at St Thomas Hospital in London. That first IOL was manufactured from Polymethyl methacrylate (PMMA), that was chosen because Ridley noticed it was inert in eyes of RAF pilots.(18) Uptake of IOLs increased slowly until the 1970s, when new and lighter posterior chamber lenses were designed (4, 5).

IOL opacification (IOLO) is a rare but known adverse event which has been reported multiple times in the literature. According to the time of presentation, the complication may be observed intraoperatively or postoperatively from a few hours after implantation to many years after surgery with opacification of hydrophilic acrylic IOLs in particular usually occurring in the late post-operative period (6, 19-22). Opacification of the IOL may cause reduced visual acuity, decreased contrast sensitivity and glare (23). In clinically significant opacification, IOL explantation is the only option for treatment, but these procedures are associated with a higher complication rate than primary implantation (24).

Although the exact causes and mechanisms leading to opacification are unknown, various pathologic processes may lead to clinically significant IOLO like: formation of deposits on the IOL surface or within its substance; excess influx of water in hydrophobic materials; discoloration by capsular dyes or medications; coating by substances such as silicone oil; or a slow degradation of the IOL biomaterial (6, 11). In most of the cases, late onset opacification, occurring several months to years post-surgery, has been associated with “calcification” – where calcium and phosphate are deposited on the surface or infiltrated into the IOL (25). Calcification has been reported for different types of lenses composed of different materials, including silicone and hydrophobic acrylic lenses, but most cases involve hydrophilic acrylic IOLs (6).

Multiple factors, in isolation or in combination, have been implicated as possible causative associations for IOLO. For example, patient factors such as associated medical conditions, or surgical techniques have been cited in the literature, and there have also been sporadic reports about opacification affecting specific batches of IOLs from individual manufacturers (8, 11, 26, 27). Material impurities and faulty manufacturing or storage as well as interactions with the packaging material have been identified in those cases (7, 11, 12).

The literature describes three types of IOL calcification (25). Type I calcification is related to or caused by the IOL itself and is typically the consequence of a problem in the manufacturing process. The calcium typically permeates into the substance of the lens (26). It is critically important to detect

these cases from the regulatory point of view in order to take appropriate action if the safety and performance of devices are compromised.

Type II calcification relates to history of pre-existing or concurrent eye disease (25). This phenomenon has been investigated in in-vitro studies suggesting a role for the nucleation and crystal growth of calcium phosphates on the IOL surface, but the mechanisms of the calcification process are still not fully understood (11, 28). Amongst the major common factors are: breakdown of the blood-aqueous-barrier and inflammation of the anterior chamber (29).

Type III calcification or pseudo-calcification, where the crystalline deposit does not contain calcium, refers to cases in which misdiagnosis may occur (25). It is not always possible to differentiate between the three types from the clinical presentation, but a laboratory analysis of an explanted device could assist in the differentiation.

IOLs are regulated as medical devices and the Therapeutic Goods Administration (TGA) is Australia's medical devices regulator. Proactively detecting potential signals of possible malfunctions or harms and thoroughly investigating outbreaks is extremely important to regulatory authorities as part of monitoring the life-cycle of any medical device. The ultimate purpose is to disseminate timely public health information and take pertinent regulatory action when appropriate in order to minimise the risks to the patients and avoid adverse public health impact. Following a structured step-by-step protocol enables a comprehensive investigation and facilitates consistent and evidence-based regulatory outcomes.

This publication is centred on analysing an outbreak of IOLO detected in Australia by the TGA through the post-market surveillance system. After receiving three Device Incident Reports (DIRs) of late onset calcification of the same implanted IOL product over a five-month period in 2017, a formal investigation was instigated in early 2018.This study explores the applicability of the standard 10 steps of disease outbreak investigation (Table 1) within the regulatory environment of medical devices (30).

Methods

Descriptive case series from September 2016 to September 2019 (cut-off December 2020).

Model "X" lens is a hydrophilic acrylic "*Lens, intraocular, posterior chamber"* which is intended to be implanted in the lens capsule of the eye during cataract surgery as a replacement for the natural lens.

The 10 steps of outbreak investigation were used to frame this investigation (Table 1) (30).

Table 1. 10 steps for conducting a field investigation applied to IOLO cases

Outbreak Investigation Step	IOLO Investigation Steps
1. Determine the existence of the epidemic	• Identify the Australian incidence of IOLO for product X and compare with incidence internationally. • Coordinate an outbreak investigation team. • Review of scientific literature.
2. Confirm the diagnosis	• Verify reports of IOLO cases (clinical diagnosis was key in this investigation).
3. Define a case and count cases	• Establish probable and confirmed case definitions. • Ascertain as many cases as possible.
4. Orient the data in terms of Time, Place, and Person	• Conduct a descriptive case study. • Obtain preliminary statistics in relation to outbreak characteristics.
5. Determine who is at risk of becoming ill	• Exclude population groups, in which the disease does not occur, helped in focusing only on those affected.
6. Develop a hypothesis that explains the specific exposure that caused disease and test this hypothesis by appropriate statistical methods	• Generate hypotheses about cause and risk factors. • Compare to similar reports available.
7. Confirm the hypothesis with the established facts	• Assess the validity of hypotheses according to investigative findings.

8. Plan a more systematic study	• Not applicable. No additional studies planned (consider the possibility of performing an epidemiologic study).
9. Prepare a written report	• Write reports (including this publication).
10. Execute control and prevention measures	• Formulate and implement recommendations.

Beside the internal information available to the TGA, publicly available databases from international medical devices regulatory agencies were searched. Data were collected and analysed in Microsoft Excel.

The ethical aspects of this project were approved by the Australian National University Human Research Ethics Committee under protocol 2017/909 Request for waiver of consent for use of data in research for Masters in Applied Epidemiology students for 'Outbreak Investigation and 'Surveillance in Public Health' projects.

Results

Determine the existence of the epidemic and confirm the diagnosis

After receiving the 3 initial reports of IOLO related to late onset (several months to years after surgery) involving deposits at least partially of calcium and phosphate on the implanted intraocular lens, an investigation commenced by planning the initial steps involved for allocating the resources and gathering the initial information including a literature review.

An initial communication with the reporter of the adverse events confirmed that the brand and model of IOL (Brand "X") and the implanting operator were the same in all three events. This ophthalmologist implanted 201 of these specific lenses in a period of 3 years. The diagnosis was confirmed clinically at the final report. This evidence was considered in light of previous cases reported to the TGA and cases reported in the literature and triggered an outbreak investigation.

Define a case and count cases

Following confirmation of the clinical diagnosis, probable and confirmed case definitions were created (Box 1) and details of the information provided by the reporter were sent to the sponsor of the product in Australia to gather more information, along with a questionnaire.

Box 1: Probable and Confirmed Case definitions for IOLO

A probable case was an initial report of any type of clinically diagnosed IOLO in Australian patients receiving model "X" intraocular lens with onset from 1 July 2016 to 31 December 2020. A confirmed case met the probable case definition and was confirmed via a final report from the product distributor of the device.

Interrogating TGA's medical device Incident Reporting and Investigation Scheme (IRIS) internal database about the model involved since its introduction to the market, identified 8 more incident reports, bringing the total reports to 11. Those incidents were previously assessed but on an individual basis. The first related incident identified in the database was reported the 16th of September 2016. Clinical advice was formally requested in April 2018 in regard to the cluster of cases related to a specific adverse event (IOLO) reported to the TGA. A new request for updated information was sent to the manufacturer.

After detecting and removing duplicate entries, 8 distinct incidents were finally confirmed. These duplicates were found in the system as the same adverse event can be reported by different sources such as suppliers, health practitioners or patients.

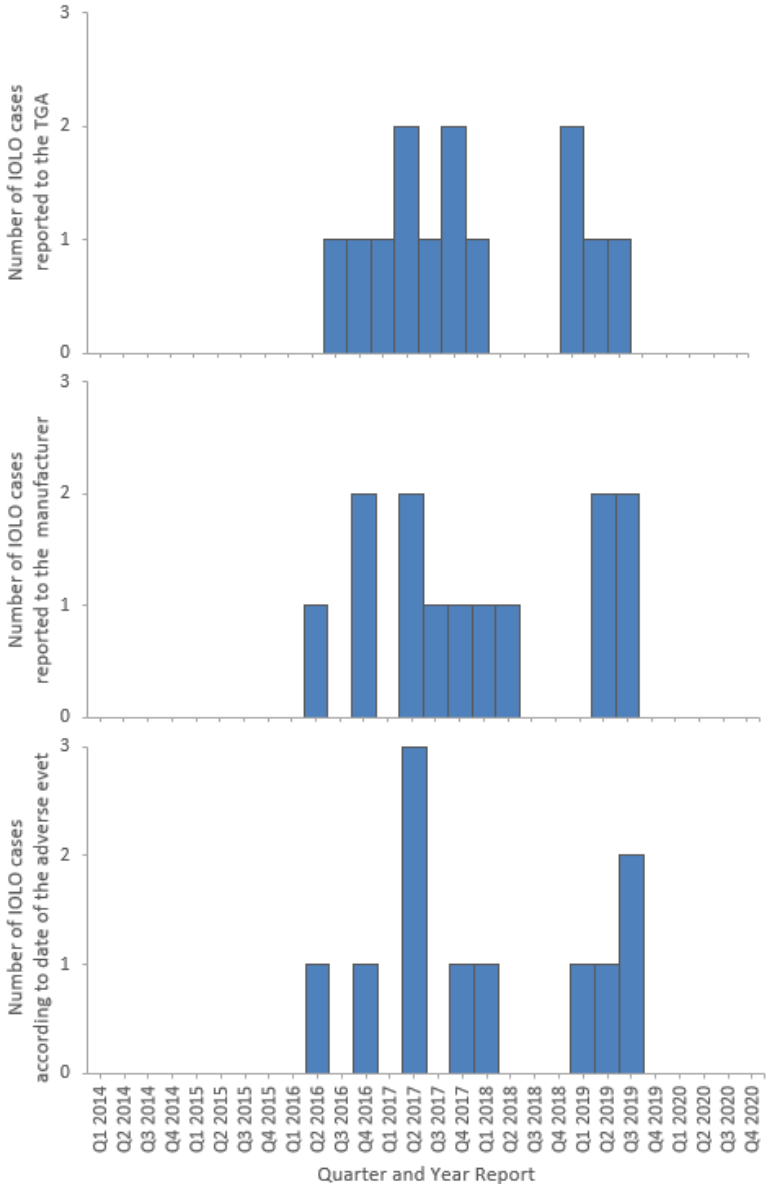
Three out of 8 of the initial incidents in Australia all occurred with one surgeon (Surgeon A). According to the initial data gathered, that ophthalmologist had an incident rate of 1.49% (3 reports for 201 implants). No implantation data were available for other surgeons.

After completing the initial evaluation, new requests for updated information were sent to the manufacturer in August 2019 and May 2021. Five new cases were identified in the IRIS database during the investigation. As a result, a total of 13 cases were associated with this outbreak.

Orient the data in terms of Time, Place, and Person

Cases of IOLO in product X were reported to the TGA during a period of 3 years (Figure 1). From those cases, the date of the adverse event was not available in the report to the TGA in two instances.

Figure 1. Epidemiological curve of Australian cases of IOLO in model X lenses, by year and quarter of report to the regulator; number of IOLO cases reported to the manufacturer; and number of IOLO cases with date of adverse event available to the regulator (Jan 2014-Dec 2020)



Beside the initial delay from when the adverse event is recognised by the health practitioner or patient until the manufacturer is made aware (median delay: 23 days; n=11, IQR 4-34.5 days), there is an additional delay for that information to become available to the regulator. The median delay in reporting the adverse event to the TGA by the manufacturer was 88.6 days (n=10, IQR: 10.5-38.5 days).

Of the patients involved in the confirmed cases, 5 were female and 2 were male (unknown for 6 cases). The median age of the confirmed cases was 66.8 years (n=8, IQR: 61.25-72.8 years). Four cases were reported in New South Wales, 5 in Queensland, 3 in Western Australia and 1 in Victoria).

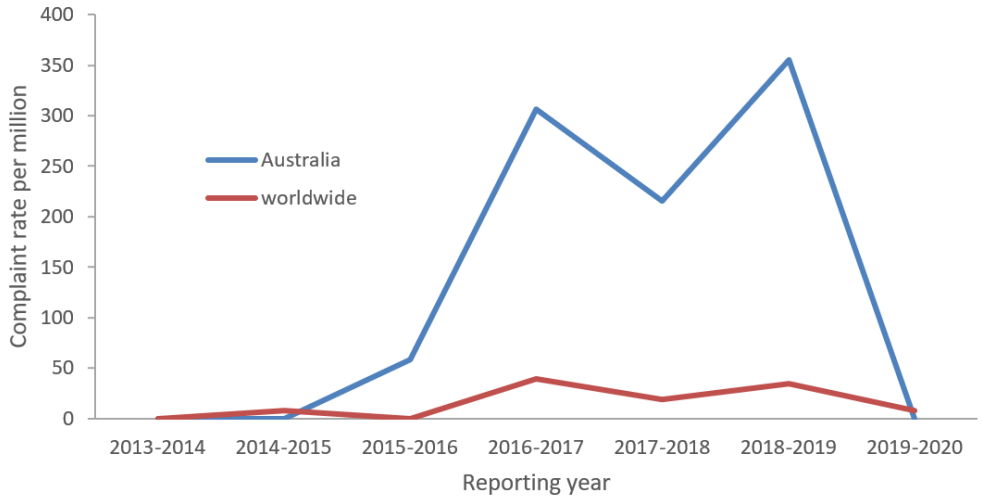
Potential contributing factors were detected for three quarters (77%, 10/13) of the patients. Two patients were diabetic and 8 other patients had relevant associated ophthalmic pathology: four patients experienced retinal detachment; and three patients required a corneal graft, two of them as Descemet-stripping endothelial keratoplasty (DSEK); and 1 case of endothelial drop after phacoemulsification. In 6/8 patients, non-standard techniques were reported including the use of gases or silicone oil.

The median duration from implantation to reporting the incident was 3.4 years (n=9, IQR: 2.90-3.86 years). At the time of the report to the TGA, for 46% (6/13) of the cases the lens had been explanted and all of them were sent for laboratory analysis by the manufacturer, and 1 more was reported as "likely to require removal " at the last follow-up available.

Ten cases (76.9%) were reported by the product distributor. The three remaining cases were reported directly by health professionals. Surgeon A performed 4 implantations, a second surgeon (Surgeon B) performed 3 implantations and the remainder were each performed by different surgeons.

From September 2013, 92,021 Brand X lenses manufactured by Company A were supplied in Australia and 994,415 units were supplied worldwide (excluding Australia) until December 2020. Besides the 13 cases identified in Australia, another cases 17 were identified by the manufacturer in the rest of the world (6 different countries) during that period of time. The total adverse event notification rate in Australia (141.3 per million implantations) during the period analysed (September 2013 to December 2020) was 7 times higher than the worldwide rate (17.1 per million implantations). See Figure 2.

Figure 2. Comparison of IOLO complaints rate per million implantations



Other incident reports related to Brand “X” have been logged into the IRIS system, but no new IOLO cases have been reported since September 2019. No specific environmental studies were developed by the TGA.

Develop a hypothesis that explains the specific exposure that caused disease, test this hypothesis by appropriate statistical methods and confirm the hypothesis with the established facts

Two hypotheses were proposed as possible causes of this cluster of cases: first that there was a medical device related issue (such as a manufacturing process) and second a different pattern of reporting of adverse events by particular individuals within the Australian ophthalmological community compared to global.

The manufacturing company was requested to provide reports and it was confirmed that biocompatibility tests and stability tests were conducted systematically each time changes were introduced in the manufacturing process. Additionally, none of the critical components, described in literature as potential IOLO causes, were identified in the device packaging. The data provided to the TGA confirmed that there were no specific materials or manufacturing lots of which affected IOLs would have been produced.

As a result of the initial steps in the investigation process, the manufacturer initiated an in vitro study in order to understand calcification as part of IOLO. The study tried to reproduce the phenomenon and include a comparison of other lenses with different raw material. Results were reviewed by the TGA but the causation of the calcification phenomenon was not elucidated. Investigations into the material and the manufacturing processes by the manufacturer of the device are still ongoing. The manufacturer also contacted surgeons who have implanted lenses in high volumes to ensure the true rate of reporting is reflective of this kind of incident, but no additional relevant data were obtained.

Laboratory analysis of explanted devices was conducted for 7 cases worldwide. Six of those cases corresponded to Australian explants and in all cases the presence of calcium deposits was verified by Energy-dispersive X-ray spectroscopy. These findings confirmed the clinical diagnosis of either type I or type II calcification, ruling out any possible cases of pseudo-calcification.

Finally, when considering the reporting source and individual surgeons in particular, it was noted that by removing Surgeon A (n=4 incidents) from the rate calculation, the rate in Australia (97.8 per million) was still 4 times higher than the worldwide rate.

Prepare a written report and Execute control and prevention measures

The relevant sections of the TGA were informed about the progress of the investigation while writing this report in order to coordinate the surveillance strategy. In the meantime, and as a consequence of the ongoing investigation and after several information exchanges, the manufacturer updated the Instructions For Use (IFU) of the device to reflect clearly the possibility of calcification on the IOL.

The TGA is actively monitoring for related adverse events and continues vigilance activities to assess subsequent progress on the ongoing investigations by the manufacturer.

Discussion

This investigation confirmed the occurrence of an IOLO outbreak over a period of 3 years in Australia. After reviewing the evidence presented by the manufacturer, no evidence was found that could indicate the possibility of type I calcification within the series. In our series, the quality of the reports is variable and it is hard to draw robust conclusions, but our findings suggest a possible type II calcification in most of the reports. It is of the upmost importance to encourage a complete and detailed report of adverse events by the sources.

Although failures of implantable medical devices are rarely reported, they carry a substantial risk of serious injury (31). Because it is impossible to design an implantable medical device without risk of failure, vigilance for reporting and collection of adverse events in relation to medical devices is a key feature of a robust post-market surveillance system. Even though this system can identify medical device failures and complications, it faces challenges and requires extensive analytic review by the regulatory agency.

Applying the methods to investigate infectious diseases outbreaks to medical devices is a more far-reaching and thorough alternative to passive surveillance and were used in this instance. The methodological approach proposed by the United States of America Centers for Disease Control and Prevention (CDC), Atlanta was chosen during this investigation. A systematic approach, targeted specifically to identify early causative factors and understand how those influence the outcome, is critical to develop effective public health measures. In this particular case, following and adapting the steps to ophthalmic devices mitigated the adverse impact of a complication related to an intraocular lens.

According to the World Health Organization, “a disease outbreak is the occurrence of cases of disease in excess of what would normally be expected in a defined community, geographical area or season” (32). This definition traditionally pertains to infectious diseases, but applying this definition

to a non-communicable conditions such as hypertension or diabetes has been well accepted within the epidemiological community (33-35). In our report, the definition of outbreak was appropriate: an excess of cases of IOLO was observed in a defined community and geographical area and lasted three years. This novel strategy can also apply to other acute onset public health events related to therapeutic goods.

Recognising an outbreak is difficult in the post-market space for medical devices. A signal could be identified for example after a sudden change in the baseline. In this series of IOLO cases, the exact onset of the adverse event was not always available and comparing epidemiological curves of the date of the report to the manufacturer against the date of the report in our internal databases showed different patterns which can lead to different conclusions. Therefore, it is critical to obtain complete and accurate onset data which permit a valid analysis. Any delays in the reporting processes to the manufacturer and to the regulator need to be minimised as well. Besides incidence, the severity of the adverse event, opacification in this particular case, needs to be considered in the analysis as less severe cases could be not reported. Due to underreporting, it is recommended that when a signal is detected, active surveillance needs to be instigated.

Another consideration is that if the information to draw a baseline is not readily available, the investigation will suffer delays. Accurate reporting is essential to create a baseline (ideally with a minimum five years' data) and a threshold. The denominator is not always available; unless a device is new to the market, in which case yearly reports are mandated, these data need to be explicitly requested from the manufacturer. There are opportunities to leverage large, device-specific clinical registries which produce robust data for monitoring medical devices safety (31, 36). In Australia, such registries are in place for high-risk devices such as orthopaedic prostheses and breast implants, but IOLs are not covered by such endeavours. Whilst the creation and maintenance of these detailed clinical registries is challenging and expensive, development of electronic health records will create new opportunities for the future and need to be considered.

Compiling data from the literature is not easy as there is no standardisation of the information reported. Some of the publications do not provide complete information and there are factors to be taken into consideration such as case definition, quality of the studies, severity of the opacification and IOL material. Therefore, the expected rate of this type of complication is difficult to ascertain. Furthermore, these are clinical trials, which follow a study protocol and will have a determined duration within a more controlled environment. On the other hand, post-market data depends on the proactive reporting of adverse events and is variable in terms of reliability according to jurisdictions. Low reporting rates limit the information available to the regulators and hence the

ability to accurately consider the benefit-risk balance associated with a given medical device (36-38). In this investigation, the rate reported in Australia was found to be higher than the worldwide rate. Differences in adverse reporting between jurisdictions are a significant source of bias to consider and highlight the importance of global harmonisation in terms of adverse event reporting. The International Medical Device Regulators Forum (IMDRF) recently proposed a harmonized terminology for reporting adverse events related to medical devices (39). These initiatives will be beneficial when adopted widely across different manufacturers and jurisdictions.

Even though the physio-pathological processes related to IOLO are not completely understood, certain associations have been observed across the literature in cases of type II calcification. Subsequent surgery or procedures is one, for example procedures using gas or silicone oil possibly affecting the lenses, but also certain types of patient comorbidities such as diabetes (6, 40-43). Reports of incidence can be found, but with high variability. For instance, undergoing surgical procedures such as vitreo-retinal surgery or keratoplasty post-IOL-implantation could be considered a risk factor: in the specific case of the latter, the incidence rate varied broadly from 2.5% in Descemet's membrane endothelial keratoplasty (DMEK) cases to almost 10% in DSEK, but it could be up to 18.5% in the sub-population with Fuchs' endothelial dystrophy (6, 44, 45). These associations with complex procedures need to be properly described in the information provided to the users of the devices so that informed consent can be given based on risks. Among the ophthalmic conditions, one of the main reported is glaucoma (6, 12). Unfortunately, details of pre-existing/concurrent conditions are not always available in post-market data.

Another factor affecting development of opacification is the time since implantation: even though the process starts within months after surgery, opacified IOLs may present many years after implantation (11). One of the limitations in post-market reports is that this information was not always available. Online platforms for reporting with compulsory fields may enhance this process. Furthermore, as showed in this series, the adverse event report could come from the company distributing the device in Australia, which is mandatory, and directly from the health practitioner or the patients. Mechanisms should be in place to automatically detect duplicates in the different databases or sources used in the investigation.

Even though the initial 3 reports related to Surgeon A instigated the investigation process, it is the view of the authors that over-reporting is not a factor to consider in our series. On the contrary, expeditious reporting is crucial in detecting possible outbreaks promptly. It is more likely that underreporting of adverse events is impacting the possibility of getting an accurate numerator in the

calculations. Under-reporting has been identified previously as a significant issue across the literature in Australia and in different comparable jurisdictions (31, 36, 38, 46-48).

Due to issues with data quality, it was not possible to dwell further into statistical methods to test the initial hypotheses, so that we have not been able to rule out or confirm either of the hypotheses. It is recommended that adverse event reporting needs to be strengthen by several pathways including more mandatory fields in the online form with targeted specific question according to the type of device, creation of registries and compulsory reporting by health practitioners. Better quality data will enable the possibility of performing robust epidemiological studies which would help us understand the root cause for this particular problem.

This outbreak appears to be settled, but as the mechanism of this adverse event remains unknown and due to the difficulties in calculating incidence accurately, active monitoring of this problem is in place by the TGA. Changes in the IFU could be considered an adequate risk mitigation strategy as they increase the awareness of the issue focusing for example on potential groups that could be at risk, either instigating the use of alternatives by the user or obtaining proper informed consent from the patients as a result. An increasing number of publications are also raising awareness on this issue and warnings in regard to the use of hydrophilic IOLs in patients at increased risk of calcification (11, 49-51).

It is important to understand the difficulties and roadblocks in applying the methods to investigate infectious diseases outbreaks to medical devices. There are several limitations in the data available from adverse events reports related to IOLs, but by following a consistent method for investigation, a clearer perspective of the problem can be made, and the likelihood of understanding a medical device “outbreak” directly affecting the ophthalmological community is increased.

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Appendices

Appendix One: Poster for RANZCO

Australian Government
Department of Health
Therapeutic Goods Administration

Applied field epidemiology in the investigation of adverse events of ophthalmic medical devices

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Australian National University

Introduction

Intraocular lens opacification (IOLO) is a rare complication after cataract surgery[1], occurring months or years post-surgery due to calcification[2]. We report the investigation of an "outbreak" of IOLO in Australia (2016-2019); detected by the Therapeutic Goods Administration (TGA) in early 2018 after 3 cases of IOLO for the same product were reported over 5 months; and conducted employing the steps of disease outbreak investigation[3] within a medical devices regulatory context.

Methods

Descriptive case series. Case Definition: clinically diagnosed IOLO in Australian patients receiving model "X" intraocular lens with onset from 1 July 2016 to 30 June 2019. Cases were confirmed when the final report was sent to the TGA, and probable cases were passively identified with the lodgement of the initial report of any type of opacification. Data were collected and analysed in Microsoft Excel.

Results

Descriptive epidemiology

During a period of less than 2 years, 9 confirmed cases of IOLO were reported to the TGA. One probable case was identified in late June 2019 and is currently under investigation (Figure 1).

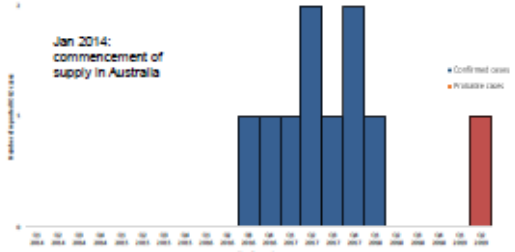

Figure 1. Epidemiological curve of Australian cases of IOLO in model X lenses, by year and quarter of report (Jan 2014-June 2019)

Of the patients involved in the confirmed cases, 5 were female and 2 were male (unknown for 2 cases). The mean age of the confirmed cases was 66 years (n=8, range: 53-82 years). Four cases were reported in NSW, 3 in Queensland and 2 in Western Australia.

Determining the existence of an outbreak

Six confirmed cases (67%) were reported by the product distributor. The three remaining cases were reported directly by health professionals. Three confirmed cases were implanted by the same surgeon, the remainder were all by different surgeons.

The total adverse event notification rate in Australia (111.6 per million) during the period analysed (September 2013 to June 2019) is 5 times higher than the worldwide figure (20.5 per million). See Figure 2.

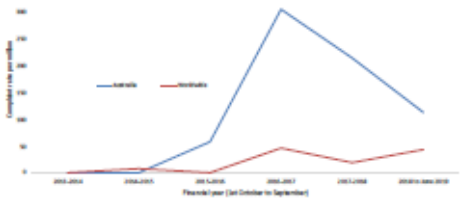

Figure 2. Comparison of IOLO complaint rates per million

Hypothesis 1: Calcification due to operator dependent factors. Removing the surgeon with (n=3) reports from the rate calculation, the rate in Australia (78.1 per million) was still higher than the worldwide rate.

Hypothesis 2: Calcification due to manufacturing fault. Manufacturing processes were reviewed to rule out non-conformities to specifications. The manufacturer of the device also conducted additional investigations in the material, trying to replicate the process of opacification in vitro.

No root cause has been identified to date.

Discussion

These cases are still under investigation by the TGA in collaboration with the manufacturer of the device. Following confirmation of the issue, an update of the Instructions For Use (IFU) has been proposed to include additional information in regards to the calcification effect.

A systematic approach to investigate medical device outbreaks increases the possibility of understanding the causes and of applying corrective actions. However, the sub-optimal quality for adverse events reporting (i.e. missing data, incongruences between different reporting sources, underreporting and lack of registry databases) poses major challenges. A more systematic study is necessary to establish any causal relationships for this particular "outbreak".

The ophthalmological community should be encouraged to report to the TGA any adverse events related to medical devices.

References

1. Tandogan T, Khoramnia R, Choi CY, Scheuerle A, Wenzel M, Hugger P, Auffarth GU. Optical and material analysis of opacified hydrophilic intraocular lenses after explantation: a laboratory study. BMC ophthalmology. 2015 Dec;15(1):170.
2. Trivedi RH, Werner L, Apple DJ, Pandey SK, Izak AM. Post cataract-intraocular lens (IOL) surgery opacification. Eye. 2002 May;16(3):217.
3. Trost SL, Spaulding A. The CDC Field Epidemiology Manual Edited by Sonja A. Rasmussen and Richard A. Goodman. American Journal of Epidemiology. 2019 Mar 29.

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TGA Health Safety Regulation

Appendix Two: Poster for PHAA

Applied field epidemiology in the investigation of adverse events of medical devices

Mario Vittorino[1,2], Ben Polkinghorne[2], Simon Singer[1]

1. Therapeutic Goods Administration (TGA)
2. Australian National University (ANU)

Australian Government
Department of Health
Therapeutic Goods Administration

Australian National University

Introduction

Intraocular lens opacification (IOLO) is a rare complication after cataract surgery[1], occurring months or years post-surgery due to calcification[2]. We report the investigation of an "outbreak" of IOLO in Australia (2016-2019); detected by the Therapeutic Goods Administration (TGA) in early 2018 after 3 cases of IOLO for the same product were reported over 5 months; and conducted employing the steps of disease outbreak investigation[3] within a medical devices regulatory context.

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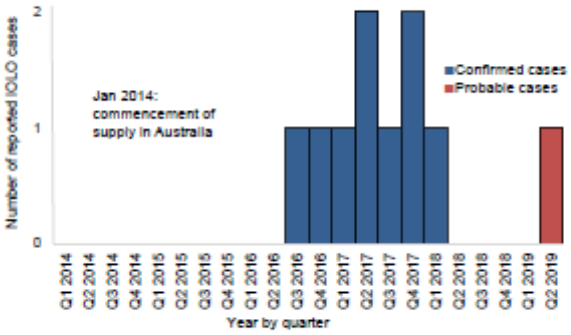

Figure 1. Epidemiological curve of Australian cases of IOLO in model X lenses, by year and quarter of report (Jan 2014- June 2019)

Of the patients involved in the confirmed cases, 5 were female and 2 were male (unknown: 2 cases). The mean age of the confirmed cases was 66 years (n=8, range: 53-82 years). See Figure 2 for the spatial distribution of cases across the country.

Figure 2. Distribution of confirmed cases in Australia (NSW=4, QLD=3 and WA=2)

Determining the existence of an outbreak

Six confirmed cases (67%) were reported by the product distributor. The three remaining cases were reported directly by health professionals. Three confirmed cases were implanted by the same surgeon, the remainder were all by different surgeons.

The total adverse event notification rate in Australia (111.6 per million) during the period analysed (September 2013 to June 2019) is 5 times higher than the worldwide figure (20.5 per million). See Figure 3.

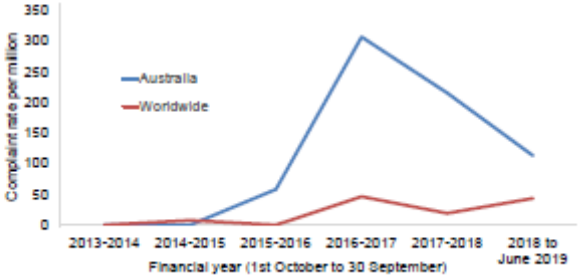

Figure 3. Comparison of IOLO complaint rates per million

Hypothesis 1: Calcification due to operator dependent factors. Removing the surgeon with (n=3) reports from the rate calculation, the rate in Australia (78.1 per million) was still higher than the worldwide rate.

Hypothesis 2: Calcification due to manufacturing fault. Manufacturing processes were reviewed to rule out non-conformities to specifications. The manufacturer of the device also conducted additional investigations in the material, trying to replicate the process of opacification in vitro.

No root cause has been identified to date.

Discussion

These cases are still under investigation by the TGA in collaboration with the manufacturer of the device. From the 10 steps of infectious disease outbreak investigation, number 8 ("Additional environmental studies") has not being performed so far . Following confirmation of the issue, an update of the Instructions For Use (IFU) has been proposed to include additional information in regards to the calcification effect.

A systematic approach to investigate medical device outbreaks increases the possibility of understanding the causes and of applying corrective actions. However, the sub-optimal quality for adverse events reporting (i.e. missing data, incongruences between different reporting sources, underreporting and lack of registry databases) poses major challenges. A more systematic study is necessary to establish any causal relationships for this particular "outbreak".

References

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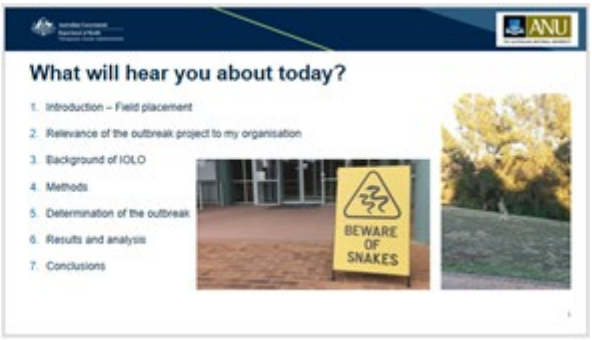
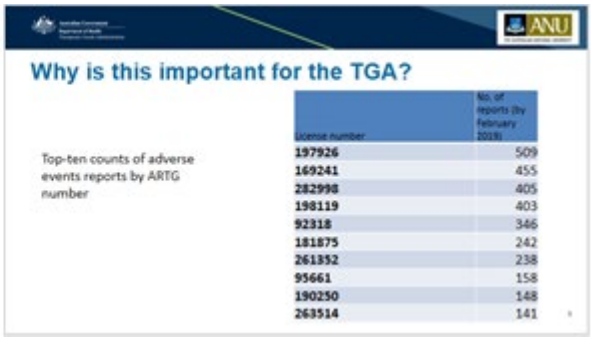
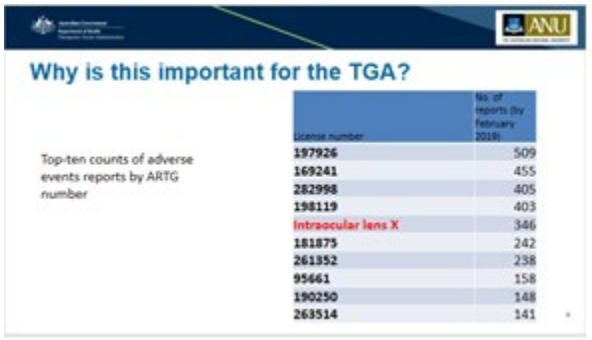
TGA Health Safety Regulation

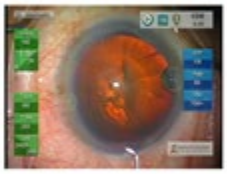
Appendix Three: Conference presentation







Intraocular lenses: bit of background



IOL opacification (IOLO): is this an outbreak?

- April 2018: clinical advice required

Few facts from the literature:

- Rare complication, usually occurring in the late postoperative period
- Exact causes: unknown
- Individual factors, such as ocular inflammation or ocular and systemic comorbidities that affect ocular metabolism, may contribute to the process
- There have been sporadic reports about high incidences of IOL opacification affecting whole batches of IOLs of individual manufacturers irrespective of secondary surgical interventions or comorbidities, so that material impurities and faulty manufacturing or storage as well as interactions with the packaging material have been suggested as causative factors in those cases.

IOLO: is this an outbreak?

- Acute health problem

- How many reports have occurred
  - Duplicates
- New incidents
  - Infoleader
- Incidents awaiting final report

Methods

- Descriptive case series which explores the applicability of the standard 10 steps of disease outbreak investigation within the regulatory environment of medical devices.

IOLO: my challenges

- My cases: ?
- My denominator: ???
- Compare to what?
- Confidentiality issues

Case definitions

A probable case was an initial report of any type of clinically diagnosed IOLO in Australian patients receiving model "X" intraocular lens with onset from 1 July 2016 to 31 December 2020.

A confirmed case met the probable case definition and was confirmed via a final report from the product distributor of the device.

A few facts

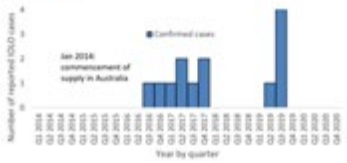
Lens(es) Y (license for 13 years):

- Almost 50 incidents in the last 5 years
- Duplicates (3) -13 cases total for this outbreak
- Mean age: 67 years (n=8, range: 56-82 years)
- Median duration implant-report: 3.4 years
- Mean delay in reporting to TGA: 102 days (n=11, range 10-583!!!)

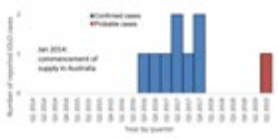
- 2 cases with Hx of DM and 8 relevant ophthalmic conditions (4 RDs, 3 corneal grafts) – 6 cases gas, 3 silicon oil
- Since late 2013 until March 2021, 105 798 lenses have been supplied in Australia and 1 082 428 have been supplied worldwide

Initial signal	Worldwide	0.002%	Australia	0.009% Too many zeroes?
2016-2020		21.4		221.3 (per million)

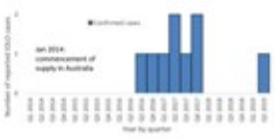
The epi curve



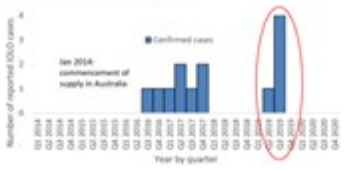
The epi curve (before)



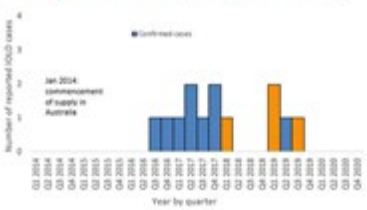
The epi curve (a bit later)



The epi curve (latest)



Epi curve (device company database)



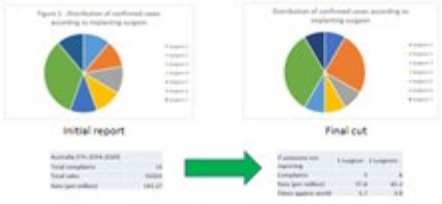
Possible explanations

Are we really a small market?
Just different regulations and rules?

Possible explanations

Who is reporting and why?
How reliable is each one of the reporting sources?

Hypothesis #1: one surgeon "super spreader"?



How do Australia compares to other countries?

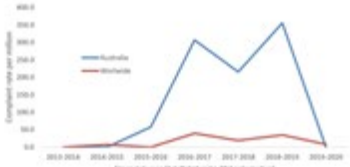


Figure 2: Comparison of IOLD complaints rate per million

Hypothesis #2: the "rogue" manufacturer

- None of the critical components, described in literature as potential opacification causes, were identified in the devices packaging.
- Manufacturing history records were reviewed with no non-conformities or deviations noted that could have contributed to the nature of these complaints.
- No specific materials or manufacturing lots of which affected IOLs would have been produced.
- In vitro study to try to reproduce the phenomenon.
- Laboratory analysis of explanted lenses.

What have we achieved so far?

The new information for use (IFU) was released in Australia (published on our website) on the 17th December 2020.

What about the future?

Conclusions

- Small market theory
- "Over-reporting" vs

- Difficult cases
- Not batch-related
- Limitations in our approach – how can we do better? UPI, better / mandatory reporting, registries?

Acknowledgements

- My supervisors (Ben and my boss at work) and the organizations
- Company Z
- My family (for the patience)

Questions?


Australian Government
Department of Health
Therapeutic Goods Administration
ANU
THE AUSTRALIAN NATIONAL UNIVERSITY

Appendix Four: Patient Information Leaflet

INTRAOCULAR LENS OPACIFICATION

Patient information leaflet

INTRODUCTION

This material will help you understand Intraocular Lens Opacification (IOLO), a rare issue that can occur after cataract surgery, and how it may be treated. IOLO is also sometimes called "calcification".

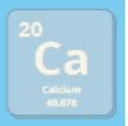
It is important to know that after removal of the cataract, the surgeon implants an artificial lens inside your eye. That lens is expected to remain clear so that it can project a sharp image in your retina, the part in the back of your eye that starts capturing images before sending the information to your brain.

WHAT IS IOLO?

IOLO is the opacification (darkening or blurring) of the lens implanted in the eye, therefore your vision could be negatively affected. If the amount of opacification is significant, then the quality of your vision is impacted and you won't be able to see well or do routine activities relying on the vision of that eye.

WHAT CAUSES IOLO?

It is not completely known what can cause IOLO, but most of the cases of IOLO have in common the buildup of calcified material on the surface of the artificial lens. Calcium is naturally found in the liquid inside your eyes. It is believed that it reacts in rare occasions with substances in the artificial lens, with left over materials from the manufacturing process or even other products used during the cataract surgery. The cause behind the formation of the deposits can differ on each case.



WHO IS MORE AT RISK?

Anyone can develop this condition after being implanted with an artificial lens, but several risk factors have been associated. For example, if you suffer from other chronic diseases (like diabetes) or require any additional surgical techniques in your eye in the future (such as a corneal transplant or a repair of a retinal detachment), there could be a higher risk of developing this issue.

WHEN DOES IOLO OCCUR?

IOLO can develop several months to several years after the cataract surgery.

WHAT WOULD YOU NOTICE IF YOU ARE SUFFERING FROM THIS CONDITION?

The most common symptoms that you can experience are similar to the symptoms you were experiencing before the cataract removal: blurry vision, "fogginess" or simply you could notice that your vision is not as clear as it was after surgery.

HOW IS IOLO DIAGNOSED?

The diagnosis of IOLO is usually clinical, based on the history and examination with the special lamp that the ophthalmologist uses during your follow-up visits. In rare cases, the diagnosis will be made only after laboratory analysis of the lens if the lens has to be removed from your eye.

It is important that your treating ophthalmologist recognises this complication in order to avoid unnecessary additional surgical procedures. Sometimes if the opacification does not affect your vision, regular visits could be the only intervention required (just to confirm that the opacification process is not getting worse).

HOW COMMON IS IOLO?

Over 200.000 artificial lens are implanted every year in Australia after cataract extraction. The chance of suffering IOLO is low: roughly 7 in 1.000 patients (less than 1%) experience calcification.

CAN YOU DO ANYTHING TO PREVENT OR WORSEN IOLO?

Actually no. But it is recommended that you:

- follow the recommendations made by your surgeon
- continue to visit you ophthalmologist for routine eye examination

This will help detect problems at an earlier stage, when they are usually easier to treat.

HOW CAN IOLO BE TREATED?

When cloudy vision begins to affect your daily activities, you may want to have surgery to correct it. The surgeon will need to remove the defective lens from your eye and implant a new one. As with any surgical procedures, the risks associated with exchanging the artificial lens should be discussed with your surgeon.

REPORTING PROBLEMS TO THE THERAPEUTIC GOODS ADMINISTRATION (TGA)

Consumers are encouraged to report problems with medical devices. Your report will contribute to the TGA's monitoring of these products. For more information, see the TGA Incident Reporting and Investigation Scheme (IRIS).

The TGA cannot give advice about an individual's medical condition, but you are strongly encouraged to talk with your ophthalmologist if you are concerned about a possible adverse event associated with the artificial lens.

Chapter 3: Towards a surveillance system for medical devices recall actions in Australia

“El que quiere azul celeste, que le cueste.”

Saying in Spanish

Literal translation: “If you want sky-blue, it'll cost you.”

Contents

Preface

My role

Because of my interest in regulation of Therapeutic Goods and my role in the Devices Clinical Section (DCS), and after considering several potential candidate projects, I identified a need for a surveillance system which was related to recalls of Medical Devices in Australia. Even though I discussed this possibility with the main stakeholders early in my MAE candidacy, the other projects were particularly challenging in terms of obtaining the data and this one was postponed until I had some progress with the others. Nevertheless, I found that starting focused work on this project towards the end of my MAE was advantageous, as I was able to apply the experience gained with the others to make the writing of this one easier.

I took the lead role in this project, guided by my academic and field supervisors. After identifying the topic, I developed the objectives and wrote the evaluation plan, including developing the methods and questionnaires for the interviews.

The interviews involved people from one main stakeholder: the Recalls Unit of the Therapeutics Goods Administration (TGA), but I also had to liaise with other stakeholders within the organization such as the devices post-market area. Being a member of DCS, I was also able to apply my own experience in providing clinical advice to the recall process.

During the writing of my first draft, I sought informal comments from the people I interviewed adding new questions as a result. This was a very interesting exercise as it was a two-way feedback which was well received by the interviewees and fed my thinking approach to the final findings and the recommendations in this report. At the same time, I was able to disseminate the key findings and recommendations back to my stakeholders. Finally, I offered my assistance with the implementation of this project.

Lessons learnt

Completing this project was challenging, particularly as it was the first time that I was involved in a project related to a surveillance system. The recalls database contains essential health-related data with a direct impact on the implementation and evaluation of regulatory practices that affect the Australian community. Ongoing, systematic collection of those data is critical; subsequent analysis and interpretation may lead to significant public health interventions which need monitoring. For example, a recall on a particular device can affect thousands of patients and it is imperative to

determine any interventions, and measure the effects of those interventions, based on data and evidence gathered through an adequate surveillance system.

An initial roadblock was to characterise what parts of the system in place for collecting data about recalls could be useful to implement a surveillance system and which parts were to be established from scratch. Characterising the different IT solutions and programs which are in use by the Recalls Unit was also challenging as the overall structure/function had to be designed. The documented standard operating procedures within the Recalls Unit were not designed with surveillance in mind, so that I could not use them as part of my evaluation, but using evaluation guidelines and other examples helped me in building a framework. It was also useful to apply what I learnt with the other projects in terms of engagement of stakeholders and project management.

The US Centers for Disease Control and Prevention (CDC) Guidelines for Evaluating Public Health Surveillance Systems was an extremely useful guide to structure my assessment. This system, which is based on key attributes, also allowed me to make recommendations on how to follow-up and evaluate the proposed system after implementation.

During the interviews, obtaining the information from experienced people in managing recalls on a daily basis was fundamental to streamline the writing and obtaining accurate information was key to inform my thought process.

Finally, this project was also beneficial for my day-to-day duties as being part of the team providing clinical advice to the Recalls Unit. I had the opportunity to discuss part of our process with them and at the same time understanding their requirements further. I hope that this will also help me improve the communication and quality of the advice focusing on the needs of our stakeholders and increasing consistency for the whole clinical section.

Public health impact

As part of this report, I recommend development of a novel surveillance system for recall actions. Even though I based my description on medical devices and the role played by the clinical section in terms of giving advice, the findings could be extrapolated to other sections of the TGA managing recalls due to similarities in the databases and processes. Furthermore, this new approach by the TGA will increase awareness of issues related to recalls and could be applicable to other regulators worldwide. This is an opportunity to be a leader in this field by increasing consistency and promoting collaboration across jurisdictions.

The implementation of the surveillance system recommended in this report has the potential to detect signals and help in targeting investigations. The current burden of work related to recalls is

significant. Recommendations, which promote modernization of IT solutions, will reduce the current workload by increasing efficiency and processing of recalls and will make data analysis more accessible for the decision making by the delegates increasing the consistency in their decisions and reducing the risks to the organization. My recommendations also suggest ways to analyse collected data for surveillance purposes.

Ultimately, these recommendations aim to help the TGA, as the regulator of therapeutic goods in Australia, meet its core objective of protecting the health and safety of the community by regulating therapeutic goods for safety, efficacy, performance and quality. The implementation of a surveillance system dealing effectively with recall actions in a routine basis has the potential to increase the efficiency of the process of recalls and lead to improvements in public health in Australia and worldwide by the utilisation of recalls data in surveillance.

Acknowledgements

Firstly, I would like to thank all the people that donated their time in interviews, phone calls, messages, emails or informal conversations. I was heavily supported in this work by a number of people in the TGA. Craig Davies and Nathan Coleman in the Recalls Unit make a huge contribution, but the whole team is amazing (Sarah Cropley, Robert Shearan and many more). It is a true pleasure to work with you. Additionally, people in devices post-market team were also really approachable and always available to my queries.

Finally, my gratitude to both my supervisors, Ben Polkinghorne and Simon Singer, for the multiple interactions and guidance along this project.

Abstract

Introduction

TGA, as the regulator which monitors and reviews the safety of therapeutic goods that are marketed in Australia, works with the medical device industry to ensure hazardous products are removed from the market or managed in a proper way to minimise any risks to patients through different recall actions. The existing recall system at the TGA is limited to the collection of data associated with the recall process.

In this project, I aimed to evaluate the current data collection of recall actions in Australia by the TGA and propose the implementation of a surveillance system.

Methodology

Attributes from the CDC guidelines for evaluating surveillance systems were used to frame the collection and analysis of information from several sources. I conducted semi-structured interviews with key stakeholders at different levels within the Recalls Unit and gathered information from sections within the medical devices branches, including my own experience as a clinical adviser in DCS.

Results and Discussion

The current system in place for managing and capturing the data from a recall by the TGA is complex and includes several different databases and IT systems, but a single database manages most of the process of a recall action. This enables a timely and stable collection of the data, but is not currently capturing all the relevant fields necessary to comprise a surveillance system. Additionally, it has limited capability to present results of searches and display information in a user-friendly format.

The absence of a robust analytic tool poses challenges for efficiency and integration of a surveillance system. Better integration between the different components and levels of governance would strengthen the system and increase its efficiency. By developing strong data analysis, it will be possible to make the large amount of routinely collected data useful and accessible for decision makers.

Updating processes in standard operating procedures and work instructions would also improve integration and clarify responsibilities. Finally, establishing and promoting a more effective international information sharing system for medical devices recalls will also have an impact on taking consistent and timely actions by increasing transparency.

Conclusions

The collection of recall data by the TGA is ongoing but it could be enhanced. Introducing an analytic tool is the key step to enable a surveillance system which would improve access to those routinely collected data by those who need to use it for public health decision making. A proper understanding of the recall data will identify emerging risks, assist in prioritising public health actions and allow the monitoring of the impact of any control measures undertaken.

Introduction

The TGA is the Australian regulator responsible for protecting the health and safety of the Australian public by regulating therapeutic goods for safety, efficacy, performance and quality including medical devices. The medical device industry is among the fastest growing industries with a very high level of research and development investment. It is fuelled by the need for superior and innovative devices in meeting the increasing demand for health care (1, 2). An inevitable reality accompanying this rapid innovation, is higher probability of quality failures such as manufacturing defects, functional defects, packaging errors, and software defects. These errors and defects present a potential health risk to the patients and personnel using these devices (2). The average number of device failures and subsequent recalls per year in this device industry is 2 to 8 times that in other industries (2). Conversely, medicines take decades to develop and after regulatory approval, subsequent modifications are not as common. Market perception of recalls is likely to be varied across industries and the tolerable risk linked to the device industry is very low due to the important consequences to the public health (2). It has been recognised for years that the confidence in medical devices reflects trust in the effectiveness and integrity of both the therapeutic goods approval and monitoring process. This confidence in the system is extremely important for our society due to the sensitivities around public health (3).

Robust evidence is necessary to characterise the risk-benefit profile of medical devices. Even though the legal framework is designed to reduce the risks associated with medical devices as far as possible, it is important to note that it will be impossible for premarket assessment and its regulation to capture all the possible issues that could end up harming patients. As stronger premarket regulation will not foresee all device-related incidents because they may not occur or be recognized for several years and also due to limitations in the sample size of clinical trials, the trend in medical device regulation has shifted toward post-market surveillance mechanisms to ensure device safety and performance.

Post-market surveillance can prospectively monitor safety and effectiveness for many patients across multiple sites and jurisdictions without impeding access to innovative devices. Several signals can be identified in the post-market space coming from varied sources such as: adverse events reporting; research publications; post-market studies; or registry data. While it cannot replace the role of high-quality clinical pre-market studies, strengthening post-market surveillance mechanisms is a critical step forward in ensuring device safety and mitigating impact against high-risk recalls (4). Widespread concern about device safety has prompted recurrent editorials in prominent medical journals advocating for enhanced premarket regulation as well as post-market surveillance (5, 6).

The TGA holds a database of the therapeutic goods that can be lawfully supplied in Australia called the Australian Register of Therapeutic Goods (ARTG). After a device enters the market, the manufacturer, sponsor, health practitioner or consumer might report complaints and adverse events as some quality defects emerge. Manufacturers and sponsors of devices are obliged to identify and report problems, but healthcare institutions and users of medical devices are not required to report problems to the TGA.

Post-market active surveillance can identify potential risks and connect device malfunction to adverse events in patients. Those post-market events may trigger recalls or advisories depending on the nature of the device problem that is identified (7). These reports may provide important information about safety and effectiveness, and have led to revision of regulatory practices for devices such as implantable cardioverter-defibrillator (ICD) leads and automated external defibrillators (8-10). Recall actions vary on a case-by-case basis depending on the risk that the identified problem poses to public health and safety. A recall action can occur in response to basic problems, such as errors in labels or packages which have occurred during the manufacturing process to more serious and complex problems, such as an unexpected increase in adverse events detected during post-market surveillance, that could be attributed to a high rate of mechanical failure of the device or microbial contamination, amongst other issues.

Post-market vigilance is definitely a valuable tool in monitoring the devices in the market space, and having different sources of evidence and information strengthens the decision making process for regulators. Timely and efficient recall actions, and a corresponding surveillance system, then play a critical role in that process. Particularly for complications that are rare but of a critical nature, it is extremely necessary to identify signals more rapidly and share efficiently that information about incidents among relevant stakeholders to avoid further events.

Medical device failures and subsequent recalls, impact almost all the key participants of the medical device supply chain. The consequences of a device recall can be easily quantified when assessing outcomes such as procedural delays and financial burden, for instance a hospital having to replace a faulty magnetic resonance imaging (MRI) scanner, but it is more complicated when assessing the damage to patients. As end users, patients tend to be the worst affected by medical device malfunctions, as they deal not only with lost time and costs but also with the severity of the impact of device malfunction ranging from minor inconvenience (e.g. a biased thermometer) to severe, sometimes fatal, injuries or disease (2).

Manufacturing companies and sponsors may be affected by recalls though increasing costs (include the costs of correcting/replacing the defective product, the transaction costs of the recall process, and the costs of unsold inventory) and damages to the overall credibility and reputation of the companies involved which are more likely to face significant disadvantages in the market (2).

TGA works with the medical device industry to ensure hazardous products are removed from the market or dealt in a proper way to minimise any risks to patients. Sponsors of therapeutic goods are encouraged to decide of their own accord, or after recommendation from the TGA, that the recall of a particular product is necessary in order to mitigate an actual or potential deficiency in relation to its safety, quality, performance or efficacy. The sponsor has responsibility for the completion of the agreed corrective action, including recovery and disposal of the goods where applicable. However, if necessary, the TGA can exercise powers under the *Therapeutic Goods Act 1989* to mandate the sponsor to recall therapeutic goods to protect public health (Division 3 - section 30F (2)):

> "The Secretary may, by written notice given to the person, require the person to take steps to recall the goods included in that batch (except any of those goods that cannot be recalled because they have been administered to, or applied in the treatment of, a person)."

As part of its duties, the TGA monitors and reviews related recall actions (Appendix 1) and the sponsors can proactively contact the TGA for advice even before a recall notification is logged. The procedures to be followed when a sponsor of a therapeutic good is required to recall a therapeutic good are set out in the Uniform Recalls Procedures for Therapeutic Goods (URPTG). The URPTG is a non-legislated guideline which provides a consistent approach for undertaking recall and non-recall actions of therapeutic goods supplied, imported into or exported from Australia. It was developed as the result of an agreement between the therapeutic goods industry and Commonwealth and State/Territory health authorities and involves several steps (Appendix 2). The purpose of the URPTG is to assist the sponsors of therapeutic goods to conduct recalls and non-recall actions using a standardised systematic procedure. Furthermore, product recalls can harm the reputation of the regulator for a faulty approval decision, and could often severely affect the manufacturer (3, 11).

A critical point to consider is that to ensure patients' safety in relation to medical devices, providing safety information to the public and relevant stakeholders such as patients, relatives, physicians and Health Technology Assessment bodies is a basic requirement. As a result, different regulatory agencies publish recall actions. Another source of recall information in the public domain, related to an ample range of medical specialties and technology areas, can be found in the literature which demonstrates the broad range of issues and the subsequent interest (4, 8, 12-16). In addition to

that, recalls of medical devices have been also used in the literature to identify issues with the approval pathways especially in the US and less commonly in other jurisdictions such as Europe, Japan, Canada or Australia (4, 7, 17-22).

Assessing or comparing recalls processes between jurisdictions is complex due to differences in the reported data which are publicly available (18, 23). There are confidential communication lines open between agencies, but more easily accessible information and transparency could enhance the processes across jurisdictions. The TGA publishes all enforcement actions including recalls, field corrections, seizures, and injunctions. Medical device recalls are published on a daily basis by the TGA on its website and contain information regarding actions emerging from agency regulation. Actions include Safety Alerts and Recalls. Safety alerts are communications issued by a manufacturer, distributor, or other responsible party or the TGA to inform health professionals or other appropriate persons or firms of a risk of substantial harm from a medical device in commercial use. Recalls are confirmed by the TGA when a reasonable likelihood of causing harm exists, and are classified according to the likelihood of causing patient harm. Class I recalls are the most serious, indicative of situations in which there is a "reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death." Class II and III recalls are less serious. TGA's Regulatory Intelligence and Investigation section can also publish enforcement reports, which may also include notice of civil or criminal proceedings or seizures of products. Other regulators such as the United States Food and Drug Administration (FDA) or the United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA) publish recall actions regularly.

Even though medical devices recalls are a complex issue, few studies have used epidemiologic methods to objectively describe the type and number of recalls for medical devices in general. While some specific devices, such as cardiac pacemakers and implantable cardioverter-defibrillators and automated external defibrillators, have been subject to frequent safety alerts, little is known about the epidemiology of medical devices and more importantly for this project, the impact of medical device recalls in Australia and worldwide (24, 25).

Currently a recalls surveillance system is not implemented in Australia. A surveillance system based on recall actions should be a critical part of the tools used by a regulator to assess those particular actions and post-market monitoring in general as it will enhance the regulator's ability to identify signals and trends and help inform regulatory decisions. At present, Australia lacks of a functioning surveillance system due to limitations in the analysis tools available. Nevertheless, after reviewing publicly available data, I was not able to identify a system with these characteristics in other jurisdictions.

This project will evaluate the current data collection of recall actions in Australia by the TGA and propose the implementation of a full recalls surveillance system which informs adequately the regulatory decisions made by the agency. In the future, the purpose of evaluating this public health surveillance system is to ensure that problems of public health importance are being monitored efficiently and effectively. These systems in general should be evaluated periodically, and the evaluation should include recommendations for improving quality, efficiency, and usefulness, which is also the aim of this project.

Methodology

Explanatory sequential mixed method study framed by the CDC guidelines for assessing surveillance systems and comprising a review of the scientific and grey literature, and TGA archival documents, and semi structured stakeholder interviews (26, 27).

The CDC Guidelines

The CDC guidelines outline a number of system attributes which can be used to assess the performance of surveillance systems (27). The system attributes I considered during this project were:

- Usefulness
- Data quality
- Representativeness
- Simplicity
- Acceptability
- Timeliness
- Flexibility
- Sensitivity
- Stability

These attributes were used to guide the collection and analysis of information about the existing database and to propose the development of a new surveillance system. The attribute of positive-predictive value was not used, as it was considered of limited utility to the purpose of this project, but it would be an interesting measurement in the future when specific studies using data obtained after implementation will allow a meaningful assessment.

Literature search

A literature search was performed utilising multiple search terms such as “medical device”, “recall”, “surveillance”, “monitoring”, “post-market” and specific terms for Australia and comparable jurisdictions or regulatory agencies (U.S. FDA, Health Canada, MHRA, European Union and Japan). This search was performed in Google scholar and PubMed in order to obtain information about state of the art in terms of implementation of surveillance systems to recall actions and to determine the information related to medical devices which is publicly available by different regulatory agencies.

Archival document review

I reviewed a number of key internal and published documents to inform aspects of this assessment. These included:

- Information available on the TGA website (https://www.tga.gov.au/recalls)
- The URPTG
- Final report prepared for the TGA by an external consultant titled "Review of work structures and processes for the Manufacturing Quality Branch". Even though it is a document with high level recommendations for the branch where the Recalls Unit sits, it helped me align my recommendations with the vision for the branch in key aspects such as streamline processes and planning for improvement in IT systems and data analytics.
- Standard operating procedures (SOPs) and working instructions (WIs) for both the Recalls Unit and DCS.

Qualitative interviews

Qualitative interviews with stakeholders were the primary methodology used for collecting information for this assessment.

Open-ended interviews were carried out after authorization from the relevant stakeholders (Recalls Unit, DCS, devices post-market areas). The objective of these interviews was to characterise the current data collection and systems in use by the TGA to process recall actions.

In order to characterise the system, I developed a semi-structured questionnaire targeted to characterising the process of a Recall in Australia and how the data are fed into the different IT systems. This basic questionnaire was used to structure the interviews, but there was flexibility to expand on certain topics if relevant using both clarifying and probing questions. I conducted four in-depth face-to-face interviews, each lasting approximately 2-3 hours and one phone interview with the devices post-market team for about half an hour. The first interview was held with the Recalls Unit Director and was aimed to gather an overview of the current resources used and available to people involved in the Recalls process and helped also in identifying the relevant interviewees. For the rest of the interviews, I included specific questions related to the CDC attributes, but the exact questions and focus of each interview were adapted to each interviewee's role and experience with the system. I used an explanatory sequential design: gathering initial data which informed the next collection and analysis, and an embedding approach for integration of the data obtained and its analysis (26).

Notes were taken through all the interviews and other features such as screen sharing or taking screenshots were necessary to obtain examples of capturing the data from recalls cases and

searches in the databases. If further questions emerged after the interview process, the interviewees were contactable by phone or email to provide specific clarifications on outcome measures or to help me understand contextual factors. After data from the interviews were gathered, a deductive thematic analysis was conducted by collating and analysing for recurrent issues referencing the relevant CDC attributes considered in the questions (28). Data obtained during the interviews were initially coded according to thematic groups and then defined by themes before including the findings in this report.

Interviews were conducted with the Recalls Unit director, Recalls Coordinators, post-market investigators and medical officers from DCS. As I am one of the medical officers in DCS, I was able to gather data from my own experience in managing the recall process from a clinical adviser perspective and sought feedback from fellow medical officers.

Additionally, feedback was received after the interviews and at the same time, dissemination of the key findings and recommendations was provided back to the main stakeholders which shaped my draft.

Results

The current system in place for managing and capturing the data from a recall by the TGA is complex and includes multiple different databases and IT systems. After gathering the views of the different stakeholders, it was patent that there are shortcomings of the current system for post-market surveillance and monitoring. In summary:

- Reliance on voluntary reporting leads to underreporting of adverse outcomes;
- Strict guidance or validation on reporting forms is lacking, leading to poor quality in submitted reports;
- Development of national or international registries, which could form part of the basis of post-market surveillance, requires considerable investment and coordination;
- Calculating adverse event rates is difficult due to incomplete numerator data on events, together with unreliable denominator data on exposures;
- Establishing causal relationships and determining whether the adverse event resulted directly from the medical device or the disease it was intended to treat is difficult due to the problems in the quality and reliability of the data available for analysis.

1. Data management during the process of a recall action

The main database that captures most of the steps in the process is called Recalls and Medicine Problems (RAMP). RAMP is embedded in a broader software platform called IBM notes, a data

storage, process management, and workflow platform, which also includes Work Management, a tool that controls some processes and tasks. This system captures all the main steps and information of the process for doing a recall. Some of the detailed data though are stored in TRIM, a secure internal governance based enterprise electronic document and records management system, but RAMP has references to it.

Fields in RAMP can be presented as free text, drop down menus, date selection and check boxes. RAMP also provides buttons to activate functions and help in the navigation. It also presents a dedicated Help button which displays the help file containing information regarding the fields and information stored on the Recall notification report. RAMP also presents icons which link to relevant documents in TRIM if required.

2. The database and IT system for storing information for the initial steps after notification

RAMP is the existing database upon which a surveillance system can be built and therefore, it will be described in more detail in this section.

If the information is sent online (preferred method), the sponsor of the product will have to fill five different tabs in the form (Table 1).

Table 1. Tabs and fields included in the online notification form

Field name	**M/V***	**Field Type**	**Field summary and comments**
Tab 1 (Notifier)			
Agent Name	M	Free text	Fields for identification of the sponsor of the product. If an agent is engaged by the sponsors to represent them (one agent could represent different sponsors), the agent field is displayed. In that case, there is an option to select either the agent or the sponsor in an additional field checkbox: Ongoing contact for further information. By selecting from the drop down list in the Contact field, the 3 subsequent fields are
Sponsor Name	M	Drop down list	
Sponsor Regulatory Address	M	Drop down list	
Contact	M	Drop down list	
Contact Person	M	Free text	

			filled automatically (from the login details stored in the system): • Contact Person • Contact Telephone • Contact Email
Contact Telephone	M	Number	
Contact Email	M	Free text	
Contact Information for General Public	V	Free text	The field Contact Information for General Public is intended to be the contact information for the action in the event users/consumers have any questions. It can be an individual person from the company or an 1800 number.
Tab 2 (Problem report)			
Proposed Problem Description	M	Free text	Fields for characterising the issue. Proposed Problem Description has a tooltip when hovering over the field: “Only include relevant recall information. Company mission statements are not necessary. Note: to avoid customer confusion, the term `Voluntary´ is not to be included.” Drop down lists show categories according to nomenclature in the URPTG.
Date First Recognised	M	Calendar selection	
Proposed Hazard Classification	V	Drop down list	
Proposed Hazard Description	V	Free text	
Proposed Action Category	V	Drop down list	
Proposed Action Level	V	Drop down list	
Proposed Action Description	V	Free text	
Has Action Been Initiated?	V	Yes/No Checkbox	
Tab 3 (Product report)			

Product Description	M	Free text	
ARTG(s)	M	Search window	Several ARTG entries could be selected. "Not on Register" could be selected when the good is not listed including when it has been cancelled (including then the cancelled ARTG ID within the Product description).
Product Code (or Catalogue/Part Number)	M	Free text	
Product Identifiers (i.e. Batch, Serial, Lot Numbers)	M	Free text	
Manufacture Date	M	Free text	Tooltip appears when hovering over the fields: "Use Australian date format (i.e. 01-Jan-2019 or Jan-2019)"
Expiry Date	M	Free text	
Release Date	M	Free text	
Batch Size	M	Free text	
Product Distribution	M	Drop down list	To select between: Australia, Australia and New Zealand, Not supplied, Unknown or Other
Product Distribution Details	M	Free text	Tooltip appears when hovering over the field: "Summarise as: XX (types of customers) in (States or Australia)"
Are the affected goods exported from Australia?	M	Yes/No Checkbox	
Tab 4 (Other actions)			
Previous actions	V	Search window	Add, remove, and edit buttons to include TGA recall Reference (RC number).

			Several TGA relevant recall or non-recall actions in the last 3 years (related to the same product or defect in the notification under assessment) can be introduced with a field available for additional information.
Current or previous overseas actions	V	Free text	To include relevant information from overseas jurisdictions, web links or documents related to the same issue which is under evaluation or that had been addressed in the last 3 years
Tab 5 (Supporting information)			
No additional naming convention beside the tab title	V	Not applicable - presented with a file name and description of the type of document	Documents as attachments (accepted file types: doc, docx, jpg, pdf, xls, xlsx, or zip). Maximum file upload size is 50Mb. Add, remove, and edit buttons are available. The following instructions are given: *Please attach any relevant information including (but not limited to):* • *Draft Customer Letter and Customer Acknowledgement Form;* • *Detailed Distribution List of Impacted Customers in the following format: State / Customer Trade Name / Suburb in MS Excel; and* • *Risk Assessment / Health Hazard Evaluation report preferably with clinical comment from a medical doctor.*

* Mandatory=M / Voluntary=V

Although some of these fields such as the Batch Size are mandatory in the online form, the sponsor enters them manually and there is no built-in validation for ensuring accuracy. Data migration from

the online form to RAMP is automated, however. When the application is submitted, a notification is created with a recall number (RC number). If the information is sent by email, email is still considered the backup option in the rare case the online form is unavailable, it is expected that the sponsor includes all the relevant information fields in the email to the Recalls Unit inbox. According to the experience of the staff in the Recalls Unit, it appears that smaller companies (with less resources and possibly less devices registered) tend to prefer the email instead of the online form.

After this initial process, the notification is available internally in the "Recalls in Tray" in RAMP for assessment by the Recalls Coordinators, with the specific date and time of that notification to the Recalls Unit automatically recorded. The notification created in RAMP has a heading with automatically populated identification details such as notification ID (RC number), date of the notification, its status and Type of Notifier (a drop down list which refers to the source of the report). Two main fields are displayed: Problem Description and Product Description (both as free texts). Although migrated from the online form, these fields usually require editing by the Recalls Coordinator to make them succinct. Additionally, five tabs are included (Table 2).

Table 2. RAMP Data Dictionary

Field name	**Corresponding name in online form**	**Field type**	**Comments**
Tab 1 (Problem Summary – Heading: Problem)			
Problem Category	-	Drop down list	For internal use only Drop down options (only one option can be selected): • Problem Seen in product Use; • Product Fails test or Specification; • Product is Contaminated; • Product is Defective; • Product Tampering; • Recall Not Following URPTG; • Regulatory Non-compliance; and • Other

Problem Subcategory	-	Drop down list	For internal use only Drop down option depends on the Problem Category (Figure 1). Only one option can be selected despite this field's title is "Select Keywords".
Date First Recognised	Same	Free text	To enable editing
Hazard Classification*	Proposed Hazard Classification	Dropdown list	Field to be reviewed by Recalls Coordinator to make sure there is agreement
Hazard Description	Proposed Hazard Description	Free text	
Proposed Action Category*	Same	Dropdown list	Field to be reviewed by Recalls Coordinator to make sure there is agreement
Action Level*	Proposed action level	Dropdown list	Field to be reviewed by Recalls Coordinator to make sure there is agreement
Proposed Action Description*	Same	Free text	Field to be reviewed by Recalls Coordinator to make sure there is agreement. This goes into SARA (System for Australian Recall Actions) as "Recall Action Instructions"
Has action been initiated?	Same	Yes/No Checkbox	
Recall Contact*	Contact Information for General Public	Free text	Reviewed by Recalls Coordinator and added details if necessary – to be published in SARA as "Contact Information"

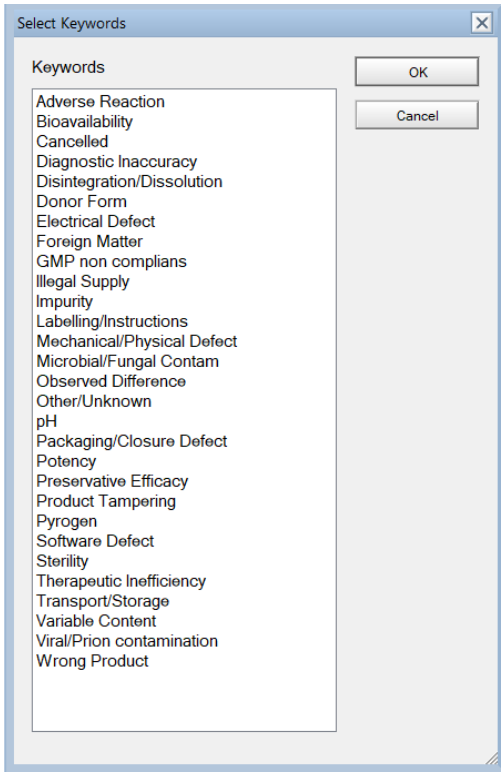
Tab 1 (Problem Summary – Heading: Product)			
ARTG Number*	ARTG	Search window	Edited with description according to ARTG entry by the Recalls Coordinator
Product Code or Catalogue/Part No.*	Product code (or Catalogue/Part number)	Free text	Reviewed by Recalls Coordinator and added details into product description
Sponsor*	Sponsor name	This field cannot be changed by the Recalls Unit.	
Product Identifiers	Product Identifiers (i.e. Batch, Serial, Lot Numbers)	Free text	N/A is populated if not information provided in the online form
Manufacture Date	Same	Free text	
Expiry Date	Same	Free text	
Release Date	Same	Free text	
Batch Size	Same	Free text	
Product Distribution	Same	Dropdown list	
Product Distribution Details XX (types of customers) in (States or Australia)	Product Distribution Details	Free text	This is a summary of the product distribution list.
Products Exported from Australia	Are the affected goods exported from Australia?	Yes/No Checkbox	
Product Exported To	Countries that the affected	Free text	

	goods have been exported to		
Tab 2 (Notification Details)			
Name	Contact Person	Automatic	Grouped under title “Notifier Details” (some of these details are captured directly from log on details in the portal). These fields cannot be changed by the Recalls Unit. The Ongoing contact field is filled with “Sponsor” by default, unless an agent was selected in the checkbox for the field Ongoing contact for further information. These fields are populated automatically from the login details stored in the system.
Ongoing contact	-	Automatic	
Organisation Name	Sponsor/ Agent Name	Automatic	
Address	Sponsor Regulatory Address	Automatic	
Phone No.	Contact Telephone	Automatic	
Fax No.	-	Automatic	
Email	Contact Email	Automatic	
Preferred contact method	-	Automatic	
Consent to release contact	-	Automatic	
Notification Notes	-	Free text	Internal fields, but not commonly used by the Recalls Unit.
Correspondence History	-	Free text	
Tab 3 (Comment History)			
No additional naming convention beside the tab title	-	Free text	Automatically generated by RAMP at certain steps I the process, for example “Notification finalised” or “Problem report assessed and new problem created”
Tab 4 (Supporting Information)			

Notifier Attachments	Supporting Information tab	Not applicable	Documents presented in a tabulated list with File name and Description, and icons with links to the attachments stored in TRIM.
Tab 5 (Other Actions)			
Previous actions	Same	Free text	Fields to be checked by Recalls Coordinator. No standardised wording format.
Current or Previous Overseas Actions	Same	Free text	

* Fields published in System for Australian Recall Actions (SARA). Besides those fields in the initial notification, SARA will extract from RAMP like the following data: type of product (medical device, medicine, biological), product name/description (product description in RAMP), reason/issue (problem description in RAMP), the TGA Recall reference (RC number) and recall action commencement date.

Figure 1. Fields selectable under all Problem Categories



The Recalls Coordinator confirmed that when a manufacturer initiates a device recall, the TGA evaluates the degree of health risk presented by the recalled product, including the severity and probability of occurrence, and reviews also its classification. For instance, safety related recall

actions (i.e., Class I and II, higher risk and seriousness) are given priority. In addition, 'Consumer level' recalls are actioned as soon as possible by the nominated Recalls Coordinator.

Central to all recalls is a recall strategy developed by the manufacturer, which involves multiple aspects (such as depth of recall, consumer and retail/wholesale level determination, public warning methods, and effectiveness checks) suited to the individual circumstances of that particular recall. The TGA reviews the adequacy of this plan and recommends changes as appropriate.

As part of this process, the Recalls Coordinator searches in RAMP for previous recalls for the particular ARTG number/name of the device involved in the recall and history of recalls for similar devices. This is captured or referenced as "Historical Background" in the WP2 form (Appendix 4), used for initial review of the recall action and its risk assessment by the Recalls Coordinator. Sometimes outcomes of the search are saved in Excel format in the specific TRIM folder.

Parts of the information included in the WP2 are captured as a field in RAMP such as identification fields of the product and sponsor, problem description, classification of the recall or proposed recall action. Other valuable information is not, for example actions needed to be undertaken by the end users, particular details of the risk evaluation such as likelihood or severity of the risk, or if they were disagreements in the strategy or push back from the sponsor of the product.

Recalls staff agreed that it is at this stage that clinical or technical advice is requested by email from different areas of the TGA when deemed necessary, for example Pharmacovigilance and Special Access Branch (PSAB), devices post-market sections or DCS. As a result of this advice, further information could be requested by email from the sponsor before giving a final recommendation or agreeing on the action plan. Those interactions with sponsors could be multiple and teleconferences may be required to reach an agreement.

3. Communication strategies

The administrative staff manually send the recall notice by email from a template generated from RAMP to the whole Recalls Distribution list. This list includes Recall Coordinators in all State and Territories and relevant internal stakeholders such as contacts in sections of devices post-market branch, DCS and PSAB. All these communications are usually done by email and a track record is kept in TRIM, but are not captured in RAMP at the present. In case of certain high-level recall actions, the TGA has a standard operating procedure to alert the Chief Medical Officer (CMO), state and territory Chief Health Officers (CHOs) and professional organisations (as appropriate).

Each state and territory health authority has a Recall Coordinator who is responsible for providing details of recalls to all relevant individuals and organisations within their jurisdiction. The relevant

parties with whom the Recall Coordinators need to communicate will depend on the type of product being recalled and the class and level of the recall.

Additionally, a TGA web statement may be published for 'Hazard Alerts' and all 'consumer level' recall actions when the TGA cannot trace the stock or there are wider safety implications. These cases are not common, but the members of the Recalls Unit expressed that they are of high significance to the TGA in terms of providing accurate and relevant information to the Australian public explaining clearly the risks associated with the recall and the actions required from the people affected. Again, files relevant to this information are stored internally in TRIM, but are not captured in RAMP.

4. Follow-up of the recall until closure

RAMP creates tasks for follow-up reports (2 and 6 weeks) and final report (12 weeks) which include data such as receipt date. But the tracking of those is captured manually in a spreadsheet in TRIM, and the recalls coordinator confirmed that there is not an automated reminder system that allows for a compliance check to the proposed timeframes. These reports and any assessments are captured in the relevant TRIM folder.

After final review of the reports and outcomes of the recall strategy, the Recalls Coordinator closes the task in Work Management. A note is entered by the system specifying "Notification finalised" in the Comment history tab and the Date Finalised field in RAMP is recorded. A final minute is stored in TRIM with detailed comments from the Recalls Coordinator.

5. Other IT systems involved in the Recalls processing and reporting

There are two other IT systems that need to be considered as they are currently used by the Recalls Unit and provide analysis or dissemination of the data captured in RAMP: Cognos and SARA (System for Australian Recall Actions).

Cognos was developed as a tool within IBM notes to interrogate the RAMP database and produce set indicators for operational reporting. These set parameters are particularly useful for obtaining statistics related to the key performance indicators reportable to the Department of Health and Aged Care. It is basically a reporting software which has predetermined searches.

Cognos data is also used in drafting the annual report on the TGA website. During the 2019-20 financial year, most of the recalls processed were classified as Class II actions (Figure 2) and the majority of them were related to devices (Figure 3). Of these 614 medical devices recalls, about 80% were class II product defect corrections.

Figure 2. All recalls in Australia by hazard classification during financial year 2019-2020 (n=790)

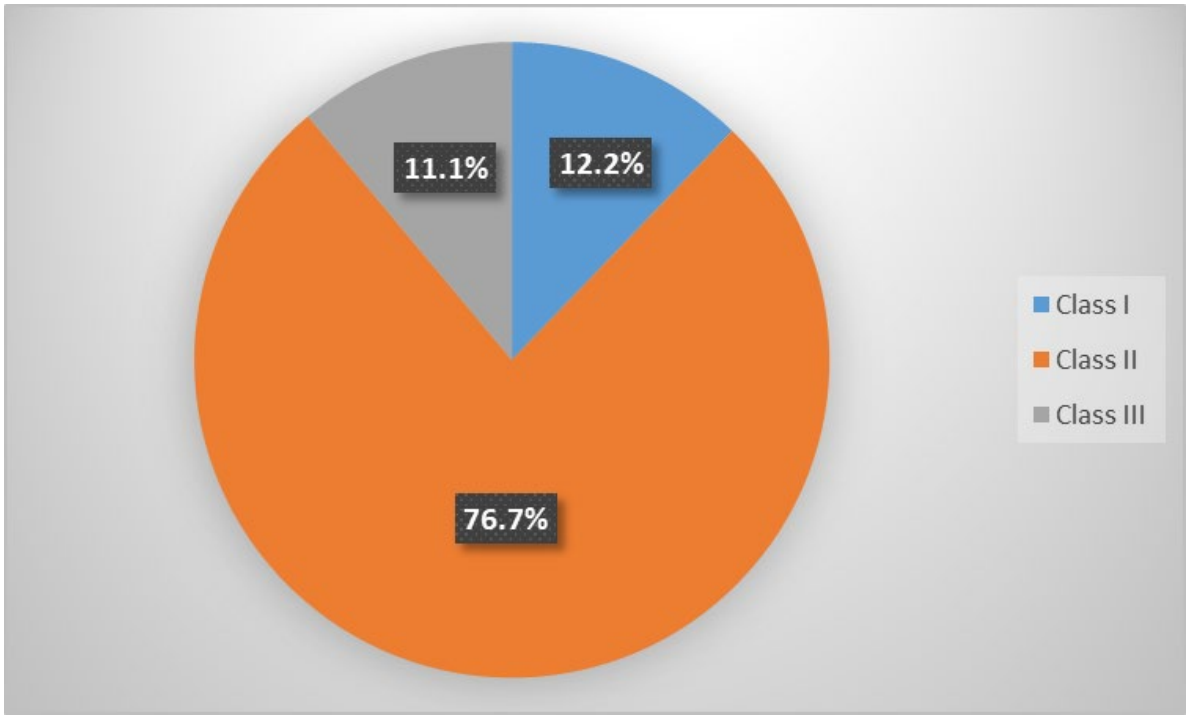
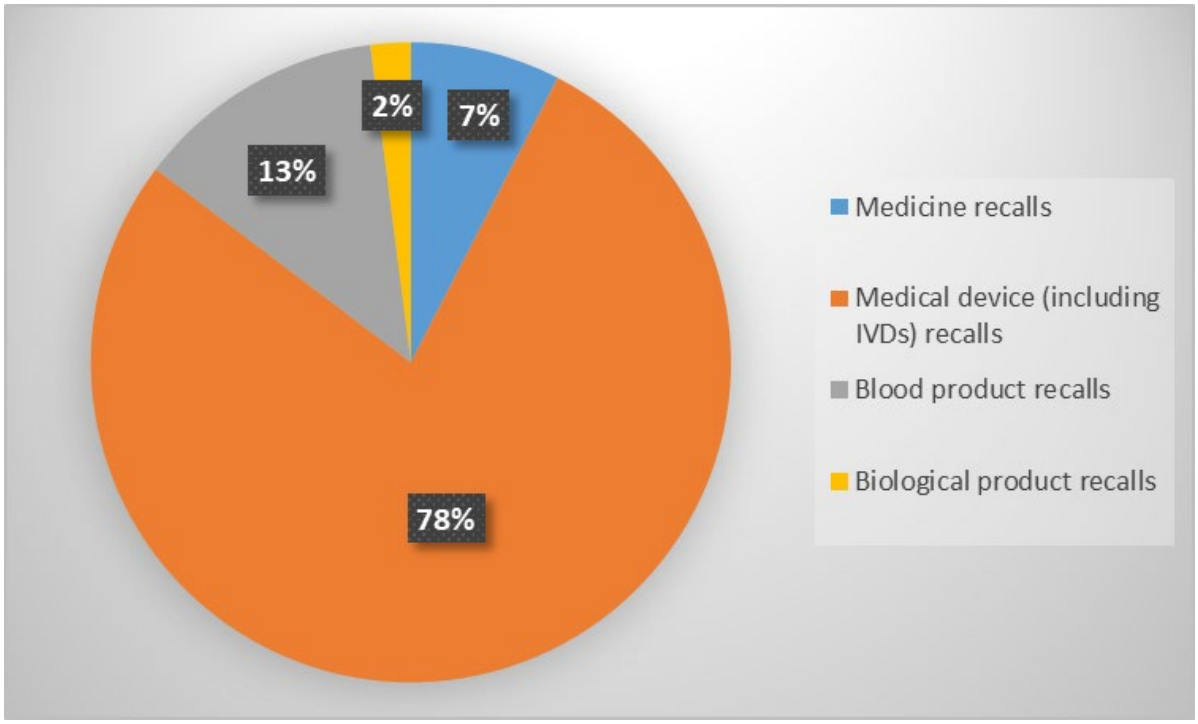
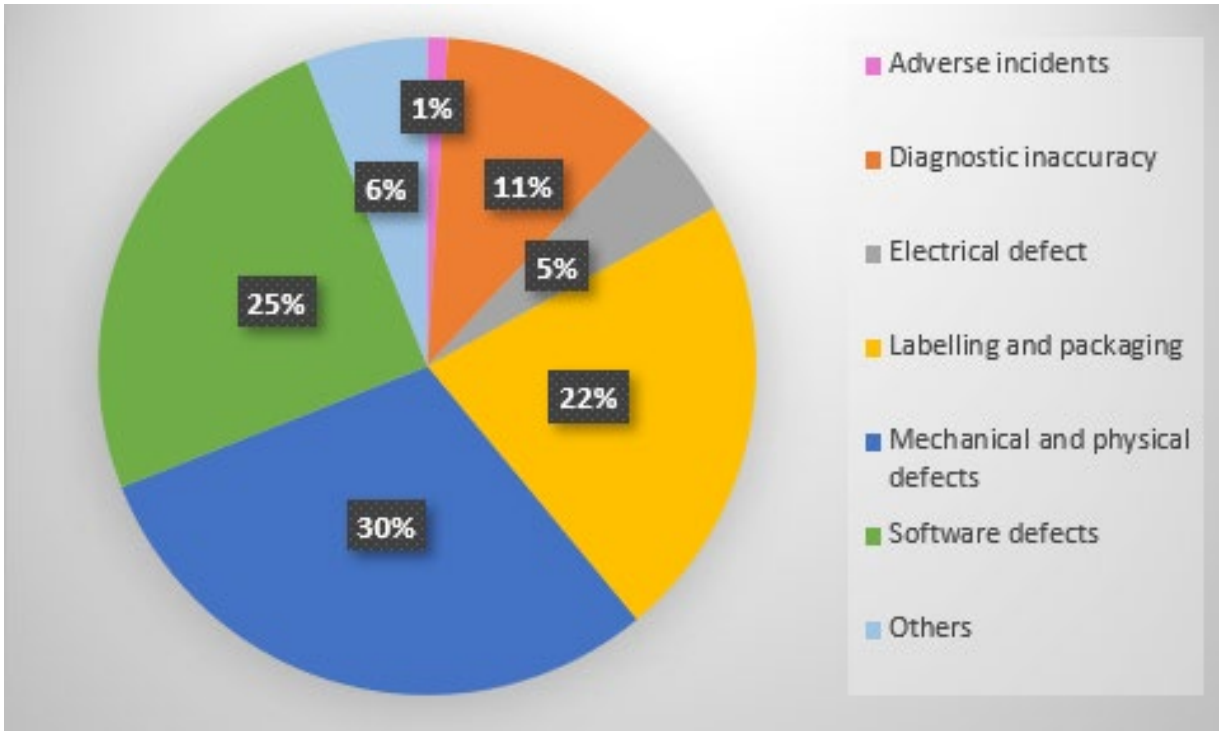


Figure 3. All recalls in Australia by product type during financial year 2019-2020 (n=790)



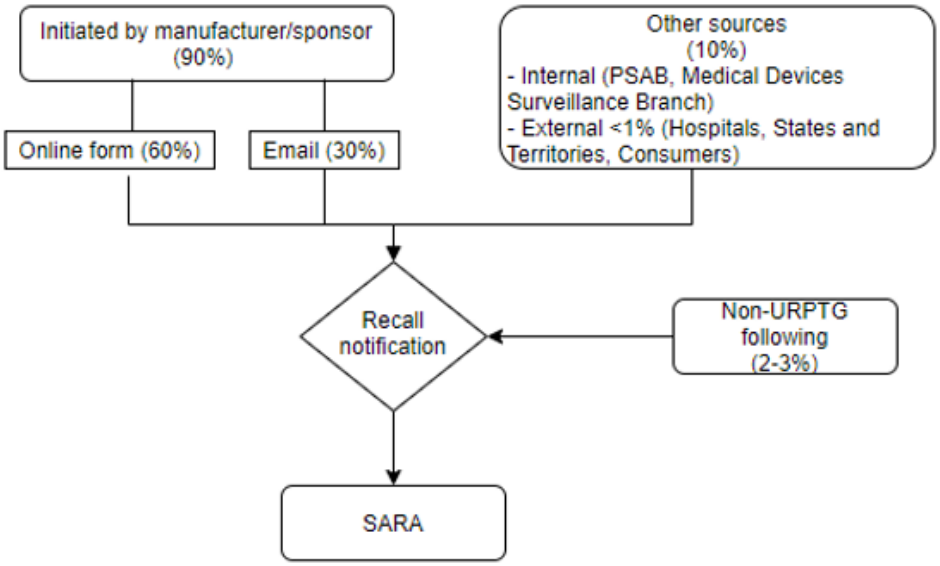
The main reason for device recall action was mechanical or physical defects (Figure 4).

Figure 4. Medical device (including IVDs) recalls by reason for recall in Australia during financial year 2019-2020 (n=614).



Generally, a recall in Australia is a voluntary action by the manufacturer or sponsor. Over 99% of the processed recall actions are initiated by the sponsor. If a recall process is officially initiated from a different source than the sponsor (Figure 5), the TGA contacts the sponsor initially to agree on initiating a voluntary process and submitting an online form. However, in rare instances the TGA may order the manufacturer to recall a product, if it deems that the product poses a significant health risk and the manufacturer fails to voluntarily recall a device.

Figure 5. Sources of recall actions published in SARA



SARA is TGA's publicly facing database[1] which provides details of recall actions. As this is a subset of information from RAMP, it will be considered for the purpose of this project as a reporting mechanism. SARA provides consumers, health care professionals, sponsors, wholesalers, hospitals and retailers with access to information about recall actions occurring in Australia for therapeutic goods. SARA could aid in the analysis and comparison by researchers of the recall reasons of each product category, as well as gathering information about number of recalls and their frequency over time. The database holds information on recall actions that have been undertaken in Australia since 1 July 2012.

SARA is searchable for therapeutic goods recall action notifications that include recalls, product defect corrections and hazard alerts (implanted medical devices and biologicals) and product defect alerts. Recall actions are included into SARA two business days after a decision is made to commence a recall action between the responsible entity and the TGA. This allows time for the responsible entity (sponsor/supplier/importer) to distribute the recall communication as per the terms reviewed and agreed with the TGA. In certain circumstances (e.g. consumer level recall actions and recall actions involving implantable medical devices), notices are also published on the alerts page on the TGA website. Alerts are issued by the TGA to advise the public about new safety information regarding therapeutic products.

The current fields captured in SARA are:

- Type of product
- TGA Recall reference (RC number)
- Product Name/Description (brand name and references to catalogue/model/batch/serial numbers)
- Recall Action Level
- Recall Action Classification
- Recall Action Commencement date (date the Recall strategy and communication was agreed)
- Responsible Entity
- Reason/Issue
- Recall Action
- Recall Action Instructions
- Contact Information (for the Recall Entity)

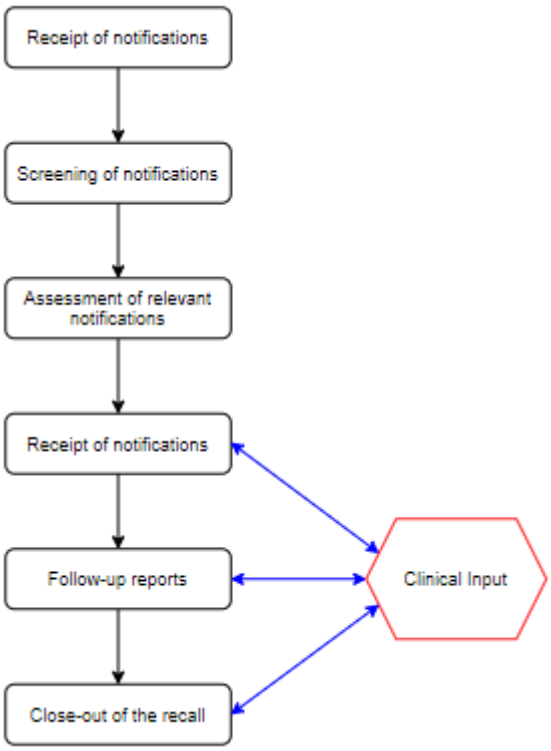
[1] https://apps.tga.gov.au/Prod/sara/arn-entry.aspx

A recent upgrade to SARA (July 2020) has improved accessibility of recall event information for the public. Users are now able to download search results of summary recall data in editable, MS Excel format, in addition to existing PDF reports. This project was undertaken in response to requests from a range of external stakeholders to provide better access to TGA recall data. Despite this, greater transparency is still requested by different stakeholders including patients (via feedback provided to TGA's website and consumer forums). Given the serious adverse events reportedly caused by device failures, continuous evaluation and improvement of dissemination strategies are needed.

6. Clinical involvement in the process of a recall action

As part of step 8 (Appendix 2), the Recalls Coordinator evaluates the medical device risk analysis report (often known as a health hazard evaluation or HHE report). According to the evaluation, clinical advice can be sought (Figure 6).

Figure 6. Simplified flowchart for the clinical input into the recall process captured in RAMP



If additional input is required from medical officers in other areas of the TGA, this is captured in the WP2 form. In particular, there are two triggers for seeking clinical advice:

1. When the clinical implications are unclear in relation to deficiency identified and/or the proposed workaround; AND/OR
2. When there is evidence of an actual death or permanent injury in any jurisdiction, including any international reports.

Additionally, any recall actions that would require a TGA web statement (i.e. hazard alerts and/or consumer level recalls, vaccine recalls and other special circumstances that have wider health implications or public health risks associated) will require clinical advice as well. Clinical advice can also be sought by email as part of steps 10 or 11 (Appendix 2) depending on the complexity of the issue.

There are three standard initial questions for the clinical advisor in the WP2 form. The first question refers to the classification of the recall (consideration is given to the proposed hazard classification) and the following questions refer to the acceptability of the proposed recall action and the communication strategy (including the customer letter). A free text section is found at the end of the document for adding comments or reasoning if required. After assessing the information, the clinical assessor responsible for the task sends an email back to the Recalls Coordinator referencing the relevant filled WP2 form and including additional information if necessary.

7. Analysis tool

There is no current analytic tool used by the Recalls Unit to systematically interrogate RAMP, except for Cognos which is very limited in scope. All other searches are done directly on RAMP according to the preferences of the user, usually looking for background history that could be related to the recall action under assessment and to provide a full picture when advice is requested from other sections of the TGA. These searches are not systematic and require manual feeding of the search terms including Boolean operators which makes them difficult to reproduce inducing a great variability in the results. RAMP has the capacity of saving previous useful searches, but this function has been inactivated as it makes the system slow. An alternative option is to use a tool called “Audit Export” which can save search parameters and extract information from RAMP, but the outcomes are output in Excel spreadsheets which are not the best option for data analysis.

Although SARA has search capabilities, those are not useful for a surveillance system as the fields and details available are extremely limited. Furthermore, doing searches by keyword could provide little context. For instance, using the term “design” in recall records cannot be used as an indication that a recall was caused by a failure in the design of a medical device.

Discussion

The existing database, RAMP, has several limitations which impede the development of a functional surveillance system. As such, the proposal is the creation of a new system.

1. Description of the proposed Surveillance System

This section proposes the objectives and components of a surveillance system for recall actions of medical devices in Australia. These components take into account the relevant legislative framework, and consider existing data collection tools used within the Recalls Unit to perform its business as usual activities.

It is important to note that this proposed plan relies heavily on a transparent and efficient communication with the sponsors of the therapeutics goods in Australia as most of the recall actions processed in Australia are initiated by the companies with the overview of the TGA. Furthermore, this plan also depends on establishing an adequate analytic tool which will enable detection of signals and analysis of trends. After this is accomplished, availability and timeliness of the data will be improved, and a consistent interpretation of the data and provision of advice will help in implementing regulatory actions.

Several aspects were considered:

- Public Health Importance of the Health-Related Event Under Surveillance.

As mentioned before, the health-related event is a recall of a medical device. There are direct implications to the Australian public if these actions are not properly undertaken.

- Objectives and Operation of the Surveillance System.

The objective of the surveillance system is to provide information about recall activities to guide regulatory actions. For that purpose, it needs to detect signals related to concerning recalls in a timely manner, support the characterization of recall actions and target interventions. An efficient surveillance system will be of great value across the TGA, because it will allow the detection of signals and the analysis of trends in a timely manner.

These objectives will be supported by two main tasks:

- Reactive analysis of surveillance data applied to specific recall actions. This will be useful for the Recalls Unit and also to any internal stakeholder from whom advice needs to be requested.
- Systematic evaluation of trends and signals from the recalls database.

Ownership of the surveillance system is with the Recalls Unit, which is a section within the Manufacturing Quality Branch (MQB). The primary function of the Recalls Unit is to coordinate and manage recall and non-recall actions of therapeutic goods in Australia. This involves liaison with the sponsor/supplier of the therapeutic good and the relevant regulatory area within the TGA. The

outcomes of these interactions may also result in the treatment of the matter as non-recall action or its referral to another advisor/stakeholder internal or external to the TGA.

Sections within the TGA such as those with responsibility for monitoring the safety of devices post-market will benefit from the system. Analysis of data will facilitate targeting of investigations and reviews, linking to other data sets, leading to early regulatory action. These data will be used to detect changes in trends for recalls associated with certain products or manufacturing companies. Additionally, it could identify families of products at greater risk of being subject to recall actions according to characteristics in common. Finally, after evaluation of the predictability of the results, this initiative could guide measures to prevent future recall actions. A consistent investigation of the cases and identifying signals is necessary to improve consistency in the recommendations and decisions from the Recalls Unit and in any subsequent regulatory actions taken by other sections within the organisation.

- Organisation of the surveillance system.

It is proposed that the surveillance plan for the recall actions should be integrated into the current main data collection system (RAMP). This plan is targeted to meet the two main actions: reactive analysis and systematic evaluation of the data generated.

Even though sponsors and manufacturing companies are important stakeholders for this process, it is relevant to remember that the key stakeholder is the Australian public as TGA's role is to safeguard and enhance the health of the population through effective and timely regulation of therapeutic goods.

The current flow of the data processing was detailed in sections 1 and 2 of the Results. Several aspects are worth further discussion.

Communications between the TGA and sponsors before notification data entry are captured in TRIM, but not currently registered in RAMP. Having this information in RAMP available for analysis will aid in building a profile of the sponsor company as these exchanges could emerge for two main reasons: the sponsor does not know sufficiently about the process or they know it, but they want to streamline it.

The different sources that could be feeding the entries and their diversity (either internal or external), as well as how this information is transmitted to the TGA, are worth considering. Details of external data sources are important as for example, recalls originated from complaints identified by hospitals or by post-market teams across the TGA could indicate that the signal was not detected by the companies in the first instance. In other instances, non URPTG following recall actions indicate

that a company is not complying with the processes and cast doubts on a correct Quality Management System (QMS) with safety implications. These data should be captured and analysed as part of the proposed surveillance system.

Furthermore, although the sponsors are legally required to submit consistent, reliable and accurate information about the product issues and there is an online form available to enter the recall notifications, this process is not always followed which creates issues related to email submissions. Although guidance can be found in the URPTG, it is not uncommon that customers' details are missing or not in the right format (even though usually only three fields are compulsory for TGA process: state, customer and suburb). This incomplete information creates delays in the processing of notifications and sometimes Recalls Coordinators have to send a template to the sponsor as a guidance. Incorporating these fields in the online form and mandating it as the preferred system for submitting recall notifications by sponsors will aid in solving the problem. The online form has validation tools ensuring that if any mandatory fields are not populated, messages will appear until all the fields are completed. There are also steps in place to verify the submitter by a declaration.

Limited uptake of the online form (60%) indicates a problem with acceptability and could affect the sensitivity of the system if the reasons for that limited uptake relates to difficulties experienced by the companies in entering the data. This does not appear to be the case, as email reporting could create a greater burden for the companies in terms of the possibility of multiple interactions due to incomplete information. Reasons behind this issue are worth exploring with the different companies involved in the process as email could be perceived as a more straightforward interaction. This obstacle also hinders data quality as if this process is not automated, there is the possibility of having incomplete information or errors when TGA staff manually re-enter the information into RAMP with the limitation that there is not a systematic system to detect and follow-up inaccuracies in those data.

Another aspect to consider of the current online form is that still requires a degree of review and manual data entry into RAMP by the Recalls Unit to ensure veracity and adequacy of proposed recall strategies. Besides that, it has a large amount of fields that are not mandatory which has a direct impact on completeness. For example, the distribution list functions as an attachment and the information in it could be presented in the wrong format or including unnecessary fields for the TGA such as addresses or telephone numbers of the contacts which increases the time needed for editing and transferring data.

Before and after transferring the data into RAMP, it was found that additional validation tools could be useful for example in the fields capturing dates. This will increase consistency in the data entered

in those fields. It is also recommended that certain fields such as Problem Category and Subcategory should be included in the online form, but this will require previous agreement on common terms with and across the industry as direct stakeholders, a process that would require consultation.

A positive aspect of RAMP is that it enables a timely and stable collection of the data. Being centralised and operated exclusively by the Recalls Unit sets a solid structure. The current fields in RAMP have been developed over many years, but actual changes to those fields have been minimal in recent years as this database has matured. RAMP has the advantage that it has a flexible format for data exchange between multiple types of databases and its own organization and structure. As a result, simplicity of the system is high but at a cost to usefulness and acceptability when considering the possibility of implementing changes and modifications as expressed by the main users (the Recalls Unit).

Additionally, the time spent in maintaining the system is minimal and staff training requirements are not onerous to the TGA. Currently, RAMP is maintained by the IT section of the Department of Health and Aged Care, and it is considered a very stable system with solid interactions with other components of the IT network. It is very secure system as an ID from the Department of Health and Aged Care is a minimum requirement to access it and special permission is required to edit any components of the program. It is backed-up twice daily into 3 additional servers, and after being transferred through several storage databases, the information is finally kept in backup tapes within a secure electronic warehouse.

The primary trade-off of this database model is that queries cannot be made as efficiently as in other models. Currently, RAMP has limited capability to present results of those searches and displays information in a rigid format which cannot be modified by the user to facilitate any subsequent analysis. Alternatives at the moment require to save results of those searches in other programs such as Excel which could decrease stability (especially when incrementing the time required to transfer, edit and manage the data). Changes to these program features or all initiatives to create/remove or modify fields need to be authorised by the Executive Level in the Department of Health and Aged Care based on demonstration of a significant business benefit or cost savings and involves the IT team. This is impacting directly on the flexibility and adaptability of the system as the process can be cumbersome and time consuming.

Other relevant information such as the background information gathered by the Recalls Coordinator is partially captured in RAMP. For example, there are fields in RAMP for related regulatory actions in Australia and overseas, but, as being free text fields, relevant details of those actions are not requested to be entered in a systematic and consistent way. Information such as identifiers of those

recall actions, associated Corrective And Preventive Actions (CAPAs), volume of affected devices distributed and implanted worldwide or commencement date and the deadline for completing the recall action if ongoing are not consistently entered into RAMP. Those extra fields in RAMP will add data quality without impacting the acceptability as part of that information is already captured by some members of the team.

The level of integration of RAMP with other systems is appropriate in terms of linkage to for example TRIM and Work Management, but there are a few issues when visualising that information within RAMP's interface which reduces its usability. For example, overdue follow-up reports are an indicator of poor compliance by the companies, but the Recalls Unit team had to create an Excel document to manage those, increasing the risk of incorrect data entry. Furthermore, automated reminders of overdue reports will be valuable for having a timely action. Even though Work Management has the flexibility of activating a feature to generate automated reminders, those would be sent by email to the nominated Recalls Coordinator and would not be captured in RAMP making any subsequent analysis of the data not easily accessible.

In terms of communication strategies, dissemination of the findings related to recall actions are usually done by mailing lists to internal or external stakeholders. The mechanisms in place reflect timeliness in the process from the notification to the TGA until the communication to the different stakeholders goes out.

Additionally, SARA is used as a database for publication on the website. Even though it is fit for its main purpose as it contains the level, classification and action description, some details of the reason for the recall and the health consequences of the problem, it has several limitations. SARA only captures a subset of fields from RAMP and is not user-friendly. It is difficult to access/find and has inconsistencies in the level of information provided. Furthermore, it does not include a mechanism to notify consumers of recalls that may affect them.

- Data analysis and interpretation.

In terms of analysis of the data for the planned surveillance system, RAMP is perceived by the Recalls Unit as a representative database as it describes the characteristics and occurrence of the health-related event. It is expected that this proposed surveillance system will have a high representativeness for recall actions in Australia due to sponsors' legislated obligations. Even though it will not describe the distribution of the health-related event by place and person as other more conventional epidemiological surveillance systems, it will describe other attributes of the actual events, including the occurrence over time.

There were severe constraints identified; RAMP is not designed to analyse the data stored in it. Furthermore, the RAMP interface is not user-friendly and will not be adaptable to presentation of data for the purpose of a surveillance system. These factors severely impact on its acceptability and therefore its usefulness.

The other IT system, Cognos, provides some basic analysis of the data, but its user interface is simplistic and it is not programmable at the moment without a significant investment in resources. Another important limitation is that it cannot be linked to individual data in the recall dataset if further clarification is needed for a specific action (or group of actions). The level of usefulness for the purpose of a surveillance system is absent.

Interpretation of the data in RAMP has several limitations at present. RAMP does not register all the relevant fields that could aid in the assessment during the evaluation of an individual recall action. It is recommended to add or modify several fields into RAMP (Table 3). These additional fields in RAMP will benefit the surveillance system in terms of the data quality, but need to be carefully planned as RAMP is not a flexible database and those changes will require involvement of IT human resources and allocation of funds.

A second extremely important limitation to consider is the quality of the inputs gathered by the system which will feed the analytic tool. Some of those aspects can be addressed in full by the implementation of the surveillance system, but others are complex issues which were confirmed during the interviews to be strong limitations. For instance, the TGA is not able to estimate the rate at which therapeutic goods are recalled unless specific information is provided by the sponsor and it is difficult to make comparisons when the denominator for similar products is not accessible directly in our databases. It is difficult to estimate the number of medical devices currently on the market as this information is not routinely captured by the regulators and a system which enables to capture that information in real time will require significant resources from the regulator and the cooperation of all the companies involved. Many products with an active license are no longer marketed for one reason or another, even though a recall has never been issued for the specific good. For example, a device may no longer be marketed, because a manufacturer has replaced an existing device with a newer or modified device. Even with an adequate data analytics tool, it will be difficult to calculate the rate at which devices are withdrawn from the market as the database will need to keep current information on all products licensed in a jurisdiction. On the other hand, the implementation of the same analytic tool will help in joining the pieces of the puzzle and it is expected that with incremental information, some of these questions will be resolved.

Another consideration is that even though the majority of data are entered into one main database (RAMP), there is valuable information captured in other systems: additional valuable information comes from documents such as root cause or hazard analyses, alerts generated in other jurisdictions or communications to customers during active investigation of a reported problem. This is partly because some of the information is stored in other programs within the Department of Health and Aged Care's IT network such as TRIM and Work Management. TRIM, due to complexity and security restrictions, does not share its content with RAMP. Therefore, those data are not readily available for internal analysis without additional steps which require data manipulation by the staff in the Recalls Unit. This makes a possible analysis more complicated and decreases the data quality as validation is not routinely implemented. This "hidden" information often provides critical details that are not readily available for surveillance analysis at the moment. Other data that could be useful for a surveillance system refer to the timelines of the recall process, such as overdue follow-up reports, are captured in Work Management. Although a link to these data is within RAMP's interface, these data are not currently analysed within a surveillance system. Other programs such as Excel are also capturing similar data.

Table 3. Recommended addition/modification of fields in RAMP

Field name	**Field type**	**Comments**
Interactions with the sponsor before notification	Number and Checkbox	Number of email/Phone interactions will be captured and allocated to two main options: a) proactive streamlining of the process b) lack of information about the URPTG.
HHE risk calculation parameters	Number	A rate of the complaint or adverse event over sales or shipments by year as per the calculations in the HHE document. Alternatively, a macro can be created to enter numeric values of the numerator and denominator to calculate the final value in the field or even entering the values of severity and probability of occurrence in a matrix according to international standards in Risk Management.

		The volume of devices distributed/implanted could be an indicator of the spread of the issue in different markets.
Customer list	Search window	Activated for recalls such as hospital level when the number of entries will be manageable.
Additional historical background	Free text	For previous recalls for the particular ARTG number/name of the device involved in the recall and history of recalls for similar devices not captured in the “Other actions” tab.
CAPAs	Yes/ No Checkbox	If “yes” selected, then a second field (Free text) will be activated to capture the CAPA ID
Commencement date of recall in other jurisdiction(s)	Date	This will help identify issues with timeliness in the response by the company to the issue.
Deadline for completing ongoing recall action in other jurisdictions(s)	Date	
Agreement on suggested recall strategy	Yes/No Check box	If “no” selected, then a second field (Free text) will be activated to describe the controversial points and required measure to solve the issue (teleconferences for example).
Clinical involvement/advice	Yes/No Check box	This field relates to complexity/severity of the recall action. An additional field will be activated if Yes is selected to capture the number of instances when advice is required during the recall process.

Interactions with the sponsor during and after notification	Number and Checkbox	Number of email/Phone interactions will be registered. A checkbox to capture teleconferences can be activated.
Alerts to CMO, CHOs and professional organisations	Yes/No Checkbox	Indicator of complexity of the recall
Media (requirement of web statements)	Yes/No Checkbox	Indicator of complexity of the recall
Report due dates (2, 6 and 12 weeks)	Date	Calendar selections for calculation of overdue follow-ups

In addition, publicly available external databases such as the ones maintained by regulators of other jurisdictions cannot be interrogated by the current system in place. Data obtained from other regulatory agencies are currently captured ad hoc in RAMP as there is not a systematic analysis of the data published by other regulators. Most of the information available to the Recalls Unit derive from email chains and the personal experience of the Recalls Coordinator. This is a lost opportunity at present for increasing data quality.

Finally, as there is not a proper analysis of trends or detection of signals based on the data captured at the moment in RAMP, it is not possible to communicate those findings. SARA is a stable tool and allows for a basic dissemination of the data, but it does not have the capacity of presenting any type of analysis.

- The analytic tool and its strategic impact on regulatory actions.

Consistency in the recall strategy depends on identifying similar cases and the correct background history (internal or from overseas regulators). Implementing an analytic tool onto RAMP will allow applying targeted search parameters and perform multiple comparisons which will inform the decision making within the Recalls Unit.

This tool is the main step to bring usefulness to the data currently captured and needs to be specifically designed to extract the data from RAMP. It is extremely important that it presents the analysis in a user-friendly interface reinforcing acceptability and enabling the TGA staff to do both regular analysis of the recall action database and targeted searches increasing the simplicity in the interpretation. Additionally, this tool will need to enable graphic representation of possible associations between fields such as similar products from different companies or products within the

same family with potentially same issue affecting them and include break down by locations of the distributed product in Australia and timelines of different recall actions.

The information should be presented in different tabs with some predetermined parameters such as timeframes, type of products, recalls characteristics such as recall classification or broken down by sponsors/manufacturers and give the user of the surveillance system flexibility for adjusting parameters of the searches if required and links to specific recall actions.

Qlik (Qlik Sense® by QlikTech International AB) is a platform for data integration and is currently part of the Department of Health and Aged Care's technology portfolio. It is classified by the Department as a business intelligence tool. It works as a self-service data visualization application which enables the user to create personalised reports and dynamic dashboards. It supports free-form analytics and allows users to build data and web applications through application program interfaces. As a result, it has the advantage that can integrate different data sources and increases the flexibility for developers in terms of designing specifically targeted views. It also has the advantage that it is generally simple enough for most users to learn without requiring special data analysis or programming skills, and basic training is available to staff. Qlik's plasticity is reflected in the courses and training in place to develop skills as a system owner and being able to introduce simple changes that could increase the usability of the interface to start with. On the contrary, any proposed changes in RAMP as a result of this evaluation will require authorization and the process could be cumbersome and time consuming as those changes and IT solutions cannot not be performed directly by members of the Recalls Unit.

Qlik offers a timely opportunity to configure it specifically for the purpose of recalls surveillance. The Recalls Unit started to explore it as a possibility for integrating data and perform targeted analysis of the data in RAMP, but this project has not progressed due to time constraints.

Qlik has been used as a tool to interrogate the recalls database by the post-market team in Medical Devices to make a correlation of recalls to adverse events. It is useful to know that this interaction (and therefore the compatibility for extracting the data) between the recalls database and this analytic tool has already been established. Currently, the information presented in the post-market Qlik app is limited to six fields:

1. Licence ID: corresponds to the ARTG number in RAMP
2. TGA ref: corresponds to the RC number in RAMP
3. Action Level
4. Hazard Class: corresponds to the Hazard classification in RAMP

5. Recall action
6. Recall reason: corresponds to the “Problem Description in RAMP”, but with a limited number of characters available for view (one sentence), and somewhat increased capacity as you roll the cursor over the field.

If further details related to that individual recall are required then the usual route will be through search by the RC number in RAMP.

Qlik has the relative disadvantage that it is not part of the formal standardised and centralised IT framework of the Department and it has been implemented by different sections independently. Although this has helped projects progress quicker, there are different stages of implementation and the potential of duplicate analyses or even the possibility of using outdated or incorrect datasets by the users is a risk if communication channels between the developers and the owners of the data are not well established.

It is important to note that at the moment there are no thresholds that could be used to inform when the surveillance system is triggered. As such, the first step will be to set-up baselines for recalls according to families of products including devices from the same manufacturer and/or devices from other companies. Depending on the baseline, a specific time-oriented timeframe needs to be designed to get recent and relevant data in the analysis. Traditionally, historical signal detection methods compare current information to 3–5 years of historical or baseline data (29-32). It is suggested to start with 5-year windows considering the evolving field of devices and the frequent iterations/modifications and versions of the products available in the market. This historical period will aid in maintaining the stability of the data.

Baselines for recall actions will enable to identify thresholds. Proper threshold selection is key. There are many algorithms published that have potential to detect a signal with good sensitivity and specificity (33-37). For simplicity and to test the system, the alert threshold initially proposed should be the mean of recall actions plus 2 standard deviations (“mean + 2SD”) which has been used previously as gold standard in the literature (38). Subsequently, threshold performance evaluation should be implemented as part of the evaluation of the surveillance system when fully implemented. These established thresholds could be compared to individual cases according to their similarities and as a result, determine if and when the identified signal deserves further investigation.

Another important feature of the analytic tool relates to searches in a broader sense. It would be useful to first establish the types of medical devices that may be prone to adverse outcomes as a mean of directing stretched healthcare resources to selectively monitor the devices most likely to be

associated with problems. An adequate recalls surveillance system will provide additional relevant information on similar recalls on different products, other recalls related to the same manufacturer or recalls done in the past for a product of the same family. Such a surveillance system will help in identifying those devices, and subsequent strategic decisions by directors of the relevant sections or the CMO on investigations or focused studies required will be evidence based.

The following fields need to be captured and analysed by the analytic tool as a minimum:

a. Sponsor of the product
b. ARTG(s) and other identifiers of the product like Global Medical Device Nomenclature (GMDN) code or Unique Device Identification (UDI) when available
c. Problem description (this field needs to allow for free text searches)
d. Problem category
e. Problem subcategory (this field needs to allow for free text searches)
f. Hazard classification
g. Hazard description (this field needs to allow for free text searches)
h. Action category
i. Action level
j. Action description (this field needs to allow for free text searches)
k. Previous actions
l. Previous or current overseas actions

Dates of the actions will need to be included as well in the analysis to enable an assessment of the efficacy of the process and comparisons of milestones. For example, date when the problem was first recognised, date when the recall action was initiated, date of the follow-up reports expected and received, timeline proposed for final closure of the recall action and actual date of finalising the recall need to be introduced as variables to monitor against. Timeliness of recall actions is of the upmost importance as delayed recall action could have impact on patients' outcomes, adverse events or even public health consequences. This attribute will be assessed by analysing data considering different points in time, such as beginning of the notification or starting of the review of the data by clinical advisors and the time taken for actioning a regulatory decision or providing advice respectively. Other parameters in relation to a timely analysis will be in relation to compliance to the proposed timeframes for reporting, time to agree and finalised the recall action or waiting times for initiating the recall assessment since notification by the sponsor. Repetitive non-compliance could lead to further investigations, and for example colour coding within Qlik's visual interface could be incorporated to flag possible signals. These features increase the usability of the

surveillance system and facilitates the analysis of data. Even automatic prompts may be generated to review cases with overdue items.

Considering different relationships between these variables within Qlik will enable to target searches according to various parameters such as type of recall, families of products or companies involved, and most importantly identify signals and trends early which can alert the decision maker of problems requiring prompt regulatory action. Regular reporting on products of interest and general trends in the database categorised by product families and sponsor/manufacturers to identify potential signals and trends should be produced at least on a quarterly basis for the post-market sections and the Recalls Unit director to identify potential projects or emerging tasks.

After Qlik implementation, regulatory actions such as initiating recalls for other products from the same or different company could be suggested and impact other sections within the TGA or other regulators worldwide. Furthermore, identifying issues that could be affecting other manufacturers which will not be aware as this information (not publicly available), could potentially implement actions at an earlier stage and the TGA can liaise to convey the message through the routine communication channels between agencies without breaching commercial in confidence interests.

Besides guiding regulatory decisions, after implementing the analytic tool, the recalls surveillance system will be crucially important to inform policy changes and in assessing research investments and maximising performance of agency resources.

An additional advantage of developing an automated data extraction and analysis process is to ensure that regular reporting does not increase the workload burden of the post-market areas and the Recalls Unit and that the projects' goals are feasible. At the same time, the dedicated platform will aid in managing the data to report in a timely manner. For example, when Qlik is developed, it could incorporate the current duties of the Cognos system for generating key performance indicators. This feature in Qlik could even save time by generating the data for annual reports of the Recalls Unit.

Support functions

- Standard and guidelines: the functioning surveillance system will support revisions of the URPTG by assessing the process and outcomes of the recall actions. Information obtained through this analysis can inform better policy directions and guidance.
- Training: with the current experience of the Recalls Coordinators and the administrative staff of the unit, minimal training will be required for the data collection and any improved processes will need to be reflected in the SOPs and WIs of the unit. IT solutions for analytics

will require new training for the staff from the Recalls Units as well as for other sections giving advice.

- Resources Used to Operate the Surveillance System: the resources to operate the surveillance system in terms of data collection and simple analysis are already deployed by the Department of Health and Aged Care as part of the routine processing of recall actions. Nevertheless, additional resources will be required to adapt the IT systems and analytics capacity to the program. Although this is an additional cost, it is noted that a recent review of the work processes done for MQB, final report dated July 2020, recommended "improved information management and data analytics".

2. Implementation of a surveillance system and recommendations

At the present time, no effective system exists to detect signals derived from recalls data. Despite the large number of recalls associated problems notified daily to the TGA, there is a concerning lack of analysis tools to mine the data available to the regulator. In particular for medical devices, better design of prospective systems for capturing adverse events specific to the growing complexity of medical devices is needed. This can ultimately provide a powerful basis to instigate recalls when necessary: with a structured analysis, signal detection will be feasible which will trigger more pro-active vigilance and finally improve patient safety.

Analysis would also support understanding the role and effect of process failures and inadequacies in the system design and risk management processes by the manufacturers of the medical devices. In addition, consideration of the economic impact of recalls is important and economic losses on the industry and health care payer side can be significant when large numbers of medical devices are recalled. Although the TGA may mandate a recall action, the majority are initiated by industry. Recalls have a negative effect on brand name therefore a coherent recalls prevention program can produce gains from recognition of previous recall actions. An efficient recalls surveillance system will assist businesses to take more preventive recall measures. For example, if a pacemaker fails due to premature discharge from certain type of batteries or there are some toxic particulates identified after a specific sterilization method used for orthopaedic prostheses, these situations could be avoided by other companies or at least identified earlier for products using similar products or processes.

Implementation of a surveillance system will provide the TGA with an efficient tool to regulate devices in the Australian market. To achieve this goal, several aspects have been identified which are susceptible of improvement and the following recommendations could be adopted:

During the interviews with the Recalls Unit, it was patent that QMS documentation is not completely up-to-date at the moment. Particularly as changes are proposed to the recall data processing and analytics, additional training for the current staff will be required, and SOPs and WIs are an integral part of that framework. This will affect the processes of different areas: the Recalls Unit, devices post-market sections and DCS.

Recommendation 1: Update SOPs and WIs to reflect the changes in the process of recalls of therapeutic goods, and implement regular (annual) updates to the QMS documents if required.

Although the implementation of an analytic tool is a priority as will be explained later, several steps can be undertaken simultaneously on the existing system with the aim to have a positive impact on data quality. Data migration from the notifications to the RAMP database should be improved. A limitation of the current system is the limited uptake of the online form (especially by small and medium sponsors).

Online forms need to be the norm for submitting recalls notifications by the companies. This will raise the accuracy of data capture and diminish the risks of communications not been entered in RAMP. A back-up pathway for communication such as email could remain open for exceptional circumstances such as failures in the system. Targeted education at sponsor groups with poor uptake is recommended.

Recommendation 2: Mandate online applications as the method for the sponsors to submit data to the TGA.

The online form can be augmented by making it more comprehensive and therefore useful for subsequent analysis. New fields, such as problem category and subcategory, should be introduced as part of the online form and those would need just verification from the Recalls Coordinators. Relevant quantitative data for calculation of the risk rating within the health risk assessment (number of complaints and devices distributed/implanted, severity and frequency scales used) should also be added. The complexity for the latter is that it will require to unify risks matrices used by manufactures and regulators for the purposes of notification in accordance with international standards.

Fields can be enhanced by introducing drop down menus for relevant jurisdictions to the TGA where a related recall action has been initiated or by adding validation steps to the distribution list which can be incorporated with a search window. The latter could be more complex if the distribution list is long as in the case of pharmacies for low risk devices. Constraining these new fields to specific

situations, for example limiting these changes to a certain recall level such as hospitals could be an option.

Recommendation 3: Review the current online form to introduce new fields or enhance existing ones.

Another step in the process is the completion of the follow-up and final reports on the same online platform. As there is already an online portal in place to submit the initial notification step of the process by the sponsor, this could be easily implemented.

At present, those reports are included as an attachment and sent in an email by the sponsors. Adding additional tabs to the online form allowing the submission of the follow-up reports and migrating that information into RAMP is the elementary solution to this issue. This change will reduce the burden to the TGA staff in terms of entering data into RAMP. Additionally, it will reduce the manual handling and risk of human error within the database.

Recommendation 4: Introduce online forms for follow-up or final reports by the sponsor.

It was important to acknowledge limitations in the data input to the system when developing the current surveillance plan in order to minimise their unfavourable effect. One of them is that not every medical device is licensed individually. For example, devices classified as associated with low to medium-high risk, do not require individual device licenses (ARTG entry) and may be marketed by manufacturers with a valid establishment license. The UDI project, which aims to implement a globally harmonised identification system for each device, could help in that regard in the near future in more accurate and faster identification of problems. The UDI System will become an important tool for improving the identification and traceability of medical devices. Therefore, UDIs will support the interoperability and data exchange between different systems used in healthcare and will add in recall tracking by the different stakeholders. When the UDI is fully operational, related data need to be captured by the proposed surveillance system.

Another issue is that capturing data for individual recalls can be complex and challenging which affects the simplicity of the surveillance system. One recall may affect several unique devices under a single license or certain lots, and some devices may be subject to a recall on more than one occasion. For example, faulty software could be installed in multiple devices from the same manufacturer and the correction will affect all of those products. Furthermore, several problems could be covered by one recall action, for instance, different software defects that will be managed at the same time within the proposed corrective action. Currently, RAMP allows for introducing

multiple ARTG entries under one recall action, but it only accepts one Problem Category and Subcategory per recall action. This complexity needs to be adequately captured by the surveillance system. Therefore, it is proposed that several fields need to be included or detailed in RAMP (Table 3) to enable data evaluation within the analytic tool.

Other fields that could be captured in RAMP, but will not be in the online form, relate to possible interactions between the TGA and sponsors previous to and after the notification. These particular fields could be used to reflect the level of engagement and cooperation of the different sponsors with the TGA.

Recommendation 5: Introduce new fields or modify current field entries in RAMP.

Choosing an analytic tool for the current data captured in RAMP by the TGA, such as Qlik which is already used within the Department of Health and Aged Care, would facilitate a timely implementation of the system in comparison to developing a complete new tool. Incorporating the analytic tool into the new surveillance system could also help in evaluating the progress of the notifications, the effectiveness of the recall strategy, any underlying investigation of root causes if applicable until full closure and the compliance of the sponsors with the specified timeframes, as in the case of follow-up reports deadlines. Additionally, some of the data that are currently captured in RAMP will definitely benefit from the implementation of the surveillance system analytic capacities specifically designed for that purpose. For example, a single search term in the recalls database may be used to consistently identify software's possible involvement in the reported problems. It is important to design specific analytic tools to target where to focus the analysis and recommend how to automate further the manually intensive and time-consuming analysis performed at the moment. The current load of the Recalls Unit is huge, and this type of analysis is unsustainable considering the year by year increase in recall actions to be processed.

Even though the experience gained with the current post-market Qlik app could be useful to facilitate the implementation of this specific tool, a completely new recalls Qlik app will need to be created specifically to cover the needs of the recalls surveillance system. It is recommended that access permission to this app should be extended to all interested sections at the TGA enhancing acceptability. Having an operational surveillance system could be feasible in less than 1 year giving consideration that authorization for developing the project may require allocation of budget resources.

Recommendation 6: Implement Qlik as a data analysis tool for RAMP.

Particular emphasis should also be placed in analysing with the analytic tool possible trends related to the source that triggers the report. It is expected that recalls not initiated by the sponsor or manufacturer will be influenced by other factors such as relevant concerns to patient groups or signals detected by other regulators. Depending on the result of this analysis, data collected from sources currently not captured by RAMP including electronic medical records or insurance claims could be an avenue in the future for detecting signals. The promise of these new initiatives includes the potential mitigation of the impact and frequency of major device recalls by earlier detection of problems. Considering that the TGA is first point of contact, this could be achieved by using the knowledge acquired through the surveillance data analysis, either to instruct the company affected to initiate a recall action which could be impacting different products or to inform other companies with similar marketed products which could be potentially affected by the same issue. A surveillance system which identifies the source of the referral which triggered the recall action will add value to the health actions taken by the TGA. Similar approach will be valid for other sources such as consumers or other regulators.

Recommendation 7: Analyse the database for specific trends according to the origin of the source which triggers the recall action.

An uncommon source of relevant information for the surveillance system could be implant registries. In the context of a post-market surveillance system, registries are helpful tools as they can facilitate communication among different stakeholders. An implant registry is a tool to deliver long-term observational data related to the performance of medical devices, but can also be regarded as an overriding tool when it comes to controlling the high incidence of adverse events. For example, within the EU, the European Heart Rhythm Association (EHRA) takes a role in helping to coordinate dialogue among stakeholders. Some unexpected performance of medical devices has been identified early to improve patient safety (23). In Australia, there are mature registries such as the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR), which are collaborating actively with the regulator to identify potential problems with devices. Increasing implant registries' input in the context of the post-market surveillance system will be achieved by including the Recalls Unit in the working groups and conversations that the TGA holds with registry initiatives in Australia. Although registries do not handle recall management per se, they have played an important role in the quick identification of patients, when a recall or adverse event occurred. In addition, registries can survey large populations, providing a powerful scientific method for long-term observational data collection. For simplicity, creating an additional entry in the drop down menu in RAMP could be achievable in a short term and will facilitate its analysis in Qlik.

Recommendation 8: Explore the possibility of gathering input from external sources such as implant registries.

Furthermore, to detect a medical device problem across jurisdictions that could harm patients, a more effective information sharing system for medical device recalls should be established with the help of the recalls surveillance system. As mentioned previously, there are legal obligations to supply accurate information and mechanisms in place to enforce these requirements, but it can be particularly difficult to identify misleading or false information. One side avenue to cross check data is when international actions have been or are undertaken at the same time as the process in Australia. For this to be more efficient, communication channels with other agencies have to be improved.

In terms of possible input avenues to the surveillance system, publicly available international recall databases have certain limitations worth considering. They do not present consistent information across jurisdictions, i.e. not all recall information is available publicly, and what is available may not contain enough information to make a definitive assessment regarding causes and contributing factors. Although not all the information will be available, including data extracted from relevant and comparable regulators public databases in the surveillance system analysis tool could help the TGA inform further its decisions and identify trends. Due to its flexibility, Qlik could be developed to interrogate multiple databases if required.

This change will increase the representativeness of the system, but it is recommended that these databases need to be built by comparable regulators ensuring that the credibility of the data is acceptable. For example, the FDA medical device recalls database is searchable online and includes data since 2002 and MHRA publishes summaries of safety alerts and recalls on its webpage. Canada also provides access to a general list of recalls, advisories and safety alerts which can be broken down by different categories including health products. Making this additional information available for analysis will further inform TGA's decisions and identify trends in a timely manner.

Recommendation 9: Include data from publicly available recall databases from other international regulators in the input of the data analysis tool.

Data from the various email subscribing lists will be harder to incorporate into Qlik. Information contained in email chains from other jurisdictions, although valuable, appear to be more complex to extract and would impact the simplicity of the system as it will need an additional step in the current process in regard to data screening and capturing.

Another point to consider is that collaboration with international regulators is of the upmost importance to detect more efficiently defects that could harm patients. A surveillance system will definitely improve that aspect if data from other jurisdictions are consistent and reliable. Establishing and promoting a more effective international information sharing system for medical devices recalls should be then the objective.

As being TGA part of different international fora and cooperation initiatives, it is recommended that the TGA takes the lead in proposing a template with minimal requirements for regulators when publishing recall actions (Appendix 5). From a practical point of view and considering that SARA is already available as the public communication strategy, only the last two fields, the deadline for completing the recall action and the description of the category or family of the affected product will necessitate to be incorporated. Even though, this proposal requires consultation with the industry as for example the disclosure of volume of sales is commercial in confidence information.

After consensus, the proposed template can be put forward to consideration of international regulatory agencies. There may be limitations due to confidentiality arrangements with different regulators. One of the avenues is to utilise established cooperation spaces such as the IMDRF (International Medical Device Regulators Forum) regular meetings. Australia is a current member of the organization.

Recommendation 10: Advocate for the adoption of an international standard for recall reporting

In terms of outputs and due to confidentiality, continuing with the email distribution lists will be probably the most recommended option. Additionally, evidence-based decisions as a result of the operation of the surveillance system will increase the efficiency of the communication with other regulators and could tailor the message according to the products available in other jurisdictions.

Finally, as this proposition implies an important change to the current processes, it is recommended that after implementation of the surveillance plan, it will be fundamental to evaluate if the proposed system is working as expected. This assessment should be done based on relevant evidence and outcomes extracted from the surveillance system following the CDC guidelines as per the surveillance system plan. A report will be delivered to the relevant stakeholders with further recommendations if applicable.

Recommendation 11: Implement a preliminary assessment of the surveillance system after operational.

In the meantime, if substantial changes cannot be immediately implemented in the regulatory processes for recalls surveillance, it should be considered as a viable alternative to place the onus on industry-supported and TGA-monitored education of health-care institutions and providers, who ultimately decide which devices are implanted in a patient to increase awareness on adverse events reporting.

Better communication of the risks associated with the product involved in the recall action should be considered to help clinicians and patients make appropriate risk assessment and allow adequate informed consent before taking a final decision on the proposed treatments.

The communication action plan agreed with the sponsor could be reinforced by close monitoring of the recall strategy by the TGA (focusing on compliance with the goals proposed during the follow-up and closure of the recall action). Furthermore, providing more detailed information in publicly available databases such as SARA about possible adverse health consequences or through additional engagement with consumer groups and the community could be beneficial.

3. Evaluation of the surveillance system using the CDC guidelines when fully implemented

Evaluation of the surveillance system plan is recommended to be carried out as a preliminary assessment at 6 months to identify any potential minor improvements. If the implementation is uneventful, a 12-month formal review is recommended. Observing how the system responds to a new demand will allow to evaluate if the surveillance system adapts easily to changing information needs or operating conditions with little additional time, personnel, or allocated funds. This assessment should be based on relevant evidence to evaluate the surveillance system for recall actions according to the level of usefulness and the nine attributes identified previously from the CDC guidelines to assess the performance of surveillance systems.

Level of Usefulness

The implementation of a fully operational surveillance system will help in the analysis and interpretation of data collected basically through RAMP at the moment. The possibility of incorporating new data fields into RAMP and interpret them with the help of an analysis tool will assist both the Recalls Unit and internal stakeholders such as devices post-market sections and DCS in their assessments. The Recalls Unit at the TGA is collecting daily a large amount of data which could be used more efficiently and have an enormous impact in the decision making processes and therefore affect positively the Australian community. A fully operational surveillance system will

identify signals specific to product problems related to certain companies or families of products and will enable opportune regulatory actions.

Having a surveillance system in place which permits analysis of trends and investigation of recalls history will guide regulatory decisions and increase the consistency of the recall action strategies. Moreover, evidence obtained from the system could be used to provide valuable feedback the sponsors and manufacturers, and have an impact on overseas regulators by communicating concerns and enhancing information exchange.

If the goal is to detect the proportion of possible recalls captured by the surveillance system, then this surveillance system is impractical. The current number of recalls that are not captured by the system will be hard to ascertain as there are no mechanisms in place to actively search for recalls that should be logged into the system but for different reasons were not initiated. However, the surveillance system could be assessed in regard to other parameters:

- discerning between sources of the recall and other characteristics such as differentiation between URPTG following or non URPTG following actions,
- detecting signals related to specific product problems related to certain companies, suppliers or families of products, or
- monitoring change in trends over time for certain recall actions or specific products.

As a result, level of usefulness will be evaluated on whether the data collected are valid and meaningful for the analysis proposed. Moreover, impact on consistency and guidance on regulatory measures could be measured by predefined metrics (such as correlation between problem category/subcategory and recall action strategy implemented across families of products) and interviews.

It is recommended to focus on the same attributes from CDC used during this project for evaluating surveillance system as this will promote a valid comparison. It is noted that from all the attributes the one that was not particularly useful for this proposed surveillance system was the “predictive value positive”, because of the difficulties in detecting what could be the proportion of cases that are actually recall actions (due to uncertainties in the denominator).

Conclusions

The existing recall system at the TGA collects data in an ongoing capacity, but is limited in terms of analysis, interpretation and dissemination of the data to improve health. At present without a proper analytic tool, those data are used (not reaching its full potential) in immediate public health action (which is part of the aim of the recall process), but still has a long road to go in terms of

program planning and evaluation and even longer in terms of research hypotheses formulation. The current interface which provides access to recall records and data, RAMP, is limited as basic search capabilities are not robust enough to support complex queries or to interrogate the actual data held. The challenge is to implement an adequate analytic tool in the brevity of time.

The TGA needs to further improve the recall process by systematically assessing recall information to identify trends and underlying causes of recalls. This analysis of the data gathered by a recalls surveillance system will enable accurate investigations and result in prompt regulatory actions. Current surveillance mechanisms are not sufficiently tailored to identify specific problems.

Enabling an adequate surveillance system will allow the Recalls Unit and other sections in the TGA, such as DCS and devices post-market areas, to respond efficiently and effectively to issues with a therapeutic good that entails or may pose a risk to public health and safety in a consistent and systematic way. Improved information management and data analytics will significantly help the TGA to undertake a more targeted, risk-based approach to the regulation of medical devices.

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Appendices

Appendix One: Classification and Management of a Therapeutic Good Recall in Australia

1. The health-related event - What is a therapeutic good recall?

A recall action in Australia is a set of market actions that are undertaken to resolve a problem with a therapeutic good already supplied in the Australian market for which there are issues, deficiencies or defects in relation to the safety, quality, efficacy (performance) or presentation of the therapeutic good. These issues may be due to non-compliance with specified standards or legislative or manufacturing requirements applicable to the therapeutic good.

Not all issues require recall actions. A non-recall action can be undertaken if:

- the therapeutic goods meet all specifications and standards AND
- there are no deficiencies in safety, quality, efficacy, performance or presentation.

There are four types of non-recall actions:

1. Safety alert: safety alerts are issued to provide information on the safe use of therapeutic goods in certain situations where, although meeting all specifications and therapeutic indications, its use could present an unreasonable risk of harm if certain specified precautions are not followed.
   A safety alert is generally used for reiterating specific precautions or instructions regarding use of the goods.
2. Product notification: a product notification provides information about a therapeutic good in a situation that is unlikely to involve significant adverse health consequences.
3. Quarantine: if a defect is identified in released goods which has the potential to raise issues related to safety, efficacy (medicines / biologicals) or performance (medical devices), a quarantine of goods could be initiated.
   A quarantine action suspends further supply and distribution of the goods pending the investigation of an issue or incident. The outcome of the investigation will determine further actions (the quarantine could be lifted or any given recall or non-recall action may occur after).
4. Product withdrawal: a product withdrawal is used to withdraw products for reasons that are not related to safety, quality, efficacy, performance or presentation, e.g. removing a previous model from the market when a new model has been released.

There are four distinct recall actions available to sponsors - recall, product defect correction, hazard alert and product defect alert.

- **Recall** - a recall is conducted to remove therapeutic goods permanently from the market or from use when there are deficiencies or potential deficiencies in safety, quality, efficacy, performance or presentation.
- **Product defect correction** - undertaken to correct a specific or potential deficiency and includes repair, modification, adjustment or re-labelling of a therapeutic good. The corrective action may take place at the user's premises or any other agreed location. In some instances, the product can continue to be used if there is robust mitigation in place until a permanent correction has been implemented.
- **Hazard alert** - a hazard alert is issued for an implanted therapeutic good with a deficiency or potential deficiency relating to its safety, quality, performance or efficacy because implanted goods (medical devices or biologicals or medicines) cannot be recalled. Usually medicines or biologicals will not be able to be retrieved from a patient after administered, but medical devices could be, and the decision to explant a device will be considered against the risks of that procedure. The hazard alert will typically contain precautionary information issued to healthcare professionals about issues or deficiencies relating to an implanted therapeutic good and advice about the ongoing management of affected patients. There may or may not be advice to consumers in the event the hazard alert is published on the TGA Website. A hazard alert may also be issued in conjunction with a recall notice for affected products that have not yet been implanted.
- **Product defect alert** - allows for the informed, continued use of defective but critical therapeutic goods, raises awareness of the issue and describes the precautionary actions that clinicians or patients may take to mitigate any associated risk. A product defect alert may later be followed by a recall once unaffected or alternative products become available. It is often the case that a product defect alert is utilised where there is no alternative product available at the time and/or for which a recall action will result in a significant interruption of patient treatment or a therapeutic good shortage, either of which would likely present greater adverse clinical sequelae than the defect itself.

Recall actions vary on a case-by-case basis depending on the deficiency of the therapeutic good and the risk the deficiency poses to public health and safety.

A recall action can occur because of straightforward problems, such as labelling or packaging errors, or for more serious and complex problems, such as an unexpected increase in side effects or microbial contamination.

2. Classification of a recall

To assist in the identification of the nature of a recall action, they are classified into one of the following classes based on the potential risk the deficiency poses to patients/consumers:

- **Class I - Most serious safety-related** - recall action occurs when there is a reasonable probability that the use of, or exposure to, the deficient therapeutic good(s) will cause serious, permanent or long term adverse health consequences or death.
- **Class II - Urgent safety-related** - recall action occurs when the use of, or exposure to, the deficient therapeutic good(s) may cause temporary or medically reversible adverse health consequences, or where the probability of serious adverse health consequences is remote.
- **Class III - Lowest risk** - recall action occurs when the use of, or exposure to, the deficient therapeutic good(s) is not likely to cause adverse health consequences and they are therefore not safety related.

Class I or class II recalls are considered to be urgent safety-related recalls, whereas class III recalls are considered to be routine non-safety-related recalls. In addition, the TGA has classified recalls based on the following:

1. The incidence of complaints

2. Distribution networks

3. Recovery procedures

4. Resources for corrective action

5. Availability of alternative products

The TGA and U.S. FDA have also defined the elements of recall strategy, including classification of recall; necessity of initiating a recall; level (or depth) of a recall, i.e., wholesale, retail, hospital, or consumer level; significance of the hazard (if any); the channels by which the goods have been distributed; and the level to which distribution has taken place. The manufacturer must also specify the method used and the level of consignees' communication for recall.

3. How are recalls managed in Australia?

Making a decision to undertake a recall action with sponsors

Australian sponsors may voluntarily notify the TGA, or be contacted in connection with the possibility of initiating a recall action for a therapeutic good as a result of reports referred to the TGA from a variety of external sources, including:

- consumers;
- manufacturers;
- wholesalers;
- retail and hospital pharmacists;
- blood and tissue banks;
- pathology departments;
- overseas regulators;
- research facilities - e.g. clinical trials; and/or
- health care professionals.

The TGA may also request agreement for a recall action as a result of:

- analysis and testing of samples of therapeutic goods;
- advice from an expert advisory committee; and/or
- information received from international regulatory authorities such as the FDA in the U.S., MHRA in the UK, European Medicines Agency (EMA) or Health Canada. These communications can come to the TGA by general mailing list subscriptions such as Rapid Alert list (mostly from European regulators) or direct emails.

Occasionally, when the recall was satisfactorily completed by the sponsor but did not follow the recommended process steps overviewed by the TGA, it is considered by the TGA as “non URPTG following”. Sponsors are reminded of their obligations when the Recalls Unit writes to them after becoming aware of such failures.

Conducting an agreed recall action

The level to which a recall action has to be undertaken is based on the significance of the risk and the channels through which the goods have been distributed. The recall levels in cascading order are:

- **Wholesale** - includes wholesalers and state/territory purchasing authorities.
- **Hospital** - includes public and private hospitals, nursing homes and other healthcare institutions, hospital pharmacists, ambulance services, blood and tissue banks and pathology laboratories as well as wholesale as appropriate.
- **Retail** - includes retail pharmacists, medical, dental and other health care professionals, supermarkets, health food stores and online stores as well as wholesale and hospital as appropriate.
- **Consumer** - includes patients and consumers, as well as wholesale, hospital and retail levels as appropriate.

Therefore, in a Retail level recall action, letters are also to be sent by the sponsor to affected wholesalers and hospitals by default.

The TGA endeavours to recall therapeutic goods to the depth of supply and as such, only affected parties need to be notified of an action as detailed in the customer or distribution list.

4. How are recalls managed from overseas?

The TGA receives information about overseas recall actions as part of its ongoing working relationship with many international agencies and overseas regulators of therapeutic goods. If the therapeutic good which has undergone a recall action overseas is included in the ARTG ("the Register") and/or has been commercially imported and distributed in Australia, then the TGA assesses whether the importer will be required to conduct a recall action for the good in Australia. Such recall actions appear in the System for Australian Recall Actions (SARA) database after two days (excluding weekends) of the recall action commencing in Australia.

Therapeutic goods that have not been supplied in compliance with local regulatory requirements, or have been imported from overseas by consumers for personal use, for example via the internet, do not appear in this system.

Information about therapeutic good recalls occurring overseas is made available online by other agencies. This includes information from the U.S. FDA, Health Canada, EMA, the UK MHRA and others.

5. Differences in managing recalls for Medical Devices

Manufacturers are responsible for analysing the potential risks associated with an adverse event, goods failure or complaint using an appropriate QMS as described in *ISO 14971 Medical devices – application of risk management to medical devices*.

Medical device manufacturers require, as part of an effective QMS (usually in accordance with *ISO 13485 Medical devices - Quality management systems - Requirements for regulatory purposes*):

- a system to recall any batch of goods by notifying sponsors or distributors
- a system to investigate any issue, including identification of root cause and implementation of corrective and preventive actions (CAPAs).

Appendix Two: Routine process for a recall action and the 11 steps in the URPTG

- Step 1 - Immediate recalls: in circumstances where a sponsor becomes aware of a serious risk associated with a therapeutic good, immediate action may be required to protect the health and safety of consumers, a company, employees or the community as a whole and the Recalls Coordinator need to be contacted immediately.
- Step 2 - Obtaining distribution and stock status: the sponsor will collect the data (such as date released, quantity of the batch, dates and quantity distributed to the Australian market and quantity supplied to customers) according to a unique identifier for the product (such as catalogue number or model reference) and manufacturing details (such as lot number or batch number). Additionally, details of any regulatory action taken overseas and sample testing (if applicable) need to be included by the sponsor in a therapeutic goods report.
- Step 3 - Conducting a risk analysis: the sponsor should receive this risk analysis report (often known as a health hazard evaluation or HHE report) when the manufacturer notifies of the device defect,
- Step 4 - Deciding the type, class, and level of recall according to the guidance in the URPTG: if, after completing the assessment, the sponsor decides the issue with the therapeutic good does not warrant a recall, then it has to be determined if a non-recall action may address the issue and Step 6 should be started.
- Step 5 - Developing a recall strategy: a draft will be submitted to the TGA for review.
- Step 6 - Drafting a communication strategy: the goal is to enable those in the supply chain to know about and comply with the recall notice including the sponsor's customer letter.
- Step 7 - Submitting recall information to the TGA: for recall (and non -recall action) the preferred method is an online notification, but email notification is still accepted.
- Step 8 - TGA assessment of the recall: the TGA conducts an independent and objective assessment to verify the strategies are appropriate to mitigate the risks posed by the affected goods including timelines and availability of alternative goods and for critical goods, the effect on future supply.
- Step 9 - Implementing the recall: the sponsor implements the communication and recall strategies once agreed. For non-recall actions agreement has to be reached that a recall is not required.

  A root cause analysis of the issues (usually done by the manufacturer) is undertaken in parallel with the recall process.
- Step 10 - Reporting on the recall: submitted by email at 2 weeks (initial report), 6 weeks (follow-up report) and 3 months or at another agreed time (final report).

- Step 11 - Reviewing the recall: the TGA verifies with documented evidence that all agreed actions were completed and that the strategy implemented provided satisfactory results.

Even though the TGA can guide the sponsors throughout the whole process, the TGA gets actively involved in Steps 8, 10 and 11 in particular.

During step 8, the TGA can provide advice and assistance in relation to letters, consumer recall notices and recall strategies. If an agreement cannot be reached with the sponsor on the appropriate recall strategy, the TGA can mandate a recall (enforce it by the law).

Recalling companies are also responsible for notifying customers about the recall and keeping the TGA informed of the recall status.

All recalls (except blood component recalls) undertaken in Australia in the publicly searchable database (SARA).

As part of conducting a recall and following TGA agreement to proceed, sponsors are required to submit progress reports at two- and six-weeks following agreement, and a final close-out report at 12 weeks. During step 10, progress reports (using specified templates) are sent to the TGA by the sponsor. The aim is to provide the necessary information to the TGA which allows to analyse the effectiveness of the recall.

Step 11 examines the progress reports. The TGA will:

- verify the sponsor has:
  - – completed all the agreed actions with documented evidence
  - – justified any discrepancies or inconsistencies
  - – provided evidence of the fate of the final goods
- determine whether the following are satisfactory:
  - – implementation of the recall
  - – the investigation of the issue or hazard that prompted the recall and the root cause identification
  - – CAPAs implemented to prevent or minimise recurrence of the issue in the future
- assess the effectiveness of the recall action
- assess ongoing compliance with regulatory requirements.

The Recalls Section reviews these reports and, once satisfied the recall action has been completed as far as practicable, issues the sponsor with a final notice advising the action is considered complete and closes the action on the Recalls and Medicine Problems (RAMP) database.

Detailed steps involved in the data collection, analysis and communication:

1. If a notification of a recall is entered online (Appendix 3), a recall number (RC number) is automatically generated and linked to that notification and will serve as identifier during the process and administrative staff of the TGA will transfer the details to RAMP.

   The alternative way of submitting the recall notification is by email. The current version of the URPTG states that:

   > "Alternatively, we will still accept email notification from you until 30 June 2020"

   This deadline is currently under review and likely extended as, even though sending the information by email increases the manual handling of the information by the Recalls Unit, email is still considered the backup option in case the online form is unavailable (a situation that has rarely happened).

   If done by email, administrative staff from the Recalls Unit get the information from the recalls generic inbox and enter the details in RAMP.
2. After this process, administrative staff from the Recalls Unit get the information from the inbox or from the online portal and save the relevant documents in TRIM. Relevant attachments, such as the Health Hazard Evaluation (HHE) or proposed customer letter, pertaining to that notification, will be stored in an individual specific folder coded with the RC number.
3. The new notification is entered into a queue of pending tasks to be processed by the Recalls Coordinator. This is done by placing the RC number to be processed into a designated group space in Webex and the Recalls Coordinator informs the rest of the team of starting that task by a message in the group space. Webex is the current team collaboration solution employed by the Department of Health and Aged Care.
4. The Recalls Coordinator verifies that the fields entered about the Recall in RAMP matches the information in the documents in TRIM and review 3 main documents:
   - Customer list
   - HHE
   - Customer letter
5. After the notification is verified by the Recalls Coordinator:
   - an RP number, which is another identifier used for continuity of internal processes in Work Management, is created in RAMP.

- "Create an incident" is activated in RAMP which is linked (manually) to the TRIM folder. This step enables the creation of all the tasks in RAMP such as reports.
- "Create letters" is activated in RAMP which creates automatic prefilled templates - forms WP2 (Appendix 4 - used for initial review of the recall action and its risk assessment by the Recalls Coordinator) and WP3 (for communicating agreement of the next steps with the sponsor). These templates are saved manually in the TRIM folder and not directly accessible from RAMP.

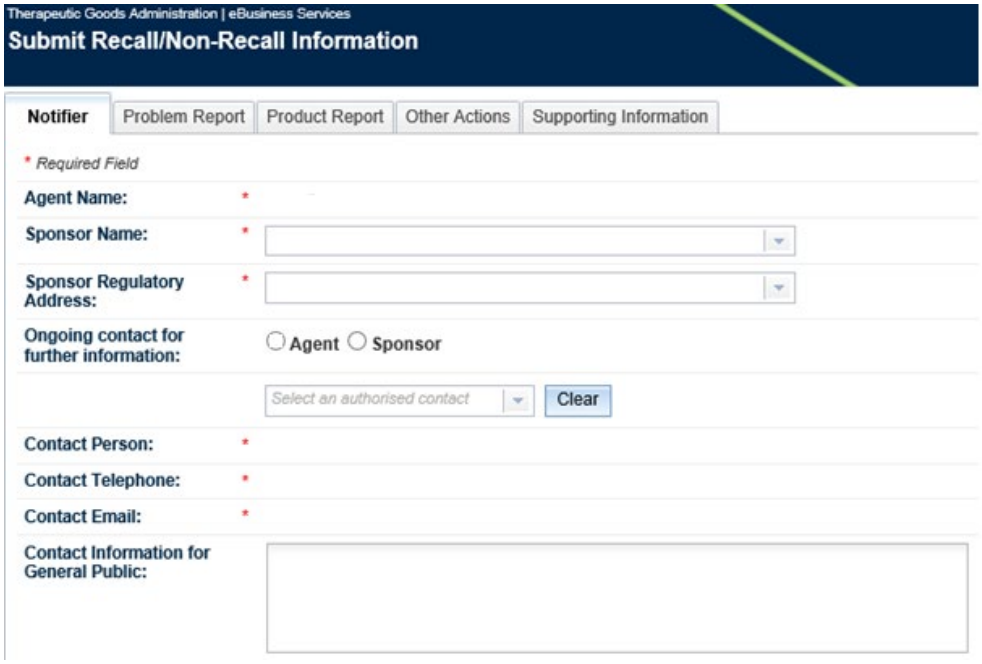
6. The Recalls Coordinator fills the WP2 form. This step that could require internal stakeholder engagement such as clinical input.
7. After the risk assessment is found acceptable, the WP3 is completed. Edits have to be made to the WP3 template manually to capture dates when the reports are due and this will be sent to the sponsor by email in an attachment alongside with a customer letter (if amendments were suggested by the TGA, those changes have to be saved manually by the Recalls Coordinator).
8. The sponsor has to send a signed copy of the final letter (within two business days) to the TGA and this final document is saved in TRIM.
9. The active task ("Initial Activity") is closed in RAMP by the Recalls Coordinator enabling SARA (System for Australian Recall Actions) to extract this information (this process is automatic).
10. Email is sent to administrative staff to register the broadcast schedule in an Excel spreadsheet. At this date (after two business days), emails will be sent to the internal and external stakeholders of the TGA.
    The email will also trigger to track the follow-up reports in a spreadsheet (input is manually done by the administrative staff).
11. At day 3, once a recall action has been initiated, the TGA notifies a number of key stakeholders including the state and territory health department Recalls Coordinators. The TGA may also notify other stakeholder groups depending on the type of product being recalled.
12. Reports: the progress of the recall is assessed at determined milestones.
    Further information from the sponsor can be requested or additional advice from the internal stakeholders (similar as in step 6).

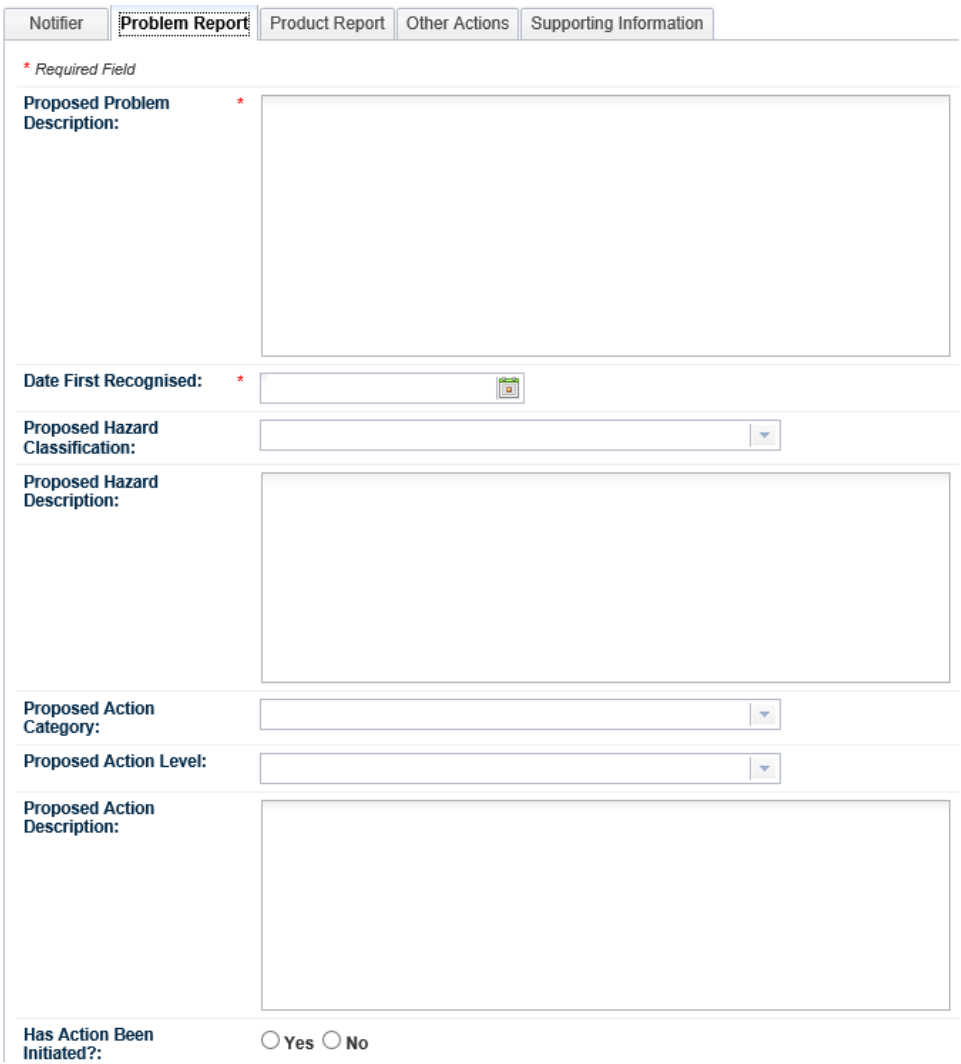
Overdue reports are followed up based on the recall classification. Priority is assigned to Class I and Class II recall actions in that order.

Critical recalls reports are monitored weekly.

13. Closure: a recall is terminated when the TGA determines that all reasonable efforts have been made in accordance with the recall plan.

Appendix Three: Online form for notification





Notifier | Problem Report | **Product Report** | Other Actions | Supporting Information

* *Required Field*

Product Description: *

ARTG(s): * Add | Not on Register

	ARTG Id	ARTG Label	Status	Type
0 item		10 | 15 | 30		
	No ARTG entries have been added			

Select not on register when the good is not listed including when it has been cancelled. Provide further details in product description field (e.g. product/model details, cancelled ARTG ID).

Product Code (or Catalogue/Part Number): *

Product Identifiers (i.e. Batch, Serial, Lot Numbers): *

Manufacture Date: *

Expiry Date: *

Release Date: *

Batch Size: *

Product Distribution: *

Product Distribution Details: *

Are the affected goods exported from Australia?: * ○ Yes ○ No

Notifier | Problem Report | Product Report | **Other Actions** | Supporting Information

* *Required Field*

Previous Actions: Add

	TGA Recall Reference	Additional Information
0 item	10 | 15 | 30	
	No previous Recalls have been added	

Provide the RC number for any previous Recall or Non Recall actions in the last 3 years that are related to the same Good(s) and/or defect in this notification.

Current or Previous Overseas Actions:

Please include relevant information, web links or documents for the same issue that's currently being addressed in an overseas jurisdiction, or has been addressed in the last 3 years.

Notifier | Problem Report | Product Report | Other Actions | **Supporting Information**

* *Required Field*

Add

Please attach any relevant information including (but not limited to):

- *Draft Customer Letter and Customer Acknowledgement Form;*
- *Detailed Distribution List of Impacted Customers in the following format: State / Customer Trade Name / Suburb in MS Excel; and*
- *Risk Assessment / Health Hazard Evaluation report preferrably with clinical comment from a medical doctor.*

	File Name	Description
No Attachments have been added		

To view any of the uploaded attachments double-click on it to open it.

Appendix Four: WP2 form

Does the proposed action meet any of the criteria for Clinical advice from a Medicines, Biologicals or a Devices Medical Officer:	☐ When the clinical implications are unclear in relation to deficiency identified and/or the proposed workaround; AND/OR; ☒ When there is evidence of an actual death or permanent injury in any Jurisdiction, including any International reports; AND/OR; ☐ All Vaccine Recalls, TGA Immunology are also to be informed via emailing vaccines@health.gov.au; AND/OR; ☐ All Medicines, Biologicals or Medical Devices supplied under the Special Access Scheme (SAS) or Authorised Prescriber (AP) Pathway are to be notified to TGAs Experimental Products Section (EPS) via emailing eps@health.gov.au AND/OR; ☐ Any recall actions that would require a TGA Web Statement. (i.e. Hazard Alerts and/or Consumer Level recalls, Vaccine recalls and other 'one-off' circumstances that have wider health implications or where a Web Statement is determined to be necessary for any reason – please specify this detail in the comments section below); ☒ Yes – Send to Clinical Delegate for advice; OR ☐ No – Recall Coordinator to sign off

Clinical Delegate advice	*I consider the hazard classification to be appropriate. (If NO, provide reasoning and suggested classification in COMMENTS section below)*	***YES/NO***
	I consider the proposed action to be appropriate. (If NO, provide reasoning and suggested change/s in COMMENTS section below)	***YES/NO***
	I consider the proposed correspondence to be appropriate. (If NO, provide reasoning in the COMMENTS section below and suggested amendments to the draft customer letter using tracked changes)	***YES/NO***
	Signed: XXX <signed electronically> *Date: xx/xx/xxxx*	

Appendix Five: Template for Public International Reporting Medical Devices Recall Actions

The following template is proposed to be used a shared document of minimal information for use by international regulators across different jurisdictions:

Public International Report for Medical Devices Recall Actions	
Product name/description	*Brand name. It needs to incorporate all relevant information including but not limited to: catalogue, model, batch or, serial number.*
UDI	*Include description according to different jurisdictions*
Type of product (kind of medical device)	*Generic reference to the product family and category or family of the affected product (for devices GMDN code or similar)*
Manufacturer	*Legal manufacturer of the product*
Responsible entity for the affected jurisdiction	*Supplier, sponsor or importer responsible to the recall action in the jurisdiction.*
Recall action type*	*Name of the type of action taken to resolve the problem.*
Recall action classification*	*According to the potential risk that the defect poses to the patient/consumers/users (usually by a numeric order).*
Recall action level*	*Level to which the recall action was undertaken. This is based on significance of the risk and channels through which the product have been distributed (for example, wholesale, hospital, retail or consumer level).*
Recall reason/issue including relevant background information (death and serious injury reports should also be highlighted)	*Brief description of the reason for the recall action. If more than one reason has been identified, those should be specified as a list.*

Volume of affected devices distributed and implanted worldwide and in local country	*Figures need to be up-to-date at least until the previous month before the detection of the defect.*
Recall action commencement date and the deadline for completing the recall action	*This could be updated as marked as final at a later stage when effectively completed with details of final outcome including the final effect and completion date.*

[*] These variables could be classified and nominated different according to the various jurisdictions, but as part of the harmonisation of the report, it is encouraged to seek consensus for them as well.

Chapter 4: Adverse event reports of hip prostheses and prediction of prostheses with higher than anticipated rates of revision

“Las cuentas claras y el chocolate espeso.”

Saying in Spanish

Literal translation: “Keep your accounts clear and your chocolate thick.”

Contents

Preface

This chapter combines two projects: data analysis and epidemiological study. For me, it was worthy to undertake them towards the end of my MAE journey as I was definitely able to apply the lessons learnt throughout other experiences, and that probably made it easier to navigate for me (although I have to admit that support was important all along the way).

Even though I was a bit disappointed in the sense that I could not develop a prediction tool as I envisaged in my initial goal, this project provided me with some important practical skills which will be a useful starting point to upcoming challenges in my career as an epidemiologist.

My role

This project was basically conceptualized by me and had input from my supervisors from that point onwards. From its conception, it served to illustrate the complexity of managing different public health databases with their own advantages and limitations.

I was the lead researcher and was responsible from the initial steps (preparing the study protocol, obtaining ethical approval, designing the data analysis plan) until the very end (analysis and writing of the results). During the project, I had to liaise and negotiate with the guardians of the data from the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) in order to obtain the basic information to proceed with comparisons (always balancing the confidentiality and the safe management of information).

Lessons learnt

This project taught me a good lesson of how data, which can be complex to start with, could become even more complex in reality, especially when merging datasets. It was a demonstration that what you have initially envisaged and planned could become more intricate when you are trying to actually do it. Easier said than done.

Noting limitations of the available dataset, this project was conceived as a proof of concept that data held by the TGA could be used to predict which joint replacement prostheses do not perform as expected in terms of revision rate identified by the AOANJRR. The objective was to determine if this concept was supported by the data and could be followed with implementation of a project to develop a machine learning model (including the use of training and validation datasets).

The data analysis part was particularly challenging as I had to deal with collecting, data cleaning and posterior matching between two distinct databases. Manual checking of details was a very time-consuming and painful process. Although looking at it in retrospective, it was definitely a great learning opportunity. Beside numerous duplicate entries, several deficiencies were found in the

data, for example: minimal details in the description of the events, no reporting dates of implant nor explant of the prostheses, initial report dates recorded as being before the final report date, spelling mistakes in the name of the devices involved, no uniform naming conventions when entering the data, inability to obtain further information from the initial reporter, devices explanted not being available for laboratory testing, previous relevant incidents not reported, or no specific information about additional devices involved in the incidents. As a result, I had to learn how to deal with incomplete and sometimes low-quality datasets, and at the same time be able to identify potential ways for making future improvements in the current systems.

Prior to starting this project, my experience with any statistical packages was extremely limited (basically knowing that they existed) as I had not worked in any formal research beyond descriptive methods. Although I have to admit that it was a steep learning curve (which I am far from done), acquiring concepts of more complex statistical analysis has paid off in the sense of a better understanding, and at the same time broaden my horizon for future research projects and the work that it could entail. I chose to use Stata for this particular task, and I have to admit that I am extremely thankful that an introduction to its use was done during the course blocks. Speaking as a non-initiated, it is not a user-friendly package (although after some initial flirting with R during the decision-making phase of which program to use, my impression is that it is a mandatory characteristic of any robust statistical package).

I sought expert advice from the biostatisticians at ANU regarding the approach I was proposing to tackle the hurdles in my project. After assessing the data which I had available to work with, the statistical analysis turned out to be very simple. Despite of this, it set a good basis for my own learning processes. I learnt about factors that can affect a predictive model and avenues to solve related problems.

Another lesson was the recognition of the importance of considering differences between databases. It is always a challenge to link information from dissimilar databases, in particular if they were not specifically designed for that purpose. This experience enlightened my knowledge about using complex databases and made me more cautious on the assertions of things that can be done with them.

Public health impact

Even though we were not able to establish a predictor model for prostheses identified by the AOANJRR as having higher than anticipated revision rates, exploring that possibility and being able to identify pitfalls in the current reporting system of adverse events is a positive outcome. These

findings can aid in the continuous improvement of TGA internal databases and set the basis for future research which eventually will increase the timeliness of evidence-based regulatory actions and, as a consequence, benefit the Australian public.

This study was presented at the 10th International Congress of Arthroplasty Registries in November 2021 (Appendix 1) and during an internal meeting of the Devices Clinical Section at the TGA.

Acknowledgements

Firstly, I would like to thank my supervisors. My field supervisor, Ben Polkinghorne for his constant support and encouragement. Thanks also to my field supervisor, Simon Singer, for his pragmatic overarching views and advice.

I am immensely grateful for the input and advice regarding stats from Dan Chateau, who kindly overtook the initial steps done by Ben O'Neill. Also credits to Jorge "George" Garcia for sharing his knowledge about the relationship between the AOANJRR and the TGA. George assisted in reviewing my chapter and provided helpful feedback and comments.

Finally, my gratitude to Dr Stephen Graves, who was my initial point of contact in the AOANJRR, and all the fabulous group of people working to make the AOANJRR such a successful enterprise, including the lovely Cindy Turner who was very patient with all my requests.

Abstract

Introduction

Early identification of poor performing hip prostheses allows for timely rectifications of quality, safety and performance as well as for the application of regulatory measures. In Australia, the major database of adverse event reports is maintained by the Therapeutic Goods Administration (TGA). The Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) captures revisions as the primary outcome. While high rates of revisions are known indicators of poor prostheses performance, correlation with adverse event data is unknown.

Patients and Methods

TGA's prostheses adverse event data related to primary hip replacements between January 2008 and December 2020 were compared with AOANJRR's historical data (2018 Annual Report) of hip prostheses with higher than anticipated rates of revisions. A total of 1512 adverse events corresponding to 132 different type of hip prostheses product families were categorised according to incidence and severity, and correlation analyses with the prostheses' revision rate were conducted.

Results

The incidence and severity of adverse event reports did not show a strong direct correlation with the AOANJRR's 76 prostheses/combinations with higher than anticipated rates of revision.

Discussion

Although adverse event reports are important signals for monitoring of the safety and performance of medical devices, neither the severity nor the incidence seem to serve as predictors of hip prostheses that were identified by the AOANJRR. Therefore, continuous collaboration between the TGA and the AOANJRR is fundamental for the identification of orthopaedic prostheses that require special vigilance and/or regulatory action.

Introduction

Total hip replacement (THR), usually undertaken for end-stage osteoarthritis, is one of the most common surgical procedures, with more than 49,000 THRs done every year in Australia (1). THR is considered a highly successful and cost-effective procedure as most hip prostheses employed perform well. For instance, in terms of implant survival, the 20 year cumulative percent revision for currently used devices undertaken for osteoarthritis is 9.0% (1). But as for any implants, there is the potential for adverse events and malfunctions with serious consequences for patients. For example, recurrent dislocations could negatively impact quality of life and function, periprosthetic fractures affect subsequent mobility or prosthetic joint infection usually requires major revision surgery (2-4). As some prostheses may perform poorly, the need for adequate pre-market assessment and vigilant post-market surveillance is paramount (5).

It's not possible to conduct randomised, double blind clinical trials of the sort that are commonly used on pharmaceutical products to determine the safety and effectiveness (performance) of medical implants. Some of the reasons are that orthopaedic prostheses undergo multiple changes and modifications over time which make performing clinical studies impractical for each of those changes, barriers for randomisation, and difficulties in determining appropriate outcomes (6). For these reasons, the regulatory approval of a certain prosthesis is often based on similarities to previously used implants, rather than direct evidence based on clinical trials. In those cases, it is accepted that making minor adjustments to the design would not have a crucial impact on the safety and performance of the new prosthesis. Even though, insufficient or inadequate preclinical data, and limited clinical studies prior to market release increase the risk to patients (7). Unfortunately, there is a history of failed innovation within the orthopaedic prostheses field, demonstrated by the failure or recall of individual products such as The Capital Hip and the Articular Surface Replacement (ASR) hip system, or whole classes of devices such as large-head metal-on-metal bearings, where significant numbers of patients experienced unusual pain due to an inflammatory response associated with metal ions affecting periprosthetic soft tissue (8-14).

This demonstrates that current pre-market preventative measures are far from perfect and highlights the relevance of an efficient post-market surveillance system to quickly identify poorly performing prostheses. The primary function of post market event monitoring is to improve the health and safety of patients by reducing the likelihood of adverse events being repeated. Various high-income nations have systems for post-market safety information collection and follow-up management for medical devices (15-18). The strengthening of post-market vigilance is significant for the following reasons:

1) it is impossible to design a medical device with zero risk of failure or adverse event; and
2) it is impractical to prospectively study before marketing or use because incremental changes are made in devices throughout their life cycles (15, 19).

Registry post-market surveillance has proven to be a powerful method for detection of increased risk of implant failure (7, 20). Joint replacement registries provide information on patient demographics, statistics for individual surgeons, a record-keeping system on joint implants, and statistics for primary and revision procedures. Arthroplasty registries are able to identify differences in outcome based on patient, surgery, or prosthesis-specific factors (21-24).

The generally accepted outcome measure of primary joint replacement surgery is time to first revision, generally estimated using the Kaplan-Meier survival method (25). This measure, focused on implant longevity, is an unambiguous and clear indication of a problem with the primary procedure, where both the patient and surgeon have agreed that it is serious enough to require further surgical intervention (5, 26, 27). As a result, arthroplasty registries have also been very effective in identifying prostheses or combinations of prostheses that are outliers with respect to revision rate, when compared to others in the same class (5, 28-30). Furthermore, registries can determine multiple factors that affect outcome, including device and non-device-related issues. These data play a critical role in providing quality post-market surveillance, as well as helping to understand prosthetic use and improve patient outcomes (31-34).

The Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) was created to record and monitor the outcomes of implanted joint prostheses. It enables a way to determine failure rates of implants over a broad range of surgeries and identify inferior orthopaedic prostheses including hips, knees or shoulders. The AOANJRR first began staged implementation and data collection on September 1999 and full nationwide implementation commenced in January 2003. The Australian Orthopaedic Association (AOA) is the data custodian of the registry and contribution by surgeons is voluntary with almost 100% compliance (7).

The AOANJRR was one of the first registries, in 2004, to formally establish a system for identifying prostheses with a higher than anticipated rate of revision (HTARR). The AOANJRR has been successful in doing this and, as a result, many outlier prostheses are no longer on the market (5). The AOANJRR analyses the rate of revision separately for acetabular and femoral components, and if there is a higher than anticipated rate, individual components are published in the Annual Report. The AOANJRR also analyses all combinations of acetabular and femoral components. Occasionally, a combination of prostheses—only when used together—has a higher than anticipated rate of

revision, and this combination is noted. An Annual Report is published in September of each year and therefore, a specific constraint of the Report is that data are up to date as of 31 December of the previous year. In general, once a prosthesis or prosthesis combination has been identified, it continues to be identified as an outlier in subsequent years and after identification of the device, the usage usually declines. This has led to a marked reduction in the number of patients exposed to devices with a higher than anticipated rate of revision (5, 11). Nonetheless, poorly performing implant designs become obvious from registry data after 5 to 7 years in some cases (35). Alternative pathways which could enable earlier identification should always be sought.

While the annual reports provide a complete synopsis of registry activity on the whole population, provision of data in a more up-to-date and targeted fashion is potentially more beneficial for the regulators, and for patients subsequently. In many countries, there is no direct collaboration between the registers and health authorities, which may delay crucial information to reach the surgeons and have severe consequences for their patients. The AOANJRR has worked closely with the Australian regulator, the Therapeutic Goods Administration (TGA), to develop robust reporting of all joint prostheses implanted in Australia enabling the TGA to independently identify devices or classes of devices which warrant further investigation and identify emerging safety and performance issues. These activities allow the TGA to identify prostheses that are performing poorly or to a level less than expected and take appropriate regulatory action to address these issues. Prompt and proper regulatory action could range from monitoring/observation to withdrawal or cancellation of a prosthesis from the Australian Register of Therapeutic Goods (ARTG) when it is deemed that the safety and performance of the prostheses are not acceptable and thereby reducing the impact on the public (11).

There are limitations to the information that a registry can produce. Revision itself is likely insufficient as a measure of success given the fact that one-year implant survivorship is nearly 100%, while 90% of total hip arthroplasty (THA) patients are satisfied one year following surgery (36, 37). Revision is affected by a number of factors (e.g. patient health status, inadequate implant monitoring, or missed diagnosis of implant failure). Additionally, patients who have died, those who undergo reoperations that are not regarded as revisions (such as debridement for infection or manipulation under anaesthetic for stiffness), and those who have poorly functioning, but unrevised, hip replacements, are all classed as “successes” (38). When success is defined based on a low number of revisions, such an approach has its restrictions, as revision oriented registries cannot determine whether unrevised implants are functioning well or poorly, or whether the patient achieved satisfactory pain relief and functional gain (8). Total joint arthroplasty is performed to

decrease pain, restore function and productivity and improve quality of life. It is, therefore, logical to measure these same outcomes when assessing the results of surgery. Therefore, it makes sense to go beyond simply time to revision and measure outcomes that quantify optimal outcomes from procedures as defined by the patient – relief of pain, restoration of function or improvement in the quality of life. Some of the international orthopaedic registries now incorporate patient-reported outcomes (PROs) and patient-reported outcome measures (PROMs) (8, 39, 40). However, these type of data have not been routinely adopted, and their incorporation into orthopaedic implants registries presents challenges (8, 37). The AOANJRR implemented a pilot study for PROMs in 2018 and they were reported for the first time in the 2021 Annual Report (1).

Similar to PROs or PROMs, additional data could be very informative. Possibilities of linkage between orthopaedic registers, other clinical quality databases and administrative health registers may be of value when performing orthopaedic register-based analysis (41). Even though these databases contain for example information about pain or additional procedures, linkage with those held by the regulator has not been explored in the literature. The ultimate goal of the regulator is to shorten the response time to alerts generated by post-marketing medical device surveillance, thereby minimising adverse events by ensuring prompt elimination of defective devices from the market. Medical device problems may surface years after they have been used or implanted in thousands of patients. The earlier and the more precise this identification takes place, then likelihood of recurrence of adverse events related to medical devices diminishes and the possibility of further harm decreases (13). As major changes to the medical device approval process are unlikely in the near future, policies intended to detect and reduce harms of medical devices must instead target the post-market surveillance space (42).

Post-market monitoring of the safety and efficacy of implants represents a feasible means of reducing the risk of adverse events that are detectable and traceable. It is an important mechanism used to detect potentially harmful but under-recognised adverse events, particularly in rare diseases and conditions where large-scale safety trials are typically not feasible. The reporting of adverse events associated with devices is the essential starting point of post-market surveillance. Reviewers at TGA examine adverse event reports to identify safety signals. Examples of adverse events are any unfavourable and unintended sign, symptom or disease, including potential harm or near misses, associated with the use of a therapeutic good. Each year, the TGA receives approximately 6000 medical device reports of suspected device-associated deaths, serious injuries, and malfunctions through the Incident Reporting and Investigation Scheme (IRIS) (43). From those, most adverse event reports received by the TGA are made by sponsors (e.g. medical device suppliers) and are

compulsory. Some reports are voluntary and made by state and territory health departments, hospitals, health care professionals, patients and consumers. All reports are risk assessed and serious adverse events are investigated immediately and given priority. Unusual incidents, incidents that led to injury, or incidents with unusually high levels of occurrence, are routinely investigated. A panel of scientific, engineering and clinical experts will assess reports and recommend the appropriate type of investigation to undertake. In numerous cases, like in the breast implant associated-anaplastic large cell lymphoma (BIA-ALCL) and urogynaecological mesh products, this system helped in identifying concerning trends (44). If post-market surveillance is not effective, patients won't be protected from potentially harmful implants and procedures.

There is no current systematic approach to correlate the ample variety of data captured by the AOANJRR as part of the TGA processes. Without the AOANJRR reports, these devices would have been identified at a much later stage, and as such the value of a registry is not to prevent device failure but to aid picking up performance issues. Although the development of new mining tools for post-market data could improve the efficiency and quality of decision-making by the regulator, an ongoing tool for analysing and combining the data of the different internal databases with the AOANJRR information has not been yet developed by the TGA. If adverse events reports related to this type of devices are captured and trends hinting that a device is problematic are identified before getting to the stage of revision (signs or symptoms like additional surgeries, malfunction or fracture of the implants, pain, metallosis or loss of function), then these early signals will trigger an investigation by the TGA. This paradigm shift would enable the early identification of implants that are performing poorly for timely remedial action.

It usually takes many procedures over many years of registry follow up to identify a poorly performing implant. A lot of patients' suffering could be prevented or alleviated if a source of early signals for late failure can be identified. This project is a search for possible early signals of orthopaedic implant failure in adverse event and incident reports received by the TGA, as a retrospective example.

Ideally, a proactive model that predicts bad performing prostheses, rather than a passive surveillance system, would greatly enhance the discussion of safety of orthopaedic implants. To date, there is no predictive tool based in adverse events reporting that specifically detects candidates of devices with HTARR. We hypothesized that there is a direct correlation between prostheses identified as suspicious of being problematic by the AOANJRR and potential signals available in the TGA post-market databases. As a result, the patients subjected to a hip replacement in Australia were the population included in this study and the report of adverse events after surgery

was the main outcome evaluated. If post-market signals currently gathered by the TGA are demonstrated to have a correlation with the actual implants identified by the AOANJRR, this will provide an additional tool for the investigation of this issue. The purpose of this project was to create and validate a predictive model for identifying earlier problematic prostheses based on post-market databases. To our knowledge, no previous studies have examined this possibility.

Patients who will be implanted in the future will benefit through the use of higher performing arthroplasty prostheses instead of prostheses identified as problematic. Establishing a predicting system which considers routine post-market data presents enduring and extensive methodological challenges. Specifically, decisions that are made about how the predictor model define and identify prostheses that are HTARR candidates have important implications. Therefore, caution must be used to build a robust model as inconsistencies can lead to regulatory decisions without an adequate evidence support. To start with, the statistical model needs to have solid basis which usually is linked to good quality data to feed it.

During this project, regulatory and privacy concerns made sharing of raw data impossible even if de-identified.

Patients and methods

Study Design and Setting

The study was based on hip joint prostheses implanted in Australia and identified as having higher than anticipated rates of revision in the 2018 AOANJRR Annual Report (45). We conducted a retrospective analysis of data from two databases: the AOANJRR and the IRIS database, which is internal to the TGA. The aim was to develop a predictive model with regression analysis, using variables captured as part of the post marketing reporting to generate outcome estimates. The research strategy was a combination of descriptive and analytical tools.

Hip prostheses data were requested from the AOANJRR by year from January 2008 to December 2020. As the annual report captures the data until December of the previous year, 10 years of data were available to the TGA before the 2018 report and 3 years after that publication. Specific data were also provided in regard to the prostheses identified as outliers by the registry in the 2018 Annual Report. Data on final reports of hip prostheses related incidents from IRIS were extracted for the same 13-year period. This time period was chosen to provide a large enough sample of incidents reported to the TGA, to be more representative of recent data, and to allow comparisons before and after the identification of the devices by the AOANJRR. While the data from the AOANJRR were provided de-identified, the principal investigator had access to the details as captured by IRIS. As

part of the data collection from the internal database, all the data were de-identified and the data analysis was undertaken using aggregated level data.

The aim for the regulator is to detect prostheses that are not performing well or have safety concerns, e.g. “problematic”. The AOANJRR was considered as our gold standard for “problematic” prostheses, which are the outliers identified by the registry as HTARR. Our research question was: does a direct correlation exist between signals available in the IRIS post-market database and prostheses identified by the AOANJRR with higher than expected revision rates? And if so, is it possible to develop a “predicting model” that will identify problem prostheses earlier than AOANJRR?

The AOANJRR collects demographic and clinical data such as age (date of birth), sex, postcode, date of surgery, diagnosis, manufacturer, prosthesis name, prostheses components, surgery methods, and if revision was needed. From the AOANJRR database, we had available the total number of implants and total number of revisions. According to the time in situ, revisions/100 observed years were calculated. It is noted that from the products used and recorded in the registry, some of them could be used in different combinations as components of a hip prosthesis system. To facilitate the matching with our internal database, devices from the same system were grouped according to the naming convention.

The IRIS internal database captures the adverse events in Australia as incident reports. Beside patient and user identifiers, it also captures basic information and details about the device, including (but not limited to) brand name, model, serial, batch or lot number, timing and source of the report, event description, severity, and type of adverse event. The devices identified in the adverse event reporting of the IRIS database were also grouped by product name if they belonged to a particular hip prosthesis system (for example femoral and acetabular component) to facilitate matching with the AOANJRR description. Keyword searches were used as descriptions of the events in the reports provided different amounts of information. For the purpose of analysing keywords, we pooled related terms into single categories as follows: revision, revised, replacement, changed to, explant and removed were pooled into a single ‘revision’ category; pain, discomfort and ache into a single ‘pain’ category; fracture, broken and cracked into a single ‘fracture’ category; loosening, subsidence and movement into a single ‘loosening” category; and dislocation, migration and malposition were pooled into a single “dislocation” category. Additional keywords searched were infection, corrosion and metallosis. Each individual report was reviewed when one or more of those keywords were identified, to confirm that it corresponded with the predetermined definition.

The cut-off provided by the 2018 Annual Report was also used to review the behaviour of adverse event reporting in the IRIS database and identify patterns or changes in trends for devices before and after they were identified as outliers by the AOANJRR.

Definitions

Four concepts were considered essential in the planning of this project:

1. Discrimination - the ability of a model to distinguish patients who experience an outcome from those who do not;
2. Calibration - comparing predicted and observed outcomes across the entire range of the data;
3. Internal validation - degree of confidence that the relationship being tested is trustworthy and not influenced by other factors or variables; and
4. External validation - the extent to which results from a study can be applied (generalized) to other situations, groups or events.

For the allocation of the keyword searches, the following definitions were used in order to group similar wording or expressions:

1. Revision: when a joint replacement needs to be replaced (it could be complete or partial)
2. Pain: localized or generalized unpleasant bodily sensation or complex of sensations that causes mild to severe physical discomfort and emotional distress
3. Fracture: cracking or breaking of the prosthesis or the surrounding bone tissue
4. Loosening: disintegration at the bone- implant interface
5. Dislocation: complete loss of articulation contact
6. Corrosion: electrochemical process releasing metal ions
7. Infection: infection involving the joint prosthesis and adjacent tissue
8. Metallosis: aseptic fibrosis, local necrosis, or loosening of a prosthetic device secondary to metal corrosion and release of metallic wear debris in periprosthetic soft and bony tissues

Variables and Outcome Measures

We identified all incidents reported to the TGA associated with hip prostheses between 2008 and 2020 and yearly incident rates were calculated. The denominator for calculating the incidence was the number of devices implanted as captured by the registry. We discriminated between devices captured by the AOANJRR and other minor components such as screws that were sometimes reported in the IRIS database. For the specific analysis of the predictive tool, we restricted our analysis to individual prostheses or systems in the AOANJRR with 200 or more implants in the 10

years previous to the cut-off line for the 2018 Annual Report to increase the precision of the anticipated estimation and decrease the error margin.

From the IRIS internal database, sponsor, manufacturer, source of reporting, actual harm, type of event, cause level, event description and investigation outcome were treated as independent variables.

Of the predictor variables tested, number of incidents (with calculated rates), severity scale measurements and keywords in the description of the adverse events were associated with each of the outcome parameters and therefore were included in regression models.
The dependent variables were the revision rates and observed years gathered by the AOANJRR, and the identification of a prostheses with HTARR. The main outcome measure was the congruence in identification of prostheses with HTARR by the post-market variables studied. Regression analyses determined the strength of the association of the chosen variables with HTARR outcomes.

Statistical Analysis

Categorical data are presented as the number of cases and percentages. Means (SDs, frequencies, and proportions) were used to describe the study patient sample. Incident report features (including patient characteristics) were reported as mean and standard deviation or proportions as appropriate. The relations of total number and type of incident reports, as the categorical dependent variables, respectively, were assessed using univariate and multivariate regression models. The logistic regression model was used to study the relationship of those characteristics and risk factors (including the keywords analysed) and the likelihood of identification of HTARR. P values < 0.05 were considered statistically significant in all analyses. Furthermore, sensitivity, specificity, positive predictive value and negative predictive value were calculated to assess the potential predictors.

For missing values in the internal dataset, we used pairwise deletion, acknowledging that some of these variables could be confounders.

We conducted all statistical analyses using StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC.

Ethics, funding, and potential conflicts of interest

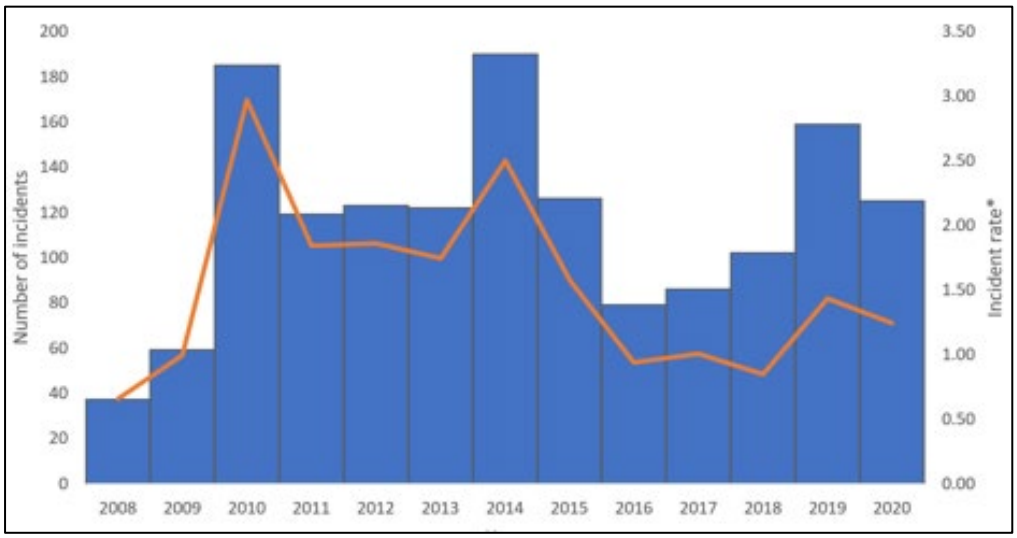
The Australian National University Ethical Committee granted ethical approval for the protocol. No grants or funding were received for the development of this project. The authors declare that there are no conflicts of interest.

Results

The 2018 Annual Report analysed 593,803 hip prostheses implanted in Australia up to 31st December 2017. Of 813 unique products or components, 471 entries remain after grouping by hip prosthesis systems for matching with the IRIS database. In that annual report, the AOANJRR identified 76 hip individual prostheses or combination of prostheses with HTARR (49 when discounted repeated name entries).

The total number of incidents related to hip prostheses reported to the TGA from 2008 until 2020 was 1512 (until 31st December 2017 the number was 1126). The annual number of incidents reported to the TGA shows fluctuation during the period analysed (Figure 1).

Figure 1. Number of yearly incidents reported to the TGA related to hip prostheses and corresponding incident rate (2008-2020)



* per 1000 implants

The number of incidents reported to us varied yearly, but the average for the 13 years reviewed was 117 incidents per year.

Although the majority of the incidents reported to the TGA do not involve an additional device (985/1510, 65.23%), 525/1510 reports implicate more than one device (median: 0; range 0-6). For instance, 362/1510 (23.97%) reports mention one additional device and 116/1510 (7.685) reports two additional devices. These devices corresponded to 305 individual products captured in the registry.

From the 1512 incident reports found during the 13-year period, 127 (8.4%) did not provide enough detail to recognise a product for matching in the registry (such as specific name, model number or a Unique Device Identification (UDI)). Among these, 101/127 (79.53%) corresponded to incidents

reported before December 2017. From the remaining 26 cases, 22 corresponded to one particular sponsor. In 14 cases, the device was clearly identifiable but not captured by the registry database (for example when solely a minor component was involved in the incident like screws).

We were able to identify 76 products in the AOANJRR database which were exclusively implanted during the 10-year period before the cut-off of the 2018 Annual Report. Of those entries, 33 (with a cumulative total of hip implants of 2226) had at least one revision (a total of 136 revisions) during the same period of time as identified by the AOANJRR. The median number of revisions was 3 (range 1-23). We compared the track record of those same products in the IRIS database, but only one incident report was captured for the same period of time. The description of the incident pointed to a revision due to a femoral bone fracture. For all the other 135 revision cases, there were no incidents reported to the TGA (even if we extended the period of follow-up in the IRIS database to December 2020). As a result, the proportion of revisions that are reported to the TGA is estimated to be less than 0.75%.

Patients involved in adverse events reported to the TGA were mostly male (494/1512 - 53.9%) with a mean age of 65.11 years and a mean weight of 91.14 kg, but missing values were a limitation in basic demographics (see Table 1). Body mass index (BMI) was not possible to be calculated as the IRIS internal database does not captures it routinely as a field in the reporting form.

Table 1. Distribution of missing values across common demographics

		n (%)		
Gender	Male	494 (32.67)		
	Female	413 (27.31)		
	Not reported	605 (40.01)		
			Median	**Range**
Weight	Reported	292 (19.31)	90 kg	38-184kg
	Not reported	1220 (80.69)	-	-
Age	Reported	709 (46.89)	66 years	13-96 years
	Not reported	803 (53.11)	-	-

Although the state/territory were the event originated was not reported in 674/1512 instances (44.58%), NSW was the state with most report followed by Queensland (see Table 2). No incidents were reported from the Northern Territory during the period analysed.

Table 2. Number of incident reports and report rate by State/Territory

State/Territory	No. incidents	Incident rate per 100000 people*
New South Wales	331	4.04
Queensland	200	3.83
Victoria	121	1.82
Western Australia	108	4.03
South Australia	51	2.88
Australian Capital Territory	23	5.32
Tasmania	4	0.74

* population as of 30 June 2021 (data extracted from the webpage of the Australian Bureau of Statistics)

Up to 9 different sources were identified in the TGA database for the incident reporting, almost all came from the sponsor of the product with 1480 (out of 1512 – 97.89%), followed by the patient in 21 and health practitioners in only 7.

From the 471 hip prostheses entries analysed in the AOANJRR, 160 had more than 200 hip implants during the 10-year pre-annual report period and of those 31 entries corresponded to HTARR. In this specific scenario, 954 incident reports were received by the TGA over the same period of time.

Regression models were run for adverse events rates against revision rates in the registry and prostheses identified by the registry because of HTARR. After linear regression, a significant link was found to revision rates in the registry (see Table 3) which is related to the fact that revision is the main complaint in over 75% of the reports to the regulator. Even though when compared to HTARR, the correlation was not strong enough to show a significant p value in a logistic regression (see Table 4).

Table 3. Comparison of incident rates (incidents reported to the TGA between 2008 and 2017) with AOANJRR revision rates (until Dec 2017)

	Incident rate (by observed years)	Incident rate (by devices implanted 2008-2017)	Incident rate (by total of devices implanted until 2017)
Coefficient	2.470*	0.393*	0.455*
	(8.00)	(8.70)	(8.36)
Constant	0.966	0.944	0.974
	(21.27)	(21.09)	(21.90)

R-sq	0.2885	0.3238	0.3067
Adj. R-sq	0.2840	0.3195	0.3023

* p<0.001
t statistics in parentheses

Table 4. Logistic regression results for adverse event rates from the IRIS database and prostheses with HTARR

Independent variable	Coefficient	Std. err.	z ratio	P value	95% C.I.
Incident rate by observed years	2.625	1.600	1.64	0.101	[-0.511 5.761]

Model χ^2 0.05
Pseudo R^2 0.03
N=159

We tested the scales and categories of severity captured by the IRIS database as possible predictors for HTARR. Actual Harm was not significantly associated with HTARR status as "serious injury" represented the vast majority (1301 out of 1380 registered entries). Problem Cause was not useful either as the causes are not specific to determine orthopaedic prostheses related issues. Even though "mechanical problems" were reported in 231 incidents (out of a total of 1232 identified causes), "unable to confirm complaint" with 671 cases and "no findings available" with 247 cases were the leading causes reported. For Problem Type, mechanical issues were mentioned in 348 incidents (out of 1485) and constituted the leading type, but no further detail was available, and the second item was categorised as "other".

The following keywords were also tested in a regression model: Revision, Pain, Fracture, Loosening, Dislocation, Corrosion, Infection and Metallosis (see Table 5). Despite the fact that pain and metallosis showed a significant p value when compared to HTARR in general, it was not possible to identify specific HTARR products based on those predictors. Additionally, we found that the sensitivity, specificity, positive and negative predictive values were a shortcoming if keywords are going to be used as sole predictors for HTARR (see Table 5).

Table 5. Coefficient p values in the regression analysis, sensitivity, specificity, positive predictive value and negative predictive value of the keywords in the IRIS database to predict HTARR prostheses

	Revision	Pain	Fracture	Loosening	Dislocation	Corrosion	Infection	Metallosis
P value	0.602	0.039	0.243	0.076	0.454	0.251	0.342	0.041

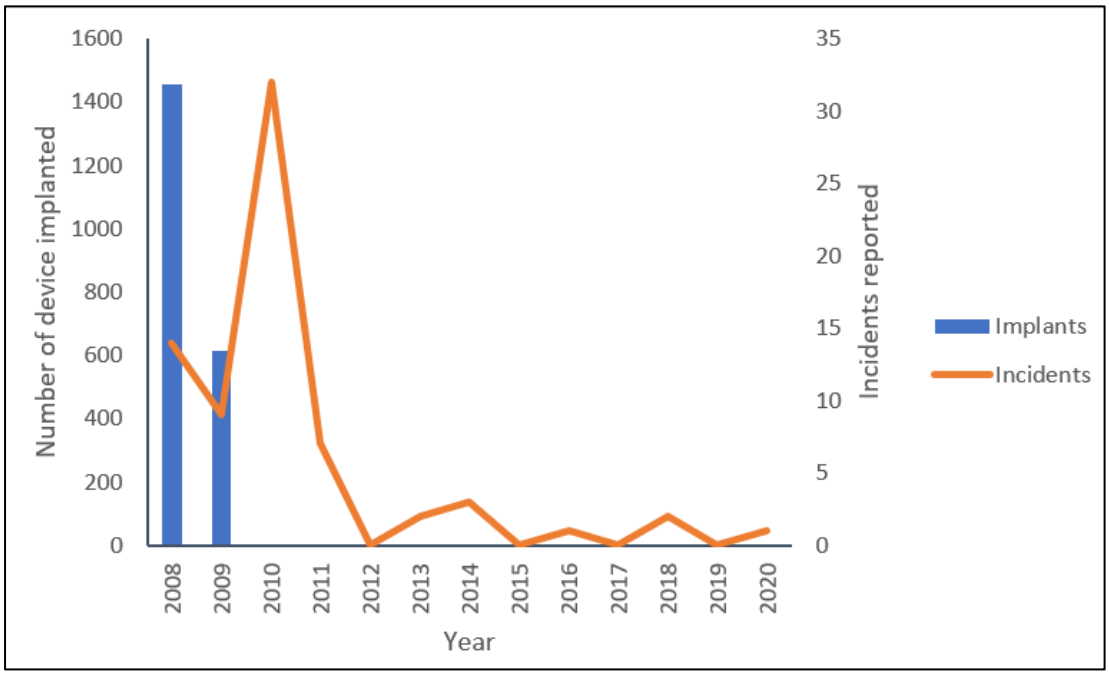
Sensitivity	47.06%	41.18%	26.47%	32.35%	11.76%	17.65%	17.65%	32.35%
Specificity	65.03%	80.37%	78.53%	79.14%	87.73%	96.32%	92.64%	96.32%
PPV*	21.92%	30.43%	20.45%	24.44%	16.67%	50.00%	33.33%	64.71%
NPV**	85.48%	86.75%	83.66%	84.87%	82.66%	84.86%	84.36%	87.22%

* Positive Predictive Value

** Negative Predictive Value

One of the reasons for this limitation is the timing of the reporting. For example, in the specific case of the ASR hip system, usage of the prosthesis declined in the first two years of our analysis (after it was first identified by the AOANJRR) with no more components of the system implanted since 2010. Despite this, the majority (66.18%) of the adverse event reporting during the period analysed came after 2010. Metallosis constituted 17.65% (12 out of 68) of all adverse events reported during that period of time and even further to 2017, incidents have been reported in minor quantities (see Figure 2).

Figure 2. Number of incidents and devices implanted for ASR hip systems from 2008 to 2020



Discussion

Although pre-market evaluation of any new orthopaedic prothesis plays an important role in determining its safety and performance, surveillance systems are becoming increasingly important as there is a shift to put more weight on post-market controls. Limited empirical research by which to refine existing or develop new post-market surveillance and reporting systems for devices have

been carried out. Most studies have been observational in nature and were targeted at identifying rates of adverse events (46-52). To our knowledge, there are currently no published, validated, and accurate predictive models of "problematic orthopaedic prostheses" (specifically for THA) based on post-market reporting to regulators. Even though we could not find a similar project in the literature, linkage between orthopaedic registers and other public health databases is possible (53, 54). Also integration of implant registry data with comprehensive clinical data from medical records can generate tailored outcome analyses (8, 55).

Detecting subtle cues can be challenging based only on the internal database partly because one critical piece of information is not routinely available: the total number of devices implanted. Therefore, we linked the IRIS database to the AOANJRR to gather that information. The AOANJRR is considered one of the more mature orthopaedic registries in the world and has a long track record. Its validity is based on coverage and registration completeness of procedures/patients associated with accuracy of registered variables. We chose hip prostheses to concentrate our efforts as this type of prostheses are common and have a longer and well established track history record in the AOANJRR. Despite this, we found that our internal database does not accurately represent event rates because most adverse events are under-reported. We also observed that comparisons between the two databases are confounded by missing data in the IRIS database, probable differences in baseline characteristics of patients and by insufficient reporting of endpoints other than revision as part of the registry database. For these reasons, this internal database needs to be used primarily to detect signals that might require further investigation.

An important negative finding of our study was the lack of association of adverse events rates and specific hip prostheses with HTARR. This is an important finding, implying that adverse event reporting data should not be viewed as strong predictors for that particular outcome. The poor performance of the post-market database as predictor for HTARR may have resulted from several factors. First, it could be a result of not reporting when signs or symptoms appear in hip implanted patients, such as pain, that could lead to revision. It seems that adverse events are reported at a late stage (when a revision surgery is already decided or performed) to the regulator. Second, the analysis is based on the presumption of having shared populations between the databases (nationwide). AOANJRR seeks to include all patients in Australia so that it minimises the patient-related or hospital-related bias. It involves a great number of patients and therefore deliver results with good validity by excellent reproducibility of findings over a relatively short period of time. The IRIS of the TGA also covers the Australian population, but the reporting rate are dissimilar due to underreporting in the regulator's internal database. Third, registry data have a core outcome which

is revision and established targeted data fields specifically designed for orthopaedic purposes while internal databases are designed to capture events related to any type of devices with several more open fields. Last but not least, the IRIS database could not be currently capturing all the data required to build a precise predicting tool.

Timing and responsibility of reporting adverse events

The reporting of device failures and adverse events associated with medical devices to manufacturers or regulators helps identify risks at the earliest possible timepoint. It could facilitate the prevention of further harm and help continuous design improvements of the devices. The unfortunate metal-on-metal THR implant recall and other cases mentioned before highlight the potential public health importance of detecting early persistent pain in a large cohort of patients. Systematic analysis of pain trends across patients may have allowed earlier detection of implant-associated morbidity and facilitated earlier warnings to clinicians, manufacturers, and regulatory agencies (8). The results in our study demonstrated that pain has a correlation with HTARR in general, but it was not possible to consider it as a good predictor for individual products probably due to limitations in the timeliness of the data of the IRIS post-market database.

Currently, it is compulsory in Australia for sponsors/manufacturers to report adverse events associated with the use of a medical device to the TGA that result in, or have the potential to result in, death or serious injury; however, this is not a requirement of healthcare professionals or facilities. A similar situation can be seen in other jurisdictions with the regional regulatory authorities. Globally, regulators encourage reporting of incidents relating to medical devices by consumers, patients, clinicians, and distributors of devices, but rate of reporting remains low and underreporting of adverse events occurs globally (56, 57). For example, the U.S. Food and Drug Administration (FDA) estimated the reporting rate as 0.5% which coincides with previous calculations in the Australian environment (16, 44). In our analysis, we confirmed that device adverse events such as revisions of hip implants are underreported to the TGA. Additionally, underreporting was pointed out by differences in reporting between Australian states and territories. Therefore, regulators and sponsors/manufacturers need to reconsider current methods used to encourage the reporting of events.

Similar to what we found in our study, adverse event reports from different sources (clinicians, healthcare facilities, sponsors/manufacturers) were associated with limitations in the consistency of the data: reports lacked details about the THR device and other possible devices implicated, patient characteristics, associated procedures, outcomes and event cause, and details of the incident investigation results. In the literature, one study compared reports of serious incidents from

clinicians and manufacturers between 1995 and 2000 (51). Findings of that study were that 4% of reports were based on the same incident, and that manufacturers tended to report fewer but more serious adverse events than clinicians. We were able to confirm several cases of duplicate reports within the database.

One of the possible causes for underreporting of device-related adverse events is that the current system is based on passive surveillance since manufacturers usually are not obliged to actively search for device malfunctions. Even though, strictly voluntary reporting of data to regulators has demonstrated also limitations. Published data provide insights into the reasons for the under-reporting of incidents in the healthcare setting which are multifactorial; these include a culture of non-reporting, lack of awareness of the role of the regulatory agency regarding medical devices by healthcare professionals and the public perceived ineffectiveness of reporting, reporters have constraints of time or are already over-burdened by administrative tasks, assumption that the rate of certain adverse event is known and acceptable, lack of recognition that the incident was related to a medical device, or, there may be a disincentive to report adverse events or device malfunctions if health care providers use them for indications or patient populations not originally approved by the regulatory authority (i.e., off-label use) (42, 44, 58, 59). Moreover, if the adverse event is a known complication, can be resolved clinically, or the device failure can be fixed by the practitioner or biomedical engineer, the issue may not be deemed necessary to report (44). After acknowledging the limitations of voluntary and mandatory adverse event reporting, the health authorities can choose among several options to encourage physicians and healthcare institutions to contribute data to adverse event databases minimising reporters' burden. The regulator could explore projects that improve the recognition of adverse events (artificial intelligence aiding in screening promptly and routinely the datasets), timeliness (such as systematic health facilities and office-based data capture, software added on to existing electronic health records that automatically reports adverse events data in near real time to the different stakeholders) or analysis of the data (use of artificial intelligence by extraction from big databases followed by machine-learning).

Data completeness and quality

When analysing adverse event reports, not only are the number of reports important but consideration also needs to be given to the type of device; different classes of device will have different levels of post-market vigilance. For example, the sponsors of class III (higher risk, such as orthopaedic prostheses) are required to provide annual reports of adverse events and complaints for the first 3 years of inclusion on the ARTG, but this is not required for lower class devices. It is important to note that orthopaedic prostheses, including hip implants were up-classified by the TGA

during the first half of the last decade. This had an impact in the nature and quality of the adverse event reporting, the fluctuation in the number of reports and the traceability of the hip prostheses involved.

Adverse event reports can also be received regarding a variety of issues: safety, quality, and performance of a device, and the vigilance and response to each kind of event may be different impacting in its description. In addition, reports may also have varying degrees of information depending on the source of the report, nature, or scales of severity of the adverse event. Moreover, reports might relate to the different stages of the lifecycle of the device, from design through to manufacture, shipping, storage, and use of the device, as well as reprocessing aspects or disposal. We looked at adverse event report descriptors and we found that they were not particularly useful (in part because the reporting form is generic: for any type of adverse event). As such, those won't be directly relevant to the clinical outcomes used for recognition of trends related to HTARR prostheses in a surveillance system if data are missing or there is not enough granularity during the collection of the data.

The weakest link remains the quality of data collection. Even though improvements in the data collection and analysis of post-market data are resource heavy, a properly set up automated system with adequate validation strategies can benefit the quality of the data. In order to improve quality of reporting, online reporting systems should be able to expand options depending on the type of adverse event or family of devices, in this case hip prostheses. These options could be aligned to recommendations for selecting relevant PROMs for orthopaedic registries so that they have good measurement properties (keeping the number of items to the minimum that is required to obtain the essential information) for patients after arthroplasty (37, 60, 61). Qualified statisticians or epidemiologists should be involved for a proper analysis and reporting of collected data. Additionally, education to reporters and active promotion will also increase awareness and possibly increase the reach of feedback. Regulatory agencies have recognised the importance of retrieving missing data with a variety of initiatives introduced to overcome these issues. For example, in Australia, the InSite programme was piloted by the TGA in two healthcare facilities in 2014 and 2015, in which an education programme was used highlighting the benefits of adverse event reporting, how to report, and what an adverse event may look like. There was a 10-fold increase in the number of adverse event reports from one of the sites during the time period that the education programme was conducted, but continued education and close interaction and collaboration is required to maintain the outcomes (44).

In 2017, of the 5,379 medical device incident reports received by the TGA, 771 (14%) were from sources other than the manufacturer's Australian legal representative (the sponsor). Sources of spontaneous reports include those from the patient or caregiver, health professionals, and departments within healthcare facilities (44). The findings in our study point out to an even lower participation (2.12%) from other sources than the sponsor. This could be related to the believe that the adverse event has been already reported to the AOANJRR and there is no need to report to the regulator. To address the lack of reporting by health care facilities and professionals, many have suggested mandatory reporting for health professionals could be an option. There are currently some initiatives exploring this possibility in Australia.

There are certain limitations as when a prosthesis is identified as HTARR, for instance the usage usually declines and could introduce a selection bias when surgeons choose a different indication as a result or according to certain patients' characteristics. Other points for consideration are that a delayed onset of a higher than expected revision rate is more difficult to identify than when the prostheses have been recently introduced, that the approach for identification could be very broad and sometimes a careful range analysis is necessary to define a particular type of problem within a group. Despite this, there was some correlation in the rates of adverse events against revision rates in the registry (see Table 3). This is not surprising, since the majority of the adverse events were related to revisions of the implants, but the correlation with each specific prosthesis identified by the registry was not particularly helpful to our objective. This was not in agreement with our main hypothesis that post-market signals in the IRIS internal database were able to predict HTARR, but it may be explained by factors such as data reporting completeness and quality, but also by the multiplicity of variables captured during adverse event reporting as opposed to a more targeted outcome measured in the registry.

Targeted reporting for hip implants

The AOANJRR is focused on core data with revision as the primary end point. If only revision is considered a failure, everything comes down to the definition of "failure" which in survival analysis is interpreted as an event instead of a process. Even though other circumstances could be considered as important modes of failures such as loosening of a component or postoperative complications. In those cases, the overall success rate would thus be an overestimation if only revision is considered as the end point (35). To make it more complex, variation in functional outcome after surgery correlates to patient attributes such as greater BMI, older age, female sex, poorer emotional health, and higher number of medical and musculoskeletal comorbidities. Other risk factors for suboptimal postoperative function include poorer self-care skills and self-efficacy (8). The implementation of

PROMs could be beneficial in those cases, but it could also be useful to correlate with internal post-market databases if better data are gathered. Patient satisfaction after surgery will continue to be an important outcome for elective joint arthroplasty, and dissatisfaction needs to be better understood. Although the associations identified in our study sometimes were not strong enough to build a predictor model, we believe that they are important in following the patients and provide signals to the regulator to investigate further into a reported issue. No single patient factor will explain all of the changes seen after surgery, so it is important to recognize that outcomes reported by patients may be influenced by a large number of variables, each exerting a small but detectable, and potentially important, influence on the overall clinical picture. This is a possibility worth of exploring in the future. In order to allow for a thorough comparison of the two databases in this study, standardisation of influencing factors is necessary. The standardisation involves the definition in the reporting of adverse events of important influencing factors, which can be implant-related, surgical related or patient-related, and their classification.

We decided to look at some keywords to search for possible predictors. Although there was some link with some specific adverse events involving pain or metallosis (see Table 5), we could not find strong predictors. Although some keywords were found to be statistically significant in general, the same correlation was not reflected when trying to identify individual or groups of hip prostheses which is the objective of the regulator. This limitation could be related to finding that during our searches for keywords, we could only consider the presence or absence of certain conditions, but not account for their severity as it was not feasible to implement scales or categories retrospectively. Alternative avenues to develop and improve prediction models, perhaps by prospectively including nonstandard or patient-collected inputs, and by predicting short- and long-term, patient-centred outcomes such as development of pain, clinical malfunction, or dissatisfaction should be explored aiming to improve predictability. A confirmation of the shortcomings of these data towards the implementation of a predictive model was that the maximum sensitivity for those keywords was less than 50% or that the positive predictive value was for most around 20-30% only (see Table 5). It is possible that the lack of strong prediction may be related to the quality of the database and lack of sufficient power due to underreporting. After adjusting these factors, a tool such as this could be beneficial for basing regulatory decisions.

Study limitations

This study has several limitations related to data quality, possibility to control for confounding, missing and erroneous registration of data and methods of ascertainment of outcome. Furthermore, due to its observational design there is the impossibility to distinguish causal associations from

associations that are derived from bias or random error. There is a constant need for validation of data regarding completeness and quality and we encounter several issues around this.

It is well established the importance of several factors on early revision risk such as age, sex, fixation strategy and surgical technique; however, other variables such as BMI, pre-operative condition (American Society of Anaesthesiologists (ASA) class), diagnosis, fixation type, patient physical status, and type of provider were also found after reviewing data from different orthopaedic registries to significantly have an influence on the survival of THAs (37, 62). All these factors are confounders. In order to overcome this confounding, comparisons between survival curves should be done using Cox multivariate or subgroup analyses, which adjust the results for influencing factors (63). We consider the fact that key demographic (age and gender) and clinical characteristics (BMI and comorbidities) of interest could be a factor in our database but despite our efforts, it was not possible to take into account important covariates/confounders in our study because the IRIS database does not present complete data. Missing data in the reports was a common theme across all the demographic categories (see figure 2); for instance, we opted not to present results adjusted for age and gender due to the quality of the data in terms of missing values in our internal database and we could not calculate BMI as height was rarely reported to us. Furthermore, the fact that the number of reports from states like Victoria with big population were less than from other states similar in size additionally points in direction of underreporting as another limiting factor.

There are also certain limitations to the data linkage between data from registries and internal post-market databases such as information bias (for example, misclassification of exposure or/and outcome) and residual confounding (factors such as detailed comorbidities and socioeconomic factors). The latter is a significant issue. Residual confounding is the term that describes the amount of variation not explained by variables included in a regression analysis, and this residual confounding can be unsettlingly large: the remaining unexplained variation can amount to more than 80% (64). The inclusion of additional confounders such as comorbidities or socioeconomic factors could reduce the amount of residual confounding and improve the predictive accuracy of a specific model (65). Even though, quality of the data was an impediment for creating a functional model from the IRIS database. Finally, implant performance is potentially confounded by the technical difficulty of inserting the implant, the knowledge and abilities of the surgeon inserting them, and the complexity of the cases (7). The capturing of these factors was inconsistent in our database.

One other more major obstacle to the effective use of post-market data is the set of severe limitations encountered with the range of nomenclatures and conventions to identify the different

products. We found many instances where the name of the device in one dataset did not correspond to the others, spelling mistakes or in cases of a product family, it was not clear to which specific devices the event was referring to or to which device was supposed to be linked in the registry database. In order to improve data collection uniformity across multiple databases (manufacturers/sponsors, registry, regulators), creating a universal bar code or identifier could be one means of circumventing this obstacle. The use of implant barcodes and catalogue numbers will help identify specific implants at risk including sizes, offset, etc. Currently the TGA is working on implementing a single UDI for the Australian market. That unique code should allow for the identification of every aspect of the device's manufacture and its tracking through the healthcare system allowing rapid identification of patients carrying implants for which alerts, recalls or other regulatory actions are generated.

Future perspectives

Based on these and many other limitations, it appears to be mandatory to increase the quality of the adverse events reporting by the different stakeholders to the TGA. The aim of this process would be to develop a consistent and structured reporting protocol which favours data completeness and creates greater transparency in the description of orthopaedic adverse events. By applying advanced analytics on available and improved post-market data, a more comprehensive and accurate framework could be created for safety surveillance and benefit-risk assessments of orthopaedic prosthesis. Regulatory approaches can be tailored to the unique datasets, and improve the timeliness, quality, and efficiency of post-market decision-making by the regulator. It is likely that full understanding of patterns of adverse events and outcomes after orthopaedic prosthesis surgery requires analysis of data from more than one source. Post-market adverse event reporting and registry data are definitely important sources of information, and can provide us with better knowledge, and a more accurate picture, of the safety and performance of the implanted devices. In the meantime, the regulator needs to continue relying on existing and trusted data, particularly data of high quality in terms of representativeness and completeness, such as those from the AOANJRR.

Conclusion

Our goal was to identify as many factors as possible within the variables captured by the adverse events reporting databases of the TGA, with the objective of eventually creating a predictive tool to help identify prostheses with HTARR before the publication of the annual report by the AOANJRR. Unfortunately, we were not successful in creating that tool. The inability to precisely predict the outcome at the individual hip product level using adverse event data is probably related to poor quality of that reporting and underreporting itself.

Despite of this, the collection of complete, accurate and targeted data has the potential to provide important information that could achieve that goal and help in the decision making by the regulator. Refinement of the data capturing system with a substantial decrease in underreporting are the obvious initial steps in this process. The TGA have several ongoing projects to improve these factors and modernize adverse event reporting and analysis so that a predictive model could be a reality in the near future.

Even though no strong correlation was found, keywords (pain is an example) could be very interesting to follow as possible predictors of outcomes. Innovative and specific methods need to be identified in order to understand how the huge amount of information held by the regulator can be improved and utilized effectively to deliver timely information about the risk-benefit balance of the products in the market. Adverse events like pain, if reported to the regulator, could affect regulatory decisions even without causing revisions. It is imperative for those data to be used and analysed to support evidence-based regulatory actions. The growth of prosthetic surgery which will occur over the next few decades lends urgency to the achievement of this objective (13, 66, 67). In the meantime, it is critical that the TGA continues cooperating with the AOANJRR as a resource to track the record of prostheses in the market.

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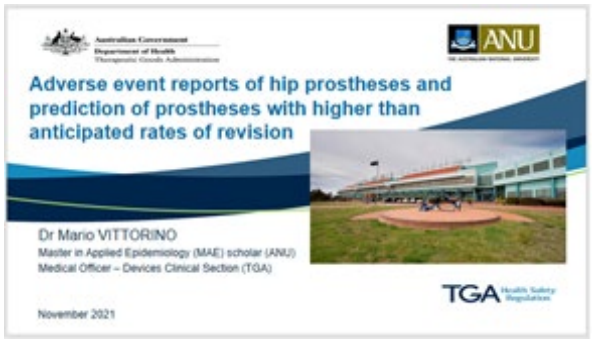
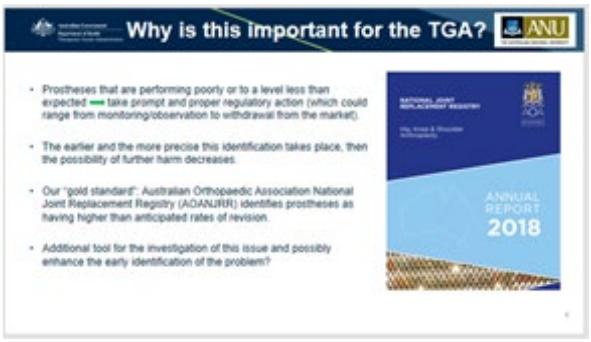
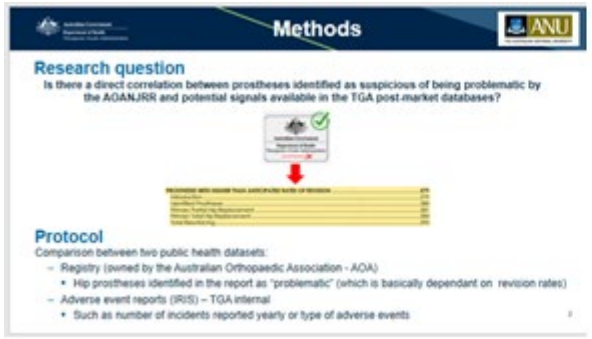
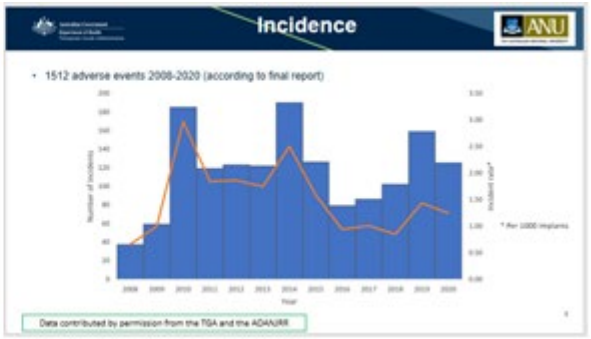
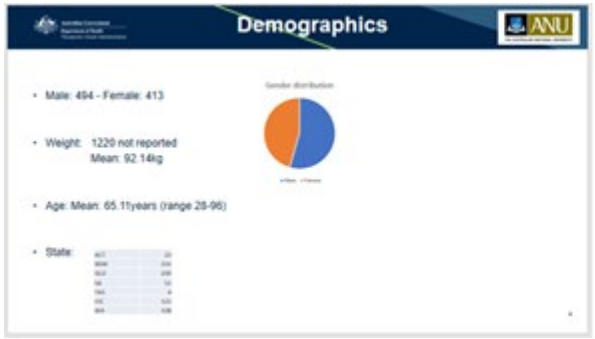
Appendix One: Conference presentation

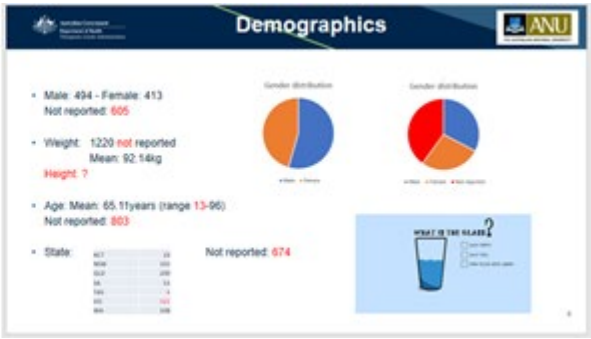


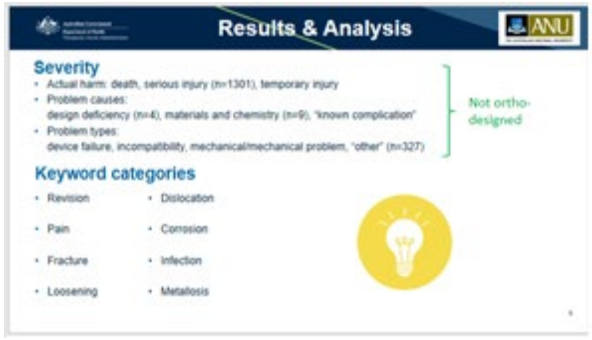


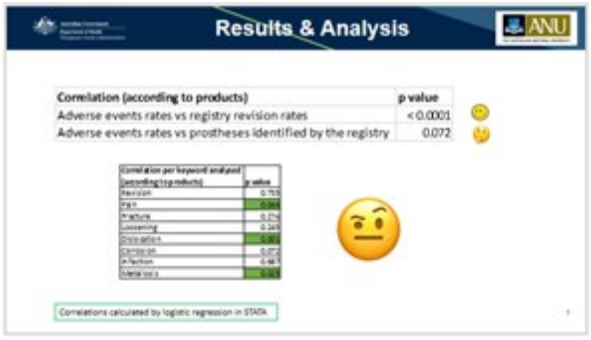












Results & Analysis

Sensitivity, specificity, PPV and NPV for keywords

	Revision	Pain	Fracture	Loosening	Dislocation	Corrosion	Infection	Metallosis
Sensitivity	47.06%	41.18%	26.47%	32.35%	11.76%	17.65%	17.65%	32.35%
Specificity	65.03%	80.37%	78.53%	79.14%	87.73%	96.32%	92.64%	96.32%
PPV	21.92%	30.43%	20.45%	24.44%	16.67%	50.00%	33.33%	64.71%
NPV	85.48%	86.75%	83.66%	84.87%	82.66%	84.86%	84.36%	87.22%

Conclusions

- Quality of post-market reporting
- Under-reporting of adverse events
- No strong direct correlation found
- Pain, for example, as possible keyword
- Continuous collaboration with the AOANJRR is critical

Australian Government
Department of Health
Therapeutic Goods Administration

ANU
THE AUSTRALIAN NATIONAL UNIVERSITY

MEDICAL DEVICES

Chapter 5: Teaching experience

“Dime con quién andas, y te diré quién eres.”

Saying in Spanish

Literal translation: “Tell me who you hang out with,

and I’ll tell you who you are.”

Contents

Preface

Rationale

This chapter outlines the teaching activities in which I was involved during my MAE candidacy. There are two requirements regarding teaching field epidemiology to achieve a minor competency. The first task is to manage a "lessons from the field" (LFF) tutorial session to a small group of colleagues of our own MAE cohort, for which I created a problem-solving exercise on pharmacovigilance. I chose this topic as challenges in pharmacovigilance are not new and include engaging the public, collaborating in partnerships, incorporating informatics, adopting a global approach, and assessing the impact of efforts (1, 2). These themes could be valuable as they are applicable to surveillance systems which is the core of one of the major competencies we have to fulfil as MAE scholars.

The second task was a group activity: to conduct a teaching session to first year MAE scholars (2019 MAE cohort). We decided to do a teaching exercise about a media communications strategy called "single overarching communication outcomes" (SOCOs). It has been recognised that communicating with the public can be confronting and using this particular strategy early in the development of communication objectives facilitates the flow of information to the media, streamlines data, and focuses on the primary audiences (3).

My role

Firstly, I actively participated in the LFF sessions organised by my peers in the allocated group and presented one LFF myself which was titled "Pharmacovigilance: how does epidemiology helps the regulators of medicines".

Secondly, as a member of the group which delivered a presentation to introduce the "SOCO" concept and its relevance to field epidemiology to first year MAEs, I had the opportunity to participate from the planning of the session to the delivery of the teaching product. After completing this teaching session, a survey was carried out among the attendees to evaluate the activity and receive feedback.

Lessons learnt

I found the two activities to be fun and fantastic opportunities to develop further concepts such as practical learning of how to teach and collaborative approach.

The LFF was particularly challenging in that I was trying to transmit to my colleagues the value of translating field epidemiology concepts to a novel topic for them, one related with therapeutic goods (medicines, vaccines). One of the advantages was that I was not the first to deliver a topic, so

that I could structure the activity considering the style of my peers using explicit teaching and questioning.

In preparation for the teaching session, the first step consisted in developing a structured lesson plan. This was a powerful tool as sometimes as a teacher, and with previous experience, you tend to avoid writing it due to sometimes fast pace and the self-confidence gained with the experience. But going over the lesson plan with your colleagues, highlighted the importance of carefully considering the objectives of a teaching session from different perspectives and gave us the ideal environment to learn about each teaching style and apply our strengths to the session. The content of the lecture was a good debate as each one of us had proposals. After agreeing on the topic, it was easier to design the problem-solving exercise and formulate the post-session questionnaire to evaluate the learning experience.

Acknowledgements

I wish to thank the other members of my LFF group: Celeste Marsh, Callum Thirkell, and Brady McPherson. Dynamism was the theme of their participation in the exercise and each one of them provided invaluable feedback.

For the MAE first year teaching, I wish to thank the other members of my teaching group: Anthea Katelaris and Stephen Hartfield. We all cooperated efficiently to develop the “SOCOs” lesson plan, presentation structure and content and evaluation questionnaire. And extra collaborative effort was placed in rehearsing the presentation. It was an enjoyable experience to work in a team in order to develop a teaching product and deliver an outcome. Our topic and delivery method were well received by the audience, as reflected in the evaluation results.

Lessons from the field

In May 2019, I had the opportunity to share my LFF tutorial as a practical lesson with my colleagues. I collated key background resources and developed activities for members of my group to work through. I had to consider that I was the only MAE scholar placed in a regulatory agency (none of the other scholars were involved in a regulatory environment, even more dealing with therapeutic goods).

The learning objectives and activities proposed were submitted to my MAE colleagues a week in advance (see Appendix 1) and they were required to prepare the material beforehand. Even though I provided links to pages and handbooks related to the topic to set the basis for a discussion, I also gave some summary within the document of important key aspects of pharmacovigilance to

highlight core information. Questions (in green) where focused on getting facts but also to promote acquiring new knowledge.

We had a one hour Zoom videoconference to review the answers and discuss further questions. The choice of the topic was praised as it was a novelty, and giving an overview and work through examples was valued by my colleagues and I received positive feedback about that strategy. I decided to finalise with a 5-question informal quiz to aid retention of the learned facts (Appendix 2 – answers in red not provided).

MAE first year teaching

Finally, for the teaching session for the 2019 MAE cohort, I worked in a group of three to create and deliver a teaching exercise on developing media messages, focussing on SOCOs. SOCOs are the overarching outcome or change desired as a result of the communication. The SOCO guides the development of a key message and supporting statements.

We decided to make the allocated 30-minute session interactive: consisting of a 10-minute background presentation, a 10- minute group activity to develop SOCOs on three issues (for which they were provided with background documents), and 10 minutes of peer feedback. We wanted to emphasise the importance of the SOCOs approach as integral tool that it could be used in different public health scenarios, including the TGA.

To reach those objectives, the lesson plan was particularly useful to coordinate appropriately the activity with my two colleagues and we had a defined road map to make sure that we cover all the proposed objectives.

Lesson plan

Table 1. First year teaching: Lesson plan

Date of session	Friday 8th March 2019
Leads	Anthea, Stephen and Mario
Topic	Creating Single Overarching Communication Outcome (SOCO)
Session Outlines	1. What is a SOCO/components. • When would you use a SOCO • SOCO examples.

	2. Students practice writing a SOCO based on scenarios provided. 3. Students report back on their SOCO, feedback is given 4. Wrap up and evaluation
Learning Objectives	Students are able to: • Describe what a SOCO is and when it can be used. • Practice developing a SOCO
Teaching	Introduce SOCOs as a useful tool to focus key communication messages. • Used widely, including by US CDC and by government health department staff. • Useful for media interviews, especially radio and news segments which may be short, and so where getting the key message across is vital. • Examples of SOCOs will be provided, (including a video of them being used if available.)
Activity & Assessment	Students will be divided into groups of 3, to each work on developing a SOCO. There will be 3 different scenarios to work on. Each group will be provided a SOCO Worksheet to assist with developing a SOCO. Each group will present their SOCO back to the class and students will be asked to provide feedback on each group's presentation. If time permits, students will be asked to volunteer to try to use their SOCO in a mock media interview.
Time	10 mins – intro to SOCOs, when to use, examples. 10 mins – each group develops a SOCO based on material 10 mins – feedback of SOCOs, wrap up and evaluation

Learning exercise

Appendix 3 contains presentation slides, and Appendix 4 the activity worksheet provided filled in with an example we wrote.

Wrap up of the session

Following the activity, we asked students to provide feedback on our exercise via a brief survey, to help improve future teaching. Our session was well received by our peers of the 2019 cohort, as reflected in the evaluation results of this session found in Appendix 5.

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Appendices

Appendix One: LFF exercise

Case study:

Please read the following report sent from an Australian doctor to an international journal in 1961[1]:

THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—Congenital abnormalities are present in approximately 1·5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide ('Distaval') during pregnancy, as an anti-emetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed from mesenchyme—i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

Hurstville, New South Wales.

W. G. MCBRIDE.

History of the Thalidomide case and lessons learnt (or not that well learnt):

Thalidomide was released in the late 1950's as a nonaddictive, nonbarbiturate sedative by the German pharmaceutical company, Chemie-Grunenthal. Thalidomide was very effective and quickly discovered to also be an effective antiemetic and used to treat morning sickness in pregnant women. Thalidomide was marketed and distributed in 46 countries around the world using different names (Distaval in Australia). Thalidomide became one of the world's largest selling drugs, and was marketed heavily and advertised as completely safe right up until it was eventually banned in November, 1961. Indeed, sample packets of the drug were given out to physicians to distribute freely to patients suffering from morning sickness. Precisely how many women were given the drug will never be known. Soon after thalidomide's release, reports surfaced of patients developing peripheral neuropathy after taking the drug. Reports of occurrences of severe birth defects affecting multiple body systems were also coming to light, that initially were not linked to, or were denied to be due to thalidomide. It was not until 1961 that thalidomide was confirmed by two independent clinicians, Lenz in Germany and McBride in Australia, to be the cause of the largest man-made medical disaster in history with huge numbers (over 10,000) of severe birth defects in children.

Oddly, no individual nor Grunenthal itself was successfully prosecuted over the disaster. It took until 2012 before Grunenthal finally offered an "apology," but stopped short of admitting liability, yet little compensation has yet been paid to thalidomide damaged survivors outside Germany. Grunenthal no longer produces thalidomide, but today is one of the world's largest Pharmaceutical companies producing drugs for pain relief.

Today, thalidomide is used to successfully treat a wide range of medical conditions, which include leprosy, multiple myeloma, and cancers, as well as Crohn's disease, HIV, and others. Thalidomide use is carefully monitored (to ensure they are not pregnant while receiving treatment). However, tragically a new generation of thalidomide survivors has occurred in Brazil. Thalidomide is used to

treat complications of leprosy in Brazil, which is sadly common and debilitating. Unfortunately, the drug is given to patients who share the medicine with others, and who do not understand or are not informed of the dangers, and damaged children are born.[2]

LFF - Pharmacovigilance: how does epidemiology helps the regulators of medicines

Learning objectives:

By the end of this session you should be able to:

- Describe the basic principles of pharmacovigilance.
- Explain differences to consider when applying pharmacovigilance principles to specific drugs such as antiretrovirals.
- Describe special considerations that apply to vaccination programmes.

Introduction

Pharmacovigilance has been defined as: The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem (WHO).[3] Pharmacovigilance is an arm of patient care. It aims at getting the best outcome of treatment with medicines. No one wants to harm patients, but unfortunately, because of many different factors, any medicine will sometimes do this. Good pharmacovigilance will identify the risks in the shortest possible time after the medicine has been marketed and will help to establish and/or identify risk factors. When communicated effectively, this information allows for intelligent, evidence-based prescribing with potential for preventing many adverse reactions and will ultimately help each patient to receive optimum therapy at a lower cost to the health system.[4]

Overview

Pharmacovigilance is now an integral part of the regulation of drug safety. Surveillance systems exist at national and international levels to ensure effective monitoring and prompt actions in response to adverse events.

The specific aims of pharmacovigilance are to:

- Improve patient care and safety in relation to the use of medicines
- Improve public health and safety in relation to the use of all medicines
- Contribute to the assessment of benefit, harm, effectiveness
- Encourage the safe, rational and effective (including cost-effective use)
- Promote understanding, education and clinical training in pharmacovigilance and effective communication of its surveillance role to the public

Origins of pharmacovigilance

The WHO Programme for International Drug Monitoring (PIDM) was established in 1968 in response to the thalidomide disaster.[5] The PIDM, now coordinated through the Uppsala Monitoring Center (UMC) in Sweden, developed an international system for detecting previously unknown or poorly understood adverse drug reactions (ADRs). ADR surveillance is responsible for detecting and responding to adverse events associated with drugs.

National regulatory authorities (NRAs) are responsible for reporting ADRs, particularly rare ones or new signals to the UMC so that they can be monitored within the global population.

In many countries, National pharmacovigilance centres are established or existing entities are designated to serve this function on behalf of the NRA. Such centres collect information about adverse events using standardized methodologies. They analyse this information and communicate regularly with NRAs to update the safety profiles of the products used in a country.

NRA'S role in the regulation of drug safety

National regulatory authorities (NRAs) are responsible for ensuring that every pharmaceutical product – including vaccines – used within the country is:

- Of good quality,
- Of known potency,
- Safe for the purpose or purposes for which it is proposed.

Whereas the first two criteria must be met before any consideration can be given to approval for medical use, the issue of safety is more challenging. There is a possibility that rare yet severe adverse events (such as those occurring with a frequency of one in several thousand) may not be detected in the pre-market development of a drug. It is therefore generally accepted that part of the process of evaluating drug or vaccine safety must happen post-market.

UMC: WHO Programme Members

The number of National pharmacovigilance centres participating in WHO's PIDM has increased from 10 in 1968 (when the programme started) to over 100 currently. The centres vary considerably in size, resources, support structure and scope of activities. Collecting spontaneous reports of suspected ADRs remains their core activity.

An up-to-date list of the countries participating in the WHO Programme for International Drug Monitoring is shown on this website: https://www.who-umc.org/global-pharmacovigilance/members/

Activity 1: which one is the organization which fulfils this role in Australia and since when is Australia member of the PIDM?

The stronger the national system of pharmacovigilance and ADR surveillance, the more likely it is that evidence-based regulatory decisions will be made for the early release of new drugs with the promise of therapeutic advances. Legislation governing the regulatory process in most countries allows for conditions to be placed on approvals, such as the requirement that there should be detailed pharmacovigilance in the early years after a drug's release.

In many countries, pharmacovigilance and NRA approvals are linked by an ADR advisory committee appointed by, and directly reporting to, the NRA. An ADR committee may include independent experts in clinical medicine, epidemiology, paediatrics, toxicology, clinical pharmacology and other disciplines. Such an arrangement inspires confidence amongst health personnel and can make a substantial contribution to public health.

While spontaneous reporting remains a cornerstone of pharmacovigilance in the regulatory environment, and is indispensable for signal detection, the need for more active surveillance has also become increasingly clear. Without information on utilization and on the extent of consumption, spontaneous reports do not make it possible to determine the frequency of an ADR attributable to a product, or its safety in relation to a similar product.[6] More systematic and robust epidemiological methods that take into account the limitations of spontaneous reporting are required to address these important safety questions.

Specific case in medicines: antiretrovirals

There is considerable experience in the developed world with the use of antiretroviral medicines. These medicines are associated with significant safety concerns including serious ADRs, with both short- and long-term effects. The outcome of these long-term adverse effects is unknown. The major events linked to the use of antiretroviral medicines include altered body fat distribution (lipodystrophy), anaemia and neutropenia, hypersensitivity reactions, hepatic disorders, acute pancreatitis, altered bone structure (osteopenia and osteoporosis), muscle damage (myopathy) of the newborn and lactic acidosis. These may damage confidence in any national ARV programme and affect patient adherence. With the erosion of confidence in the safety of medicines and of the programme, patients may stop taking these life prolonging medicines leading to problems for themselves and for society as a whole. Poor adherence is known to lead to failure of therapy in the patient and in addition, to increase the possibility of development of drug-resistant viral strains leading to reduced efficacy. Little is known about the toxicity profile of ARVs in developing countries. These countries have special factors and conditions that are very different from those of the developed world and medicine use and its safety may therefore vary considerably. The relevant factors and conditions include the existence of comorbid conditions such as a high prevalence of tuberculosis (TB), malaria and other infections of all types; malnutrition; reliance on traditional and/or alternative therapies; insufficient numbers of trained doctors and pharmacists; irrational use of prescription medicines; and likelihood of medicine interactions. In addition, some local systems for the delivery of health care may rely on people who have limited training, knowledge or expertise, and medicine regulatory systems that are either rudimentary or non-existent and are not adequately equipped to deal with medicine safety issues.[4]

Activity 2: go to section C of the practical handbook on the pharmacovigilance of antiretroviral medicines (https://www.who.int/hiv/topics/pharmacovigilance/arv_pharmacovigilance_handbook.pdf?ua=1) and:

1. find which type of reporting is the most common method of surveillance in the world for antiretrovirals?
2. what would be the advantages and disadvantages of it?

Why vaccines are different and what the specific needs and expectations are towards vaccine surveillance?

Vaccines are considered drugs but require different "immunization safety" surveillance systems to monitor adverse events. Some of the key differences are:

	Vaccines	**Other drugs**
Target population	Usually, healthy people including infants.	Usually, sick people.
Purpose	To prevent disease.	Usually to treat disease.
Source / provider	Vaccines are often administered through public health programmes. In some countries, vaccination may be a prerequisite for enrolment in school.	Often administered by a medical doctor or pharmacist.
Timing	Most childhood vaccines are administered at specific ages, or in relation to special circumstances such as outbreaks or travel. The age at the time of vaccination may coincide with the emergence of certain age-related diseases (e.g. neurodevelopmental disorders).	Normally at time of illness.

Acceptability of risk	Low acceptance of risk. Intensive investigation of severe AEFIs, even if rare, is necessary. Minor AEFIs also should be carefully monitored because they may suggest a potentially larger problem with the vaccine or immunization, or have an impact on the acceptability of immunization in general.	Acceptance of adverse events often depends on the severity of illness being treated and the availability of alternative treatment options.
Quantity	8–15 Childhood vaccines globally recommended.	Thousands of drugs are available.

Although vaccines represent less than 1% of all drug products, their use and purpose is very specific and requires a modified ADR system able to detect and respond adequately and rapidly to occurring adverse events. An ADR related to vaccination is called AEFI (an Adverse Event Following Immunization. According to WHO's definition[7], it is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

Activity 3: considering your previous knowledge on vaccines and the information provided above, imagine the occurrence of a vagal syncope in a child following vaccination. Please answer the following questions:

1. When the parents bring their child for immunization, why may they have a low tolerance for any adverse events that follow such as a vagal syncope?
2. You will be in charge of investigating this event (in particular your supervisor asked for a "causality assessment" as the parents need to know ASAP). Even if you get further information, do you believe it could be possible to establish a definite causal association in this case? What would be the main issue?
    - Hint: yellow box in https://www.who.int/vaccine_safety/publications/aevi_manual.pdf?ua=1

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Appendix Two: Quiz

Q 1. Pharmacovigilance includes:

a. Detection of drug adverse events
b. Assessment of drug-related problems
c. Understanding and Prevention of drug adverse events
d. Just a and b
e. All of the above

(Answer: all of the above)

Q 2. National regulatory authorities (NRAs) are responsible for ensuring that every pharmaceutical product – including vaccines – used within the country is:

a. Of good quality
b. Of known potency
c. Safe for the purpose or purposes for which it is proposed
d. Only a and c
e. All of the above

(Answer: all of the above)

Q 3. Post-market surveillance is key for the safety a drug could as there is a possibility that rare yet severe adverse events may not be detected in the pre-market development of a drug or vaccine:

- True
- False

(Answer: true)

Q 4. Which one of these is not a major event linked to the use of retrovirals:

a. Lipodystrophy
b. Anaemia and neutropenia
c. Haemolacria
d. Myopathy
e. Acute pancreatitis

(Answer: c)

Q 5. Acceptability of vaccine adverse events often depends on the severity of the illness to be prevented (more acceptable for more severe illness). Therefore minor adverse events are not monitored routinely as there will be always a positive risk-benefit balance.

- True
- False

(Answer: false)

Appendix Three: Presentation slides

SOCOs

Stephen Harfield
Anthea Katelaris
Mario Vittorino

Lesson outline

1. **What is a SOCO (10mins)**
   - When would you use a SOCO
   - SOCO examples
2. **Students develop a SOCO (10 mins)**
3. **Students report back on their SOCO (10 mins)**
   - Wrap up and evaluation

Learning objectives

Students are able to:

- Describe what a is SOCO
- When it can be used.
- Practice developing a SOCO

What is this "SOCO"?

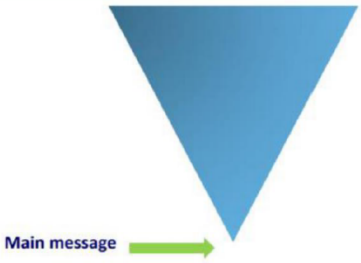
- Google it!
  "Scenes of Crime Officer?"
- Wikipedia:

What is SOCO?

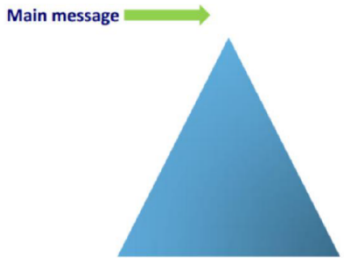
Single Overarching Communication Outcome

- Outcome (or objective) or change you want to see as a result of communicating the SOCO.
- It is NOT your message.
  – (But closely informs your key message)

Scientists and experts speak like this!



Tip 2: Get to the point!



Components of a SOCO

Answer four questions before a communication process:

1. What is your issue?
2. Why do you want to focus on this issue and why now?
3. Who needs to change behaviour (target audience)?
4. What is the change that you want to see in your audience as a result of your communications (THIS IS YOUR SOCO)

SOCO example

- https://www.facebook.com/WesternSydneyHealth/videos/news-western-sydney-local-health-districts-dr-shopna-bag-was-interviewed-by-nine/1661260774143169/

Components of a SOCO

Answer four questions before a communication process:

1. What is your issue?
2. Why do you want to focus on this issue and why now?
3. Who needs to change behaviour (target audience)?
4. What is the change that you want to see in your audience as a result of your communications (THIS IS YOUR SOCO)

Template

SOCO

- What is the objective or outcome you want to achieve?

Key message

- Include in 1 sentence (or 2) the key message.

Supporting statements

- This should include three to four supporting statements.

Background

- Background information and data that would be useful to know but not necessarily say to the media.

When to use?

- All media!
  - Well suited to radio/TV grabs
  - To structure media releases
    - Public health alerts
    - Media on your research
- Elevator pitch/briefings

Let's do it!

- Developing a SOCO Group activity
  - Salmonella
  - Measles
  - Mosquitoes

Your turn

Single Overriding Communications Objective (SOCO) Worksheet

Topic / incident
Target audience Who is the main audience or population segment you would like this message to reach?
SOCO What is the objective or outcome you want to achieve?
Key message 1(to 2) sentences. This should be the message that if they quote nothing else, you would want them to play.
Supporting statements This should include three to four supporting statements (key facts). These are not they key messages but supporting additional statements that contain useful additional information.
Background This section should include background information and data that would be useful to know but not necessarily say to the media. It might include context regarding frequency of events or responses that have already been undertaken.

Learning objectives

Students are able to:

- Describe what a is SOCO
- When it can be used.
- Practice developing a SOCO

Appendix Four: Activity worksheet example

Topic / incident	Wild mushroom poisoning
Target audience Who is the main audience or population segment you would like this message to reach?	General public (especially people who pick wild mushrooms)
SOCO What is the objective or outcome you want to achieve?	A small cluster of wild mushroom poisonings was detected on 25/4/18. While the overall number of wild mushroom poisonings is not above numbers detected in previous years, it is important to remind the public of the risks associated with eating wild mushrooms, so people do not eat wild mushrooms (and therefore exposure to the hazard is reduced).
Key message 1(to 2) sentences. This should be the message that if they quote nothing else, you would want them to play.	The Ministry of Health recommends that people do not eat wild mushrooms as it is difficult to distinguish between edible and poisonous mushrooms.
Supporting statements This should include three to four supporting statements (key facts). These are not they key messages but supporting additional statements that contain useful additional information.	- Eating poisonous mushrooms can cause severe abdominal pains, nausea, vomiting, diarrhoea and hallucinations. Some varieties of mushrooms can cause death due to kidney and liver damage. - In Australia, there are poisonous wild mushrooms that look similar to edible wild mushrooms found in Europe and Asia. - Because there is no reliable way to distinguish between edible mushrooms and poisonous mushrooms, it is recommended that you only eat mushrooms you have purchased from the supermarket or green grocer.

	- Cooking wild mushrooms does not make them safe to eat.
Background This section should include background information and data that would be useful to know but not necessarily say to the media. It might include context regarding frequency of events or responses that have already been undertaken.	Clinical presentation - Gastrointestinal symptoms usually occur relatively soon after eating poisonous mushrooms, typically within 6 hours. The more serious complications of liver and kidney failure usually take 24-48 hours to develop. - Anyone who experiences symptoms following eating wild mushrooms should contact the Poisons Information Centre (13 11 26) or seek medical treatment through their doctor or local Emergency Department. Season - The wild mushroom season usually occurs from late February to late May (weather-dependent).

Appendix Five: First year teaching session evaluation survey results

All questions were scored on a scale from 1 (worst) to 5 (best), except for question 3, where the middle answer was the optimal answer. N=16 responses.

Question	Option range	Mean	Standard deviation	Range
1. Were the objectives and purpose of the session clear to you?	1 – not at all clear 5 – very clear	4.7	0.5	4 - 5
2. Was the presentation style engaging?	1 – not at all engaging 5 – very engaging	4.9	0.3	4 - 5
3. How did you find the pace of the session?	1 – far too slow 3 – just right 5 – far too fast	3.0	0.4	2 - 4
4. How useful was the content?	1 –not useful at all 5 – very useful	4.3	0.7	3 - 5
5. How likely are you to use SOCOs in the future?	1 – very unlikely 5 – very likely	4.1	0.9	3 - 5