Improving the reporting of adverse drug reactions by healthcare professionals in Australia: a mixed methods study

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Statement of originality

This is to certify that to the best of my knowledge, the content of this thesis is my own research undertaken from 2018 to 2022. The thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Raymond Li

Authorship attribution statement

Dr Ronald Castelino, Professor Kate Curtis, and Dr Connie Van formed the higher degree supervisory team. External support was also received from Professor Timothy Chen, and associate professor Syed Tabish Razi Zaidi on various aspects of this research. Published manuscripts form part of the higher degree award of Doctor of Philosophy undertaken by Raymond Li. The following information outlines the published and submitted manuscripts embedded in this thesis and authorship attribution statements indicating the contributions of the thesis author.

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I designed the study with my co-authors, collected the data, analysed the data, and authored the manuscript.

I am the lead author and corresponding author for all the publications above.

Raymond Li

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As supervisor(s) for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

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Abstract

Introduction

Adverse Drug Reactions (ADRs) are a significant cause of hospitalisations and are associated with considerable morbidity and mortality. Under-reporting of these ADRs is a significant healthcare problem as it causes delays in identifying safety issues for medicines resulting in more patient harm. Various strategies have been implemented to improve the quantity and quality of ADR reporting, however these have only been temporarily effective in nature with reporting rates returning to pre-intervention levels within 12 months post cessation of the intervention. Therefore, there is a need to create an effective solution that can provide a sustained long-term improvement in ADR reporting.

Objectives

This thesis aims to identify factors that influence ADR reporting by healthcare professionals to help inform the design of future interventions to provide a more sustained improvement in the quality and quantity of ADR reporting.

Methods

An embedded experimental mixed methods study design was used to investigate the factors associated with ADR reporting by healthcare professionals. In phase one, a retrospective analysis of hospital admission records was conducted to identify whether ADR related hospitalisations were reported to the national regulator. An analysis of a regulatory intervention to improve ADR reporting was also conducted using a time series analysis to assess any improvement in ADR reporting over a 24-month period. In phase 2, a mixed methods survey was deployed to hospital-based healthcare professionals to identify the barriers and facilitators of ADR reporting. Quantitative results were analysed using descriptive statistics and qualitative data were analysed using content analysis. The study identified barriers and enablers to clinician behaviour and categorised them to one of 14 influencers of behaviour per the Theoretical Domains Framework (TDF). These barriers were then mapped to interventions to address these barriers using the Behaviour Change Wheel.

In phase 3, the evidence from this research was integrated to generate a proposed intervention to improve ADR reporting as the final outcome of the thesis.

Results

A total of 5521 hospital admission records were reviewed of which 496 were considered ADR related hospitalisations (9.0%). Patient age (OR 1.04, 95%CI 1.03-1.05) and the number of medicines (OR 1.13, 95%CI 1.11-1.15) were associated with ADR related hospitalisations. Up to 99% of all known ADRs had not been reported to the national regulator. The results of the impact of a regulatory intervention 'the black triangle scheme' on ADR reporting showed that there was a slight increase in the quantity (monthly increase of 0.41 reports per medicine, 95%CI 0.02 – 0.80) and an almost 3-fold improvement in the quality of reporting (22.2% high quality reports post intervention vs 7.6% high quality reports pre intervention, $p<0.001$). Regarding the survey, which was completed by 133 healthcare professionals, knowing how to report ADRs (OR 3.58, 95%CI 1.05 – 12.2) and encountering ADRs as part of everyday clinical practice (OR 18.6, 95%CI 5.52 – 62.5) were significant predictors of ADR reporting. Content analysis identified three categories: modifying the ADR reporting process, enabling clinicians to report ADRs, and creating a positive ADR reporting culture. After integrating the quantitative and qualitative results, they were mapped to 3 TDF domains: knowledge, environmental context/resources, and beliefs about consequences. An ADR reporting framework was created based on the evidence generated.

Conclusion

ADR under-reporting is highly prevalent in Australia and current regulatory actions to improve ADR reporting have only been modestly successful. The findings from this mixed methods research suggest that a multifaceted approach specifically targeting the behavioural domains of knowledge, environmental context/resources, and beliefs about consequences would be required to improve the quantity and quality of reporting.

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List of abbreviations

ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
AEMS	Adverse Event Management Service
AHPRA	Australian Health Practitioner Regulation Agency
AIHW	Australian Institute of Health and Welfare
ARTG	Australian Register of Therapeutic Goods
BCW	Behaviour Change Wheel
DAEN	Database of Adverse Event Notification
eMR	Electronic Medical Records
GP	General Practitioner
HCP	Healthcare Professional
HREC	Human Research Ethics Committee
MRN	Medical Record Number
NHMRC	National Health and Medical Research Council
NPS	National Prescribing Service
PASS	Post Authorisation Safety Study
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QPPV	Qualified Person for Pharmacovigilance
PBS	Pharmaceutical Benefits Scheme
REDCap	Research Electronic Data Capture
REMS	Risk Evaluation and Mitigation Systems
SJS	Stevens Johnson Syndrome
TGA	Therapeutic Goods Administration
UMC	Uppsala Monitoring Centre
WHO	World Health Organisation

Publications related to this thesis

Li R, Zaidi STR, Chen TF, and Castelino RL. Effectiveness of interventions to improve adverse drug reaction reporting by healthcare professionals over the last decade: a systematic review. *Pharmacoepidemiol Drug Saf* 2020; 29(1): 1-8

Li R, Curtis K, Zaidi STR, Van C, Thomson A, and Castelino RL. Prevalence, characteristics and reporting of adverse drug events in an Australian hospital: a retrospective review of hospital admissions due to adverse drug events. *Expert Opin Drug Saf* 2021; 20(10): 1267-1274

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Li R, Curtis K, Van C, Zaidi STR, and Castelino RL. A new paradigm in adverse drug reaction reporting: consolidating the evidence for an intervention to improve reporting. *Expert Opin Drug Saf* 2022; doi 10.1080/14740338.2022.2118712

Conference presentations

Li R. A showcase of innovation in pharmacovigilance 2017 Association of Regulatory and Clinical Scientists (ARCS) conference, Sydney

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Grants and scholarships

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1 Introduction

1.1 Introduction

All medicines can cause side effects and as such, it is important to document these so that a comprehensive safety profile can be obtained for each medicine to facilitate their appropriate prescribing and use. As such, it is the responsibility of all healthcare professionals (HCPs) and consumers to report side effects to contribute to this knowledge and enhance the science of pharmacovigilance, which is defined as the "activities relating to the detection, assessment, understanding and prevention of adverse drug reactions (ADRs) or any other possible drug related problems".(1) This thesis, which contains peer-reviewed publications, investigates the facilitators, barriers, and perspectives of HCPs towards reporting ADRs with a view to inform strategies to improve the quantity and quality of ADR reporting in Australia.

This chapter provides the context of ADR reporting by introducing the common definitions used in pharmacovigilance, the mechanisms of ADR reporting systems available, and the overall impact of ADRs on the healthcare system in Australia. The evidence gap in ADR reporting is then discussed, which leads into the research objectives, aims and questions. The significance of this research and the author's positions on this are then presented. This chapter concludes with an overview of the structure of this thesis including an outline for each chapter and the location of each peer-reviewed publication embedded within this thesis.

1.2 Background

This section introduces the background on ADR reporting in Australia to provide context to this research. This includes an outline on the common definitions used, the roles and responsibilities of the national regulator in Australia, the ADR reporting channels available, and an overview of the spontaneous reporting system including a discussion on its strengths and weaknesses. This section will also present the challenges and impact of ADR under-reporting, which demonstrates the evidence gap associated with creating effective

strategies to improve ADR reporting and the need to create such evidence-based interventions.

1.2.1 What is the difference between an adverse drug event and adverse drug reaction?

An adverse drug event (ADE) is defined by the International Council of Harmonisation as "any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment."(2) An ADE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. ADEs include adverse drug reactions (ADRs), which is defined as "any noxious and unintended response to a drug which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function."(3) The phrase *response to drug*- suggests that a causal relationship between the medicine and the reaction is at least a reasonable possibility. ADEs also include medication errors , which are usually preventable and can lead to patient harm caused through product confusion, packaging and labelling issues, dispensing and prescribing errors, gaps in communication, and incorrect routes of administration.(4) Based on these definitions, it is important to collect information about ADEs for medicines rather than only ADRs given that a causal relationship may not be obvious at the time of occurrence. This also assists in establishing a more comprehensive safety profile for medicines.

1.2.2 ADRs in the Australian healthcare system

ADRs are estimated to be the direct cause of 2-3% of hospitalisations in Australia with an overall rate of 2 medication errors for every 3 patients at the time of hospital admission.(5) This is equivalent to approximately 230,000 hospitalisations annually for medication-related issues. The Australian Institute of Health and Welfare (AIHW) data showed that the rate of ADR related hospitalisations increased from 4.8 to 5.4 events per 100 hospitalisations between 2007-08 to 2015-16.(6) In addition, ADRs resulting in emergency hospital admissions (9.7 events per 100 hospitalisations) were more than double the rate for non-emergency hospital admissions (3.9 events per 100 hospitalisations) in 2015-16 highlighting

the complexities and seriousness of medication-related issues. (Figure 1.1) ADRs were also more likely to result in surgical admissions than non-surgical admissions (7.7 and 4.7 events per 100 hospitalisations respectively).

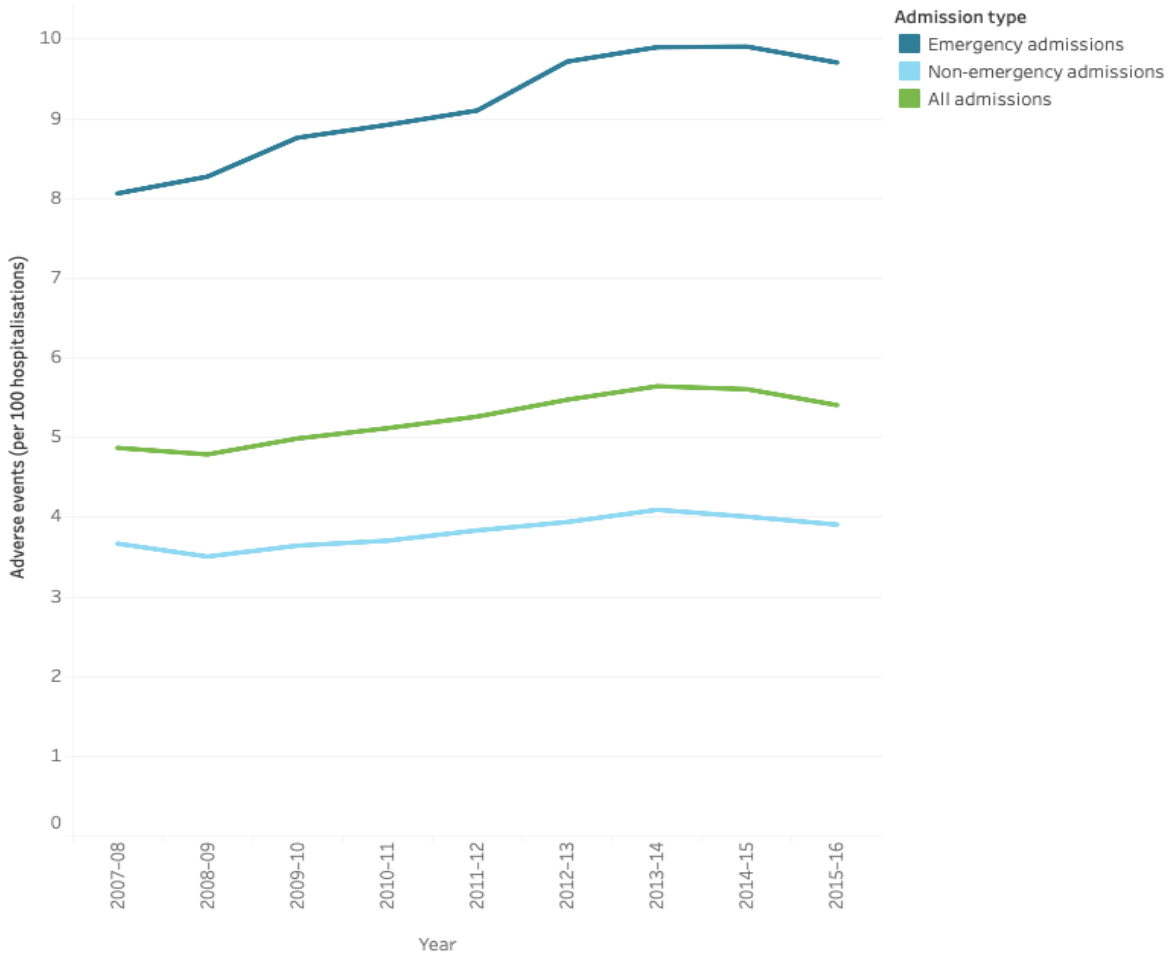

Figure 1.1: Hospitalisations involving an ADR by urgency of admission, 2007-08 to 2015-16

More importantly, the majority of detected ADRs in Australian hospitals are considered preventable with studies showing that this can be as high as 75%. (7) This suggests that some medicines are being inappropriately prescribed given the number of medicines a patient takes is significantly associated with or is an independent predictor of ADR related hospitalisations.(8) Inappropriate prescribing is defined as using medicines that are not clinically indicated, not cost effective, or are causing more harm than benefit for patients. (9) Furthermore, it is likely that some patients may already be suffering from conditions caused by ADRs, and when new medicines are initiated to treat these conditions, it triggers a prescribing cascade whereby a new medicine is prescribed to treat an ADR of another

medicine in the mistaken belief that a new medical condition requires the treatment.(10) This leads to more potential harm for patients and adds an unnecessary cost burden to the healthcare system. It is important to recognise that these costs not only include the expenditures of the hospital stay, but also costs associated with additional clinical investigations, staff wages, disposable goods, missed days from work and other associated morbidity caused by the ADR.(11) A literature review from Australia showed that the average cost per hospitalisation was $5,204 AUD in 2011-12 and based on the medication-related hospital admission rate of 230,000 in the same year, the overall annual cost of ADR related admissions can be estimated at $1.2 billion AUD.(12)

1.2.3 ADR reporting in Australia

All HCPs and consumers can voluntarily submit an ADR report to the Therapeutic Goods Administration (TGA), which acts as the national regulator responsible for monitoring the safety of all approved medicines in Australia. They can do so through a number of means including phone, fax, email, posting an ADR blue card, or completing an online report using the TGA Adverse Event Management Service (AEMS).(13) The TGA encourages reports of all suspected and unexpected ADRs as well as those that are suspected of causing death, danger to life, hospital admission, prolongation of an existing hospitalisation, increase in treatment costs, birth defects, and absence from productive activity. Reports received are collated and analysed by a TGA medical officer and shared with the World Health Organisation Uppsala Monitoring Centre (WHO-UMC) along with ADR reports from the national regulators of 166 nations.(14)

The overall reporting rates by HCPs in Australia comprise only a small proportion of all ADRs reported to the TGA with the pharmaceutical industry submitting the most reports due to mandatory pharmacovigilance requirements. For example, in 2017, only 6% of ADR reports were received from community pharmacists and 3% were received from general practitioners (GPs), both of which were lower than those reported by consumers (7%). (15) In addition, the overall trend of reporting rates from these HCP groups were flat to declining from 2013 to 2017. This is in contrast to the pharmaceutical industry who submitted 54% of the ADR reports in 2017 with an increasing trend during the same period. (Figure 1.2) This may be due to several reasons including the reliance on a spontaneous reporting system for

HCPs and consumers whereby reporting ADRs is voluntary versus mandatory reporting requirements for pharmaceutical companies that is strictly monitored and enforced by the TGA under its pharmacovigilance inspection program.(16)

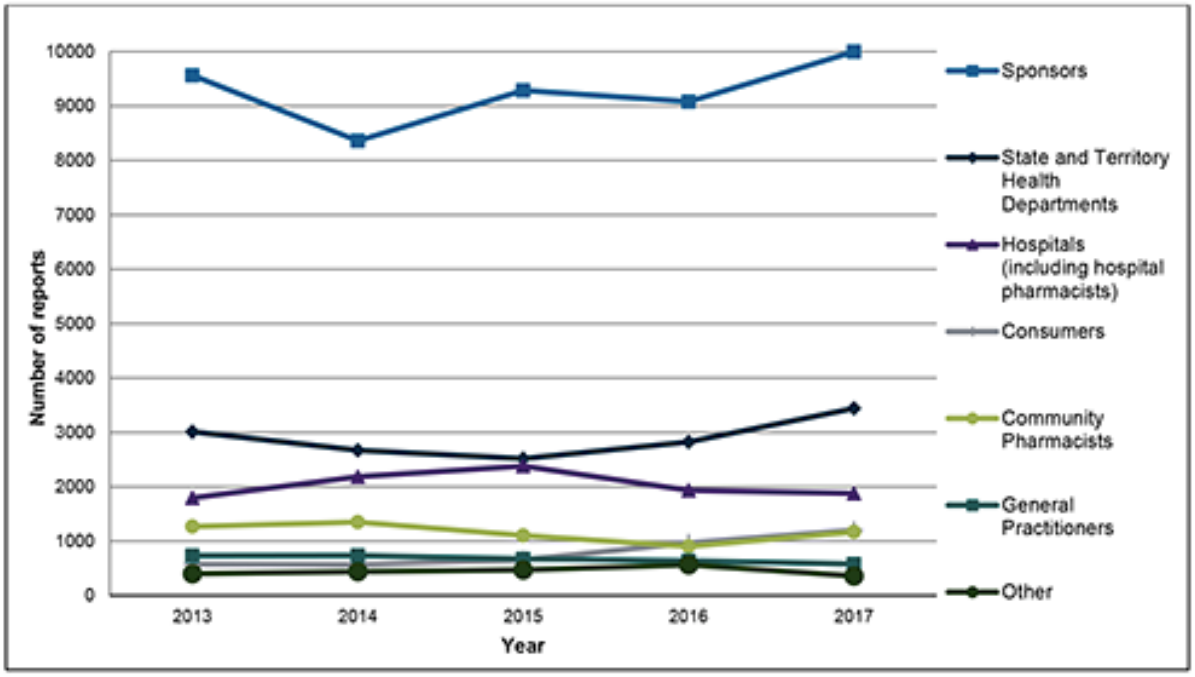

Figure 1.2: Origin of medicine and vaccine adverse events received by the TGA 2013-17

The low rate of ADR reporting by HCPs and consumers in Australia has been recognised by the TGA, who have enacted several strategies to create awareness and encourage reporting. In 2014, the National Prescribing Service (NPS) introduced two learning modules to highlight the importance of safety reporting and how to build a culture of ADR reporting into everyday practice.(17) In addition, the TGA has rolled out integration features within existing GP prescribing software and pharmacy dispensing software to report directly into the TGA AEMS module.(18, 19) To encourage ADR reporting for new medicines, the TGA also introduced the black triangle scheme in January 2018, which involves the inclusion of a black triangle symbol in Product Information and Consumer Medicines Information alerting consumers and HCPs to report ADRs.(20) A similar scheme has been used in the European Union since 2013, however the literature showed that the success of this scheme was suboptimal. (21, 22) Prior to this doctoral research the impact of the black triangle scheme in Australia had not been evaluated.

1.2.4 Spontaneous reporting system

A spontaneous reporting system is defined as a passive surveillance system whereby reports of ADRs are voluntarily submitted by consumers and HCPs to the national regulatory agencies. There have been studies to suggest that spontaneous reporting is the best method for ADR collection during the post-marketing phase of the drug life cycle due to convenience, low cost and feasibility.(23) It also benefits from the fact that safety information is collected from real-life clinical situations as opposed to clinical trials where vulnerable patients are often excluded from the trial and trial duration is limited.(24) As such, the spontaneous reporting system has been adopted worldwide as the primary form of post-marketing surveillance for approved medicines. However, it is estimated that only 2-4% of non-serious and 10% of serious ADRs are reported spontaneously by HCPs.(25) In addition, the spontaneously reported ADRs are usually of very poor quality with lots of missing information.(26) There are also limitations in calculating ADR incident rates from spontaneous reports with only frequencies of ADR occurrences available and information on the population exposed to the drug are lacking.(27) Another issue with the spontaneous reporting system is the inability to categorically determine a causal relationship between the suspect drug and the ADR as each case report can involve patients with multiple concurrent disease states and taking multiple concomitant medications.(24) Finally, there are always inherent reporting biases in a spontaneous reporting system where consumers and HCPs are more likely to report ADRs that have been mentioned in the media or published in the literature. Well known or trivial ADRs are less likely to be reported and medicines that have been on the market for a long time attracts less ADR reports compared to medicines that are newly registered. This may create false safety signals for existing medicines or spikes of ADRs associated with newer medicines.(28)

1.2.5 Impact and significance of ADR under-reporting

Unfortunately, not all ADRs associated with a medicine are identified during the clinical trial stages of the drug development process. The high cost of running interventional clinical trials imposes several limitations including small patient sample size, restricted patient populations with strict inclusion and exclusion criteria, and limited study duration.(29) Therefore, clinical trials may only be able to detect ADRs that are common and that develop

over a short period of time. The patient population in clinical trials may not be representative of patients who may receive the treatment post-marketing and who may be more susceptible to ADRs (e.g. elderly, patients with concurrent illnesses, women of child-bearing age). This is further emphasised by the fact that ADRs are poorly reported in the literature. A review of 113 randomised controlled studies published in high impact journals found that 15% did not provide quantitative data on ADRs, 27% did not provide information on the severity of ADRs, and 48% did not include information on patient discontinuations due to ADRs.(30) Therefore, it is difficult to generalise the safety information collected from clinical trials into actual everyday practice as after a medicine is marketed, previously unknown and potentially serious ADRs will occur and this can alter the benefit risk profile of that medicine. Examples include natalizumab, which is associated with progressive multifocal leukoencephalopathy,(31) rosiglitazone and rofecoxib which is associated with significantly increased cardiovascular risk,(32, 33) and diethylstiloestrol which is associated with increased risks of stillbirth, neonatal death, infertility and vaginal adenocarcinoma.(34) In Australia, lumiracoxib was recalled from the market in 2007 due to significant liver toxicity leading to transplantation and death.(35) All of these safety issues were identified post-marketing and have caused significant harm in patients who were exposed. This is a significant healthcare problem and highlights the significant healthcare impact when there are delays by regulatory agencies to identify safety issues for medicines. This is reinforced by a systematic review of all medicines removed from the market for safety reasons which showed that the median time from drug launch to drug withdrawal was 10 years.(36) Therefore, health authorities around the world must rely on additional phase IV observational and epidemiological safety studies to identify new ADRs associated with medicines. For example, the European Regulatory Agency has recently made the conduct of post authorisation safety studies (PASS) legally binding on the pharmaceutical company through the implementation of EU guidance document EMA/813938.(37) This document provides regulatory agencies with the legal authority to mandate the execution of PASS as a condition of granting marketing authorisation.

1.3 Evidence Gap

Various strategies have been implemented to improve the quantity and quality of ADR reporting. These have primarily focused on traditional interventions such as educational sessions, providing reminders, provision of an incentive such as remuneration or continuing medical education points, or enhancing the availability of the reporting form. Results have consistently shown that these strategies are effective in improving ADR reporting, however this was only temporary in nature with ADR reporting rates returning to pre-intervention levels within 12 months post the cessation of the intervention.(38) This calls for a different approach to increase ADR reporting that would result in a more persistent and sustained improvement in the quantity and quality of reporting.

Digital enhancements in healthcare have progressed significantly over the past decade with the implementation of various forms of e-prescribing, e-medical records, e-medication management, health related mobile apps, and the use of artificial intelligence to assist with mining and integrating large datasets to streamline processes for routine medical administrative activities.(39-41) Some of these technologies already exist in Australia such as electronic medication management and electronic medical records, which are used in hospitals in New South Wales. However, there is some variation across other states and regions of Australia and is dependent on whether a local health area network has adopted digital technologies.. Therefore, there is an opportunity to develop a digital tool that can encapsulate these features to facilitate ADR reporting and allow for the assessment of its effectiveness post intervention.

To better help inform the development of this digital intervention, specific barriers and perspectives of HCPs towards ADR reporting should be identified. There is a wealth of literature on what these are including studies from Australia, (42-49) however, these were not collected based on the domains within a formal behavioural change framework and hence could not be utilised to inform the development of an intervention that would specifically address these barriers. As such, there is a need to utilise an evidence-based behavioural change tool to collect information on HCP perspectives and barriers towards ADR reporting so that this information can be integrated into the final electronic reporting tool.

1.4 Research objectives and aims

The primary objective of this research is to generate evidence to help inform the development of a digital tool to improve the quantity and quality of ADR reporting by HCPs within the hospital setting in Australia. As part of phase 1 of the project, I identified the prevalence, characteristics, and reporting of ADRs in the hospital environment. This helped to identify the electronic systems and datasets available that can be integrated to improve ADR reporting as well as determining whether there are specific medicines or disease states that require additional focus in terms of ADR reporting. At the same time, I reviewed the effectiveness of an intervention recently introduced by the TGA to improve the quality and quantity of ADR reporting for newly approved medicines. This helped to inform whether newly approved medicines should be a focus for our digital tool and what complementary features may be required to enhance the effectiveness of the intervention. I then proceeded to phase 2 of the project by reaching out to HCPs to understand their perspectives towards reporting ADRs as well as identifying the associated facilitators and barriers to ADR reporting by using a behavioural change framework. All of this information was then synthesised to achieve the overall objective of informing the design of a digital tool to improve ADR reporting by HCPs in Australia (phase 3).

1.5 Research questions

Phase 1 – Reviewing existing literature on ADR reporting

1. What is the prevalence of ADR related hospitalisations and what are their characteristics?
2. What proportion of ADRs are reported to the Australian regulator?
3. How successful was the implementation of the regulatory initiative 'black triangle scheme' on improving the quantity and quality of ADR reporting and are there any opportunities to further enhance the effectiveness of this intervention?

Phase 2 – Identifying behavioural factors associated with ADR reporting to inform future interventions

4. What are the perspectives, facilitators and barriers of HCPs working in the hospital environment towards the reporting of ADRs?

Phase 3 – Integrating the evidence

5. What evidence can be used to inform the design of a strategy to improve the quality and quantity of ADR reporting in Australia?

1.6 Significance of this research

The early identification, quantification, and analysis of ADRs is critical to understanding the safety profile of a medicine. As there is only limited safety information available at the time of a medicine being approved for use on the market, it is critically important to have in place a mechanism to collect and report ADRs post marketing so a complete safety profile can be obtained. Furthermore, effective risk management strategies can be put in place to address any significant safety issues identified. For example, the use of carbamazepine was associated with severe Stevens Johnson Syndrome (SJS) especially in the Asian population, which was only identified during post-marketing surveillance activities and analysis of ADR reports.(50, 51) It was concluded that the Asian population was significantly more at risk of SJS due to the presence of an allele HLA-B*1502 and as such, a risk management strategy was put in place which mandates additional monitoring for SJS when physicians prescribe carbamazepine in Asian patients.(52, 53) This helped to significantly reduce morbidity and mortality in these patients and could not have been achieved without the collection and reporting of ADRs for carbamazepine post-marketing. Therefore, any potential under-reporting of ADRs must be addressed, especially for newer medicines as their safety profiles are limited.

Understanding the characteristics and prevalence of ADRs occurring in hospitals helped to tailor interventions that may be specific to a certain medicine class or disease state area where poorer outcomes in patients are more frequent. Assessing the effectiveness of existing strategies also helped to inform any potential shortcomings and synergies that can be exploited in the design of future interventions to improve ADR reporting. In addition, exploring HCPs attitudes, perspectives, and barriers towards reporting ADRs helped to determine the specific factors that must be addressed from both an operational and contextual level. The integration and application of the findings from this research informed

the design of an intervention that will incorporate digital advancements from the last decade to improve the quantity and quality of ADR reporting.

1.7 Position of the thesis author

I am a registered pharmacist in Australia and have practiced for over 10 years in the field of pharmacovigilance within the pharmaceutical industry, including acting as the qualified person for pharmacovigilance (QPPV) for a major pharmaceutical company in Australia for over 4 years. This has allowed me to appreciate the importance of monitoring the safety profile of medicines given the day-to-day role of interacting with the TGA on maintaining a positive benefit risk profile of all medicines sponsored by my company. This has encouraged me to become curious about one of the key deficiencies of our national pharmacovigilance surveillance system, namely the voluntary reporting of ADRs by HCPs who manage and treat ADRs as part of their everyday patient care versus the mandatory reporting requirements imposed on pharmaceutical companies who are not responsible for the daily clinical management of patients.

There has been a growing need to improve ADR reporting given the significant length of time it takes regulators to remove medicines with unacceptable safety profiles from the market.(36) Traditional strategies to improve ADR reporting such as educational sessions, reminders, and/or incentives have only been modestly successful and the effects of these interventions subside significantly to pre-intervention levels within 12 months. Developments in artificial intelligence and natural language processing to identify ADRs for pharmaceutical companies has driven me to see whether there is an opportunity to apply such technologies to help HCPs identify and report ADRs. By taking on this project as part of my PhD, I hope to generate the evidence required to support the development of a digital tool to encourage ADR reporting allowing for the faster identification of medication safety issues.

1.8 Thesis overview

This thesis was written to investigate potential ways to improve ADR reporting by collecting information on the prevalence, characteristics and the current ways HCPs report ADRs in

Australia, as well as their perspectives and perceived barriers to ADR reporting. Given the incorporation of digital technologies into healthcare in the last decade such as eMedical Records, eMedication Management System (eMEDS), digital health apps etc., I aimed to generate the evidence required to inform the development of a digital tool to improve ADR reporting.

This thesis is organised and written according to the requirements of a thesis by publication. It contains five peer-reviewed publications which are embedded within the content of the various chapters to provide a unified body of evidence.

1.8.1 Overview of thesis chapters

The first chapter provides an introduction into the background of ADR reporting in Australia and establishes the context and rationale for this thesis. The definitions of ADRs versus ADEs are explained to clearly differentiate what should be collected and reported as part of the post-marketing surveillance system. The prevalence of ADRs in Australian hospitals is discussed along with statistics on its current trends and costs to the healthcare system. In addition, this chapter also highlights the current under-reporting of ADRs by HCPs and the strategies introduced by the TGA to encourage reporting. From this, I explored the potential reasons of ADR under-reporting by discussing the strengths and weaknesses of a spontaneous reporting system and analysing the potential impact of delays in identifying safety issues for medicines.

Chapter 2 provides a comprehensive literature review into understanding the effectiveness of interventions that have been implemented to improve the quantity of ADR reporting. This chapter contains the first peer-reviewed publication which specifically focused on studies published between 2010 and 2019 as a previous systematic review was already published for studies published prior to 2010.(38, 54) An updated literature review including studies published from 2019 to 2021 was conducted to identify any new evidence on this topic and the findings from this are reported in this chapter.

Chapter 3 describes the research methods that were used for this thesis including a discussion on the theoretical and philosophical principles of the exploratory embedded mixed methods research design. The rationale for using the mixed methods approach is presented along with the ethical considerations that were taken into account during the conduct of this research project. An overview of the study site, participants, sources of data collection including its analysis, management and integration is also provided.

Chapter 4 presents the findings of this research and includes three peer-reviewed publications that are embedded. Publication 2 reports on the prevalence, characteristics and reporting of ADRs in an Australian hospital answering research questions 1 and 2.(55) Publication 3 presents the results of the effectiveness of the recently introduced black triangle scheme to improve the quantity and quality of ADR reporting in Australia, which answers research question 3.(56) Publication 4 presents on the perspectives, facilitators and barriers of HCPs towards reporting ADRs in the hospital environment including both qualitative and quantitative data and this answers research question 4.(57)

Chapter 5 integrates all of the findings from this research and includes the fifth and final publication of this thesis. This includes a discussion of all the evidence generated from this research project to inform future interventions that can be implemented to improve ADR reporting by HCPs in Australian hospitals. This answers research question 5.

Chapter 6 is the final chapter of this thesis and provides a summary of the key findings, recommendations, and directions for future research. It explains how recommendations from this research can further enhance the development of digital interventions to improve ADR reporting as well as strategies to improve its uptake as part of everyday clinical practice. The initial implementation of a digital tool to improve ADR reporting at Blacktown Hospital will be discussed. This chapter also includes a discussion on the strengths and weaknesses of this research.

2 Literature review

2.1 Introduction

This chapter presents a literature review of the existing evidence surrounding the effectiveness of interventions to improve ADR reporting. The research questions are first presented, followed by a summary of a systematic review of studies published between 2010 and 2019. This period was selected as a similar systematic review of the same topic was already published for the period up to 2010.(38) Our systematic review was published in the peer-reviewed journal *Pharmacoepidemiology and Drug Safety* and is embedded within this chapter.(54) The results from an updated literature review from July 2019 to February 2022 are also presented.

2.2 Literature review questions

The following questions for the literature review were guided by the Participants, Interventions, Comparisons and Outcomes (PICO) framework: (58)

1. What are the types of interventions used to improve ADR reporting?
2. How successful have these interventions been in improving the quantity of ADR reporting and are certain types of interventions more effective than others?
3. Are multifaceted strategies more effective than single interventions in improving ADR reporting?
4. Are electronic digital technologies being adopted as a strategy to improve ADR reporting and are they more effective than traditional strategies?

2.3 Literature review overview

An integrative review method was utilised to investigate the research questions as this enables a comprehensive analysis of the literature employing a combination of diverse methodologies from a variety of sources.(59) An initial scoping review showed that there are a variety of different interventions that have been assessed to improve ADR reporting, however, these were primarily based on traditional methods such as educational workshops, providing an incentive, reminders, or making available the ADR reporting form.

Given the incorporation of digital tools to assist with healthcare related activities in the last decade, a more recent literature review was required. By conducting a systematic review, the depth of knowledge that can be obtained allows for a comprehensive analysis of the available evidence despite the challenges in analysing a large volume of search results that is expected from this methodology.(60)

A systematic search of the literature was conducted using the databases MEDLINE-PUBMED, and EMBASE according to guidance from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.(61) Furthermore, a horizontal review of the references from the included studies was undertaken to identify any publications that were not included from the original search. The search terms used were based on the previously published systematic review but amended slightly to match the updated standardized keywords adopted by EMBASE. The inclusion criteria were any study type that investigated the effectiveness of an intervention to improve ADR reporting. As the previous systematic review included all studies that were published to December 2010, we selected the time period from 01 July 2010 to 17 June 2019 in our systematic review to allow for any potential 6-month publication delay. Studies that were already included in the previous systematic review were excluded along with publications not in the English language. The quality of the included studies was evaluated using the same methodology as the previously reported systematic review to ensure consistency. The specific results and methods of this literature review are presented in the following publication.

2.4 Publication 1

Li R, Zaidi STR, Chen TF, and Castelino RL. Effectiveness of interventions to improve adverse drug reaction reporting by healthcare professionals over the last decade: a systematic review. *Pharmacoepidemiol Drug Saf* 2020; 29(1): 1-8

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REVIEW

WILEY

Effectiveness of interventions to improve adverse drug reaction reporting by healthcare professionals over the last decade: A systematic review

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Abstract

Background: Various strategies have been studied in the literature to address the significant underreporting of adverse drug reactions (ADRs) in healthcare systems worldwide.

Objectives: We conducted a systematic review of the literature that assessed the impact of various strategies to improve ADR reporting published in the last decade and compared this with the strategies identified in a previous systematic review.

Methods: MEDLINE and EMBASE databases were used to retrieve papers published from 01 July 2010 to 17 June 2019. We included papers in the English language that investigated the quantitative impact of strategies used to improve ADR reporting.

Results: A total of 10,021 articles were retrieved using our search criteria, of which 13 met the inclusion criteria. Multifaceted strategies resulted in a point estimate increase in ADR reporting of 9.26-fold (−2.21–17.11, 95% CI) versus 7.19-fold (−5.29–32.68, 95% CI) for single interventions. Using electronic reporting tools was more commonly identified as an interventional strategy with a point estimate increase of 13.69-fold (−5.29–32.68, 95%CI) versus 4.42-fold (0.66–8.19, 95% CI) for traditional educational methods. The quality of the majority of publications included in this review was low.

Conclusions: Developments in digital technology in the last decade has led to the increased use of electronic reporting tools to improve ADR reporting. Higher quality studies investigating the impact of these electronic methods are needed to fully explore its role in improving ADR reporting.

1 | INTRODUCTION

Underreporting of adverse drug reactions (ADRs) is one of the pressing issues affecting medication safety in clinical practice. Overreliance on spontaneous reporting system coupled with lack of accountability means the majority of ADRs goes unnoticed until such incidents result in patient harm.[1] A recent systematic review found that over 9 out of 10 ADRs identified by healthcare professionals (HCPs) were not reported.[2] Furthermore, the spontaneously reported ADRs usually contain inadequate information to allow for an informed judgment in confirming any causal relationship with the suspect medicine. These deficiencies can delay regulatory actions with a systematic review showing that the median interval from drug launch to drug withdrawal was 10 years for drugs with an unacceptable safety profile.[3] These

delays significantly increase the healthcare costs associated with the management of ADRs as they are a major cause of hospital admissions, prolongation of an existing hospitalization, morbidity and mortality.[4] A Canadian study showed that the overall cost for the management of a single ADR related hospital admission was $7528, and this increased to $10,388 if the patient was admitted to the intensive care unit.[5,6]

The key factors that influence ADR reporting are HCP's knowledge, their underlying perspectives, and operational barriers. Several studies have shown that HCPs with better knowledge on what and how to report ADRs were more likely to do so, however the majority of them had very low knowledge on this topic.[7-9] HCP's perceptions also play a significant role in the under-reporting of ADRs with one survey showing that 87% of physicians believed that all serious reactions will be well documented by the time a drug is marketed and that 71% thought that a single case report will not contribute to medical knowledge.[10] Operational barriers such as lack of remuneration, competing priorities in patient care, and difficulty in accessing ADR reporting forms also significantly influence reporting rates.[11-14] A 2014 systematic review also summarized that the primary themes of indifference, diffidence, ignorance, insecurity and lack of time were the main causes of under-reporting.[13] These factors contribute significantly to the low rates of ADR reporting with studies showing that 50-97% of HCPs admitting that they have not reported any ADRs in the last 12 months.[15]

To address these barriers, a number of initiatives and interventions have been designed to help improve the ADR reporting rates. These have been traditionally in the form of providing educational sessions on ADR reporting, simplification of the ADR reporting process, providing incentives such as continuing education points or remuneration, and enhancing the availability of reporting forms. A systematic review examined the evidence for the effectiveness of various interventions on improving ADR reporting and included all studies published until December 2010.[16] This was a comprehensive analysis of 43 studies which focused on the traditional interventional strategies described above. However, there have been significant developments in the area of digital technology in the last decade across the healthcare sector with the introduction of a number of electronic health initiatives. These include e-prescribing, natural language processing tools to identify ADRs, electronic medical records, and health-related mobile apps, which can significantly improve the convenience of undertaking routine health related tasks and provide a streamlined process for medical administrative activities.[17-19]

1.1 | Objective

This literature review will provide a more recent assessment on the features and successes of the various strategies undertaken to improve ADR reporting by HCPs, and propose alternative initiatives that may enhance these existing methods. This review will also examine whether the recent initiatives were more successful than previous strategies as reported in the earlier review.

2 | METHODS

2.1 | Search methodology

A literature search of MEDLINE and EMBASE databases from 01 Jul 2010 to 17 June 2019 was conducted following the PRISMA statement.[20] The following search terms were used in MEDLINE and EMBASE: *('adverse event'/exp OR 'adverse event' OR 'adverse drug reaction'/exp OR 'adverse drug reaction') AND ('drug surveillance program'/exp OR 'drug surveillance program')*. All were Emtree search terms.

These dates were selected to avoid studies already identified in the previous systematic review and to allow for a potential 6 month publication delay. The inclusion criteria was any randomized studies on individual or aggregate levels (e.g. cluster randomized studies), quasi-experimental studies, and ecological time series studies that investigated the impact of an intervention to improve ADR reporting by HCPs. Studies that were already included in the Gonzalez-Gonzalez systematic review were excluded. The other exclusion criteria included publications in non-English language, no full text availability, not providing sufficient description of the actual intervention, not reporting quantitative results of the intervention, and not including HCPs as the study population.

2.2 | Data extraction

The abstracts of the retrieved scientific papers were initially screened by the primary author with a view to exclude review articles, conference presentations, editorials, or letters. The full text articles of the remaining publications papers were then independently reviewed by the primary author and included if it assessed an intervention that aimed to improve the rate of ADR reporting. All included articles were then independently reviewed by a second author to ensure they met the inclusion criteria. In case of disagreement, the publication was reviewed by a third author who made the final decision.

The following data were extracted for each of the included studies:

1) Study design: quasi-experimental, randomized controlled, cluster-randomized controlled and ecological time series.
2) Country where study was conducted
3) Type of intervention: educational sessions such as presentations or workshops to inform HCPs on the importance and process of ADR reporting, reminders, economic incentive, providing feedback to reported ADRs, making the ADR report form more available through distribution, telephone intervention, and electronic ADR reporting tools such as eHealth records, hyperlinks, or online reporting.
4) Study duration
5) Target population and setting: physicians, pharmacists or other healthcare professionals to whom the intervention is targeted in a primary care or hospital setting.
6) Sample size

2.3 | Data analysis

An intervention was classified as successful if there were any quantitative increase in ADR reports after the intervention. The magnitude of this success was calculated as a ratio of the number of ADR reports post intervention versus pre intervention (x-fold) if this was not already reported in the included studies. The magnitude in increase of ADR reports for studies with multiple interventions was compared with studies investigating the impact of single interventions. The types of interventions identified in this systematic review were also compared with the types of interventions identified in a previous systematic review with a focus on the quantitative impact of the electronic reporting tools identified in both studies.

2.4 | Quality analysis

As there are significant limitations in the current tools that are used to assess the quality of studies included in systematic reviews, we have used the following criteria to classify the quality of our included studies.[21]

1) Quasi-experimental and time series studies: these were classified as high risk of bias as the lack of a control group can influence the results. Some confounding factors include seasonal variation in reporting, media reports of ADRs of interest, public health campaigns, or changes in reporting protocols which may inflate the number of ADRs collected.
2) Randomized/non-randomized controlled studies: these were classified as medium risk of bias as there was no randomization or the process for randomization was not described. This can bias the selection of participants but controls for external influences mentioned above.
3) Cluster-randomized controlled studies: these were classified as low risk of bias as the authors clearly specified the method of randomization and the use of spatial clusters across different hospital networks that prevented the possibility of cross-contamination between the intervention and control groups.

2.5 | Statistical analysis

Statistical analysis of the magnitude of increase in ADR reporting was performed using IBM SPSS (version 25.0) with significance levels set at $P < .05$. The non-parametric Mann Whitney U test was used for comparing the ADR reporting rates between multifaceted versus single interventions as well as electronic reporting interventions versus traditional methods.

2.6 | Ethics approval

As this is a systematic review of studies containing fully anonymized data, no ethics approval was required.

3 | RESULTS

3.1 | Publication selection

Using the keywords in the computerized searches in MEDLINE and EMBASE, a total of 10,021 publications were identified. After removing duplicates and excluding publications based on language, full text availability, and article type, 2688 abstracts were screened for relevance to the topic. The full texts of 58 publications were then reviewed for potential inclusion based on the inclusion criteria. There were 48 publications excluded for inadequate description of the intervention, not providing sufficient results of the intervention, not including HCPs as the study population, or the study did not aim to investigate the impact of the intervention. A horizontal review of the remaining papers' references resulted in 3 additional studies identified. Consequently, a total of 13 publications were included in this review. (Figure 1)[22-34] Table 1 provides a summary of the publications that met the inclusion criteria.

3.2 | Setting and population

The majority of the included studies were conducted in Europe (61.5%) with 2 in Asia (15.4%), 2 in North America (15.4%) and 1 in Africa (7.7%). Almost two thirds of the studies were undertaken exclusively in the hospital setting (61.5%) while two were reported in the primary care environment (15.4%). Three of the studies (23.1%) were also carried out in both a hospital and primary care setting.[22,30,32] Just over half of the studies (61.5%) involved multiple HCPs (physicians, pharmacists and/or nurses) while 30.8% exclusively targeted physicians.[23,26,30,31] The duration of these studies ranged from 5 to 102 months.[24,29]

3.3 | Study designs and measures

The most common study design of the included publications was quasi-experimental (53.8%), followed by randomized controlled studies (30.8%), and ecological time series studies (7.7%). All publications included quantitative parameters as a measure of the success of each intervention such as the increase in the absolute number of ADRs reported or the rate of ADR reporting. The majority of these publications (53.8%) also included qualitative parameters such as quantity of new ADRs, serious ADRs, unexpected ADRs and high causality ADRs.[24-27,30,32,33]

3.4 | Quality assessment of included studies

Table 2 below presents the results of the quality assessment of the included studies. There were 3 that were classified as low risk of bias,[26,30,32] one study as medium risk,[27] and 9 studies were classified as high risk..[22-25,28,29,31,33,34]

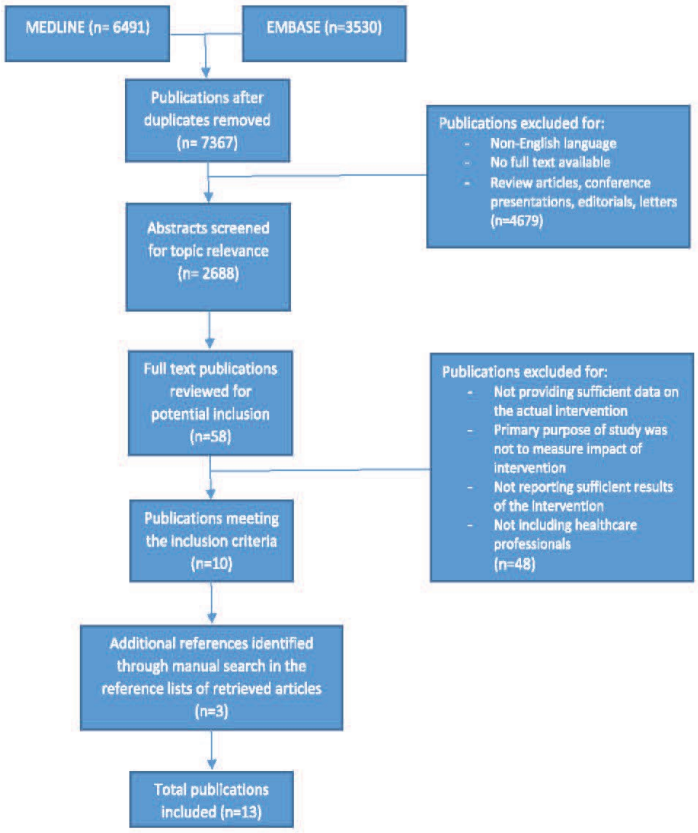

FIGURE 1 Flow chart of literature selection process [Colour figure can be viewed at wileyonlinelibrary.com]

3.5 | Interventions and outcomes

The majority of the studies (61.5%) examined the effectiveness of a single form of intervention to improve ADR reporting[22,23,27-30,33,34] while the rest investigated the impact of multifaceted approaches.[24-26,31,32] As the authors of 5 papers included 2 or more activities as part of their intervention, we included a total of 19 interventions from the 13 publications for this analysis.[24-26,31,32] The most common strategy was the provision of educational session(s) such as a presentation or workshop (31.6%),[25,26,30-32,34] while using an electronic reporting tool to improve ADR reporting was also a popular strategy utilized in 26.3% of the studies.[22,24,28,29,33] Other initiatives include sending reminders (15.8%), offering an economic incentive (10.5%), using telephone interventions (10.5%), and providing feedback to reported ADRs (5.3%).[23-27,31,32] The results showed that all interventions were effective in increasing the absolute number of ADRs reports, or the percentage or rate of ADR reporting. The point estimate of increase in reporting rates was 9.26-fold (−2.21–20.74, 95% CI) for multifaceted approaches versus 7.19-fold (−2.73–17.11, 95% CI) for single interventions (P = .42). For electronic reporting tools, the point estimate of increase in ADR reporting was 13.69-fold (−5.29–32.68, 95% CI) versus 4.42-fold (0.66–8.19, 95% CI) for traditional educational methods (P = .153). Out of the 4 randomized controlled studies that were included in this review, all interventions resulted in a statistically significant increase in the quantity of ADR reports.[26,27,30,32]

3.6 | Comparison with previous systematic review

The use of electronic reporting tools to improve ADR reporting was more commonly identified as an interventional strategy in this systematic review. In the Gonzalez-Gonzalez review, only 3 of the 46 interventions (6.5%) identified from 1986 to 2010 investigated the impact of an electronic ADR reporting tool whereas this review identified 5 out of 19 interventions (26.3%) over a period of less than 10 years.[16] The electronic reporting tools identified in this review included the integration of electronic health records to automatically populate ADR reports,[29] which was not a feature of earlier electronic reporting tools identified in the previous systematic review.[16]

TABLE 1 Characteristics of included studies

Reference and country	Study population and setting	Study period	Sample size	Study design	Type of intervention	Increase in reporting (fold)	95% Confidence interval
Linder et al, 2010, USA	Healthcare professionals in hospital	5 months	26	Quasi-experimental	Electronic ADR reporting	36.17	16.07–81.39
Johansson et al, 2011, Sweden	Physicians and nurses in hospital	12 months	151	Randomized controlled	Reminders	1.52	0.19–1.81
Ribeiro-Vaz et al, 2011, Portugal	Pharmacists in hospital and primary healthcare	12 months	1467	Cluster randomized controlled	Educational session Telephone intervention	3.22	1.33–7.80
Herdeiro et al, 2012, Portugal	Physicians in primary care	20 months	6579	Cluster randomized controlled	Educational session Telephone intervention	3.97	3.86–4.08
Ribeiro-Vaz et al, 2012, Portugal	Healthcare professionals in hospital	48 months	Not reported	Ecological time series	Electronic ADR reporting	2.50	0.49–12.89
Lander et al, 2013, Denmark	Healthcare professionals in hospital	12 months	140	Quasi-experimental	Electronic ADR reporting	5.4	4.56–6.24
Biagi et al, 2013, Italy	Physicians in primary care	24 months	737	Quasi-experimental	Reminders	1.49	1.08–2.05
Abadie et al, 2014, France	Healthcare professionals in primary care and hospital	18 months	Not reported	Quasi-experimental	Electronic ADR reporting	1.45	1.16–1.83
Lopez-Gonzalez et al, 2015, Spain	Physicians in hospital and primary care	22 months	7498	Cluster randomized controlled	Educational session	2.31	1.46–3.68
Morales Rios et al, 2016, Mexico	Physicians in pediatric emergency department of hospital	16 months	62	Quasi-experimental	Educational session Reminders Inclusion of reporting form Feedback	14.68	4.99–43.21
Chang et al, 2017, China	Physicians and pharmacists in hospital	102 months	Not reported	Ecological time series	Economic incentive Electronic ADR reporting	22.96	16.97–25.80
Fang et al, 2017, China	Physicians, pharmacists and nurses in hospital	66 months	943	Quasi-experimental	Educational session Economic incentive	1.49	1.34–1.66
Terblanche et al, 2018, South Africa	Healthcare professionals in hospital	18 months	547	Quasi-experimental	Educational session	6.7	2.83–15.72

TABLE 2 Quality assessment of included studies

Reference	Study design	Method of randomization described	Risk of bias
Ribeiro-Vaz et al, 2011	Randomized controlled	Yes, spatial cluster	Low
Herdeiro et al, 2012	Randomized controlled	Yes, spatial cluster	Low
Lopez-Gonzalez et al, 2015	Randomized controlled	Yes, spatial cluster	Low
Johansson et al, 2011	Randomized controlled	No	Medium
Linder et al, 2010	Quasi-experimental	N/A	High
Lander et al, 2013	Quasi-experimental	N/A	High
Biagi et al, 2013	Quasi-experimental	N/A	High
Abadie et al, 2014	Quasi-experimental	N/A	High
Morales Rios et al, 2016	Quasi-experimental	N/A	High
Fang et al, 2017	Quasi-experimental	N/A	High
Terblanche et al, 2018	Quasi-experimental	N/A	High
Ribeiro-Vaz et al, 2012	Ecological time series	N/A	High
Chang et al, 2017	Ecological time series	N/A	High

4 | DISCUSSION

This review showed that all strategies were effective in increasing the ADR reporting rate and the magnitude of this increase was significant with 53.8% of the studies reporting at least a threefold improvement.[24,26,28,29,31,32,34] This is not surprising as the literature showed that under-reporting of ADRs was extremely high and therefore at pre-intervention, there were very low numbers of ADRs reported. Compared to previous systematic reviews, the use of electronic reporting tools was more commonly identified as an interventional strategy and this demonstrates an important advance in utilizing digital technology to facilitate the reporting of ADRs. For example, Linder et al captured electronic health records using an application to trigger an ADR report when a clinician discontinued a medication due to the ADR.[29] It took the clinicians a mean of 53 seconds to send each report and this resulted in a 35-fold increase in reporting rates. Therefore, the integration of electronic health data and automatic capture of this information to facilitate ADR reporting appears to be an extremely successful strategy, however higher quality randomized controlled studies are required to fully investigate its benefits. It is also important to note that other electronic methods identified in this review only achieved a more modest 1.45- to 5.4-fold increase in ADR reporting rates.[22,28,33] This can be attributed to the fact that electronic reporting tools are only a passive facilitator that improves the convenience of reporting ADRs, whereas traditional methods such as educational sessions and/or reminders are active facilitators that directly promote ADR reporting. Therefore, a multifaceted interventional approach utilizing both strategies would be paramount to its success. This was demonstrated in a study where educational sessions in combination with reminders, providing feedback, and making reporting forms more accessible resulted in a 14-fold increase in reporting.[31] Studies that investigated single forms of intervention in education and reminders only achieved a modest 2.3-fold and 1.5-fold increase, respectively.[27,30] This can be explained by the fact that different interventions may have different effects on individual HCPs and that some interventions may work synergistically with each other. However, it is difficult to characterize the exact influence of each individual intervention as part of a multifaceted strategy on the final outcome.

There were no studies identified in this review that were conducted in the Oceania region. In Australia, a pharmacy software vendor integrated an Adverse Event Recording module into the dispensing software of community pharmacists that allowed them to report ADRs directly to the local regulator.[35] This program was initially successful as the volume of ADRs reported in the first three quarters of 2014 was almost as high as the total number of ADRs reported by community pharmacists in the previous year.[36] However, ADR reporting rates fell again in 2015 indicating that this initiative did not provide a long-term solution.[37] Other strategies such as educational sessions may be useful as one study reported that almost 90% of community pharmacists in Australia would be encouraged to report more ADRs if education was provided on this topic.[14] Based on the results of this review, a multi-faceted approach including education, reminders, and electronic reporting would likely to be the most successful.

It is also important to note that improvements in the quality of ADR reports are also a critical measure, and unfortunately this was not investigated in any of the included studies. Studies have shown that the filling quality of ADR reports in national pharmacovigilance databases are extremely poor resulting in the inability to apply algorithms to determine any possible causal relationships between the medicine and ADR.[38,39] This may be due to constraints within global pharmacovigilance legislations that mandate ADR reporting for pharmaceutical companies, who would focus on reporting ADRs just to comply with these regulations, even for cases with minimal information.[40,41] The same studies showed that the quality of ADR reports from HCPs are much higher than those received from the pharmaceutical companies indicating that those who choose to report are more motivated or had better knowledge of pharmacovigilance.[38,39] Therefore, the focus of strategies should be to address the barriers associated with the voluntary nature of HCP reporting to increase the quantity of reports that are of high quality.

4.1 | Limitations of this review

One of the key limitations of this review is publication bias with one study showing that statistically significant results are almost 3 times

more likely to be published.[42] Therefore, the effectiveness of the interventions to improve ADR reporting may have been overestimated. In addition, there is significant heterogeneity in the designs and sample sizes of the included studies making it difficult to compare their results without adjusting for confounding variables. Furthermore, the quality of the included studies were poor with the majority lacking a control group and therefore it is difficult to assess whether the improvements in ADR reporting was solely due to the intervention.

4.2 | Future directions

With the development of digital technologies and automation, there is a great opportunity to utilize these methods to assist with improving ADR reporting rates. This can include the development of systems such as mobile apps or software in personal digital assistants that can integrate with existing databases so that it reduces manual input of data. These novel approaches can decrease the time it takes submit an ADR report, minimize manual entry errors and therefore encourage timely and high quality reports. Another area for further research would be to investigate whether interventions also improved the quality of ADR reports as this would significantly assist with signal detection activities to identify or confirm a potentially new safety issue.

5 | CONCLUSION

To address the high rate of underreporting, multiple strategies have been studied and found to be effective in increasing the ADR reporting rates by HCPs. However, ensuring the improved ADR reporting rates are maintained after ceasing the intervention remains a significant challenge. Developing mobile apps and software that integrate with existing databases presents an opportunity to create a more permanent solution but would require high quality studies to investigate the impact of this novel approach.

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2.5 Update of literature review (June 2019 to April 2022)

An updated literature review was conducted using the same systematic strategy as the original systematic review. The objective of this was to identify any new publications that would enhance the evidence base around any potential novel strategies that have been assessed to improve ADR reporting. The updated search was performed for the period between 18 June 2019 and 30 April 2022 in MEDLINE-PUBMED and EMBASE. The search terms used, and the inclusion and exclusion criteria applied were identical to the original literature review. A horizontal review of the references included in this systematic review was also performed to identify any publications that were not identified in the first search.

This resulted in a total of 2448 articles retrieved. After removing duplicates, the titles and abstracts of 2265 articles were screened for potential inclusion. The full text of 18 articles were reviewed to ensure they met the inclusion criteria. A total of 4 publications were included in this updated literature review. The PRISMA diagram for article search, screening, and inclusion is provided below. (Figure 2.1)

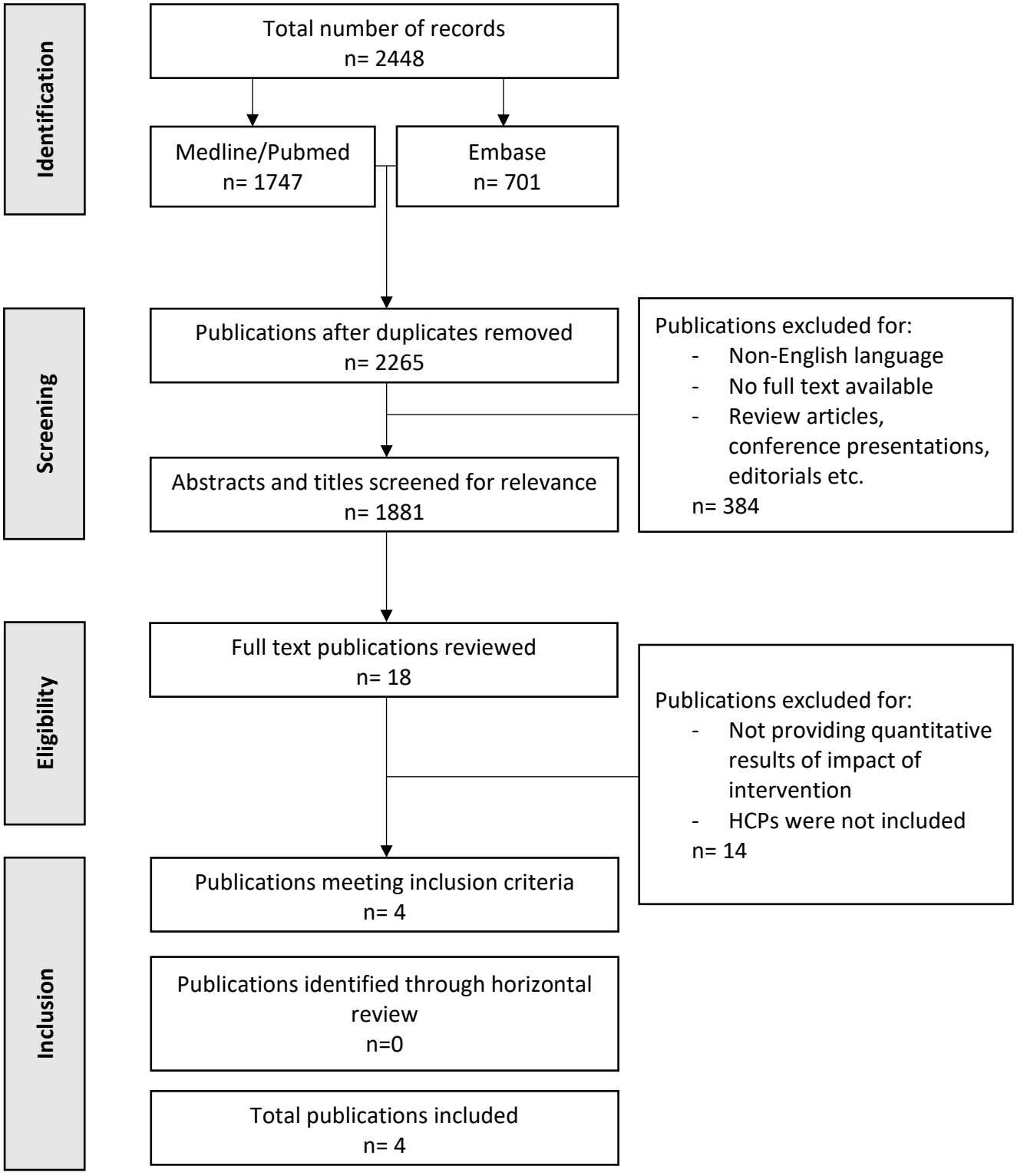

Figure 2.1 PRISMA diagram for article selection process

2.6 Results of updated literature review

There were 4 additional primary research studies that met the inclusion criteria. One was a randomized controlled study,(62) whilst the other three were of a quasi-experimental pre-post design.(63-65) Two of the studies utilized a multifaceted intervention including educational sessions, SMS text message reminders, and posters; one study used an electronic ADR reporting tool; and the other investigated the impact of mandatory ADR reporting as an intervention. Three of the studies were conducted exclusively in a hospital setting while one study was conducted in both hospital and primary care environments. A summary of the included articles is provided in Table 2.1.

The updated literature review showed that all interventions successfully improved ADR reporting rates over the duration of each study. Using a multifaceted approach improved ADR reporting by 1.3-fold and 6.0-fold across the two studies while single interventions of mandatory reporting and using an electronic reporting tool increased ADR reporting by 1.27-fold and 2.0-fold respectively. These results are consistent with the findings of our original systematic review on this topic and reinforce the need for more effective interventions to improve ADR reporting. (54)

2.7 Publication 1: Summary

The literature review presented in this chapter reported the evidence around the effectiveness of interventions to improve ADR reporting for the period July 2010 to January 2022. This showed that despite the initial success of these interventions, ADR reporting rates returned to previous levels once the intervention was ceased. Furthermore, electronic reporting tools were more commonly identified as an intervention in the last decade and were more successful than traditional strategies at improving ADR reporting. However, these interventions were not designed based on any framework that would specifically address the barriers that influence behaviour change. In addition, the quality of these studies was low. Some additional limitations of this review include the exclusion of papers not in the English language, and this may have excluded high quality studies and bias the outcomes. Furthermore, impact of any potential publication bias could have been measured using funnel plots. This knowledge gap warrants further research to understand the

facilitators and barriers towards reporting ADRs, so that the evidence generated can be used specifically to inform the development of a digital tool to improve reporting. The following chapter reports on the study design and methods to achieve this.

Reference and country	Study population and setting	Study period	Sample size	Study design	Type of intervention	Increase in reporting (fold)
Correa et al, 2019, Argentina	Healthcare professionals in hospital	6 months	21	Quasi experimental	Electronic reporting tool	2.0
Sonowal et al, 2020, India	Nurses in hospital	16 months	195	Quasi experimental	Educational session, diary, poster, SMS	6.0
Opadeyi et al, 2021, Nigeria	Healthcare professionals in hospital	15 months	4912	Randomized controlled	Educational session, SMS	1.32
Candore et al, 2022, European Union	Healthcare professionals in primary care and hospital	84 months	275,190	Quasi experimental	Mandatory reporting	1.27

Table 2.1 Characteristics of included studies

3 Study Design and Methods

3.1 Introduction

This chapter presents the overall study design, methods and theoretical framework used to conduct this research. Firstly, a philosophical overview of pragmatism which underpins and informs the mixed methods approach is discussed. This is followed by a discussion on the justification for employing the mixed methods approach to investigate the interventions used to improve ADR reporting. From this, an overview of the research objectives is presented along with how the research methods address each of these aims. The research participants, study site, sources of data collection, ethics and governance, data analyses and management are also presented in this chapter. A comprehensive description of the research methods are also provided in publications 2, 3, and 4, which form part of chapter 4. (56)

3.2 Research approach

Research is an essential and continuous activity to achieve scientific progress and aims to find responses to worthwhile scientific questions using a systematic approach.(66) It has been described as being the fuel to advance medical knowledge and has been associated with significantly shaping perspectives and evidence in medicine and healthcare. In our research, we aimed to generate new evidence to inform the development of an intervention to improve the quantity and quality of ADR reporting so that a comprehensive safety profile can be obtained for medicines improving appropriate prescribing and patient safety.

There are three dimensions of reasoning described in medical research, namely inductive, deductive and abductive.(67) Deductive reasoning is associated with quantitative research methods and aims to test theories to generate data and form a logical conclusion. In our research, deductive reasoning was used as part of the initial phase to identify the prevalence, characteristics and reporting of ADRs in Australian hospitals. It was also used to assess the quantitative impact of an intervention on ADR reporting in Australia, as well as identifying the facilitators and barriers to reporting ADRs in the hospital setting. Inductive reasoning utilizes existing knowledge, experiences and observations to develop a theory or

generate a conclusion.(68) This approach was utilized as part of the qualitative component of this research when exploring the perspectives, barriers and challenges HCPs face when reporting ADRs. Finally, abductive reasoning is purposed to address some of the weaknesses of the deductive and inductive approaches by taking incomplete observations from experience to generate a new theory or modify an existing one.(69) This approach was adopted as part of the final integration phase of our research to inform an evidence-based approach to improve ADR reporting.

The choice in methodology was guided by assessing each of the following overarching components: philosophy, methods, approaches, strategies, and techniques.(70) (Figure 3.1) A mixed methods research design was adopted, and this consisted of interconnecting components showing the philosophical worldview, a strategy of enquiry, and specific techniques and procedures that explored knowledge acquired both subjectively and objectively.(71) These components are shown in Figure 3.2.

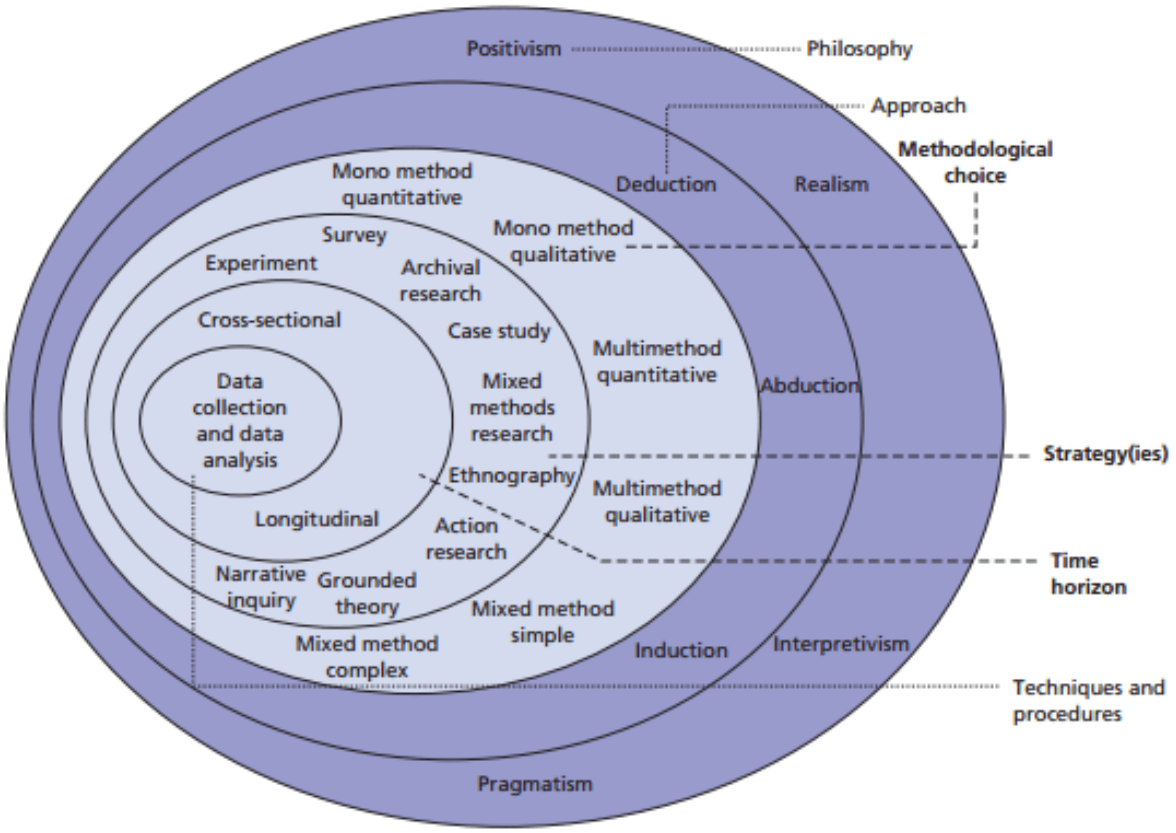

Figure 3.1 The Research Onion – adapted from Saunders, Lewis and Thornhill 2012 (70)

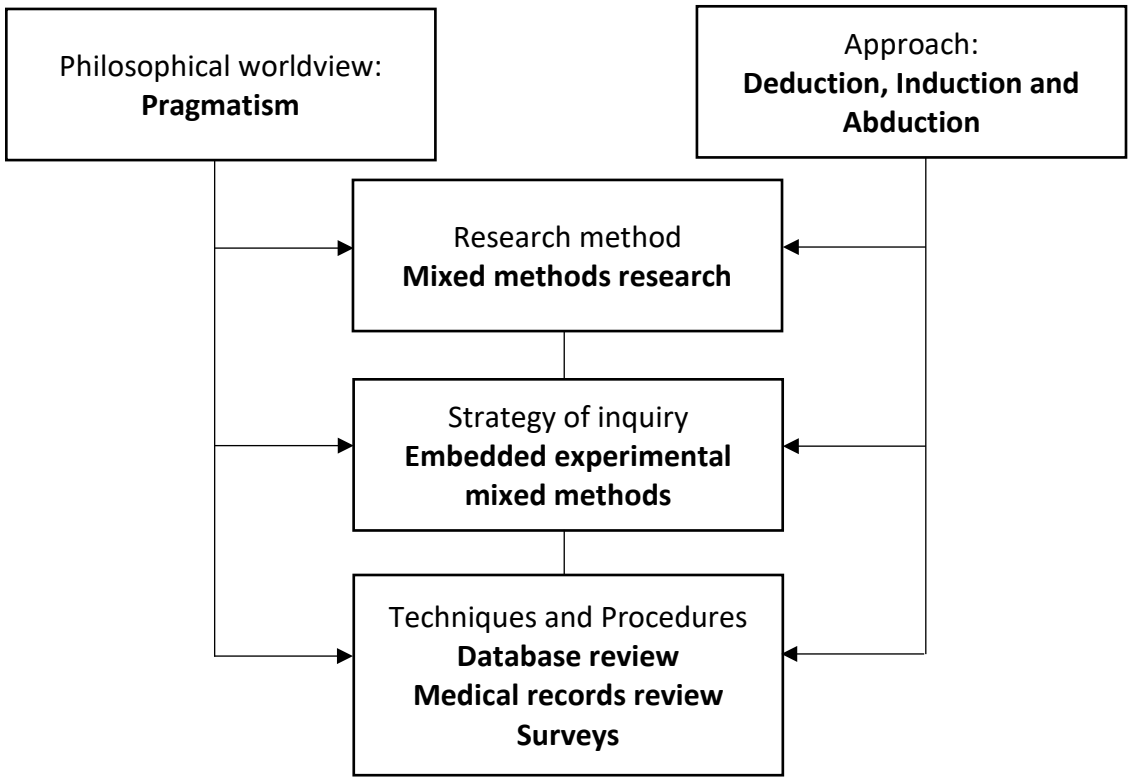

Figure 3.2 Research design framework to generate evidence for informing the design of an intervention to improve ADR reporting

3.3 Philosophical worldview: pragmatism

Philosophical worldviews or paradigms was one of the key influencing drivers of the type of research that was conducted and this included the research questions, study design, methods and practices.(71) These paradigms are shaped by certain attributes such as the researchers' profession, the researchers' and supervisors' predispositions, assumptions, and past research experiences.(72, 73)

Prior to this research, the author of this thesis participated as the primary researcher in projects about ADR reporting and was responsible for study design using quantitative methods, recruitment, data collection, and data analyses. In his role as a pharmacist practising in the area of pharmacovigilance within the pharmaceutical industry, he has extensive experience in understanding the role of the TGA in monitoring and analysing the safety profile of medicines. In addition, these responsibilities also included the collection

and analysis of ADR reports from consumers and HCPs, which allowed for a thorough understanding of the challenges of encouraging HCPs to complete ADR reports and submitting complete safety information for these reports to allow for an informed analysis on the causal relationship between the ADR and the medicine. The research supervisors consist of two research pharmacists with extensive experience in hospital pharmacy systems and processes, and an emergency nurse researcher with extensive experience in translational research and instigating behaviour change in HCPs. Furthermore, all researchers are extremely experienced in all methods of research including quantitative, qualitative and mixed methods approaches. This wide collection of perspectives and worldviews were synthesized to determine the best approach to investigate and generate the evidence required to develop an intervention to address ADR under-reporting by HCPs in Australia.

The philosophical worldview of pragmatism was adopted for this research. Pragmatism is based on the proposition that researchers should adopt the methodological approach that would work best to investigate a specific research problem.(74) It embraces a plurality of methods and takes the assumption that knowledge can be generated from actions, experiences, and learnings.(75) In addition, it focuses on the outcomes of the research and the research questions rather than specifically on the methodology.(71) Pragmatism also accepts that there can be multiple realities that are subject to empirical enquiry rather than focusing exclusively on the metaphysical notions such as reality and truth.(76)

In mixed methods research, there is general consensus that pragmatism should be adopted and the literature reports that this is the most common paradigm reported. This is primarily based on the fact that mixing qualitative and quantitative methods provides significance to understanding and developing the research question.(77) This minimizes the epistemological and ontological philosophies and allows for the utilization of a feasible and practical approach to investigate and conduct the research. Given the independence afforded to researchers who do not have to commit to a specific methodology in a pragmatistic model, a diverse methodological combination can be employed, and this was what was required for our research.

There is also a clinical focus to this research namely to understand the specific perspectives, facilitators and barriers towards reporting ADRs and generate this evidence to inform the design and development of an intervention to improve ADR reporting in Australian hospitals. The first chapter discussed that the study conception was initiated by the thesis author who has extensive experience in pharmacovigilance and has a passion for improving patient safety outcomes. It was identified through this work that HCPs frequently do not respond to requests for information about ADRs during a pharmaceutical company's follow up processes for more information, which in turn is a significant healthcare problem as it does not allow for a comprehensive analysis of any potential causal relationship between the ADR and the medicine. Upon further investigation, the same problem occurs at the TGA and the significant under-reporting of ADRs detrimentally impacts the work of the regulator to ensure a positive benefit risk profile of all medicines on the Australian market. Therefore, the thesis author had a desire to research the extent and causes of this problem with the overall objective of creating an intervention leveraging developments in digital technologies to improve the quantity and quality of ADR reporting. Pragmatism was adopted as it was flexible and provided the theoretical framework to conduct this research using a myriad of methods.

3.4 Theoretical perspective

From the pragmatic paradigm discussed above, the mixed methods approach integrates both quantitative and qualitative methods to successfully achieve research objectives and outcomes. In healthcare research, quantitative methods are traditionally employed to assess the numerical extent of an observation (i.e. incidence of ADR related hospitalisations and its associated under-reporting) while qualitative methods are utilized to understand the reasons for these observations (i.e. why are ADRs under-reported). Finally, the combination of both methodologies helps to identify the key factors that influence behaviour, and the necessary actions for promoting a change in practice.(78)

There are a variety of subcategories within the mixed methods research approach and researchers can select from four major models. These include the embedded or nested model, explanatory sequential model, exploratory sequential model, and the triangulation

model.(79) Each model is associated with a specific methodology and set of processes that warrant careful consideration from researchers especially with regards to any challenges posed by their choice of model and planning for strategies to overcome these challenges. Furthermore, the timing associated with data collection, how these data will be used, and the emphasis given to the balance of quantitative versus qualitative approaches along with its synthesis should also be taken into consideration when selecting the category of mixed methods. The final strategy of enquiry selected for this thesis is described in chapter 3.5 below.

3.4.1 Interventions for changing clinician behaviour

The application and implementation of knowledge into clinical practice requires a meaningful change in behaviour. Its success is predicated upon the identification and understanding of the facilitators and barriers, and then designing an intervention that would specifically address these barriers.(80, 81) There is some evidence that interventions informed by theoretical frameworks have been more successful at changing behaviour than non-theoretical based frameworks.(82) However, in a systematic review of implementation strategies to change behaviour, less than a quarter were linked to a specific theory.(83) Furthermore, the vast majority of interventions did not have a clear justification for using a specific theory and the selection was not informed by any assessment of the intervention and the problem.(84) As such, there was a need to create clear guidance on how researchers can appropriately link a behavioural change intervention to specific domains within a theoretical framework so that research knowledge can be successfully applied into clinical practice. Examples of these include the guidance given on how to best implement the theoretical domains framework and the behaviour change wheel which are described in further detail in the following section. (85, 86)

3.4.2 Theoretical Domains Framework

The theoretical domains framework was developed by a team of psychological theorists, health service researchers and health psychologists and aimed to integrate the abundance of behavioural change theories into a simple instrument so that it can be applied to research from all disciplines.(87) It is a comprehensive framework that applies theory to assess a

research problem involving the determinants of behaviour with the aim of informing the design of an appropriate intervention to address the specific barriers. The outcome of the initial theoretical domains framework was the identification of 12 domains, which was later expanded to 14 domains covering 84 theoretical constructs after a second revision by researchers.(85, 88) The domains are presented in Table 3.1 below.

Table 3.1 The Theoretical Domains Framework domains and component constructs

Domain	**Constructs**
Knowledge	Knowledge (including knowledge of condition/scientific rationale); Procedural knowledge; Knowledge of task environment
Skills	Skills; Skills development; Competence; Ability; Interpersonal skills; Practice; Skill assessment
Social/professional role and identity	Professional identity; Professional role; Social identity; Identity; Professional boundaries; Professional confidence; Group identity; Leadership; Organisational commitment
Beliefs about capabilities	Self-confidence; Perceived competence; Self-efficacy; Perceived behavioural control; Beliefs; Self-esteem; Empowerment; Professional confidence
Optimism*	Optimism; Pessimism; Unrealistic optimism; Identity
Beliefs about consequences	Beliefs; Outcome expectancies; Characteristics of outcome expectancies; Anticipated regret; Consequents
Reinforcement*	Rewards; Incentives; Punishments; Consequents; Reinforcement; Contingencies; Sanctions

Intentions*	Stability of intentions; Stages of change model; Transtheoretical model and stages of change
Goals	Goals; Goal priority; Goal/target setting; Action planning; Implementation intention
Memory, attention, and decision processes	Memory; Attention; Attention control; Decision making; Cognitive overload/tiredness
Environmental context and resources	Environmental stressors; Resources/material resources; Organisational culture/climate; Salient events/critical incidents; Person x environment interaction; Barriers and facilitators
Social influences	Social pressure; Social norm; Group conformity; Social comparisons; Group norms; Social support; Power; Intergroup conflict; Alienation; Group identity; Modelling
Emotion	Fear; Anxiety; Affect; Stress; Depression; Positive/negative affect; Burn-out
Behavioural regulation	Self-monitoring; Breaking habit; Action planning

*Optimism, reinforcement and intentions were newly added domains to the latest version of the theoretical domains framework. The Nature of Behaviours domain was removed.

The theoretical domains framework has been used extensively to understand the specific facilitators and barriers towards the determinants of behaviour so that the appropriate intervention can be developed. Examples include research conducted in the areas of hand hygiene, blood transfusion practice, and tobacco use prevention.(89-91) In Australia, this framework was also successfully utilised to inform interventions to address challenges in the areas of acute lower back pain, blunt chest injury and the adoption of eMR in hospitals.(92-

94) Therefore, in this thesis, we have also adopted the theoretical domains framework to identify the facilitators and barriers that HCPs face when identifying and reporting ADRs. The specific mechanisms of how to implement behaviour change including its context will help inform the intervention that was designed to improve the quality and quantity of ADR reporting.

3.4.3 Behaviour Change Wheel

The behaviour change wheel (BCW) (Figure 3.3) was developed after a systematic review of existing behavioural change frameworks showed that none provided comprehensive coverage for the full range of interventional operations and that only a minority provided adequate association with an existing behavioural model.(95) As such, a new framework was created to provide a systematic process for designing an intervention that can address a specific behaviour change in any context. The core of the BCW contains the behavioural system which embodies capability, opportunity and motivation. This is surrounded by nine categories of interventions that can be used to address any identified deficiencies within the behavioural system. Finally, the outer rim of the BCW is comprised of seven categories of policy which can be used to assist with the execution of the interventions. The incorporation of at least one of the BCW components have guided the development of interventions used to change eating behaviours, reduce sedentary behaviour post stroke, and promote physical activity using a mobile app.(96-98) Furthermore, a systematic review showed that interventions guided by the behavioural change wheel were very successful in improving rates of intravenous thrombolysis with an almost 100% increase in the uptake.(99) In this research, the BCW was adopted as it provides an evidence-based framework for implementing research evidence to inform an intervention to improve ADR reporting.

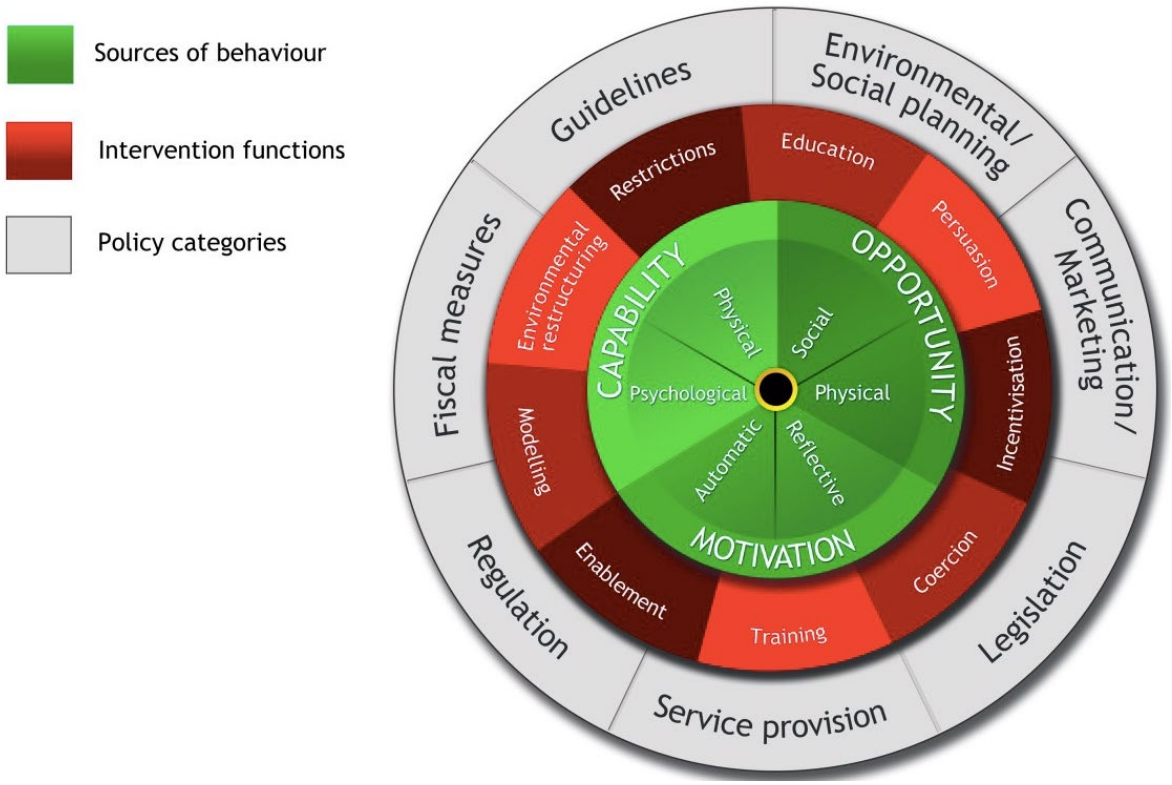

Figure 3.3 The Behaviour Change Wheel

3.5 Research design

Research design describes the various strategies used to collect and analyse data, as well as integrating this information to inform future research. Quantitative analysis involves the collection of measurable data and is considered to be more scientifically credible than information that is unmeasurable. However, there are scenarios where quantitative methods cannot explain the how or the why for certain experiences and as such, qualitative methods are required to explore the complexities of human behaviour and provide a narrative understanding of the phenomena of interest to help address these questions.(100) These may be in the form of focus groups, interviews, open ended questions in surveys and other forms of qualitative observation to collect information. There has also been more advocation for a pluralist position whereby the researcher is afforded a more diverse research approach incorporating both quantitative and qualitative methodologies. This mixed methods approach has been defined as the integration of qualitative and quantitative research questions, methods, designs, techniques for data collection/analyses, and the reporting of results.(101) For this research thesis, the mixed methods approach was

adopted because of its pragmatism and flexibility to allow for an objective and comprehensive understanding of firstly, the quantifiable aspects of the research phenomenon (i.e. magnitude of ADR under-reporting in Australian hospitals) and secondly, using qualitative methods to investigate key human behaviours that may be responsible for this phenomenon. Finally, by mixing the collected data, the evidence can be generated to help inform the design of an intervention to address the problem associated with the phenomenon.

3.5.1 Strategy of enquiry: embedded experimental model

There are primarily four different models within the mixed methods approach which are the triangulation model, embedded model, explanatory model and exploratory model. The choice is made based on how the researcher plans the study phases, the timing and order of data collection, the importance placed on the qualitative and quantitative components in the research, and the approach taken to mix the data.(79)

The embedded experimental model of the mixed methods approach was utilized for this research. This design allows for data to be combined from two different methodological approaches and is based on the premise that a single form of data is not sufficient to answer the research question.(79) The model describes the use of a specific dataset in a secondary capacity to support a primary dataset obtained using a different methodological approach. This research thesis was predominantly a quantitative study with the overall objective of measuring the magnitude of any increase in rates of ADR reporting after the implementation of an intervention. To achieve this, it was also necessary to quantify current ADR reporting rates without any intervention. However, it was important to understand the human behaviours associated with reporting ADRS and to identify the facilitators, barriers and perspectives of HCPs towards ADR reporting and as such, a qualitative component was required to help explain the rates of ADR reporting and inform the design of an intervention to improve reporting. Therefore, the embedded experimental model was utilized with the qualitative data acting in a supporting role and embedded into the primary quantitative data to help explain the measurable observations. (Figure 3.4)

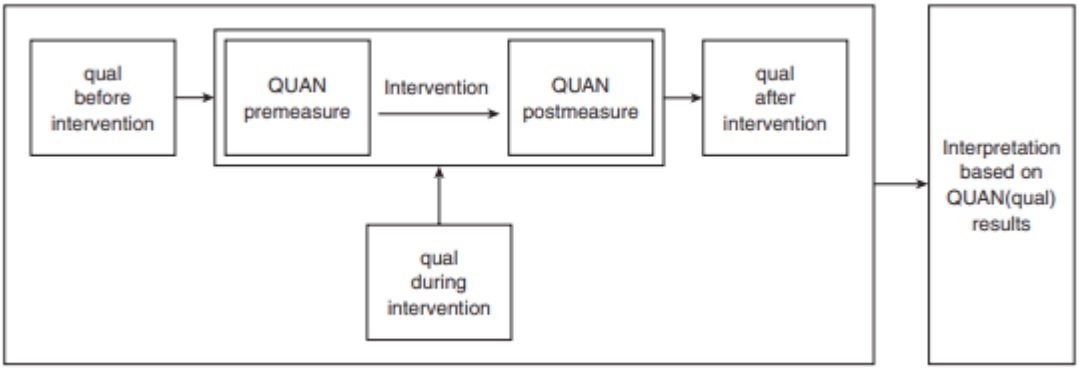

Figure 3.4 The embedded experimental model

The literature review in chapter 2 demonstrated that an evidence gap existed around the application of evidenced-based interventions that are informed by a behavioural framework, to improve ADR reporting. Furthermore, there was a lack of published data on the magnitude of ADR under-reporting in Australia. This highlights a need to investigate the extent of this problem along with a thorough understanding of the factors that influence it. By adopting a pragmatist worldview, a qualitative strand to understand human behaviours was incorporated into a primarily quantitative study and formed the embedded experimental mixed methods research approach that was selected for this research. Table 3.2 demonstrates the various sources of data collection and forms of data analyses used in each of the research methods along with their integration.

	Quantitative methods (primary)	**Qualitative methods (secondary)**	**Integration**
Data collection	- Hospital medical records - TGA pharmacovigilance database - Survey	- Open ended questions within survey	- Hospital medical records - TGA pharmacovigilance database - Survey
Data analyses	Statistical analyses	Textual analyses	

			- Statistical analyses - Textual analyses
Data interpretation	Statistical interpretation	Content analysis	- Statistical interpretation - Content analysis

Table 3.2: The integration of qualitative and quantitative approaches

3.6 Study Methods

3.6.1 Study objectives

The primary objective of this research is to generate evidence to help inform the development of a digital tool to improve the quantity and quality of ADR reporting by HCPs within the hospital setting in Australia. This includes understanding the current prevalence and practices of ADR reporting as well as analysing the effectiveness of any interventions already implemented to improve ADR reporting by using quantitative techniques. Qualitative methods will then be applied to understand the facilitators and barriers and the results will be integrated to inform the final approach to improve ADR reporting.

3.6.2 Research questions

Phase 1

1. What is the prevalence of ADR related hospitalisations and what are their characteristics? (Quantitative)
2. What proportion of ADR related hospitalisations are reported to the hospital safety committee and/or the Australian regulator? (Quantitative)
3. How successful was the implementation of the regulatory initiative 'black triangle scheme' on improving the quantity and quality of ADR reporting and are there any opportunities to further enhance the effectiveness of this intervention? (Quantitative)

Phase 2

4. What are the perspectives, facilitators and barriers of HCPs working in the hospital environment towards the reporting of ADRs? (Quantitative and qualitative)

Phase 3

5. What is the evidence required to inform the design of a strategy to improve the quality and quantity of ADR reporting in Australia? (integration)

3.6.3 Research phases

This research consists of three phases, quantitative, qualitative, and the integration phase. In the first quantitative phase, the information on the pre-intervention reporting of ADRs was collected by reviewing existing hospital records (research questions 1 and 2). In addition, the quantitative effect of existing interventions implemented to improve ADR reporting was measured (research question 3). In the next step, quantitative and qualitative data on the perspectives of HCPs towards ADR reporting was collected to identify the key facilitators and barriers that may explain the results identified in phase 1 of the research (research question 4). Finally, the results from both the quantitative (primary) and qualitative (secondary) steps were integrated to generate the evidence required to inform the design of a strategy to improve ADR reporting (research question 5).

3.6.4 Data collection, analyses and integration

In phase 1 where we aimed to identify the prevalence and characteristics of ADRs and the associated reporting in the hospital setting, the following information was collected: length of stay, ADR description, classification of ADR by type, causal relationship and seriousness, suspect medicine causing the ADR, and the quantity of ADR reports made to the Australian regulator. Furthermore, the effectiveness of an intervention to improve ADR reporting was measured by comparing the number of ADRs reported pre and post the intervention. In the second phase, the perspectives and experiences of HCPs towards ADR reporting were explored to collect information on the key factors that influence ADR reporting behaviours. Finally in phase 3, this information was synthesized to inform a strategy to improve the quantity and quality of ADR reporting. A research plan was created to address the study objectives (Figure 3.5)

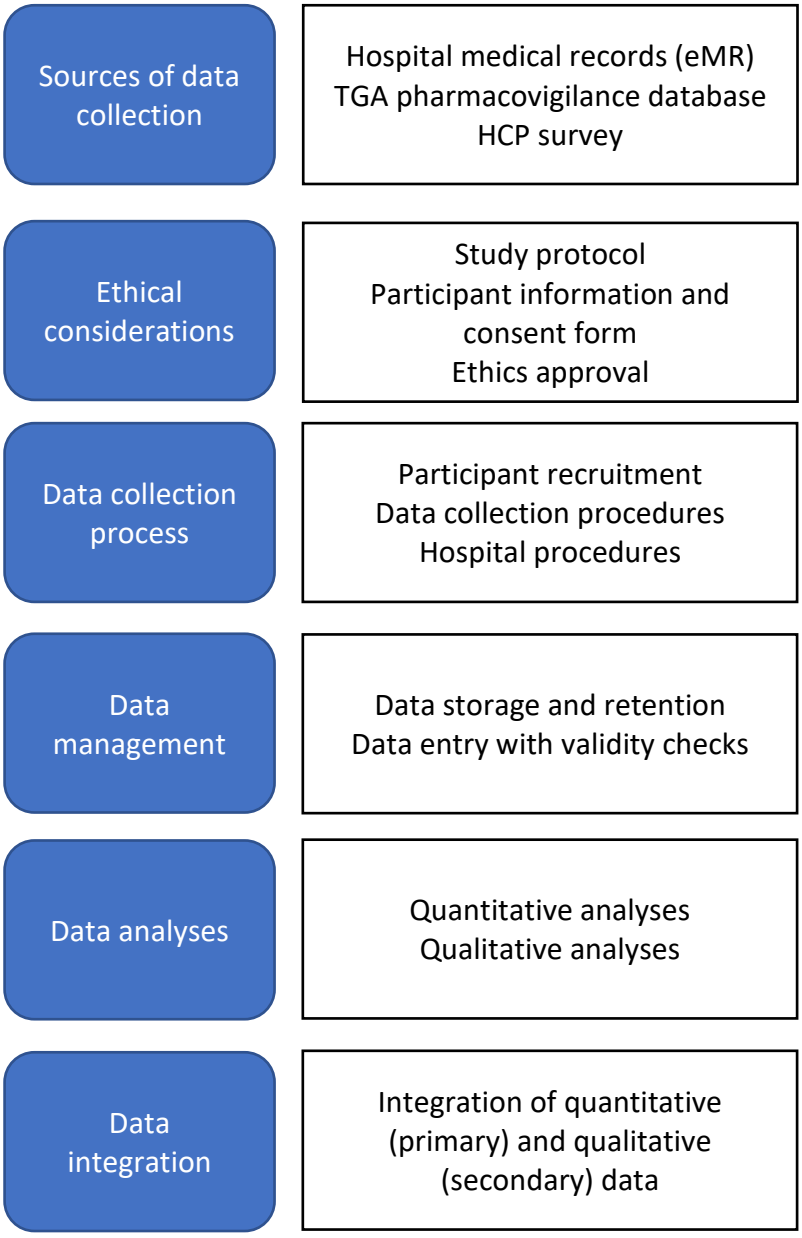

Figure 3.5 Research plan for data collection, management, analyses and integration

3.7 Study site: Blacktown Hospital

Blacktown hospital is a 534-bed tertiary referral hospital that serves one of the fastest growing geographic populations within the Western Sydney Local Health District of New South Wales.(102) It serves as a major teaching hospital for Western Sydney University with a clinical school located onsite for medical students. Clinical services provided include intensive and high dependency care, surgical services, obstetrics, specialist adult acute

medical care, newborn care, mental health services, renal dialysis centre, chemotherapy and oncology, drug and alcohol service, and primary care in community health. The 24-hour emergency department is one of the busiest in Sydney and there were approximately 55,000 presentations in 2019/2020. (103)

3.8 Study participants

There were two groups of study participants that were included in this research:

1. Patients, over 18 years of age, who experienced an ADR and presented to emergency for treatment/management.
2. Physicians, nurses, and pharmacists working at Blacktown hospital. These HCPs were selected as they are involved in the day-to-day clinical care of patients, which can involve the treatment and management of ADRs and the reporting of ADRs to the TGA.

3.9 Sources of data collection

The various sources of data collection were outlined in Figure 3.5 and additional details describing each of these sources including the information that was extracted for this research are described below.

3.9.1 Electronic Medical Records (eMR)

Blacktown hospital implemented the eMR program on 1st August 2015 as part of the eHealth strategy for NSW Health to deliver integrated care for patients with the aim of improving the quality of care and health outcomes.(104) This system provides more complete clinical information about patients and facilitates improved communication between HCPs within the hospital and across the wider healthcare network. In addition to information about the patient demographics and the dates of hospitalisations, the eMR provides detailed information about the patient's medical history, concomitant medications, diagnoses, blood test results, investigations ordered, progress notes and outcomes. More importantly, the eMR is able to document the patients' admission notes from the clinician (including emergency department notes), as well as their discharge summary, which provides a comprehensive summary of the patient's journey throughout their hospital

admission. The eMR was accessed remotely through a secure electronic network server of the Western Sydney Local Health District. The records for all patients who presented to the emergency department between October 2019 and December 2019 were retrospectively reviewed to verify whether the presentation was ADR related. This included a review of the emergency department admission notes written by a physician as well as the patient's discharge summary. The inclusion and exclusion criteria that were applied to determine whether a hospitalisation was considered ADR related is provided in section 3.11.1.

For each hospitalisation that was assessed to be ADR related, the following information was extracted from the eMR: patient demographics, dates of hospitalisation, description of the ADR, details about the suspect medication, relevant patient medical history, concomitant medications and the management pathway (short stay unit, emergency admission, or intensive care unit). These were collected using a data collection form (See Appendix 1)

More detail on the methods for this study, which answers research questions 1 and 2 is presented in Publication 2 "Prevalence, characteristics and reporting of adverse drug reactions in an Australian hospital: a retrospective review of hospital admissions due to adverse drug reactions" and embedded in chapter 4.2.1

3.9.2 TGA pharmacovigilance database

The TGA pharmacovigilance database, called the Database of Adverse Event Notification (DAEN) was implemented in January 2012 to increase transparency and provide a mechanism for the TGA to share ADR information for all medicines approved on the Australian market.(105) It is a publicly available database that includes all ADRs reported to the TGA from January 1971 and is the primary source by which the TGA undertakes analyses of the safety information to identify potential safety issues using both quantitative and qualitative signal detection methods.(106) The ADR reports can come from a wide variety of sources including the pharmaceutical industry, state and territory health networks, hospitals, general practitioners, nurses, community pharmacists, other HCPs, and members of the public (consumers and/or relatives of patients). As a member country of the WHO,

information from DAEN is shared with the Uppsala Monitoring Centre to support worldwide safety monitoring and surveillance activities.(14)

There are important limitations to note about the data captured within DAEN as well as the results of any search conducted within this database. Firstly, the degree of causal relationship between the suspect medicine and the ADR cannot be fully established, and this determination is primarily based on the observations of the individual reporter of the ADR. Secondly, the ADR report made to the TGA may not contain all the necessary information that is required to warrant a thorough analysis of the ADR, and it may be just a coincidence that the ADR occurred at the time a medicine was taken by the patient. In addition, the search results from DAEN cannot be relied upon exclusively to determine the frequency of an ADR for a medicine, or to compare frequencies of ADR occurrences for different medicines. This is because of varying patient exposure rates to the medicine depends on its therapeutic area, as well as the overall quantity of units being supplied by the manufacturer in Australia depending on its reimbursement status. Finally, the reports made to the TGA are voluntary in nature and this may be significantly influenced by external factors such as any publicity of the medicine in the media, the length of time the medicine has been on the market, existing reports of certain ADRs published in the literature, or any overseas regulatory actions taken against the medicine.(106)

Despite these limitations, this research was undertaken within the context of the shortcomings of a spontaneous reporting system (see section 1.2.4 for more details) with the overall aim of informing a strategy to improve ADR reporting in Australia. As such, the DAEN was searched to verify whether ADR related hospitalisations identified by reviewing eMR was reported to the TGA. This was conducted by searching specific fields within DAEN such as patient age, gender, suspect medicine, ADR description and date of the report to match the information retrieved from eMR for ADR related hospitalisations.

The DAEN was also used as the primary source of information to determine whether the introduction of an intervention (black triangle scheme) to improve the quantity and quality of ADR reporting in Australia was successful. More information about this intervention was provided in section 1.2.3. The list of black triangle and newly approved medicines in 2017

were retrieved by searching the Australian Register of Therapeutic Goods (ARTG) and the TGA annual summary report for 2017.(107, 108) Information about ADRs reported for these medicines were collected by reviewing DAEN. The following information was extracted: month and year of medicine approval, brand name of medicine, active ingredient, reporter type, patient age, patient gender, drug start date, ADR description, ADR onset date, outcome, and patient medical history.

More detail on methods for this study, which answers research question 3 is presented in Publication 3 "Effect of the black triangle scheme and its online educational campaign on the quantity and quality of adverse drug event reporting in Australia: a time series analysis" and embedded in chapter 4.3.1

3.9.3 HCP survey

An HCP survey tool was created to understand the perspectives and attitudes of HCPs towards reporting ADRs as part of their everyday clinical practice, which helped to address research questions xx. The questions in the survey tool were informed by the theoretical domains framework, as well as previous research that was conducted by the thesis author on this topic, but within the setting of community pharmacists.(85, 109) The theoretical domains framework (TDF) was selected as it provides the 14 domains that influence clinician behaviour change. As such, each question in the survey tool were designed and aligned with at least one of the 14 domains. To ensure content and face validity the survey tool was reviewed by hospital clinicians from the investigators' network who were known to have an interest in this topic. Table 3.3 demonstrates how some of the questions were aligned to the TDF. The final survey tool included 27 individual items that addressed all 14 domains of the TDF. They were divided into 3 sections that collected information on the knowledge, perspectives, and practices of HCPs towards ADR reporting. The question types included multiple choice, 5-point Likert scale from strongly agree to strongly disagree, and open-ended questions. (See Appendix 2 for final survey tool).

Table 3.3 Development of the survey tool using the 14 domains within the Theoretical Domains Framework

Domain	Sample questions/statements
Knowledge	Can you define an ADR? a) Yes b) No
Skills	I know how to report ADRs in the hospital a) Yes b) No c) Not sure
Social/professional role and identity	I have a professional obligation to report ADRs a) Strongly Agree b) Agree c) Neutral d) Disagree e) Strongly Disagree
Optimism	I don't report ADRs because it won't make a difference a) Strongly Agree b) Agree c) Neutral d) Disagree e) Strongly Disagree
Beliefs about consequences	I don't report ADRs because there are no results or actions taken based on ADRs I report a) Strongly Agree b) Agree c) Neutral d) Disagree e) Strongly Disagree
Reinforcement	I'm more likely to report ADRs if I receive an acknowledgement a) Strongly Agree b) Agree c) Neutral d) Disagree e) Strongly Disagree
Intentions	I'm more likely to report ADRs if it was for a new medicine a) Strongly Agree b) Agree c) Neutral d) Disagree e) Strongly Disagree
Memory, attention and decision processes	I don't report ADRs because I forget to report at the time of the reaction a) Strongly Agree b) Agree c) Neutral d) Disagree e) Strongly Disagree
Environmental context and resources	I'm more likely to report ADRs if an electronic tool was available that automatically populates information from existing health datasets such as eMeds.

	a) Strongly Agree b) Agree c) Neutral d) Disagree e) Strongly Disagree
Social influences	I don't report ADRs because I've been encouraged not to a) Strongly Agree b) Agree c) Neutral d) Disagree e) Strongly Disagree
Emotion	I don't report ADRs because it would cause stress and burnout in my workload a) Strongly Agree b) Agree c) Neutral d) Disagree e) Strongly Disagree
Behavioural regulation	I'm more likely to report ADRs if there is someone monitoring our ADR reporting a) Strongly Agree b) Agree c) Neutral d) Disagree e) Strongly Disagree

More detail on methods for this study, which answers research question 4 is presented in Publication 4 "Why hospital-based healthcare professionals do not report adverse drug reactions: a mixed methods study using the theoretical domains framework" and embedded in chapter 4.4.1.

3.10 Ethics and governance

The conduct of this research abides by the ethical requirements outlined in the National Health and Medical Research Council (NHMRC)'s Statement on Ethical Conduct in Human Research.(110) An application was made to the Western Sydney Local Health District under the low/negligible risk category to collect information on ADR related hospitalisations addressing the first two research questions. This was approved on 9th March 2020 – HREC reference: 2019/ETH13102 (Appendix 3). Corresponding site approval was granted on 18th March 2020 (Appendix 4). The documents that were submitted for consideration by the ethics committee included the study protocol (Appendix 5) and the data collection form (Appendix 1). For research question 3, the primary source of data was the publicly available database DAEN, which contains only de-identified patient data. Therefore, no ethics application was required, and an exemption was granted by the University of Sydney HREC

(Appendix 6). To address research question 4, a low/negligible risk ethics application was made to the Western Sydney Local Health District and this was approved on 20th August 2020 – HREC reference: 2020/ETH00597 (Appendix 7). Corresponding site approval was granted on 19th October 2020 (Appendix 8). The documents that were submitted as part of the application include the study protocol (Appendix 9), survey tool (Appendix 2), participant information sheet/consent form (Appendix 10), email communication to clinicians (Appendix 11), and an advertising brochure with QR code (Appendix 12).

There were no foreseeable harm or discomfort for the participants taking part in this research. The only identified risk was inconvenience that was associated with the time taken to complete the survey. All participants were offered the Participant Information Sheet/Consent form, which provided the necessary information around participating in this research. They were free to withdraw from the study at any time without consequence. However, once the survey was completed, participants could not withdraw their consent as the collected data was anonymous with no mechanism to match a survey response to a specific participant.

3.10.1 Researcher bias

Bias is defined as any form of deviation or trend away from the truth at any timepoint within a research project such as during study design, data collection, analysis, interpretation and final publication.(111) Research bias can be intentional or unintentional and is a significant cause of erroneous conclusions. It is important to recognise that all research contain confounding factors and limitations and it is important to identify these so that mitigating actions can be taken to minimise their impact on the final results and research conclusions.

Researcher bias occurs when the researchers' own perceptions and perspectives on the research topic affects the overall conduct of the study.(112) This can occur during the study design where the researcher may favour one methodology over another, as well as during data collection where only selective information is included based on the researchers' previous knowledge and experiences on the research topic. More importantly, this bias may

be unintentionally transferred to study participants in a way that affects their responses and behaviours. This 'Hawthorne effect' occurs when study participants inadvertently display traits of conformity and social desirability when they become aware of being observed so that they can meet the expectations of the researcher.(113) In this research, a potential source of bias may relate to participants reporting that they report ADRs more frequently than their actual practice in order to appear 'socially desirable' to the researcher.

It is also important to recognise the impact of the 'halo effect' as a source of researcher bias. This occurs when the researchers' own knowledge and perceptions on a topic influences their evaluation of open-ended responses provided by research participants.(114) This can significantly bias the research findings and risks the internal validity of any data analyses. Addressing this source of bias is important given the HCP survey contains open ended questions that requires coding and evaluation.

Another source of researcher bias relates to the implementation of an intervention where the researcher is actively involved in its concept and design.(112) If the researcher has pre-conceived thoughts around the potential superiority of the new intervention over existing strategies, the outcomes of the research may be unduly influenced. This is particularly relevant for this research given that one of the objectives is to generate the evidence to inform a novel strategy to improve the quantity and quality of ADR reporting.

To minimize the impact of the various sources of researcher bias identified above, the thesis author undertook a collaborative approach with his research supervisors during all phases of the study concept, design, data collection, analyses, and publication. This helped to ensure that an objective mindset was adopted during any discussions on the concept and design of a research study. Furthermore, data analyses were always conducted by the thesis author in conjunction with one or more of the research supervisors to enhance reliability. This was particularly important during the content analyses and data interpretation of the qualitative datasets as the coding and themes generated can be influenced by researcher bias. Therefore, consultation and agreement among all researchers was conducted to ensure validity and reliability.

3.11 Data collection

This research involved the collection of QUANtitative and qualitative data from various sources. An overview of the processes involved at each stage of this research is presented in Figure 3.6 below.

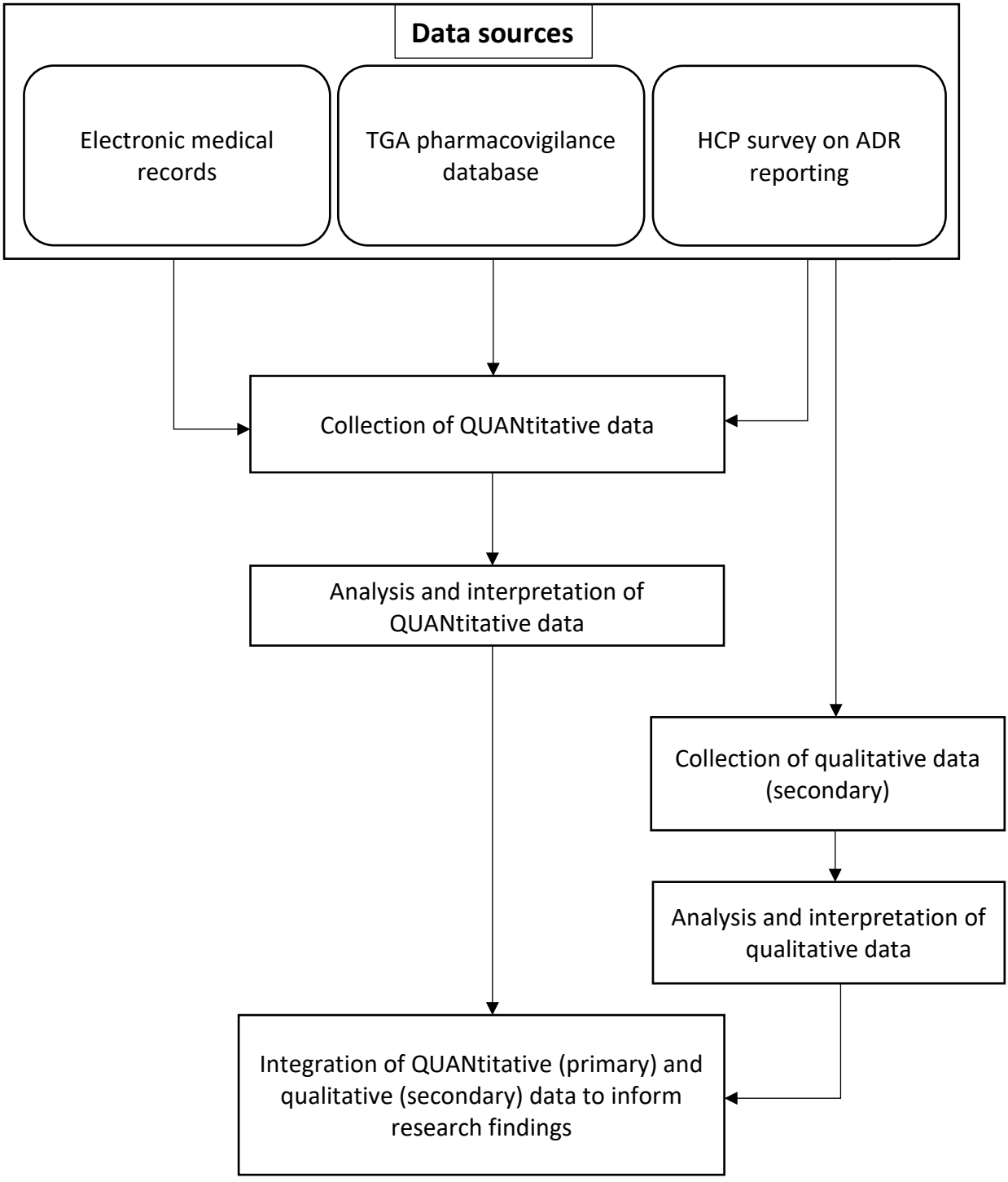

Figure 3.6 Overview of data collection, analysis and integration

3.11.1 Data inclusion and eligibility for each research question

To answer the first and second research questions, data were extracted from eMR for all presentations to the emergency department at Blacktown hospital between October and December 2019. Inclusion and exclusion criteria were used to assess whether hospitalisations were related to an ADR:

Inclusion criteria:

1. The clinician suspects an ADR related event as documented on the admission record; or
2. Any known ADR of the medicine is listed on the admission record
3. An unknown ADR of the medicine is listed on the admission record that must have a:
    - Plausible temporal relationship between the onset of the event and start of the medicine; AND
    - The ADR cannot be explained by the patient's existing medical conditions
    - Note: this includes reactions that may not be documented as an ADR, but occurred in the patient

Exclusion criteria

1. No plausible temporal relationship between the ADR and any medicine

Once a hospitalisation was assessed as ADR related, it was further classified by the type of suspect medicine using the Anatomical Therapeutic Classification system ,(115) the type of ADR using the Medical Dictionary for Regulatory Activities, (116) the strength of the causal relationship between the medicine and the ADR using the WHO-UMC algorithm, (117) the preventability of the ADR using the Hallas criteria, (118) and the expectedness of the ADR using the approved Product Information for each medicine. The TGA DAEN database was searched to check if the ADR was reported to the TGA as described in section 3.9.2.

Further information about the process for data inclusion and analysis are described in section 4.2, publication 2.

To address research question 3, a time series analysis was conducted using data extracted from the TGA DAEN database. The total time period for this analysis was 24 months which includes the ADRs retrieved for newly approved medicines from 2018 (black triangle intervention), and ADRs identified for newly approved medicines in 2017 (comparator group). The quantity of ADRs were compared pre and post the black triangle intervention in January 2018. The quality of the ADR reports was measured by determining whether sufficient information was provided to warrant the application of the WHO-UMC criteria for assessing a causal relationship between the suspect medicine and the ADR.

Further details about the data collection, inclusion and analysis are described in section 4.3, publication 3.

For research question 4, an HCP survey collecting both quantitative and qualitative data was implemented to understand the perspectives and practices of HCPs towards reporting ADRs so that facilitators and barriers to this process can be identified. The inclusion criteria for survey respondents include all pharmacists, physicians and nurses practising at Blacktown hospital and registered with the Australian Health Practitioner Regulation Agency (AHPRA).

3.11.2 Recruitment of survey participants

Participants were invited to participate primarily via email sent by their head of department on behalf of the research team (Appendix 11). In addition, a brochure containing a QR code was distributed to the pharmacy, nurse stations, and physician offices at Blacktown hospital. Reminder emails were sent every 2 weeks by the head of department to those who were invited to complete the survey. Due to the COVID-19 pandemic, access was restricted to only employees of Blacktown hospital and this posed significant challenges to physically promoting the survey on site. As the thesis author was not an employee of this hospital, the promotion of the survey to participants was reliant on a single research supervisor who was an employee on only 1 day a week. This significantly hampered the recruitment rate and as a result, the period for which the survey was open for completion was extended beyond the

initial 8-week completion period (January and February 2021) to a 16-week period (January to April 2021).

3.11.3 Completion of survey

All survey participants who accessed the survey were provided with an introduction describing the aims and objectives of the survey with a link to the Participant Information Sheet/Consent Form. It was estimated that the survey would take 10 minutes to complete. All questions in the survey were marked as mandatory to avoid incomplete responses being submitted/included in the data analyses.

Further information regarding the conduct of the survey such as sample size calculations, data collection and recruitment are described in section 4.4, publication 4.

3.12 Data Management

3.12.1 Data entry with validity checks

3.12.1.1 Data from eMR

Information from all patients who presented to the emergency department at Blacktown hospital from October 2019 to December 2019 extracted into an Excel spreadsheet which contained the following fields: patient Medical Record Number (MRN), admission pathway (emergency, short stay, or intensive care), gender, age, date of emergency department arrival, and date of discharge. All fields in this spreadsheet were screened for completeness and any duplicate lines were identified and removed. The patient MRN was then used as the primary search term in eMR to collect information about the patient's hospitalisation. Information from the uploaded emergency department notes and the discharge summary were then reviewed to verify whether the hospitalisation was ADR related. If it was considered ADR related, the data collection form (Appendix 1) was completed with the information transferred to another Excel spreadsheet for import into IBM Statistical Package for Social Sciences (SPSS) to assist with data analyses.

3.12.1.2 TGA ADR data

ADR information for black triangle medicines and newly approved medicines in 2017 were extracted from the TGA DAEN database into an Excel spreadsheet which contained the following fields: drug name, report date, onset date of event, gender, age, ADR description, ADR outcome, reporter type, and concomitant medications. Completeness of this information was not checked as it was expected that not all details about the ADR may be reported due to the voluntary nature of spontaneous reporting and it was one of the objectives of the study to investigate the quality of ADR reports. Any duplicate entries were reviewed and removed. The data was then imported into IBM SPSS for data analyses.

3.12.1.3 HCP survey data

Survey data was captured using Research Electronic Data Capture (REDCap), which is a web platform used for building and managing surveys hosted via the University of Sydney.(119) The anonymised data were then exported directly into IBM SPSS for analyses.

3.12.2 Data storage and retention

All research data were collected and stored on a secure password protected computer at the Blacktown Hospital Pharmacy Department. For data analyses, de-identified data was transferred to a password protected University of Sydney computer using the Cloudster portal, which is hosted on a secure university server allowing for secure data transfer. Access to the data was limited to the thesis author and his supervisory research team. All records will be retained for 5 years in accordance with the University of Sydney and hospital ethics committee requirements. After this time period expires, the research data will be destroyed using secure methods that will ensure that it cannot be retrieved in accordance with the NHMRC Australian Code for the responsible conduct of research.(120)

3.13 Data Analysis

3.13.1 Quantitative analysis

Quantitative analyses were conducted in SPSS with the significance level set at $p<0.05$. Parametric and non-parametric statistical tests (Mann Whitney U, Pearson chi squared x^2), were employed depending on sample size and normality of distribution, which was assessed

using the Shapiro-Wilk test. For normally distributed data, the means and standard deviations were reported whilst for non-normally distributed data, medians and interquartile ranges were reported. Categorical data were reported using counts and percentages. Multivariate logistic regression was employed to identify factors that may be associated with ADR related hospitalisations. (see section 4.2 publication 2 for more details) A time series analysis using segmented regression was utilized to compare the ADR reporting rates pre and post an intervention. (see section 4.3 publication 3 for more details).

3.13.2 Qualitative analysis

A conventional content analysis approach was conducted for the qualitative data collected through the HCP survey without bias towards any pre-existing theories or frameworks on this topic.(121) Firstly, the thesis author familiarised himself with the data by reviewing it several times to achieve an understanding of the overall meaning. The data were then analysed by searching for terminology that reflect a key concept and these were considered sub-categories. These sub-categories were then assigned labels and notes to help further classify these into higher level categories. The entire process was conducted by the thesis author and two research supervisors (CV and KC) using a consensus approach. The categories generated from this process were reviewed and discussed by the entire research team and adjusted to ensure they accurately reflected the content of the collected data. Further details on the qualitative methodology are described in section 4.4 publication 4).

3.14 Data integration

The final step of the mixed methods approach was the integration of the QUANtitative and qualitative data to generate the evidence required to inform a strategy to improve ADR reporting. After the collection and analysis of these data, they were compared, contrasted and combined to support the overall interpretation. The quantitative results measured the characteristics, prevalence, and reporting of ADRs as well as the effectiveness of a strategy to improve ADR reporting. In addition, quantitative results from the HCP survey helped to understand the facilitators and barriers towards ADR reporting. Qualitative data from the HCP survey was then used to help explain the human perspectives and behaviours that lead to the quantitative results. The incorporation of the qualitative data in a secondary capacity

to the primary quantitative component helped to achieve the final objective of this research.

3.15 Summary

This chapter described the theoretical paradigms and perspectives including the determinants of behaviour that informed the embedded mixed methods study design of this research. The study objectives and research questions were then established along with a description of each research phase (data collection, analyses, integration) and how this would address each of the objectives. An overview of the study site and study participants was also provided. The sources of data collection were described along with the methodology involved in the data collection activities. Finally, the ethical and governance considerations, how the collected data was managed, and the methods of data analyses and integration were explained. Further details are provided within the embedded publications in chapters 4 and 5.

4 Study Results

4.1 Introduction

This chapter provides details on the results of this research and includes 3 peer reviewed publications. The first article reports on the quantitative results on the topic of the prevalence, characteristics, and reporting of ADRs which addresses the first 2 research questions of this thesis. The second article describes the quantitative results on the effectiveness of an intervention used to improve ADR reporting in Australia addressing the third objective of this thesis. The third publication contributed to both the quantitative and qualitative components of this research. It reported on HCP perspectives and attitudes towards reporting ADRs and the identification of facilitators and barriers of ADR reporting. This addressed the fourth research question of the research thesis.

4.2 Publication 2: Summary

This publication quantified the prevalence of ADR related hospitalisations and described the features and characteristics of the ADRs. The results showed that ADRs are responsible for almost 10% of hospitalisations and that nervous system medicines were responsible for the highest proportion of these hospitalisations. ADRs were also preventable and over 99% of these were not reported to the TGA. An additional limitation of this study is that the preventability assessment using the Hallas criteria was only undertaken by one investigator, which may have affected the reliability of this assessment. This paper demonstrates that there is a significant problem with regards to ADR under-reporting in Australia and highlights the need for an effective intervention to improve ADR reporting.

4.2.1 Prevalence, characteristics and reporting of ADRs in an Australian hospital

Li R, Curtis K, Zaidi STR, Van C, Thomson A, and Castelino R. Prevalence, characteristics and reporting of adverse drug reactions in an Australian hospital: a retrospective review of hospital admissions due to adverse drug reactions. *Expert Opin Drug Saf* 2021; 20(10): 1267-1274

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ORIGINAL RESEARCH

Prevalence, characteristics, and reporting of adverse drug reactions in an Australian hospital: a retrospective review of hospital admissions due to adverse drug reactions

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ABSTRACT

Background: Adverse drug reaction (ADR) related hospitalizations is a major cause of morbidity and mortality in Australia. This study investigated the prevalence, characteristics, and reporting of ADR related hospitalizations at a tertiary hospital in Australia.

Research design and methods: A retrospective review of all ADR related hospitalizations from October to December 2019 was conducted using eMedical Records. They were classified by medicine class, ADR type, preventability, and the strength of causal relationship. ADRs were searched within the regulator's safety database to verify whether it was reported.

Results: A total of 496 ADR related hospitalizations were identified from 5521 records (9.0%). Nervous system agents (32.3%) were responsible for most ADR hospitalizations and were more likely to cause psychiatric disorders (RR 9.71, 95%CI 4.98–18.87). They were also more likely to cause preventable ADRs (HR 1.62, 95%CI 1.46–1.81). Patient age (OR 1.04, 95%CI 1.03–1.05) and the number of medicines (OR 1.13, 95%CI 1.11–1.15) were associated with ADR related hospitalizations. Under-reporting to the national regulator was over 99%.

Conclusions: ADR under-reporting is highly prevalent in Australian hospitals. Further research into identifying specific barriers toward reporting ADRs are needed to inform strategies with a focus on healthcare professionals involved in prescribing, dispensing, and administrating nervous system agents.

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Pharmacovigilance; reporting; adverse drug reaction; medication safety

1. Introduction

Adverse drug reactions (ADRs) are a major cause of mortality and hospitalizations globally with studies showing that they are responsible for 4.2% to 30% of hospitalizations in the USA and Canada, 2.5% to 10.6% of admissions in Europe, and 7.2% to 11.0% of admissions in Australia [1–3]. This proportion increases in high-risk populations with the literature estimating that 20–30% of admissions for those aged 65 or over were medication related [4]. Furthermore, the prevalence of ADR-related hospitalizations has also increased with the Australian Institute of Health and Welfare data showing that the rate of ADR-related hospitalizations increased by 21% from 8.0 per 100 hospitalizations in 2007/08 to 9.7 per 100 hospitalizations in 2015/16 [5]. In addition, there is strong evidence that ADRs also lead to significant prolongation of existing hospitalizations with a study showing that the mean length of stay (LOS) was increased from 8 to 20 days [6]. A substantial proportion of ADRs were identified as preventable with the Quality in Australian Healthcare study estimating that 51% of ADRs were highly preventable resulting in increased LOS and permanent disability as an outcome [7]. This is a significant healthcare problem as the direct and indirect costs associated with managing ADRs in Australian hospitals is estimated at 1.2 USD billion annually [8].

The Australian regulatory agency Therapeutic Goods Administration (TGA) encourages all healthcare professionals to report suspected and unexpected ADRs to assist with monitoring the safety profile of medicines [9]. However, the reporting rates are extremely low with only 19% of the overall ADR reports coming from healthcare professionals in 2017, with the majority being reported by the pharmaceutical industry [10]. In January 2018, the TGA introduced the black triangle scheme to encourage the reporting of ADRs by healthcare professionals and consumers for newly approved medicines. This scheme enhances the safety monitoring of these medicines as there is a limited understanding of its safety profile due to their recent approval on the market. However, a recent study showed that there was only a modest effect on improving the quantity and quality of reporting for these new medicines [11]. This is consistent with the international literature which shows that despite the awareness on the importance of reporting ADRs, the median global under-reporting rate was 94%, and this increased to 96% for studies measuring ADR reporting in hospitals [12]. With an estimated 230,000 medication-related hospitalizations in Australia each year and an average of 2,034

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ADR reports received from Australian hospitals annually, the rate of under-reporting in Australian hospitals can be estimated at over 99% [5]. The lack of reporting contributes to delays in identifying new safety issues and regulatory action taken to revoke the approval status of medicines with unacceptable safety profiles. This causes more harm in patients resulting in increased morbidity and hospitalizations leading to higher healthcare costs.

There have not been any published studies that investigated the characteristics of ADRs in Australian hospitals and the magnitude of any potential ADR under-reporting in this setting. This study will analyze the characteristics of ADR related hospitalizations including the causality, preventability and the type of medicines causing them. We will also examine whether certain ADRs are more likely to be caused by certain types of medicines, and whether these ADRs have been reported to the TGA. The results of this study will assist with informing the type of medicines that should be the focus of any interventions designed to improve the quantity and quality of ADR reporting. It will also shape the design of future digital tools that would automatically report specific types of ADRs for specific medicines that are of interest to regulatory agencies.

2. Methods

We conducted a retrospective review of all hospital admissions due to an ADR at a tertiary hospital in New South Wales, Australia from 1 October 2019 to 31 December 2019. All patients aged over 18 years who presented to hospital emergency and were admitted to a ward, short stay unit, or the intensive care unit were included in this study. Short stay units are designed to admit clinically stable patients who display low to moderate risk and complexity and can be expected to be discharged in the short term with optimal diagnostic support and clinical management [13].

To determine whether the hospitalization was ADR related, the electronic patient admission records and discharge summaries for each patient were extracted from eMedical Records and reviewed by the primary investigator (RL). Hospitalizations were considered ADR related if the clinician documented a suspected ADR-related event, or if the records included any diagnosis of a known ADR to a medicine as the reason for hospitalization. This may be based on a clear diagnosis of an ADR on the hospital record, or an inferred diagnosis based on information described by the clinician. In addition, if the records contained an unknown ADR to a medicine but there was a plausible temporal relationship between the onset of the event and the start date of the medicine, this was also included as an ADR related hospitalization. This may include reactions that are unpredictable and non-dose dependent. All patients were followed up until hospital discharge and those that were included as an ADR related hospitalization were verified by a second investigator (RC). After reviewing each record, the following information was collected: patient age, gender, dates of hospitalization, location of admission (ward, short stay unit, or intensive care) suspect medicine name and dose, description of ADR, total number of medicines taken by the patient, and the patient's medical history. Ethics approval for the study was obtained from the Western Sydney Local Health District ethics committee (HREC approval number: 2019/ETH13102).

2.1. Classification of suspect medicines

All suspect medicines associated with ADR related hospitalizations were classified into therapeutic classes using the Anatomical Therapeutical Classification System (ATC) [14]. This system divides medicines into different groups according to the body organ or system on which they act and is controlled by the World Health Organization Collaborating Center for Drug Statistics Methodology.

2.2. Classification of adverse drug reactions

All ADRs were classified into various system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA) [15]. This is a standardized medical terminology created by the International Collaboration of Harmonization (ICH) and adopted by the World Health Organization (WHO) as a means for international standardization in communicating ADRs among the various health authorities. The ADRs were further classified into type A (augmented), B (bizarre), C (chronic), D (delayed), E (withdrawal) and F (unexpected failure of therapy) [16]. Each ADR was also assessed for expectedness using the Therapeutic Goods Administration approved Product Information for each medicine. The incidence of specific ADR related hospitalizations by type was calculated by determining the total number of patients hospitalized due to a specific ADR type as a percentage of the overall number of patients hospitalized due to ADRs.

2.3. Assessment of causal relationship

The strength of the causal relationship between the ADR and the suspect medicine was assessed using the World Health Organization Uppsala Monitoring Center (WHO-UMC) algorithm which classified the causality as certain, probably related, possibly related, conditional, or unlikely [17]. This algorithm was used as the health authorities of 166 nations share their ADR reports to the WHO for analysis and classification.

2.4. Assessment of preventability

Each hospital admission record was assessed for preventability using the Hallas criteria, which classified ADRs as definitely preventable, possibly preventable, or not preventable [18]. Due to the clinical nature of this assessment, the preventability was assessed by a registered hospital pharmacist in Australia.

2.5. Reporting of ADR to the TGA

The Australian regulator requests that any ADR that is considered at least possibly related to a suspect medicine and unexpected are reported to its national pharmacovigilance database, the Database of Adverse Event Notification (DAEN)

[19]. This publicly available database contains all ADRs reported to the TGA from 1971 and is used for signal detection to identify new safety issues. Therefore, we searched the DAEN to check whether any of the ADRs determined in this study to be at least possibly related and unexpected have been reported. Search criteria included matching patient age, gender, suspect medicine details, description of the ADR, and date of reporting that was within 3 months after the date of hospital admission.

2.6. Statistical analyses

Analyses were performed using IBM SPSS version 27.0 with significance levels set at $p < 0.05$. The Mann–Whitney *U* test (continuous variables) and Pearson Chi Square test (categorical variables) were used to compare the characteristics between ADR and non-ADR related hospitalizations. Multivariate logistic regression was conducted to identify factors associated with ADR-related hospitalizations. Relative risks and the corresponding 95% confidence intervals were calculated for medicine class and ADR type associated with preventability.

3. Results

There were 5521 presentations to the study hospital emergency department between 1 October 2019 and 31 December 2019, of which 496 (9.0%, 95%CI 8.2–9.8%) were considered ADR related. A total of 720 individual ADR events were experienced by these 496 patients. More than a third of these patients (34.1%) experienced multiple ADRs of which 8.5% experienced 3 or more different ADRs as part of their admission. The majority of all ADRs (60.9%) were considered preventable, while 30.0% were unexpected (Table 1). Patients taking five or more medicines were more likely to experience multiple ADR types compared to patients taking less than 5 medicines (RR 1.67; 95%CI 1.11–2.52). They were also more likely to experience preventable ADRs (RR 1.28; 95% CI 1.03–1.60).

Table 1. Classification and characteristics of ADR.

MedDRA classification*	n (%)
Blood and lymphatic system disorders	16 (2.2)
Cardiac disorders	36 (5.0)
Eye disorders	3 (0.4)
Gastrointestinal disorders	142 (19.7)
General disorders and administration site conditions	15 (2.1)
Hepatobiliary disorders	13 (1.8)
Immune system disorders	4 (0.6)
Infections and infestations	32 (4.4)
Injury, poisoning, and procedural complications	115 (16.0)
Investigations	8 (1.1)
Metabolism and nutrition disorders	65 (9.0)
Musculoskeletal and connective tissue disorders	2 (0.3)
Nervous system disorders	60 (8.3)
Psychiatric disorders	53 (7.4)
Renal and urinary disorders	95 (13.2)
Reproductive system and breast disorders	1 (0.1)
Respiratory, thoracic and mediastinal disorders	16 (2.2)
Skin and subcutaneous tissue disorders	2 (0.3)
Vascular disorders	42 (5.8)
ADR classification	
Type A	195 (39.3%)
Type B	42 (8.5%)
Type C	153 (30.8%)
Type D	5 (1.0%)
Type E	11 (2.2%)
Type F	90 (18.1%)
Expectedness	
Expected	347 (70.0%)
Unexpected	149 (30.0%)
Multiple ADRs	
Yes	169 (34.1)
No	327 (65.9)
Preventability	
Definitely preventable	143 (28.8)
Possibly preventable	159 (32.1)
Not preventable	194 (39.1)
Causal relationship by WHO-UMC algorithm	
Certain	6 (1.2)
Probably related	170 (34.3)
Possibly related	254 (51.2)
Conditional	46 (9.3)
Unlikely related	20 (4.0)

*The MedDRA system organ class classification also contained congenital, familial, and genetic disorders; ear and labyrinth disorders; endocrine disorders; neoplasms benign, malignant and unspecified; pregnancy, puerperium and perinatal conditions; social circumstances; surgical and medical procedures; and product issues, of which none of the ADR-related hospitalizations identified in this study were classified into.

3.1. Suspect medicine and ADR type

Of the 496 ADR related hospitalizations, 32.3% were caused by medicines acting on the nervous system, such as analgesics, anti-epileptics, antidepressants, etc. The second most common ATC class of medicines causing ADR related hospitalizations were those that target the blood and blood forming organs such as antithrombotics, antiplatelet agents, etc. (22.8%), and this was followed by medicines that affect the cardiovascular system, such as antihypertensives, lipid modifying agents, diuretics, etc. (21.4%). (Figure 1) The most frequently reported type of ADR by MedDRA classification was gastrointestinal disorders (19.7%) followed by injury, poisoning, and procedural complications (16.0%), and renal and urinary disorders (13.2%). Type A ADRs were also the most common (39.3%). (Table 1)

Patients taking medicines affecting the nervous system were almost 10 times more likely to experience psychiatric disorders and 3 times more likely to have injury, poisoning, and procedural complications compared to patients not taking these medicines (Table 2). Furthermore, these medicines were more likely to cause preventable ADRs leading to hospitalization, whereas antineoplastic and immunomodulating agents were less likely to do so (Figure 2). Cardiac system medicines were also more likely to cause renal and urinary disorders while medicines affecting blood and blood forming organs were more likely to cause gastrointestinal disorders. Gastrointestinal disorders overall were less likely to be preventable whereas psychiatric disorders, injury, poisoning, and procedural complications were significantly more likely to be preventable.

3.2. Preventability of ADR related hospitalizations

Of the 496 ADR-related hospitalizations, 302 were considered at least possibly preventable (60.9%). The primary reason for ADR-related hospitalizations being assessed as preventable

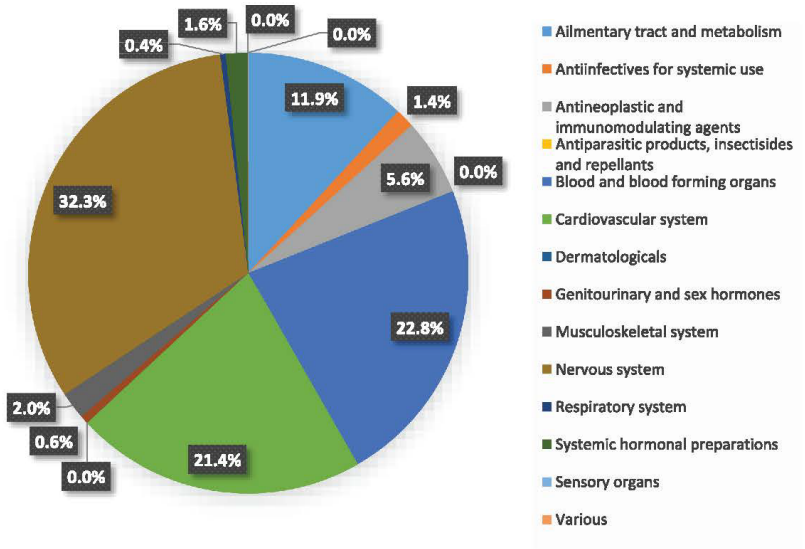

Figure 1. Therapeutic area of suspect medicines by ATC coding.

was that the prescribing of the medicine was inappropriate based on the patient's medical history and inconsistent with best medical practice (49.7%) (i.e. no documented indication for a medicine). In addition, drug–drug interactions accounted for 33.1% of preventable ADRs and the remaining 17.2% consisted of medication errors and/or dose-related issues. Nervous system agents were found to have caused the highest proportion of preventable ADR-related hospitalizations, most of which were the inappropriate prescriptions of quetiapine, diazepam, pregabalin, clonazepam, and oxycodone for clinical indications that were not documented. The majority of preventable ADRs were expected (69.2%), and this was higher for nervous system agents (78.9%) compared to other medicine types. Examples of some preventable ADRs are provided in Table 4.

3.3. Characteristics of ADR related hospitalizations

Patients admitted for ADR-related problems were older, taking more medicines, and stayed longer in hospital compared to patients admitted for non-ADR-related issues. (Table 3) They were also more frequently admitted to the hospital ward rather than the short stay unit compared to patients admitted for non-ADR related issues. Multivariate logistic regression showed that patient age and the total number of medicines were significantly associated with ADR related hospitalizations (Table 5).

3.4. Causal relationship and reporting to TGA

The vast majority of ADRs causing hospitalization were considered at least possibly related to the medicine (86.7%) with only 4.0% considered definitely unrelated using the WHO-UMC algorithm. The remaining 9.3% were classified as conditional indicating that these were previously unknown reactions that would warrant further investigation. There were 129 ADR-related hospitalizations that were classified as at least possibly related and also unexpected, which would warrant an ADR report to the TGA. After searching the DAEN database, only 1 ADR was reported (TGA reference: 488,490 – Digoxin causing rapid atrial fibrillation and urinary tract infection) representing an under-reporting rate of over 99%.

4. Discussion

Adverse drug reactions are responsible for a significant number of hospital admissions and the complexities associated with the management of ADRs lead to longer stays. Our study showed that the prevalence of ADR-related hospitalizations was 9.0%, which was consistent with other Australian studies which ranged from 7.2% to 11.0% [3,20]. Older age and taking more medicines were significantly associated with being admitted for ADR related issues, which was also demonstrated in a number of other studies [2,21,22]. Our results also showed that ADR related hospitalizations resulted in a longer LOS, which can be explained by the additional clinical investigations and resources required to manage and treat ADRs as well as longer times needed to recover from any associated morbidity. This is reinforced by the finding that more patients with ADR-related hospitalizations were admitted directly to a ward rather than a short stay unit where lower risk patients are managed. Patients admitted for ADR related issues were also taking significantly more medications compared to patients admitted for non-ADR related issues. It may be

Table 2. Incidence of ADR-related hospitalization by type associated with medicine class.

	Incidence rate of ADRs leading to hospitalization (%)			
Class of medicine causing ADR type	**Patients taking this medicine and experiencing this ADR type**	**Patients not taking this medicine and experiencing this ADR type**	**Relative risk (95% CI)**	**P value**
Nervous system medicines causing psychiatric disorders	19.5	2.0	9.71 (4.98–18.87)	<0.001
Nervous system medicines causing injury, poisoning and procedural complications	29.4	10.0	2.93 (2.11–4.10)	<0.001
Cardiac system medicines causing renal and urinary disorders	22.6	10.3	2.19 (1.51–3.17)	<0.001
Blood and blood forming organ medicines causing gastrointestinal disorders	28.0	17.4	1.61 (1.18–2.19)	0.003

plausible that these patients may be already suffering from conditions caused by ADRs, which trigger a prescribing cascade where new medicines are initiated for conditions that may not have been recognized as an ADR to an existing medicine. This leads to inappropriate prescribing causing additional preventable ADRs, which was found to be more than 60% in our study.

We also identified that almost a third of ADR-related hospitalizations were caused by medicines that target the nervous system, such as anxiolytics, antipsychotics, antidepressants, analgesics, etc. These patients were 10 times more likely to experience a psychiatric related ADR, and almost 3 times more likely to experience injury, poisoning, and procedural complications, of which 92.5% and 73.9% were found to be preventable, respectively. In addition, almost 82% of patients taking these nervous system medicines experienced at least one preventable ADR leading to hospitalization, which suggests that these medicines were inappropriately prescribed. This is supported by a national population study in Korea showing that the rate of inappropriate prescription of psychotropic and nervous system drugs was 53.4% [23]. Furthermore, another Swedish population study concluded that inappropriate prescriptions increased the odds of experiencing ADRs by over two-fold (OR 2.47; 95%CI 1.65–3.69) and 50% of these ADRs resulted from taking a medicine affecting the nervous system [24]. In contrast, antineoplastic and immunomodulating agents were less likely to cause preventable ADRs suggesting that these medicines were carefully prescribed and managed to help treat essential conditions in the oncology and hematology setting. Other reasons include that only specialist physicians can prescribe antineoplastic agents with strict monitoring protocols as part of the overall patient management plan whereas nervous system agents can be prescribed by any general physician without such a monitoring protocol. These findings suggest that interventions to improve ADR reporting should be focused on nervous system medicines and educational strategies should be created to enhance its appropriate prescribing.

All ADR-related hospitalizations are considered serious according to the ICH E2A criteria [25], which is adopted by regulatory agencies worldwide and as such, any ADR considered at least possibly related and unexpected in our study should be reported to the TGA. However, the under-reporting rate was greater than 99%, which was consistent with numerous other studies where this was consistently over 95% [22,26,27]. This may be explained by the finding that 70% of ADRs leading to hospitalization were expected, and therefore did not qualify for reporting to the TGA. However, the under-reporting of the remaining unexpected ADR related hospitalizations is a significant healthcare problem as it causes delays for regulatory agencies to identify any new safety signals and take the necessary action to remove medicines with unacceptable safety profiles from the market. A systematic review including 462 medicines with canceled registrations due to safety concerns showed that the median time from drug launch to drug withdrawal was 10 years [28]. These delays contribute further to increasing healthcare costs resulting from ADR-related hospitalizations and its associated morbidity and mortality. In addition, studies have also found that ADRs

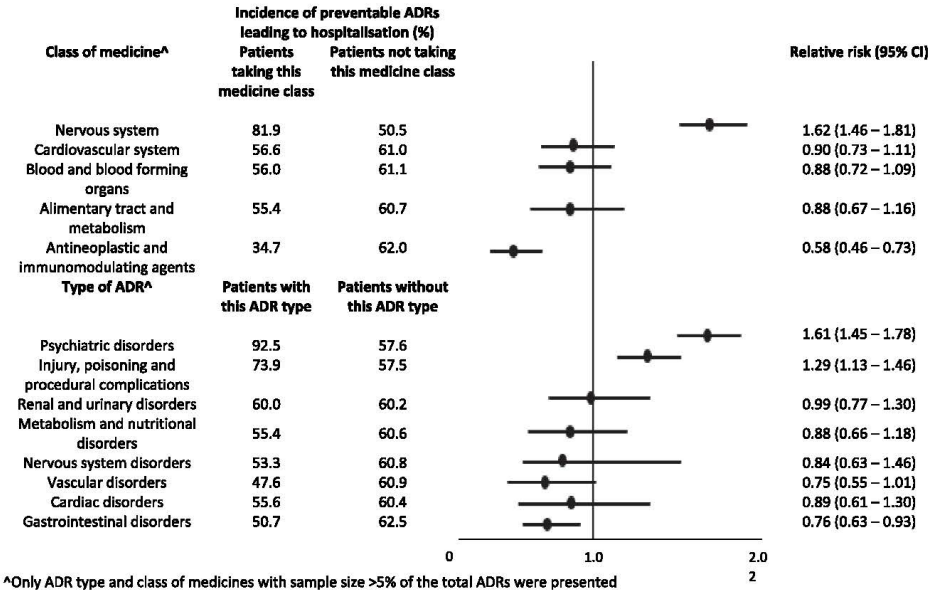

Figure 2. Relative risk of medicine and ADR type being preventable.

Table 3. Characteristics of patients admitted to hospital for ADRs vs non-ADRs.

	ADR related hospitalization (n = 496)	Non-ADR related hospitalization (n = 5025)	P value
Median age (IQR)	74 (58–83)	55 (35–72)	<0.001
Female gender – no. (%)	264 (53.2)	2760 (54.9)	0.47
Median Length of Stay – days (IQR)	5 (2–9)	3 (2–6)	<0.001
Median number of medicines (IQR)	10 (6–14)	4 (0–9)	<0.001
Admitted to ward – no. (%)	369 (74.4)	2517 (50.1)	<0.001
Admitted to short stay unit – no. (%)	118 (23.8)	2389 (47.5)	<0.001
Admitted to intensive care – no. (%)	9 (1.8)	119 (2.4)	0.43

are poorly documented and those reported are of extremely low quality [11,29,30]. For example, a recent study showed that only 4.4% of reported ADRs had adequate information to assess a causal relationship between the medicine and the ADR [30]. This further contributes to ADR underreporting and does not allow regulatory agencies to conduct any meaningful signal detection activities to identify new safety issues.

The barriers associated with ADR reporting have also been extensively reported in the literature. These primarily include lack of knowledge, time, active support from management, and problems related to ADR diagnosis and the organization of the pharmacovigilance system [31,32]. In addition to these barriers, the lack of ADR reporting may also be attributed to a lack of implemented procedures and delegated responsibilities for ADR reporting within the hospital. Another explanation could be that healthcare professionals may not have realized that an ADR was the cause of the hospitalization, and as such would not consider reporting this to the regulatory agencies. Healthcare professionals in hospitals should develop awareness on the importance of ADR reporting due to the high prevalence of ADR related issues and strategies such as electronic reporting and continuous education should be implemented to facilitate this reporting. A systematic review showed that electronic tools facilitating ADR reporting were more effective than traditional methods, such as educational workshops, offering incentives, or providing reminders [33]. Future studies should focus on firstly identifying specific barriers to ADR reporting within a hospital environment through either surveys or focus groups. An intervention should then be developed that specifically addresses these barriers and then tested to verify its success.

4.1. Limitations

This study has several limitations. Firstly, a 3-month period of data inclusion at a single hospital does not provide an adequate reflection of all ADR related hospitalizations in Australia. In addition, the incidence data is specific to ADR related hospitalizations and no conclusions can be drawn on the overall incidence rate of an ADR associated with a medicine in the entire population. However, the sample size of over 5500 hospitalizations analyzed does provide a snapshot into the characteristics, features, and prevalence of ADR related

Table 4. Examples of preventable ADRs.

Patient age and gender	Suspect medicine(s)	ADR leading to hospitalization	Clinical issue with medication(s)
41 yr old female	Amitriptyline, clonazepam, olanzapine, pregabalin, valproic acid	Syncope, fall, suicidal ideation	No documented indication for amitriptyline or pregabalin use.
69 yr old male	Venlafaxine, quetiapine, phenelzine	Muscle contractions, tachycardia, confusion, high BP	Medication combination caused serotonin syndrome
77 yr old male	Apixaban	Stroke recurrence, fall	Incorrect dose of 2.5 mg prescribed as patient did not meet criteria for dose reduction
75 yr old male	Oxycodone, naloxone, transdermal fentanyl	Opioid induced delirium	Patient did not require an increased dose of fentanyl
81 yr old female	Rivaroxaban, aspirin	Gastrointestinal bleeding, bleeding gums	Patient's rivaroxaban dose was at 20 mg despite her moderate renal impairment with her CrCl at 39 mL/min.

issues and the type of medicines causing them. Secondly, the classification of preventability of the ADRs was performed by a single hospital pharmacist. This reduces the reliability of this assessment which could be improved by including other healthcare professionals, such as nurses and physicians. Nevertheless, the rate of preventable ADRs detected in this study was comparable to other studies, with a systematic review showing that the mean percentage of preventable ADRs leading to hospitalization was 49% and increasing to 63% in the elderly population [34–36]. Finally, there is usually seasonal variability in the reporting of ADRs and this may have influenced the reporting rate to the TGA detected in this study. Modeling in the literature shows that our study period of October to December 2019 is associated with a higher rate of ADR reporting and this may have underestimated the degree of ADR underreporting [37].

Table 5. Factors that predict ADR related hospitalizations.

Factor	Adjusted odds ratio (95% confidence interval)	P value
Age	1.04 (1.03–1.05)	<0.001
Female gender	1.07 (0.89–1.29)	0.47
No. of medicines	1.13 (1.11–1.15)	<0.001

5. Conclusion

ADR-related hospitalizations are highly prevalent in Australia and patients with older age and taking more medications are at higher risk resulting in a longer length of stay. Medicines affecting the nervous system were responsible for the greatest proportion of ADR-related hospitalizations of which 82% were considered preventable. These medicines were also more likely to cause psychiatric disorders and injury, poisoning and procedural complications. ADR underreporting was significant and future research into identifying specific barriers to ADR reporting in a hospital setting would be essential so that interventions can be designed to specifically address these with a focus on healthcare professionals involved in prescribing, dispensing, and administrating nervous system medicines.

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4.3 Publication 3: Summary

This publication reports on the effectiveness of a recent intervention, the black triangle scheme which was implemented by the Australian regulator, to improve the quantity and quality of ADR reporting in Australia. The results showed that reports from HCPs and consumers were infrequent with the majority of reports coming from the pharmaceutical industry. Despite an extensive advertising campaign promoting the black triangle scheme, this intervention was only marginally successful in improving the quantity of ADR reporting. However, there was a higher proportion of serious and unexpected ADR reports for black triangle medicines. It would be ideal if the majority of ADRs associated with black triangle medicines are reported to the regulatory agency, however this is hard to measure as it is difficult to estimate the number of patients exposed to these medicines. This is also dependent on the frequency of prescribing of these medicines. The quality of ADR reporting was improved, however further interventions are required to enhance the overall pharmacovigilance system in Australia.

4.3.1 Effect of the black triangle scheme and its online educational campaign on the quantity and quality of ADE reporting in Australia

Li R, Curtis K, Zaidi STR, Van C, and Castelino R. Effect of the black triangle scheme and its online educational campaign on the quantity and quality of adverse drug event reporting in Australia: a time series analysis. *Expert Opin Drug Saf* 2020; 19(6): 747-753

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ORIGINAL RESEARCH

Effect of the black triangle scheme and its online educational campaign on the quantity and quality of adverse drug event reporting in Australia: a time series analysis

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ABSTRACT

Objectives: The black triangle scheme was introduced to Australia in January 2018 to improve the significant under-reporting of adverse drug events (ADEs). The authors investigated the impact of the black triangle scheme on the quantity and quality of ADE reports submitted to the Therapeutic Goods Administration.

Methods: An interrupted time series analysis with segmented regression was conducted to compare the quantity of ADE reports pre and post the black triangle intervention for the period between January 2017 and December 2018. The quality of reports was measured by the ability to apply the World Health Organization – Uppsala Monitoring Center algorithm to evaluate a causal relationship between the medicine and ADE.

Results: A total of 384 ADE reports were extracted for the 33 medicines approved in 2017 and 135 ADE reports for the 36 black triangle medicines. Time series analysis showed that there was a monthly increase of 0.41 reports per medicine (95%CI, 0.02–0.80, p = 0.039) post the black triangle intervention. There was a higher proportion for high quality reports for black triangle medicines versus 2017 medicines (22.2% vs 7.6%, p < 0.001).

Conclusion: The black triangle scheme was marginally successful in improving ADE reporting and additional strategies are required to enhance the overall pharmacovigilance system in Australia.

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1. Introduction

Under-reporting of adverse drug events (ADEs) is highly prevalent in Australia and around the world. A 2006 systematic review demonstrated that the global rate of under-reporting by healthcare professionals is 94% [1]. In 2017, only 10% of the 18,600 ADE reports received by the Therapeutic Goods Administration (TGA) were from hospitals, 7% from consumers, 6% from community pharmacists, and 3% from general practitioners versus 54% from pharmaceutical companies [2]. Furthermore, the quality of ADE reports have been reported as poor with only 4.4% to 11.5% of reports containing adequate information to allow for an analysis of the causal relationship between the suspect medicine and ADE [3,4]. This severely impedes the ability of regulators to identify and validate new safety signals which may adversely impact the benefit risk profile of a new medicine.

The main barriers to reporting ADEs have been studied extensively in the international literature with lack of time, different care priorities, uncertainty about drug causing the ADE, difficulty in accessing reporting forms, and lack of awareness of the requirements for reporting being the key concerns [5–8]. Healthcare professionals' attitudes also play a significant role in the under-reporting of ADEs with one survey showing that physicians believed that all serious reactions will be well documented by the time a drug is marketed and that a single case report will not contribute to medical knowledge [9]. All of these barriers contribute to the substantial under reporting of ADEs with studies showing that 50–97% of healthcare professionals admitting that they have not reported any ADEs in the last 12 months [10,11].

In January 2018, the TGA introduced a black triangle scheme to increase awareness and promote the reporting of ADEs by consumers and healthcare professionals [12]. This involves the inclusion of a black triangle symbol ' 'onto the Product Information and Consumer Medicines Information along with mandatory accompanying text alerting consumers and healthcare professionals to report ADEs. This symbol applies for a minimum of 5 years to; all newly approved medicines (except biosimilars and generics) and existing medicines with a new indication that is for a significantly different condition, or use in a significantly different patient population.

A similar scheme has been in operation in the United Kingdom (UK) since January 1976 and the European Union since 2013 [13]. A 1995 UK survey reported that 64% of healthcare professionals understood the purpose of the black triangle scheme, but only 38% were able to correctly define its

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meaning [14]. In a 2018 questionnaire to oncology healthcare professionals in the UK, 26% did not understand the purpose of the black triangle and 54% would not alter their reporting habits in the presence of a black triangle [15]. This suggests that the implementation of the black triangle scheme has not been effective.

To promote the successful implementation of the black triangle scheme in Australia, with the goal of increasing ADE reporting, the TGA conducted an educational advertising campaign through social media (Facebook and LinkedIn), Google advertising, and online health journals from February to May 2018 [16]. These activities reached more than 1.2 million unique users and achieved more than 7.2 million advertisement impressions via Google resulting in a 100 fold increase in unique visits to the TGA black triangle scheme webpage [16]. Furthermore, the average time spent on the webpage per unique user was longer than prior to the advertising campaign. Overall, this campaign improved awareness, however it is unknown whether this has translated to a meaningful improvement in the quantity and quality of reporting. This study will examine the effect of the black triangle scheme on the quantity and quality of ADE reports submitted to the TGA one year after its implementation.

2. Methods

The Australian pharmacovigilance system requires mandatory reporting from the pharmaceutical industry as a condition of approving the registration of a medicine, however it is voluntary for healthcare professionals or consumers [17]. As all ADE reports originate from a consumer or healthcare professional, the pharmaceutical industry is seen as an intermediary between the reporter and the regulator. All reports can be submitted either electronically via the TGA Adverse Event Management System, as a CIOMS-I form, or by using the standard 'blue card' adverse reaction reporting form as part of the Australian system for pharmacovigilance [18–20].

A retrospective analysis of all ADE reports submitted to the TGA for new medicines approved in 2017 and 2018 was conducted. This includes all reports received for these medicines from January 2017 to December 2018. The reports were extracted from the adverse event management database managed by the TGA pharmacovigilance office. The information recorded include: date of report, reporter type, report source, patient age, gender, suspect drug name, suspect drug start date, ADE description, onset date, outcome, and concomitant medications. The study was determined to be of negligible risk and was exempted from ethics by the University of Sydney Human Research Ethics Committee for the condition: 'involves the use of existing collections of data or records that contain only non-identifiable data about human beings'.

2.1. Quantity and type of reports

The quantity of reports per month for new medicines approved in 2017 (control group) was compared with those reported for black triangle medicines approved in 2018 (intervention group) over a cumulative period defined as the number of months these medicines were approved on the Australian market. Seriousness of the ADE was assessed using the International Conference of Harmonization criteria (e.g. fatal, life-threatening, hospitalization, congenital anomaly, persistent disability, other medically significant, or non-serious) and expectedness was evaluated using the TGA approved Product Information for each medicine [21].

2.2. Quality of reports

Each report was assessed to determine if it contained enough information to use the World Health Organization – Uppsala Monitoring Center (WHO-UMC) algorithm for evaluating a causal relationship between the suspect medicine and ADE [22]. This algorithm was selected as the national regulators of 166 countries share their safety reports to the WHO for analysis [23]. Reports were classified as 'high quality' if it was possible to determine a causal relationship based on the reported safety information, or 'low quality' if it was not possible to conduct a causality analysis. The minimum information required to establish a causal relationship based on the WHO-UMC algorithm was: suspect medicine, medicine start date, event onset date, event description, and concomitant medications. For reports classified as high quality, the strength of the causal relationship was further evaluated using the WHO-UMC algorithm.

2.3. Analysis

The quality of the reports were independently assessed by two investigators (RL and RC) against the WHO-UMC algorithm. In case of discrepancies, the report was then evaluated by a third investigator (STRZ) and an agreement reached within the group.

Analyses were performed using IBM SPSS (version 25.0) with significance levels set at $p \leq 0.05$. The mean number of ADE reports pre and post the introduction of the black triangle scheme were also analyzed using an interrupted time series analysis. Segmented regression analysis was conducted to estimate the effect size of any change in the quantity of ADE reporting as well as to detect any month to month variations prior to and post the black triangle intervention. The Durbin Watson statistic was used to assess autocorrelation. The Mann Whitney U test was used for comparing the quantity of reports between the intervention and control groups.. A Chi Square Test of Association was used to compare the quality of reports between the intervention and control groups.

3. Results

3.1. Type of medicine and therapeutic area

A total of 33 new medicines were approved in 2017 versus 36 black triangle medicines approved in 2018. This includes 6 existing medicines with a newly approved indication in 2018 that warranted its inclusion as a black triangle medicine. A breakdown of the therapeutic areas for the indications of these medicines is listed in Table 1.

Table 1. Indications of newly approved medicines by therapeutic area.

Therapeutic area for indication	Newly approved medicines in 2017 (n (%))	Black triangle medicines (including new indications) approved in 2018 (n (%))
Antineoplastic and hematology	11 (33.3)	10 (27.8)
Cardiovascular and thrombosis	1 (3.0)	0 (0)
Endocrinology and metabolic	5 (15.2)	4 (11.1)
Eye, ear and skin disorders	0 (0)	3 (8.3)
Gastroenterology	2 (6.1)	2 (5.6)
Neurological and neuromuscular	4 (12.1)	8 (22.2)
Reproductive	1 (3.0)	0 (0)
Respiratory	2 (6.1)	1 (2.8)
Vaccine, anti-infective and anti-allergen	7 (21.2)	8 (22.2)

3.2. Quantity and type of reports

A total 384 reports were reported to the TGA for newly approved medicines in 2017 over a cumulative period of 568 months on the Australian market. For black triangle medicines in 2018, 135 reports were collected over a cumulative period of 222 months. Two thirds of 2018 black triangle medicines had zero reports submitted to the TGA versus 45.4% of new chemical entities approved in 2017. There was no difference in the rate of ADE reports received for 2017 medicines versus 2018 black triangle medicines (0.68 ADE reports/medicine/month versus 0.61 ADE reports/medicine/month, $p = 0.294$).

The vast majority of reports were received from the pharmaceutical industry (87.7%), with health care professionals (10.2%) and consumers (2.1%) being the other direct sources to the TGA. Over 90% of reported ADEs were serious, and almost half (45.9%) were considered both serious and unexpected ADEs. There was an increase in the proportion of serious and unexpected ADEs reported for the black triangle medicines in 2018 versus the newly approved medicines in 2017 (64.4% vs 39.3%, $p < 0.001$) – Table 2.

Interrupted time series analysis showed that the trend of ADE reporting rates were very low prior to the introduction of the black triangle scheme, with a mean of 0.149 reports per medicine (95%CI, 0.05–0.264) (Figure 1). Post intervention, the mean number of ADE reports per medicine increased to 0.726 (95%CI, 0.588–0.878). Based on the segmented regression model, the effect estimate of the mean number of ADE reports per medicine at baseline was 0 reports per month (95%CI, −0.292–0.292). There was no significant month to month change in the number of ADE reports per medicine 0.029 (95%CI, −0.011–0.068, $p = 0.151$) during the pre-intervention period. Immediately after the introduction of the black triangle scheme intervention, there was an increase of 0.41 ADE reports per medicine (95%CI, 0.021–0.80, $p = 0.039$) with no significant trend of monthly variations in ADEs reported to the TGA for up to 12 months post intervention (−0.03, 95%CI −0.089–0.023, $p = 0.298$). There was no evidence of autocorrelation as the Durban-Watson scores were 1.60 and 1.77 for the regression models pre and post intervention.

Table 2. Type and source of report.

Variable	ADE reports for newly approved medicines in 2017 (n (%))	ADE reports for black triangle medicines (including new indications) approved in 2018 (n (%))
Reporter of ADE		
Pharmaceutical industry	337 (87.8)	118 (87.4)
Healthcare professionals	40 (10.4)	13 (9.6)
Consumers	7 (1.8)	4 (3.0)
Seriousness and expectedness of ADE		
Fatal	10 (2.6)	10 (7.4)
Serious	342 (89.1)	122 (90.4)
Non-serious	32 (8.3)	3 (2.2)
Expected	221 (57.6)	46 (34.1)
Unexpected	163 (42.4)	89 (65.9)
Serious and unexpected	151 (39.3)	87 (64.4)

3.3. Quality of reports to determine a causal relationship

The majority of reports were poor in quality throughout the study period. Only 11.3% contained adequate information to allow for an assessment of the causal relationship between the medicine and adverse reaction using the WHO-UMC algorithm. Only 18.3% of reports provided a drug start date and 29.1% provided an event onset date. The quality of the reports from health care professional and consumers was superior to those from the pharmaceutical industry, 60.9% of reports from healthcare professionals and consumers contained enough information to be able to assess a causal relationship versus 4.4% from the pharmaceutical industry ($p < 0.001$). In particular, health care professionals and consumers provided the drug start date (78.1% vs 10.1%, $p < 0.001$) and the event onset date (87.5% vs 20.9%, $p < 0.001$) at a higher frequency. (Figure 2).

There was also a difference in the quality of reports received for newly approved medicines in 2017 versus the 2018 black triangle medicines. The drug start date (25.9% vs15.9%, $p = 0.01$), outcome (37% vs 16.4%, $p < 0.001$), and concomitant medications (42.2% vs 30.2%, $p = 0.011$) were completed more frequently for black triangle medicines versus for 2017 medicines (Figure 3). Less than a quarter of reports for black triangle medicines contained adequate information to allow for a causality assessment using the WHO-UMC algorithm, although this was still higher than the report quality for 2017 medicines (22.2% vs 7.6%, $p < 0.001$). There was no difference in the proportion of high quality reports for the black triangle medicines received from health care professionals/consumers versus the pharmaceutical industry.

3.4. Causality analysis using the World Health Organization – Uppsala Monitoring Center algorithm

Of the 59 reports that contained adequate information to perform a causality assessment between the suspect medicine and the ADE, the causality of 40.7% of ADEs were considered probable/likely, 1.7% possible, and 10.2% unlikely (Table 3). The remaining ADEs (47.4%) were assessed as conditional/unclassified indicating these were new and previously unknown reactions that warrant further investigation. The proportion of such reports for the 2018 black triangle

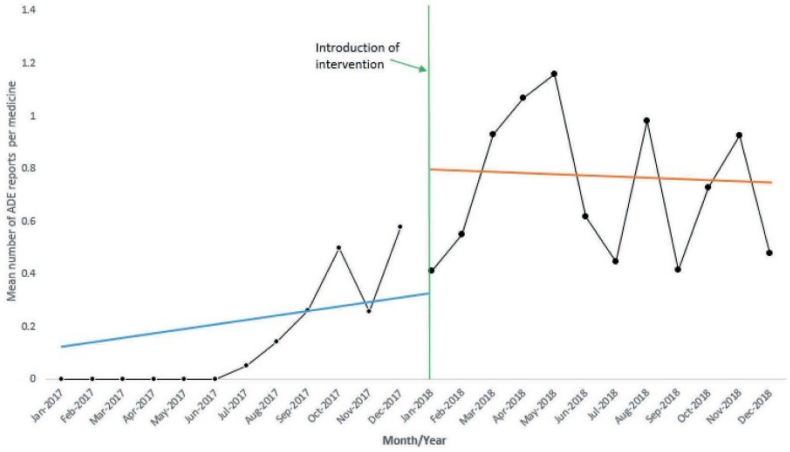

Figure 1. Mean number of adverse drug events per medicine reported to the Therapeutic Goods Administration from January 2017 to December 2018.

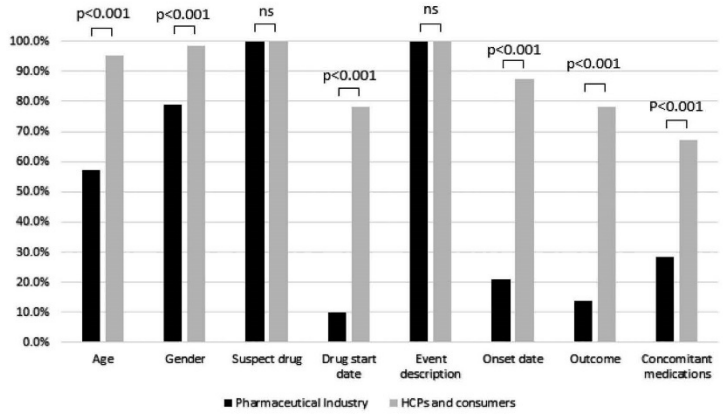

Figure 2. Percentage of completed fields within a report by healthcare professionals and consumers vs pharmaceutical industry.

medicines versus the 2017 medicines was not different (56.7% vs 37.9%, p = 0.15). Only 4.8% of all reports for new medicines approved in 2017 and 2018 couldn't be determined as causally related to the suspect medicine and 5.4% of reports contained enough information to suggest that it may be a new or previously unknown reaction.

4. Discussion

Regulators around the world rely on spontaneous reporting of ADEs to supplement safety information collected during clinical trials to identify previously unknown safety issues, especially for newly approved medicines. However, this study showed that reporting rates in Australia were extremely low with no ADEs reported for more than half of the newly approved medicines in 2017 and 2018. Due to mandatory reporting requirements for sponsors of medicines in Australia [17], it was not surprising to see that the vast majority of ADE reports originated from the pharmaceutical industry, although their quality was poor. This could be due to the time constraints mandated within the Australian pharmacovigilance legislation where pharmaceutical companies must report all serious ADEs (even those with minimal information) to the TGA within 15 calendar days [17], hence, the focus may be to comply with these requirements rather than providing the detail necessary for the identification of new safety signals. In contrast, the quantity of reports from health care professionals and consumers was extremely low but of superior quality. It is plausible that health care professionals and consumers who decided to report ADEs were more motivated or had better knowledge on the importance of pharmacovigilance resulting in higher quality reports. This presents an opportunity for the TGA and other regulators around the world to provide

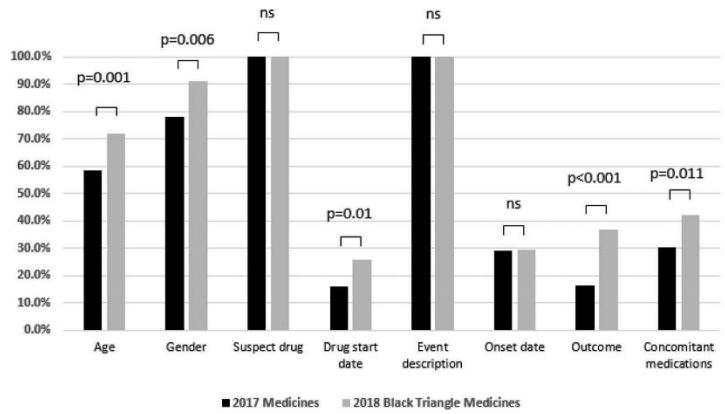

Figure 3. Percentage of completed fields within a report for 2017 medicines versus 2018 black triangle medicine.

Table 3. Causality analysis of adverse drug events using the WHO-UMC algorithm.

	2017 medicines (n = 29)	2018 black triangle medicines (n = 30)
Certain	0 (0)	0 (0)
Probable/Likely	15 (51.7)	9 (30.0)
Possible	1 (3.4)	0 (0)
Conditional/ Unclassified	11 (37.9)	17 (56.7)
Unlikely	2 (6.9)	4 (13.3)

education to health care professionals and consumers on the importance of providing complete safety information in their interactions with the pharmaceutical industry. Pharmaceutical companies should also work with these stakeholders to identify and address any barriers to providing the requested information in these follow up requests.

The results also showed that despite the awareness campaign conducted by the TGA to promote the black triangle scheme, the implementation was not very successful in increasing the quantity of ADE reports for black triangle medicines. This can be due to several factors. Firstly, the advertising campaign promoting the black triangle scheme was exclusively conducted using social media channels, and therefore consumers and healthcare professionals without access to these would not have been aware of this intervention. Secondly, the lack of increase in ADE reports can be a result of the 'Weber effect' which suggests that ADE reporting peaks at the end of the second year after a regulatory authority approves a medicine [24]. However, it is important to note that this effect was based on only a single class of medication prescribed in 1984 and a 2014 study showed that this effect was not present in the United States [25].Therefore, it is difficult to fully attribute these results to the Weber effect as it has not been comprehensively evaluated in Australia. Finally, the lack of success of this intervention may also be due to delays in the clinical uptake of the newly approved medicines. This study showed that almost 50% of the newly approved medicines in 2018 were in the hematology, neurology and oncology therapeutic areas, and the high cost associated with these medicines may be a barrier to broad access. This may also help to explain the high proportion of medicines where zero ADEs were reported. To further enhance the effectiveness of the black triangle scheme to improve the quantity of ADE reporting, additional strategies should be implemented as part of a multifaceted approach with a recent systematic review showing that electronic and multifaceted interventions were more successful than single, traditional methods [26]. Furthermore, these strategies should address both the quality and quantity of ADE reports given the significant underreporting bias detected for different types of medicines [27].

The results also showed that there was an improvement in the overall quantity of reports for all new medicines post intervention. Furthermore, the overall quality of reports for black triangle medicines were improved especially with regards to the more frequent provision of drug start dates and concomitant medications. This information is essential in most causality analysis algorithms as it allows for the establishment of a temporal association as well as to rule out ADEs caused by confounding factors such as other medications [22,28,29]. Despite the improvements in quality, there were still over three quarters of reports that lacked the adequate information required to perform a standard causality analysis. This is especially problematic as large volumes of safety data within pharmacovigilance databases cannot be used to evaluate new safety signals. This is reinforced by our finding that only 5% of ADE reports for new medicines approved in 2017 and 2018 included enough information to indicate that the report contained a previously unknown reaction that warranted further investigation. The black triangle scheme would perhaps be more successful if implemented using strategy that incorporates a clear understanding of the associated barriers to, and facilitators of change. In addition, human behavior is central to successful sustained compliance with policy and uptake of new guidelines. Interventions to ensure compliance are most successful if principles of behavioral

change psychology are applied. Three validated tools to use to achieve this either in isolation or together are the Theoretical Domains Framework, the Behavior Change Wheel and the Behavior Change Technique Taxonomy (BCTT) [30].

4.1. Limitations

This study had several limitations. It is difficult to attribute the black triangle scheme as the sole reason for the improvements in the quality of reporting. Other factors such as media reports of ADEs and/or publication of ADEs in the literature may have had influence. Secondly, this analysis was conducted for medicines that were approved in 2017 and 2018. A dataset of ADE reports from years prior to 2017 would enhance the time series analyses of estimating the trend of ADE reporting prior to the introduction of the black triangle scheme to better substantiate the effect of this intervention. However, given that the overall quantity of ADE reports did not significantly vary from 2013 to 2017, it is unlikely that including this additional data would significantly affect the outcome of this study [2].

Finally, differences in the therapeutic areas of the indications for the new medicines makes it difficult to compare their ADE reporting rates given the differences in population exposure rates in different disease states.

4.2. Future research directions

Future research should investigate healthcare professional and consumers' understanding of the black triangle scheme. This may focus on their perceptions on whether its implementation will drive a change in their practice of ADE reporting as well as explore factors that may be considered as barriers. Furthermore, a large volume of ADE reports exists within the Australian pharmacovigilance database where inadequate information limits the ability to apply a traditional causality algorithm, and this is also likely to be the case for other pharmacovigilance databases of health regulators around the world [3,4].Therefore, further research can be conducted to investigate advanced forms of analyses such as natural language processing or artificial intelligence to see if validated safety signals can be identified from ADE reports with missing data.

5. Conclusion

Although the black triangle scheme improved the overall quality of ADE reports submitted to the Australian regulator, there was no meaningful increase in the quantity of reports. Reports from healthcare professionals and consumers were infrequent, but superior in quality to those received by the pharmaceutical industry. Further interventions to improve the quantity and quality of ADE reports are required to enhance signal detection and the post marketing surveillance system in Australia.

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Author contributions

Conception and design: R Li. Analysis and interpretation of data: R Li, K Curtis, C Van, STR Zaidi, R Castelino. Drafting of paper: R Li. Revising it critically for intellectual content: R Li, K Curtis, C Van, STR Zaidi, R Castelino. Final approval of version to be published: R Li, K Curtis, C Van, STR Zaidi, R Castelino. All authors agree to be accountable for all aspects of this publication.

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4.4 Publication 4: Summary

This publication reported on the knowledge and perspectives of HCPs towards ADR reporting to help understand the facilitators and barriers to this process. The questions were mapped to the 14 domains within the TDF and both quantitative and qualitative data were collected. The quantitative results showed that a substantial proportion of HCPs do not report ADRs. Knowing how to report ADRs and encountering ADRs in their practice were significant predictors of whether they made an ADR report. Qualitative data were mapped to 3 categories: Modifying the ADR reporting process, enabling clinicians to report ADRs, and creating a positive ADR reporting culture. The domains identified as requiring attention in future interventions to improve ADR reporting included knowledge, environment context/resources, and beliefs about consequences.

4.4.1 Why hospital-based healthcare professionals do not report adverse drug reactions: a mixed methods study

Li R, Curtis K, Van C, Zaidi STR, Yeo CY, Kali CA, Zaheen M, Moujalli GT, and Castelino R Why hospital-based healthcare professionals do not report adverse drug reactions: a mixed methods study using the theoretical domains framework. *Eur J Clin Pharmacol* 2022; 78: 1165-1175

European Journal of Clinical Pharmacology (2022) 78:1165–1175
https://doi.org/10.1007/s00228-022-03326-x

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Why hospital-based healthcare professionals do not report adverse drug reactions: a mixed methods study using the Theoretical Domains Framework

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Abstract

Purpose Adverse drug reaction (ADR) underreporting is highly prevalent across the world. This study aimed to identify factors associated with ADR reporting and map these to a behavioural change framework to help inform future interventions designed to improve ADR underreporting.

Methods A mixed methods survey was distributed to healthcare professionals at a tertiary hospital in Sydney, Australia. Quantitative data was analysed using logistic regression to identify factors that predict ADR reporting. Qualitative data was evaluated using content analysis. These were then integrated and mapped to the 14 domains within the Theoretical Domains Framework (TDF) to identify target areas relevant for improving ADR reporting.

Results One hundred thirty-three healthcare professionals completed the survey. Knowing how to report ADRs (OR 4.56, 95%CI 1.95–10.7), having been trained on ADR reporting (OR 2.72, 95%CI 1.29–5.77), and encountering ADRs as part of clinical practice (OR 10.3, 95%CI 3.59–29.4) were significant predictors of reporting an ADR. Content analysis identified three categories: modifying the ADR reporting process, enabling clinicians to report ADRs, and creating a positive ADR reporting culture. After data integration, the three target TDF domains were knowledge, environmental context/resources, and beliefs about consequences.

Conclusion Future interventions designed to improve ADR reporting should address these target domains to instigate behaviour change in healthcare professionals' reporting of ADRs.

Keywords Pharmacovigilance · Adverse drug reactions · Reporting · Theoretical domains framework

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Introduction

Adverse drug reactions (ADR) are defined as any untoward medical occurrence in a patient administered a pharmaceutical product where a causal relationship is suspected [1]. They are a major cause of morbidity and mortality and directly responsible for up to 18% of hospital admissions and 27% of deaths in Australia [2]. The costs of ADRs are considerable due to the complexities associated with ADR treatment in a patient group who are generally older and taking more medications [3, 4]. The rate of ADR-related hospitalizations in Australia has increased by 21% from 8.0 per 100 hospitalizations in 2007/08 to 9.7 per 100 hospitalizations in 2015/16. Up to 60% of these were considered preventable [5].

Some ADR-related hospitalizations may be related to the poor characterization of the safety profiles of medicines due to underreporting of ADRs once a medicine is marketed [6]. In addition, most ADR reports are of very low quality, with missing information that is required to make an informed assessment of the frequency, severity, and causal relationship between the ADR and medicine [6–8]. This causes delays for regulatory agencies to remove medicines with unacceptable safety profiles. A 2016 systematic review reported the median time taken to withdraw a medicine for safety reasons was 10 years after its launch [9].

Barriers to ADR reporting by clinicians include lack of time, competing clinical priorities, uncertainty about the causal relationship between the drug and ADR, difficulties in accessing the reporting form, length of reporting form, lack of a user-friendly electronic ADR reporting platform, lack of awareness, and a belief that all serious reactions are well documented by the time a medicine is marketed [10–14]. In addition, ADRs are diagnosed over time and may require the input of multiple healthcare professionals, while most ADR reporting forms only allow for reporting of ADRs at a specific time point [15]. Interventions to improve ADR reporting have not been designed to specifically address the known barriers. A 2020 systematic review of interventions to improve ADR reporting concluded that their effectiveness was modest and that there was a lack of consideration of theoretical frameworks in the design of interventions [16, 17]. In addition, end-user input from healthcare professionals into the design of ADR reporting systems is lacking with only the needs of regulatory agencies taken into account [18]. As such, a knowledge gap exists in the creation of an intervention that is designed specifically to address the key determinants of behaviour change required to improve the quantity and quality of ADR reporting.

This study investigated medical officer, nurse, and pharmacist perspectives of ADR reporting in a hospital setting, so target areas can be identified to inform the development of a tailored intervention to improve ADR reporting.

Methods

Study design

This was an embedded mixed methods study where a qualitative component was added to a primarily quantitative study and the data were collected and analysed together [19]. We conducted a cross-sectional survey of medical officers, nurses, and pharmacists practising at Blacktown Hospital, a tertiary referral hospital with 570 beds in Western Sydney [20]. Currently, healthcare professionals in this hospital report ADRs by completing a 'blue card' reporting form and submitting it to the Australian regulator, the Therapeutic Goods Administration (TGA), through an online portal, or by email, fax, or post [21]. However, other aspects of patient care in this hospital have migrated to electronic platforms such as eMedical Records and eMedication Management.

Ethics was obtained from the Western Sydney Local Health District (HREC reference: 2020/ETH00597).

Survey development

We were interested in 3 specific areas, namely, knowledge, perspectives, and practices of ADR reporting based on a previous survey conducted for community pharmacists practising in Australia [22]. In addition, development of the survey was also guided by the Theoretical Domains Framework (TDF). The TDF was developed and validated by an international collaboration of behavioural scientists and implementation researchers to identify key factors that would influence behaviour change among healthcare professionals [23]. This led to the establishment of 14 domain areas including knowledge; skills; social/professional role and identity; beliefs about capabilities; optimism; beliefs about consequences; reinforcement; intentions; goals; memory, attention and decision processes; environmental context and resources; social influences; emotion; and behavioural regulation, of which any one or combination of these domains may be needed to cause behaviour change. The TDF has been used extensively in healthcare research in Australia to identify barriers that need to be addressed to increase uptake of a new process or system. Examples include the successful adoption of an electronic medicine management system in hospitals, implementing a blunt chest injury care bundle, and adopting guidelines for the management of acute low back pain [24–26]. The TDF was selected as it identifies a wide range of determinants of behaviour and can be mapped to the behaviour change wheel to identify suitable

behaviour change techniques (BCT) to inform interventions for improving ADR reporting (Supplementary Index, Figure S1) [24].

A pool of questions for each of these areas was generated based on each of the 14 domains within the TDF, with the question selection based on consultations with senior clinicians from the investigators' network with an interest in this topic and practising in hospital nursing, pharmacy, and medicine.

We created a draft survey tool containing questions answered on a 5-point Likert scale from strongly disagree to strongly agree and open-ended questions to collect additional information about ADR reporting. This was piloted with a group of hospital pharmacists and nurses ($n=5$) for feedback, and the wording of two questions was revised to enhance their clarity to the audience. The final version of the survey tool contained 25 items and is shown in Appendix S1 (Supplementary index).

Data collection and recruitment

All medical officers, nurses, and pharmacists at Blacktown hospital were emailed an invitation to participate in this study from their departmental director/manager. This email correspondence contained the participant information sheet and an electronic link to the survey. Posters with QR codes were circulated around the hospital inviting participants to complete the survey. Data were captured using the Research Electronic Data Capture (REDCap), which is a secure web-based database application maintained by the University of Sydney.

Statistical analyses

Statistical analyses were conducted using IBM SPSS (version 27.0) with significance levels set at $P<0.05$. Adjustment for multiple comparisons was made using the Bonferroni correction. Descriptive statistics were reported using medians and interquartile range (IQR) as the Shapiro–Wilk and Kolmogorov–Smirnov tests displayed significance indicating the data is not normally distributed. The Kruskal–Wallis test was used for comparing the perspectives towards ADR reporting between pharmacists, medical officers, and nurses, as well as those who reported ADRs versus those who didn't. Multivariate logistic regression was used to identify factors that predict whether a healthcare professional reports an ADR.

Qualitative data from free text responses were analysed using the conventional content analysis approach to identify new themes and categories without bias towards pre-existing theories or frameworks on this topic [27]. Initially, the researchers familiarized themselves with the data by repeatedly reading through the entire content to achieve immersion and obtain an overall meaning. The data were then carefully analysed by searching for terminology that may capture a key thought or concept (sub-categories). Notes were made for each of these concepts, and labels were then assigned to help classify these into categories. This entire process was conducted by 3 researchers (RL, KC, and CV) independently. If there were discrepancies, the researchers discussed these, and a consensus approach was taken.

The quantitative and qualitative data were then integrated and mapped to each of the 14 TDF domains using a consensus approach by 3 investigators (RL, KC, and CV). Quantitative results that had a median score of 5 or greater (equivalent to strongly agree on 5-point Likert scale) were included in this integration phase. The domains were then classified as target domains if 3 or more quantitative or qualitative results were mapped to that domain. This helped to identify the most important domains to target when designing future interventions to improve ADR reporting.

Results

The survey was completed by 133 healthcare professionals comprised of 16 pharmacists (12.0%), 76 nurses (57.1%), and 41 medical officers (30.8%). Most respondents had encountered ADRs in their clinical practice (66.4%) indicating that they have either treated an ADR for a patient or a patient reported an ADR to them in a consultation. However, less than half of these healthcare professionals have reported an ADR (41.8%). Over one third of healthcare professionals did not know how to report ADRs to the hospital safety committee (34.3%) or the TGA (35.1%). Almost two thirds of healthcare professionals (64.9%) indicated they had not received any training on ADR reporting. The vast majority (94%) were not aware of the recently introduced TGA black triangle scheme, and very few were subscribed to receive TGA safety alerts (15.7%).

Quantitative: differences among pharmacists, medical officers, and nurses

Most healthcare professionals agreed that ADR reporting is important for patient care (94.7%) and that they have a professional obligation to report ADRs (94.0%). Pharmacists and nurses reported better knowledge on how to report ADRs to the hospital safety committee as well as the TGA than medical officers (reporting to hospital committee, 75% and 76.3% vs 41.5%, $P<0.001$, and reporting to TGA, 100% and 72.4% vs 36.6%, $p<0.001$). Furthermore, more pharmacists reported they had received training on ADR reporting than medical officers (43.7% vs 22.0%, $P=0.013$). Three quarters of pharmacists have reported an ADR, and this was substantially more than medical officers (46.3%) and nurses (31.6%) even though there were no differences

among the three healthcare professional groups in encountering ADRs in their clinical practice (Table 1). Multivariate logistic regression showed that knowing how to report ADRs to the hospital committee (OR 4.56, 95%CI 1.95–10.7), having been trained on ADR reporting (OR 2.72, 95%CI 1.29–5.77), and encountering ADRs as part of clinical practice (OR 10.3, 95%CI 3.59–29.4) were significant predictors of making an ADR report (Table 2).

Quantitative: perspectives of healthcare professionals towards ADR reporting

Healthcare professionals agreed that ADR reporting should be made mandatory (median [IQR], 5 [3–5]) is important for patient care (median [IQR], 5 [4, 5]) and that they have a professional obligation to report ADRs (median [IQR], 5 [4, 5]) with no significant differences in these perspectives among physicians, nurses, or pharmacists. Healthcare professionals believed they were more likely to report ADRs if there was an electronic tool that automatically populates information from existing datasets (median [IQR], 5 [4, 5]). The median scores for the perspectives of healthcare professionals towards ADR reporting are presented in Table 3.

Qualitative: content analysis

There were 110 healthcare professionals who responded to the qualitative component of the survey. Their responses were classified into 245 sub-categories. These were then synthesized into 3 main categories: modifying the ADR reporting process; enabling clinicians to report ADRs, and creating a positive ADR reporting culture (Table 4).

Table 1 Characteristics of respondents by healthcare professional type

	Medical officer	Nurse	Pharmacist	Overall	*P* value
N (%)	41 (30.8)	76 (57.1)	16 (12.0)	133	
Median no. of years of clinical practice (IQR)	3.0 (1.0–5.5)	8.0 (3.0–14.75)	5.0 (1.5–10.75)	5 (2–12)	
Median no. hours per week (IQR)	40 (39–42.5)	40 (38–40)	40 (38–40)	40 (38–40)	
Qualification					
Undergraduate (%)	39.0	50.0	43.8	45.9	
Postgraduate (%)	61.0	50.0	56.3	54.1	
Know how to report ADRs to hospital safety committee					
Yes (%)	41.5	76.3	75.0	65.4	<0.001[a]
No (%)	58.5	23.7	25.0	34.6	<0.001[b]
Know how to report ADRs to TGA					
Yes (%)	36.6	72.4	100	64.7	<0.001[a]
No (%)	63.4	27.6	0.0	35.3	<0.001[b]
Received training on ADR reporting					
Yes (%)	22.0	36.8	43.7	34.6	0.013[a]
No (%)	78.0	63.2	56.3	65.4	
Aware of black triangle scheme in Australia					
Yes (%)	2.4	3.9	18.8	5.3	n.s
No (%)	97.6	96.1	81.2	94.7	
Subscribed to receive TGA safety alerts					
Yes (%)	7.3	17.1	25.0	15.0	n.s
No (%)	92.7	82.9	75.0	85.0	
Encountered ADR in clinical practice					
Yes (%)	73.2	59.2	81.3	66.2	n.s
No (%)	26.8	40.8	18.8	33.8	
Have reported ADR					
Yes (%)	46.3	31.6	75.0	41.4	0.001[c]
No (%)	53.7	68.4	25.0	58.6	

Significance value was set at 0.017 after applying the Bonferroni correction

n.s. not significant

[a]Medical officer vs pharmacist

[b]Medical officer vs nurse

[c]Nurse vs pharmacist

Table 2 Factors associated with healthcare professional reporting of ADR

Factor	Absolute number (Y/N)		Crude odds ratio (95% CI)	Adjusted odds ratio^ (95% CI)	*P* value
Know how to report ADR to hospital safety committee	**87**	**46**	**4.61 (1.99–10.7)**	**4.56 (1.95–10.7)**	**<0.001**
Know how to report ADR to TGA	86	47	3.42 (1.55–7.61)	3.34 (1.49–7.46)	0.003
Received training on ADR reporting	46	87	2.60 (1.25–5.42)	2.72 (1.29–5.77)	0.009
Awareness of TGA black triangle scheme	7	126	9.43 (1.10–80.7)	9.25 (0.35–55.8)	0.25
Subscribed to receive TGA safety alerts	20	113	1.51 (0.58–3.92)	1.36 (0.51–3.67)	0.54
Encountered ADR in clinical practice	88	45	10.5 (3.79–29.2)	10.3 (3.59–29.4)	<0.001

^results were adjusted for no. years of clinical practice, no. of hours per week, and highest qualification

Modifying the ADR reporting process

Modifying the ADR reporting process, particularly through streamlining, improving, and mandating ADR reporting by healthcare professionals, was the most identified category, represented by 133 comments. Of these, there were 29 comments specifically on 'making the ADR reporting process easier' and 18 comments on making ADR reporting mandatory through monitoring, protocols, or setting key performance indicators. There were 11 respondents that highlighted forgetfulness at the time of ADR occurrence as a barrier to reporting and that reminders would serve as an important intervention to assist with the reporting process:

Make the whole process easier, formulate a protocol, and screen databases using automation. (Medical officer, respondent ID 052).

However, even if mandated, there remains several barriers to this as there were 50 comments on a 'lack of time and/or resources to report ADRs:

Lack of time due to workload – staff won't have time for breaks. (Nurse, respondent ID 070).

Enabling clinicians to report ADRs

Enabling clinicians to report ADRs by increasing their knowledge, awareness, and understanding of both the importance and process of ADR reporting was highlighted by 96 respondent comments. There were 62 comments that highlighted the need to provide education around ADR knowledge and awareness while 21 comments emphasized the importance of offering training sessions on the ADR reporting process. Thirteen comments indicated any 'uncertainty of a causal relationship between the ADR and the medicine' and 'non-serious reports' would be barriers to submitting an ADR report:

Being unsure of the causal relationship between the reaction and the drug, as well as often needing to confer with other healthcare professionals about whether or not they would consider something to be an adverse drug reaction or a natural progression of a patient's condition. (Pharmacist, respondent ID 003).

Creating a positive ADR reporting culture

Creating a positive ADR reporting culture was highlighted by 16 comments as being important to facilitate ADR reporting. These include providing encouragement for colleagues to report ADRs ($n=7$), providing acknowledgement and/or feedback for reported ADRs ($n=3$), and incentivizing the reporting of ADRs ($n=4$). Fear of legal repercussions was identified as a barrier to creating that positive ADR reporting culture ($n=2$):

Reporting culture will definitely help increase rates of ADR reporting, this will need to be facilitated/encouraged/embedded by senior clinicians/managers/executives. (Pharmacist, respondent ID 001).

Integration: mapping of quantitative and qualitative results into domains within the TDF

Quantitative items with scores > 4 and categorized qualitative results were mapped to 9 TDF domains: knowledge; social/professional role and identity; beliefs about consequences; reinforcement; intentions; memory, attention and decision processes; environment context and resources; social influences; and behavioural regulation. From this, the 3 domains selected as targets for future interventions to improve ADR reporting were determined to be knowledge [7 results]; environment context and resources (7 results); and beliefs about consequences (4 results) — see Table 5.

Discussion

This study identified several influences on clinician behaviour that need to be addressed in any future intervention designed to improve ADR reporting, in particular, knowledge, the work environment/resources, and beliefs about consequences.

Table 3 Perspectives of medical officers, nurse, and pharmacists towards ADR reporting (1–5 Likert scale)

Question (TDF domain)	Median (IQR), overall	Median (IQR), medical officer	Median (IQR), nurse	Median (IQR), pharmacist
Reporting ADRs is important for patient care (beliefs about consequences)	5 (4–5)	4 (4–5)	5 (4–5)	5 (4–5)
Reporting ADRs should be mandatory for HCPs (behavioural regulation)	5 (4–5)	4 (4–5)	5 (4–5)	4.5 (4–5)
I have a professional obligation to report ADRs (social/professional role and identity)	5 (4–5)	4 (4–5)	5 (4–5)	5 (4–5)
The safety profile of medicines is well characterized by the time it is marketed (knowledge)	4 (3–4)	3 (3–4)	4 (3–5)	3 (2–4)
I'm interested in reading about ADRs in medical literature (reinforcement)	4 (3–5)	4 (3–4)	4 (3–5)	4.5 (4–5)
I'm more likely to report ADRs if:				
There was an incentive (reinforcement)	3 (3–4)	3 (2–4)	3 (3–4)	3 (2–4)
There was an electronic tool that automatically populates information from existing datasets (environment context and resources)	5 (4–5)	4 (4–5)	5 (4–5)	5 (4–5)
I'm mandated to report and there is a consequence if I don't (beliefs about consequences)	4 (3–4)	4 (3–4.5)	4 (3–4)	4 (3–4.75)
There was a hospital protocol mandating ADR reporting (behavioural regulation)	4 (3–5)	4 (3–4)	4 (3–4.75)	4 (4–5)
I see that there are other HCPs reporting ADRs (social influences)	4 (4–5)	4 (4–4)	4 (3–5)	4 (3–5)
There was a reminder (environment context and resources)	4 (3–4)	4 (3–4)	4 (3–4)	4 (2.25–5)
It was serious and unexpected (beliefs about consequences)	5 (4–5)	5 (4–5)	4 (4–5)	5 (4–5)
It was for a new medicine (intention)	4 (3–5)	4 (4–5)	4 (3–5)	5 (4–5)
It has a strong causal association with the medicine (beliefs about consequences)	4 (3–5)	4 (4–5)	4 (3–5)	4 (3.25–5)
There is someone monitoring our ADR reporting (behavioural regulation)	4 (3–4.5)	4 (3–4)	4 (3–4)	4 (3.25–5)
I receive an acknowledgement (reinforcement)	4 (3–4)	4 (3–4)	4 (3–4)	3 (3–4)
I'm less likely to report ADRs because:				
I don't have the time (environment context and resources)	3 (2–4)	4 (2.5–4)	3 (2–4)	4 (2.25–4)
I fear there may be legal repercussions (beliefs about consequences)	2 (2–3)	2 (2–3)	3 (2–3)	2 (1–2)
There are no results or actions taken based on ADRs I report (beliefs about consequences)	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)
I forget to report at the time (memory, attention, and decision processes)	3 (2–4)	3 (2–4)	3 (2–4)	4 (3–4)
It was non-serious and expected (knowledge)	3 (2–4)	4 (3–4)	3 (2–4)	4 (3–4)
I don't have enough information to warrant a report (environment context and resources)	3 (3–4)	3 (3–4)	3 (2–4)	4 (2.25–4)
I don't know how to report (skills)	3 (2–4)	4 (3–4)	3 (2–4)	2 (2–3)
I'm uncertain of the causal relationship (knowledge)	3 (3–4)	4 (3–4)	3 (2–4)	3 (2.25–4)
I would rather have it published in the medical literature (intentions)	3 (2–3)	3 (3–4)	3 (2–3)	2 (1–2.75)
I don't know when I'm supposed to (knowledge)	3 (–4)	4 (3–4)	3 (2–4)	2 (1.25–3)
It won't make a difference (optimism, beliefs about consequences)	3 (2–3)	3 (2–4)	3 (2–3)	2 (1–3.75)
My colleagues don't (social influence)	3 (2–3)	3 (2–4)	3 (2–3)	2 (1–3.75)
It would cause stress and burnout in my workload (emotion)	3 (2–4)	3 (2–4)	3 (2–4)	2.5 (1.25–3.75)
I have been encouraged not to (social influence)	2 (1–3)	2 (1–3)	2 (2–3)	2 (1–2)

IQR interquartile range

Table 4 Categorization of qualitative data

Category and *sub-categories (number of respondent comments and TDF domain)*
Modifying ADR reporting process
Automate the reporting process (n = 6) (environment context and resources)
Make ADR reporting mandatory/through protocols (n = 18) (behavioural regulation)
Use electronic tools/software to assist ADR reporting (n = 5) (environment context and resources)
Lack of time to report ADRs (n = 50) (environment context and resources)
Forget to report ADRs (n = 7) (memory, attention, and decision processes)
Make ADR reporting easier (n = 29) (environment context and resources)
High workload/lack of resources (n = 14) (environment context and resources)
Creating reminders to assist ADR reporting (n = 4) (environment context and resources)
Enabling clinicians to report ADRs
Provide education to drive knowledge and awareness of ADR reporting (n = 62) (knowledge)
Provide training on ADR reporting process (n = 21) (knowledge)
Uncertain of causal relationship to warrant an ADR report (n = 10) (knowledge)
Non-serious ADRs do not need to be reported (n = 3) (knowledge)
Creating a positive ADR reporting culture
Providing acknowledgement/feedback for reported ADRs (n = 3) (reinforcement)
Incentivize the reporting of ADRs (n = 4) (reinforcement)
Fear of legal repercussions for reporting ADRs (n = 2) (beliefs about consequences)
Provide encouragement for colleagues to report ADRs (n = 7) (social influences)

We have applied the first two steps of French et al.'s [28] four-step model for change; the identification of (1) what and who needs to change, (2) what barriers and facilitators need to be addressed, (3) what interventions could be used to overcome the barriers, and (4) the evaluation of any intervention [28]. This study identified that (1) staff and systems within the workplace need to change and (2) barriers to be addressed include knowledge, environment, reinforcement, and memory. The next step would be to create a multifaceted intervention designed to overcome these barriers utilizing education, training, and environmental restructuring [29].

Knowledge was a key gap identified as over one third of respondents did not know how to report ADRs to either their hospital safety committee or the Australian regulator, while sub-categories collected from qualitative comments include the need to provide education and training on the importance of ADR reporting and process. This is consistent with previous studies which showed that a significant number of healthcare professionals were not educated or trained on ADR reporting, impacting their ability to report ADRs in their clinical practice [11, 22]. Consideration needs to be given in including ADR reporting into the curriculums of university healthcare degrees as well as part of continuing education workshops for healthcare professionals. Furthermore, training on ADR reporting can be included as part of the onboarding process for new healthcare professionals employed in a hospital setting.

Environment context and resources was also influential in healthcare professionals reporting of ADRs. Most healthcare professionals agreed that they would be more likely to report ADRs if the process was amended by adopting an electronic tool that is capable of automation. In addition; 'modifying the ADR reporting process' through making reporting mandatory, automating the reporting process, and utilizing electronic tools/software was proposed to facilitate ADR reporting. This is consistent with other literature which showed considerable interest among healthcare professionals towards uptake of new technologies to assist with ADR reporting [30]. A 2020 systematic review also showed that electronic strategies were more successful at improving ADR reporting rates than traditional interventions such as providing education and training [16]. However, it is also important to note that mandatory ADR reporting has not been shown to significantly improve ADR reporting in jurisdictions that have adopted this as it causes an excessive burden [31]. Therefore, any future interventions designed to improve ADR reporting should be developed around a digital framework to simplify and automate the process.

Lack of time, resources, and high workload were also identified as significant barriers to ADR reporting. This was expected as healthcare professionals are more likely to focus on treating the ADR at the time of occurrence, rather than thinking about reporting it. This is reinforced by staff indicating they are more likely to report ADRs if a reminder was created within the ADR reporting pathway. These results are also consistent with previous studies which showed that lack of time and resources are key issues that need to be overcome to encourage ADR reporting [32–36]. In addition, qualitative studies in Canada showed that reporting required duplication of documentation resulting in time constraints, and many ADR reporting systems were too complex and poorly fitted into clinical practice [14, 15]. Therefore, simplification of the reporting process so that ADR reporting is not perceived as an administrative burden is an essential consideration when designing future interventions.

Table 5 Quantitative and qualitative results mapped to the TDF to identify target domains that inform future interventions to improve ADR reporting

Domain (description)	Quantitative result(s)	Qualitative result(s)	Target domain (Y/N)
1. Knowledge (an awareness of the existence of something)	65.7% know how to report ADRs to the hospital safety committee 64.9% know how to report ADRs to the TGA 35.1% have received training on ADR reporting	**Facilitators:** Providing education to drive knowledge/awareness of ADR reporting Provide training on ADR reporting process **Barriers:** Uncertain of causal relationship to warrant ADR report Non-serious ADRs do not need to be reported	Y
2. Skills (an ability or proficiency acquired through practice)			N
3. Social/professional role and identity (a coherent set of behaviours and displayed personal qualities of an individual in a social or work setting)	I have a professional obligation to report ADRs (median score 5 out of 5)		N
4. Belief about capabilities (acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use)			N
5. Optimism (the confidence that things will happen for the best or that desired goals will be attained)			N
6. Beliefs about consequences (acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation)	More likely to report if the ADR was serious and unexpected (median score 5 out of 5) Reporting ADRs is important for patient care (median score 5 out of 5)	**Barriers:** Fear of legal repercussions for reporting ADRs	Y
7. Reinforcement (increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus)		**Facilitators:** Providing acknowledgement/feedback for reported ADRs Incentivize the reporting of ADRs	N
8. Intentions (a conscious decision to perform a behaviour or a resolve to act in a certain way)			N
9. Goals (mental representations of outcomes or end states that an individual wants to achieve)			N
10. Memory, attention, and decision processes (the ability to retain information, focus selectively on aspects of the environment, and choose between two or more alternatives)		**Barriers:** Forget to report ADRs	N
11. Environment context and resources (any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behaviour)	More likely to report if there was an electronic tool that automates ADR reporting (median score 5 out of 5)	**Facilitators:** Automate the reporting process Use electronic tools/software to assist ADR reporting Creating reminders to assist ADR reporting **Barriers:** Lack of time to report ADRs Make ADR reporting easier High workload/lack of resources	Y

Table 5 (continued)

Domain (description)	Quantitative result(s)	Qualitative result(s)	Target domain (Y/N)
12. Social influences (those interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviours)		**Facilitators:** Provide encouragement for colleagues to report ADRs	N
13. Emotion (a complex reaction pattern, involving experiential, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter or event)			N
14. Behavioural regulation Anything aimed at managing or changing objectively observed or measured actions)	Reporting ADRs should be mandatory for HCPs (median score 5 out of 5)	**Facilitators:** Make ADR reporting mandatory through protocols	N

Beliefs about consequences were the final target domain assessed as relevant to inform future interventions to improve ADR reporting. The quantitative results clearly showed that healthcare professionals were more likely to report ADRs if it was serious and unexpected or if there was a strong causal relationship between the medicine and the ADR. This may be due to the perception that regulators are more likely to take action and their report will be of consequence to characterizing the safety profile of the suspect medicine. In addition, a very strong perception that ADR reporting is important for patient care was identified. This was reinforced by the finding that HCPs in our study felt a very strong professional obligation to report ADRs. However, there were a couple of respondents who noted in the qualitative comments that fear of legal repercussions was a barrier for them to report ADRs despite a very neutral effect when this question was asked in the quantitative component of the survey.

The three TDF domains identified in this study were also identified in a 2015 Iranian study by Mirbaha et al. involving hospital pharmacists and nurses [10]. In that study, respondents admitted that they had low awareness on what ADRs should be reported (poor knowledge) and that special education and training should be provided on what and how ADRs should be reported. Within the domain of environment context and resources, the authors identified lack of time, complicated administrative procedures in the reporting process, and limited access to appropriate resources for submitting ADR reports, which were similar themes captured in our study. In the area of beliefs about consequences, comments around the importance of ADR reporting to enhance patient care and quality use of medicines were identified, which was also similar to our study. Mirbaha et al. also mapped their results to 3 additional TDF domains which were not classified as target domains in our study; these were skills, intention, and social influences. These differences may be explained by the different hospital working environments and culture experienced by clinicians in the management of ADR reporting.

Future intervention at the study site to improve ADR reporting must adopt a multifaceted approach using mechanisms known to address the identified barriers [16, 37]. An electronic tool incorporating automation and integration with existing hospital electronic health records/medication management systems can be deployed to help simplify the ADR reporting process to save time and resources, addressing the needs within the domain of environment context and resources. A systematic review showed that digital reporting tools were moderately successful with a doubling in the quantity of ADR reports; however, these tools required promotion to healthcare professionals [38]. Therefore, educational sessions on the importance and process of ADR reporting should be combined with any training sessions on how to use

the new ADR reporting system. This would enable clinicians to report ADRs and address the gaps within the knowledge domain. Finally, a focus should be placed on ADR reporting for reactions that are serious, unexpected, and/or has a strong causal relationship with the suspect medicine. This would assist regulators with identifying new safety issues for medicines and fully characterize their safety profile.

Study limitations

One of the key limitations for this study was the limited sample size of 133 healthcare professionals at a single hospital, indicating that these results may not be representative of the perspectives of all clinicians. This also had an impact on the results of the logistic regression as shown by the relatively wide confidence intervals. The low rate of participation was mainly due to the challenges of lock-down due to surging COVID-19 cases in Australia at the time this survey was deployed. Secondly, respondents completing this survey may be subject to social desirability bias [39]. Some healthcare professionals may feel guilty for not reporting ADRs and therefore are not likely to admit this. In addition, the respondents may have provided 'socially desirable' responses about their perspectives towards ADR reporting resulting in inflated scores in this area. However, the use of anonymized surveys may have reduced the impact of this bias. Thirdly, this study focused its enquiry specifically on behaviour change, which limited the exploration of other important factors such as end-user involvement in the design of any future ADR reporting tool. This is critically important as the needs of frontline clinicians must be considered to ensure any future interventions are successful. A study undertaken to pilot an electronic health record-based ADR reporting form with pharmacists showed that this was a critically important step to help inform the design and enhance the functionality of these features prior to its full implementation [40].

Conclusion

A substantial proportion of healthcare professionals do not report ADRs. By using behaviour change theory, the factors associated with ADR reporting were mapped to three target domains of knowledge, environment context and resources, and beliefs about consequences. A multifaceted intervention addressing these domains should be implemented to instigate behaviour change in healthcare professionals' reporting of ADRs.

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Declarations

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4.5 Chapter Summary

This chapter reported the quantitative and qualitative results of this mixed methods research. The results from the retrospective review of hospital admissions showed that a substantial proportion of hospitalisations are ADR related. In addition, ADR under-reporting was highly significant highlighting the need for effective interventions to improve this. The analysis of the impact of the recently introduced black triangle scheme in Australia concluded that it was only marginally successful in improving the quantity and quality of reporting, and that further interventions are required. The mixed methods survey reported the quantitative and qualitative results of HCP perspectives towards ADR reporting and identified domains within the TDF that should be targeted in the design of future interventions. The results showed that a substantial portion of hospital-based HCPs do not report ADRs. The TDF domains that should be targeted in the design of future interventions to improve ADR reporting include knowledge, environment context/resources, and beliefs about consequences. The next chapter of this thesis will integrate the quantitative and qualitative data reported in this chapter to generate the evidence and help inform the design of a strategy to improve the quantity and quality of ADR reporting in Australia.

5 Discussion

5.1 Introduction

This chapter provides details on the final integration of all the evidence generated from the results of this research and includes the fifth peer reviewed publication. The quantitative data on the prevalence, characteristics and reporting of ADR related hospitalisations, the effect of the black triangle scheme on ADR reporting, as well as the quantitative HCP survey findings are combined with the qualitative results describing the factors relevant for ADR reporting. This chapter addresses the final objective of this research, which was to generate the evidence required to inform the design of future interventions to improve ADR reporting. In addition, strategies to help with the uptake of these potential interventions was discussed within the context of digital transformation in the healthcare setting.

5.2 Publication 5: Summary

This publication integrated all of the evidence generated from the prior studies in this research to help inform the design of an intervention to improve ADR reporting. It explored the current literature on the magnitude of ADR under-reporting and analysed the perspectives and barriers faced by HCPs in this area. The effectiveness of various types of interventions that have been implemented to improve ADR reporting was also discussed with a focus on identifying the more effective strategies and current gaps. Taking into account the impact of digital transformation in the healthcare setting especially in the area of automation and artificial intelligence, a digital tool would be considered an essential element to facilitate ADR reporting. In addition, the features and rollout of this tool will need to take into account the factors assessed as relevant for ADR reporting as determined by behavioural change frameworks. The intervention should also remove as much 'human element' from the ADR reporting process as possible to overcome current challenges in the continuous and sometimes costly educational and reminder campaigns, which would be required to maintain any increase in ADR reporting rates post implementation of the intervention. Moving into the future, complete automation and adoption of artificial intelligence in the screening and reporting of ADRs of interest for new medicines should be the gold standard.(122) Investment into creating this wholistic approach is necessary to address the significant ADR under-reporting rates and can be adopted into other pharmacovigilance activities such as signal detection.

5.2.1 Publication 5: A new paradigm in adverse drug reaction reporting: informing the design of an intervention to improve reporting in the next decade

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A new paradigm in adverse drug reaction reporting: consolidating the evidence for an intervention to improve reporting

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Abstract

Introduction: Adverse drug reaction (ADR) under-reporting is highly prevalent internationally and interventions created to address this problem have only been temporarily successful. This review aims to investigate how to leverage digital applications and automation across the healthcare industry to improve the quantity and quality of ADR reporting.

Areas covered: This review investigated the significance of ADR under-reporting, the barriers of reporting ADRs, and the magnitude of success of various interventions to improve ADR reporting by searching the EMBASE and MEDLINE databases to include studies published between January 2000 and February 2022. This data was integrated with a view to describe a future ADR reporting framework.

Expert opinion: Digital transformation has presented a significant opportunity with vast quantities of patient health data becoming available in electronic formats. The application of artificial intelligence to detect ADRs and then using automation to report these directly to regulatory agencies without human input would significantly enhance the quantity and quality of ADR reporting. Emphasis should be placed on ADRs identified for newly approved or black triangle medicines. Future studies are needed to measure the success of this ADR reporting framework in reducing the time taken to identify new safety issues and improving patient outcomes.

Keywords: pharmacovigilance, digital, drug safety, automation

Article Highlights

- Despite the implementation of various interventions, ADR under-reporting remains highly prevalent delaying the identification of new safety signals.
- The most common factors associated with ADR reporting that are mapped to a behavioural framework include knowledge, motivational factors/goals, and environmental constraints.
- Interventions to improve ADR reporting have only been modestly effective as their designs were not informed by behavioural change frameworks that would specifically address the identified barriers.
- A comprehensive multifaceted approach leveraging artificial intelligence to identify ADRs from health databases and applying automation to report these to regulatory agencies should be the gold standard of ADR reporting in the future.
- Significant challenges remain in the adoption of automation and artificial intelligence in ADR reporting due to the infancy of technology in this area and future research should be directed to help inform the design and features of

1. Introduction

Understanding the complete safety profile for medicines is essential to support the quality use of medicines. However, this is extremely difficult to achieve given that medicines are approved on the market based on clinical trial data alone. The high cost of operating interventional clinical trials imposes limits on study duration restricting the ability to collect long-term adverse drug reactions (1). Furthermore, clinical trials are limited to a certain patient sample size with strict inclusion and exclusion criteria. As such, the patient population included in clinical trials are not representative of real-world patients who may be more susceptible to ADRs such as those who are elderly, have multiple concurrent illnesses, pregnant women, children, or those with complex health histories (2).

It is during the post-approval phase of a medicines' lifecycle that its' safety profile is better characterised as more patients are exposed to the medicine. However, the collection and reporting of safety information during this time period is voluntary in contrast to the mandatory reporting of safety information during the course of a clinical trial (3). ADR reporting rates are extremely low during this post-approval phase when rarer, unexpected ADRs start to occur, some of which may adversely impact the benefit risk profile of a medicine. This causes significant delays in regulatory action taken to remove medicines from the market due to new safety concerns as shown by a systematic review which concluded that the median time taken to revoke a medicine registration due to safety issues was 10 years after launch (4). Examples include natalizumab, which was associated with progressive multifocal leukoencephalopathy (PML), rosiglitazone and rofecoxib which were associated with significantly increased cardiovascular risk, and diethylstiloestrol which was associated with increased risks of stillbirth, neonatal death, infertility and vaginal adenocarcinoma (5-8). These safety issues were all identified post approval of these products and have resulted in the product either being removed from the market or having significant restrictions imposed upon the label such as the Risk Evaluation and Mitigation Strategies (REMS) in the USA or a black box warning in Australia.

Delays in regulatory action expose patients to unnecessary risk, and in addition to causing harm to the patient, lead to excessive burden on the overall healthcare system. It is estimated that ADRs are the primary cause of up to 19% of hospital admissions internationally (9). The overall cost of a single ADR in an inpatient setting is estimated to cost $2,262 USD, however this increases to $19,685 if the patient is admitted to the intensive care unit (10, 11). The costs of preventable ADRs were found to be significant with a 2012 Canadian study showing that $159 million out of a total of $348 million CAD resulted from the management of preventable ADRs (12). ADR costs not only include the expenditures of the actual hospital stay, but costs associated with additional clinical investigations, staff wages, disposable goods and medications, missed days from work, and morbidity such as stress caused by ADRs (13). The cost of ADRs has also been shown to be significantly higher than the cost of the illness alone. They can trigger a prescribing cascade where new medications are prescribed to treat conditions that may or may not be recognised as an ADR to another medicine (14).

The 1995 Quality in Australian Health Care study estimated that 43% of adverse drug events (ADEs) were predictable or potentially preventable (15). Another Australian study showed that 61% of ADRs resulting in hospitalisations were preventable (16). These high preventability proportions demonstrate the need to take further action to reduce the burden of ADRs. The prevention of ADRs is also the most important objective of pharmacovigilance and good practices can significantly reduce the financial costs of national healthcare systems around the world.

Digital initiatives have been introduced in the last decade to transform the management of patients in healthcare setting. Examples of these include the adoption of eMedical Records, eMedication Management, ePrescribing, digital health records, and mobile apps (17-20). Natural language processing and artificial intelligence in healthcare have also been introduced in areas of clinical decision support, information management, data analysis of electronic health records for diagnosis, as well as the provision of personalised healthcare (21, 22). These measures can support improvements in adherence to guidelines for healthcare professionals, increase cost savings, enhance patient satisfaction, and promote efficiency across hospital processes. Therefore, there exists an opportunity to leverage digital technologies to improve the process and experience of reporting ADRs.

This review integrates the literature on the significance and magnitude of ADR under-reporting with the perspectives and barriers faced by healthcare professionals and consumers in this area to generate evidence-based recommendations to improve ADR reporting.

2. Methods

This review consolidates the findings from three key areas in the ADR literature; (1) the extent of ADR under-reporting, (2) the barriers faced by healthcare professionals and consumers to ADR reporting and (3) the effectiveness of interventions that have been implemented to improve ADR reporting. Firstly, studies that reported a quantitative estimate of ADR under-reporting in both the primary care and hospital settings identified in a 2006 systematic review were included in this review (23). We also included any literature that were published post this review using the same search strategy reported in the systematic review of EMBASE and MEDLINE databases between January 2000 to February 2022 (Table 1). Secondly, the literature around perceptions and barriers towards ADR reporting for consumers and healthcare professionals were reviewed by analysing studies that were included in previous systematic reviews (24, 25). We also included studies published post these reviews using the same search strategy in EMBASE and MEDLINE databases between January 2000 to February 2022 (Table 2 and 3). Then, the effectiveness of various types of interventions that have been implemented to improve ADR reporting was presented (26-28). (Figure 1) Finally, we integrated the evidence and investigated possible designs of a future digital initiative informed by evidence based behavioural science, and how these may be complemented with existing interventions as part of a multifaceted approach to improve ADR reporting.

3. Significance of ADR under-reporting

3.1 Problems with a spontaneous reporting system

Regulatory agencies around the world rely on a spontaneous reporting system for post-marketing surveillance activities due to its feasibility, convenience and low cost (29). This system also benefits from the fact that safety information is collected from real-life clinical situations as opposed to clinical trials where vulnerable patients are often excluded and trial duration is limited. However, a recent systematic review reported that the median rate of under-reporting was 94%(23). Not only is the under-reporting of ADRs a significant healthcare problem, the spontaneously reported ADEs are usually of very poor quality with lots of missing information (30, 31). There are also limitations in calculating ADE incidence rates from spontaneous reports with only frequencies of ADR occurrences available, but information on the population exposed to the drug are lacking (32). Another issue with the spontaneous reporting system is the inability to categorically determine a causal relationship between the suspect drug and the ADR as case reports can involve patients with multiple concurrent disease states and taking multiple concomitant medications (29). Finally, there are always inherent reporting biases in a spontaneous reporting system where consumers and HCPs are more likely to report ADRs that have been mentioned in the media or published in the literature. Well known or trivial ADRs are less likely to be reported and medicines that have been on the market for a long time attracts less ADR reports compared to medicines that are newly registered. This may create false safety signals for existing medicines or spikes of ADRs associated with newer medicines (32).

3.2 ADR under-reporting in the primary care setting

There have been several studies that measured the magnitude of ADR under-reporting in the primary care setting. These studies have primarily adopted the methodology of using intensive monitoring over a pre-defined period to identify the quantity of ADRs and whether they have been reported to the national regulator through the spontaneous reporting system. The five studies included in this analysis showed that under-reporting rates ranged from 34% to >99% with a median under-reporting rate of 91% (Table 1) (33-37). These results are very similar to an earlier systematic review, which showed that the median ADR under-reporting rate in primary care setting was 95% (23). However, it is important to note that a key limitation of both reviews is that the included periods of intensive monitoring are limited and only provides a cross-sectional snapshot rather than an adequate representation of the entire population.

3.3 ADR under-reporting in the hospital setting

There were 7 studies included in this review that investigated the quantity of ADR under-reporting in the hospital setting (Table 1) (16, 38-43). The results showed that the median rate of under-reporting was 96% ranging from 72% to 100%. This was similar to a previous systematic review, which also showed that the median ADR under-reporting rate was 96% for hospital physicians (23). It is important to highlight that ADRs leading to hospitalisations are serious in nature and would more likely be reported. On the other hand, the majority of ADRs occurring in primary care includes non-serious and common ADRs that are unlikely to

be reported. However, the median under-reporting rate in the hospital setting appeared to be slightly higher than the primary care setting. This may be explained by the fact that hospital doctors may be more focused on the clinical care of patients that require immediate attention in the hospital setting. Therefore, they would not have as much time to undertake administrative tasks such as documenting and reporting ADRs when compared to doctors practising in the primary care setting.

4. Barriers for healthcare professionals and consumers to report ADRs

4.1 Perspectives and knowledge of HCPs

There have been numerous studies that investigated the reasons for ADR under-reporting and most have been in the form of surveys. A recent study that investigated the knowledge and perspectives of Australian community pharmacists towards ADR reporting showed that knowledge, training, and time are key determinants of ADR reporting (44). In addition, a case control study involving both general practice physicians and hospital physicians showed that motivational themes of diffidence, complacency, insecurity, indifference and ignorance were important determinants of ADR reporting (45). This was reinforced by a systematic review which demonstrated these similar motivational themes as being important factors in ADR reporting (25). Another recent study showed that process complexities and perceived importance of ADR reporting were additional influencing factors (46). Overall, there were 18 studies that identified 8 themes that influenced ADR reporting for healthcare professionals (Table 2) (25, 44-60). The most common theme identified was 'environmental constraints', which was identified as a key determinant of ADR reporting in two thirds of the included studies. This was followed by 'knowledge' and 'training' identified in 61.1% and 44.4% of studies respectively. These themes are consistent with similar studies undertaken to investigate the perspectives of HCPs into the causes of ADRs in patients including medication errors (61).

Some of these determinants were also mapped to behavioural change frameworks as this helps to inform the design of future interventions to improve ADR reporting. For example, the theoretical domains framework, which outlines 14 domain areas that would influence behaviour change, was used to help identify factors that would be essential to instil a mindset shift to improve ADR reporting by healthcare professionals (62). A qualitative study in Iran showed that the 6 key domains that would influence ADR reporting were knowledge, environmental constraints, motivational factors, skills, social influence, and beliefs about consequences. This is reinforced by a more recent study in Australia which showed that the domains of knowledge, environmental constraints, and beliefs about consequences were the key factors that will need to be addressed in any intervention to improve ADR reporting (60).

4.2 Perspectives and knowledge of consumers

There have also been numerous studies that investigated the perspectives and knowledge of consumers towards reporting ADRs (63-79). The factors associated with their reporting behaviours were very different to those of healthcare professionals and there were 6 key

determinants identified. "Confusion/poor awareness" was the most identified factor impacting ADR reporting by consumers and this was reported in 12 out of 17 (70.6%) of included studies. The seriousness of the ADR and whether it resolved was also a significant factor in determining whether a consumer reported the ADR as this was identified in 8 out of 17 (47.1%) of the studies. Other key determinants for ADR reporting for consumers include whether they receive feedback or acknowledgement to their ADR report (5 out of 17, 29.4%), any form of HCP enablement (e.g. physician asks a patient to report) (5 out of 17, 29.4%), and their perceived importance in enhancing ADR surveillance (5 out of 17, 29.4%). (Table 3)

5. Interventions to improve ADR reporting

5.1 Education

A variety of educational strategies have been implemented to improve ADR reporting and these have been primarily in the form of educational workshops, face to face visits, presentations, eLearning modules, or provision of general information through pamphlets (80-87). As a single intervention, these strategies have been shown to be modestly effective in improving ADR reporting with a median point estimate of 3.44-fold (95%CI 2.31 – 8.00) increase in reporting rates for the 8 included studies in this review.

5.2 Reminders

Using reminders was also an intervention that has been investigated to improve ADR reporting. There were 4 studies included in this review and these included reminders in the form of a letter, emails, monthly newsletter, and a quarterly drug safety bulletin (88-91). As a sole intervention, using reminders to improve ADR reporting was not very effective and resulted in a median point estimate of 1.40-fold (95% CI 1.15 – 1.51) increase. It was important to highlight that one of the studies, which utilized reminder emails, did not result in any improvement in the quantity or quality of ADR reporting (91).

5.3 Electronic tool

In the last decade, there has been an increased uptake of information technology including digital tools to improve ADR reporting. There were 5 studies identified in this review with all electronic interventions being implemented in a hospital setting (92-96). The type of interventions included an automated tool that reported ADRs directly from electronic health records, inclusion of a hyperlink to an online ADR reporting form within electronic patient records, and a web based adverse drug event manager reporting tool. The effectiveness of these interventions was modest resulting in a median point estimate of 3.60-fold (95% CI 2.50 – 5.40) increase in ADR reporting.

5.4 Multifaceted vs single interventions

There are 15 studies included in this review that investigated the impact of multifaceted interventions on ADR reporting (97-111). These include combinations of two or more of the following strategies: educational initiatives (face to face or eLearning), economic incentives, electronic tools, reminders, providing feedback, telephone interviews, improving accessibility to ADR reporting forms, and/or provision of continuing medical education credits. These multifaceted interventions resulted in a median point estimate of 5.40-fold (95%CI 3.22 – 10.00) increase in ADR reporting rates versus an overall 2.73-fold (95%CI 2.00 – 3.97) increase for single interventions (P=0.038, Mann-Whitney U test). (Figure 1)

6. Future strategies to improve ADR reporting (integration of the evidence)

There is tremendous potential to leverage recent developments in digital technologies to improve ADR reporting. Traditional methods such as education, reminders, feedback etc. have only been temporarily effective in improving ADR reporting rates with the effect diminishing substantially within 6-12 months post the intervention (86, 108, 109). Even those implemented by national regulators did not have any significant impact on ADR reporting (112). Furthermore, these interventions will need to be continuously implemented to maintain the improved ADR reporting rates, which may not be feasible given the high cost of time and resource in maintaining education, reminders etc. As such, digital initiatives are an attractive option to increase ADR reporting rates for the long-term.

These digital technologies are already in existence in the areas of automated detection of ADRs, screening large datasets for ADRs, as well as signal detection activities to identify new ADRs (113-115). Furthermore, tremendous advancements have been made in the area of artificial intelligence and machine learning in the detection of ADRs, with one study showing an 80% success rate in automated ADR detection in the hospital setting (116). However, the detection of ADRs is a passive process, which is very different to the active process involved in reporting ADRs that is also dependent on behaviour change from reporters. Therefore, the implementation of a digital tool as the sole intervention may not be adequate as shown by the modest improvement in our identified studies. In addition, multifaceted strategies were also found to be significantly more effective than single approaches. A comprehensive approach which addresses both the uptake and utilisation of the digital reporting tool in addition to automation is required to be successful in improving the quality and quantity of ADR reporting.

6.1 Mobile app

The European Union has recently piloted a digital mobile application to support ADR reporting in the United Kingdom, Croatia and the Netherlands. This was based on previous experience in this area in the United States, which found mobile apps were promising in engaging consumers and healthcare professionals in medication safety reporting (117). However, it is important to also consider potential barriers in the uptake of this digital technology and concerns around data privacy, secure storage, and potential misuse of personal health information are key issues that need to be addressed (118). A qualitative study exploring the factors associated with usage of a mobile app to report ADRs showed that the characteristics within the app such as functionality, language, ease of use, layout,

and operating system were significant influencers (119). In addition, the respondents emphasised the importance of two-way communication including a feedback mechanism within the app to further enhance the uptake of the mobile app. Therefore, the final version of the app included patient friendly language with a simple layout, allowed reporters to save and access the ADR reports they have submitted, and provided data/statistics on the incidence rates of reported ADRs for medicines. In addition, a safety update function was built into the app so that healthcare professionals and consumers were alerted to new safety issues identified for medicines, and this also served as a reminder for users to report similar ADRs related to the safety issue.

Promotion of the app to consumers and healthcare professionals was also considered essential to enhance awareness of its capability and availability (120). Recommendations were made to ensure that any launch of the mobile app was linked to a publicity strategy on the importance of ADR reporting. Furthermore, continuous publicization of the app over a long period of time was required to enhance uptake and awareness. For example, the yellow card reporting app in the UK was launched in July 2015 to coincide with an educational campaign on the recently introduced black triangle scheme in the European Union. This resulted in the highest number of new user registrations during this period. A second significant surge in new user registrations occurred when the app was promoted on the UK regulatory agency's website. However, this continuous promotion is difficult to maintain and reflects the same challenge as other interventions that need to be continuously applied to maintain improvement in ADR reporting rates. In addition, there was no evidence that the implementation science of behavioural change was applied during the design of the app, which may have further encouraged ADR reporting by users. Finally, the app lacked an automation feature and users were still required to manually enter information to generate an ADR report.

6.2 What does a comprehensive ADR intervention look like?

A current project is underway in Australia to incorporate an electronic ADR reporting tool within the hospital's eMedical Records to facilitate reporting by healthcare professionals. Features of this tool include automation, when ADR information is recorded into a patient's eMedical record,the patient's demographics, medical history, suspect medication, time of occurrence, ADR information, and the reporter's profession is then automatically extracted into an ADR report ready for submission. This automation within the ADR reporting tooladdresses environmental constraints such as lack of time and resources.

In addition, it is important to consider additional complementary interventions that address the 6 domains of knowledge, motivational factors, skills, beliefs about consequences, social influence and environmental constraints within the theoretical domains framework identified from previous research (50, 60). Based on the suggested interventions within the behavioural change wheel (121), an electronic educational module is being developed to provide the knowledge, enhance social influence, and motivation to report ADRs, whilst a hospital protocol is being generated to address the skills gap and beliefs about consequences. The launch of this digital tool can be timed with the recent implementation of the black triangle scheme in Australia, which was shown to be only modestly successful in improving the quantity and quality of ADR reporting (30). Overall, this multifaceted

approach that has been designed based on a behavioural change framework addresses the shortcomings of previous interventions and future research should be undertaken to investigate the magnitude of its success in improving ADR reporting and more importantly, whether this can be maintained over an extended period of time.

7. Conclusion

ADR under-reporting remains a significant problem across healthcare systems worldwide with multiple studies showing that the magnitude of under-reporting was consistently over 90% across both the primary care and hospital settings. The factors associated with ADR reporting are well characterised by a wealth of literature clearly establishing the facilitators and barriers, however the vast majority of studies have not mapped these to a behavioural change framework, which is essential to inform the design of an effective intervention. As such, the majority of interventions implemented to improve ADR reporting were only modestly successful and only for a short duration with reporting rates returning to pre-intervention levels within 6-12 months post implementation. Future interventions should incorporate digital technologies leveraging automation and artificial intelligence in conjunction with additional strategies that specifically address the key factors, which are mapped to a behavioural change framework as part of a comprehensive multifaceted approach to improve the quantity and quality of ADR reporting.

8. Expert opinion

Encouragingly, the chronic under-reporting of ADRs is getting much needed attention as evident from increasing literature in this area. Several barriers remain though emerging technologies and digital transformation over the last few years presents a tremendous opportunity in the new era of healthcare management. It is evident that a vast quantity of personal health data exists digitally across multiple channels in health insurance databases, reimbursement datasets, eHealth records etc. and this presents a tremendous opportunity for the adoption of automation and artificial intelligence to analyse and extract ADR data. Existing technologies already exist in this area for the detection of ADRs, and the future lies in taking the next step of reporting this information to health regulators at an individual level. Emphasis should be placed on newly approved medicines and black triangle medicines where their safety profiles have not yet been fully characterised. In addition, ADRs that are new and/or unexpected should be prioritised for reporting. Therefore, an all-in-one digital tool that automatically identifies and reports specific ADRs for selected medicines is the gold standard to aspire towards for future ADR reporting. This would significantly enhance real world outcomes of patient safety as understanding the safety profile of new medicines leads to more informed prescribing and considered use of these medicines in the right patient populations. This would also reduce the extent and severity of ADRs occurring in patients if they are well known and can be adequately managed.

The current mobile app developed in the EU is an attractive tool to facilitate ADR reporting. The value of this app can be further enhanced by supporting reporting of quality issues for medicines to help identify manufacturing faults and/or batch related issues. This could be complemented by a camera function where images of quality faults can be uploaded in real

time to allow for faster investigation and evaluation. Enhancements can also be made to alert app users of emerging safety issues so that those involved in the management of patients taking these medicines can be closely monitored. This would also encourage further reporting of similar ADRs related to the safety issue allowing for real-time application of pharmacovigilance. The outputs from the 2018 EU SCOPE project would further enhance the adoption of this digital tool with e-learning modules, IT systems, and reporting tools supporting the overall ADR reporting process (122).

The key challenge to the successful utilisation of any digital technology in ADR reporting lies in strategies that drive a substantial uptake. This is an area where the behavioural framework of implementation science comes to the fore. However, it is extremely difficult to identify the full range of factors that impact ADR reporting. This information has been traditionally collected through surveys, which are collected from a limited sample of respondents within a specific cross-sectional timepoint. These studies are also inherently influenced by selection bias where respondents who are motivated and/or interested in ADR reporting are more likely to participate, and therefore their perspectives may not be representative of the entire cohort of healthcare professionals and consumers, especially those who lack such motivation. In addition, the different work environments across multiple hospitals and health networks pose different barriers for healthcare professionals, and therefore it would be difficult to implement a solution that addresses the wide variety of factors. Continuous promotion of the digital tool over long periods of time is also a significant barrier. Materials that are developed such as infographics must be targeted and clear for all to understand on public sources.

To overcome these limitations, it would be prudent to limit any 'human factor' in the process of ADR reporting with more consideration given to automation and artificial intelligence in the reporting process. However, there are still significant challenges in the technological implementation of these automation tools given the infancy of expertise in this area. Currently, no large scale automated digital tool exists to assist the screening of large healthcare datasets for ADRs and then reporting those to regulatory agencies. Furthermore, automation may not improve the quality of ADR information and human intervention is still required in the evaluation of ADR reports. This area would be an exciting focus for future research to gradually build the evidence for finding the right balance in adopting technology into the ADR reporting process.

It is unlikely that ADR reporting rates will evolve significantly in the next 5 years as the research in the last 2 decades have focused on traditional interventions that are entirely driven by human actions. We are now at the stage where we are starting to incorporate automation and digital initiatives to facilitate ADR reporting along with human input that is based on evidence based behavioural change frameworks. A proposed framework for ADR reporting describing the end-to-end process is shown in Figure 2. It would be interesting to measure the magnitude of improvement in the quality and quantity of ADR reporting for these digital initiatives compared to the traditional methods. Furthermore, it is important to investigate the impact of increased ADR reporting on earlier identification of new safety issues and improvements in patient health outcomes as measures of success. Moving into the future, full automation and utilisation of artificial intelligence in the screening and reporting of ADRs of interest for selected medicines should be adopted in conjunction with

human reporting that is supported by digital technologies. Investment in working towards this wholistic approach is necessary to address the significant under-reporting rates, which have not shown any significant improvement over the last few decades.

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Table 1: Estimate of ADR under-reporting

Study, year	Country	Study duration	Sample size and setting	No. of ADRs reported to national pharmacovigilance centre	No. of ADRs detected	Rate of under-reporting (%)
Lewis M et al, 2001	Germany	3 months	50 GP practices	894 per 100 000 patients	1389 per 100 000 patients	36
Lacoste-Roussillon et al, 2001	France	5 days	254 GPs	328	6236	95
Heely et al, 2001	United Kingdom	2 years	Not reported	4211	376	91
Gonzalez-Rubio et al, 2011	Spain	12 months	6 urban health centres	543	357	34
Grange et al, 2012	France	12 months	Not reported	388,502	759	>99
Pouyanne et al, 2000	France	14 days	33 hospitals	6371	134,159	95
Backstrom et al, 2004	Sweden	5 years	5 hospitals	15	107	86
Mittman et al, 2004	Canada	5 years	22 hospitals	25	674	96
Rydberg et al, 2016	Sweden	1 year	1 hospital	2	146	99
Dittrich et al, 2020	Netherlands	1 month	1 hospital	0	132	100
Khalili et al, 2021	Iran	1 year	2 hospitals	67 per 100,000 admissions	237 per 100,000 admissions	72
Li et al, 2021	Australia	3 months	1 hospital	1	496	99
Median under-reporting rate for hospital setting					**96%** (IQR 90.5-99%)	
Median under-reporting rate for general practice setting					**91%** (IQR 36-95%)	
Median under-reporting overall					**95%** (IQR 86-99%)	

GP = General Practitioners; IQR = interquartile range

Table 2 Domains of ADR reporting by healthcare professionals

		Theme/domains of ADR reporting							
Study, year	**Setting**	**Knowledge[1]**	**Training**	**Motivation factors[1,2]**	**Skills[1]**	**Perceived importance**	**Environmental constraints[1,3]**	**Social influence[1]**	**Beliefs about consequences[1]**
Herdeiro et al, 2005 Portugal(45)	Primary care and hospital			X					
Lopez-Gonzalez et al, 2009 (systematic review) (25)	Primary care and hospital			X		X	X		
Santosh et al, 2013 Nepal(48)	Primary care and hospital	X	X				X	X	
Hadi et al, 2013 Malaysia(49)	Hospital	X	X				X		
Mirbaha et al, 2015 Iran(50)	Hospital	X		X	X		X	X	X
Terblanche et al, 2017 South Africa(51)	Hospital		X	X		X	X		
Li et al, 2018 Australia(44)	Primary care	X	X		X		X		
Moinuddin et al, 2018 Saudi Arabia(52)	Hospital		X			X	X		X
Nisa et al, 2018 Pakistan(53)	Hospital	X					X		X
Al Shammari et al, 2018 Saudi	Hospital	X					X	X	

Arabia(54)									
Kasser et al, 2019 Ethiopia(55)	Primary care	X							
Hughes et al, 2019 United Kingdom(56)	Primary care			X			X		
Le et al, 2019 Vietnam(57)	Hospital	X	X				X		
Guner et al, 2019 Turkey(58)	Primary care	X				X			
Adegbuyi et al, 2020 Nigeria(59)	Primary care and hospital	X	X			X			
Haines et al, 2020 South Africa(47)	Primary care	X	X						
Gahr et al, 2021 Germany(46)	Primary care					X	X		
Li et al, 2021 Australia(60)	Hospital	X					X		X
Overall (%)		**66.7**	**44.4**	**27.8**	**11.1**	**33.3**	**72.2**	**16.7**	**22.2**

[1] Knowledge, motivational factors, skills, environmental constraints, social influence, beliefs about consequences are domains of the Theoretical Domains Framework (TDF)
[2] includes diffidence, indifference, apathy
[3] includes barriers such as process difficulties, lack of time

Table 3: Domains of ADR reporting by consumers

		Theme/domains of ADR reporting					
Study, year	Country	Confusion and poor awareness	Process related	ADR seriousness and/or resolution	Perceived importance	HCP enablement	Feedback receipt
Bukirwa et al, 2008(63)	Uganda			X			
Braun et al, 2010(64)	Australia	X		X			
Van Hunsel et al, 2010(65)	Netherlands			X	X	X	X
Avery et al, 2011(66)	United Kingdom	X		X	X	X	X
Krska et al, 2011(67)	United Kingdom	X					
Lorimer et al, 2012(68)	United Kingdom	X	X	X			
Salvo et al, 2013(69)	Italy	X					
Arnott et al, 2013(70)	United Kingdom	X			X	X	X
Harmark et al, 2013(71)	Netherlands				X	X	X
Robertson et al, 2013(72)	Australia	X		X			
Elkalmi et al, 2014(73)	Malaysia	X					
Jha et al, 2014(74)	Nepal	X	X				
Parella et al, 2014(75)	Australia	X					
Rolfes et al, 2014(76)	Netherlands				X		

Matos et al, 2015(77)	Portugal	X		X			X
Sales et al, 2017(78)	Saudi Arabia	X	X				
Aslani et al, 2018(79)	Australia			X		X	
Overall (%)		**70.6**	**17.6**	**47.1**	**29.4**	**29.4**	**29.4**

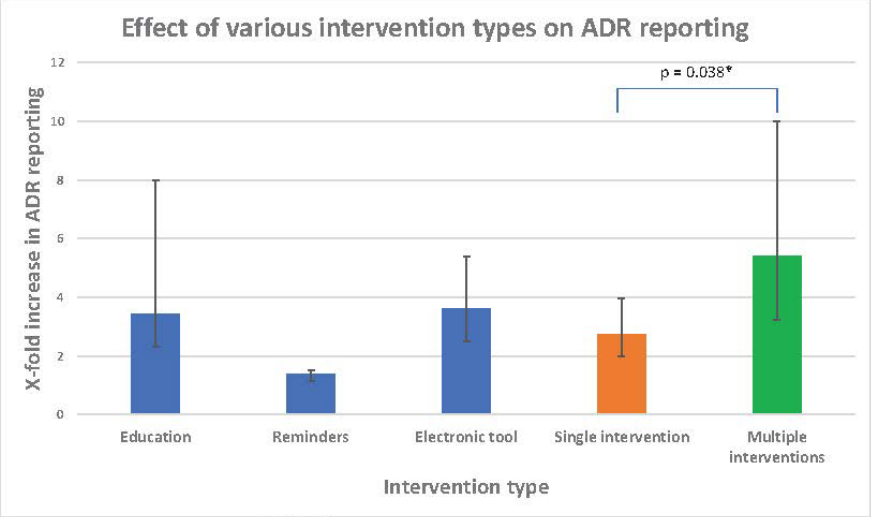
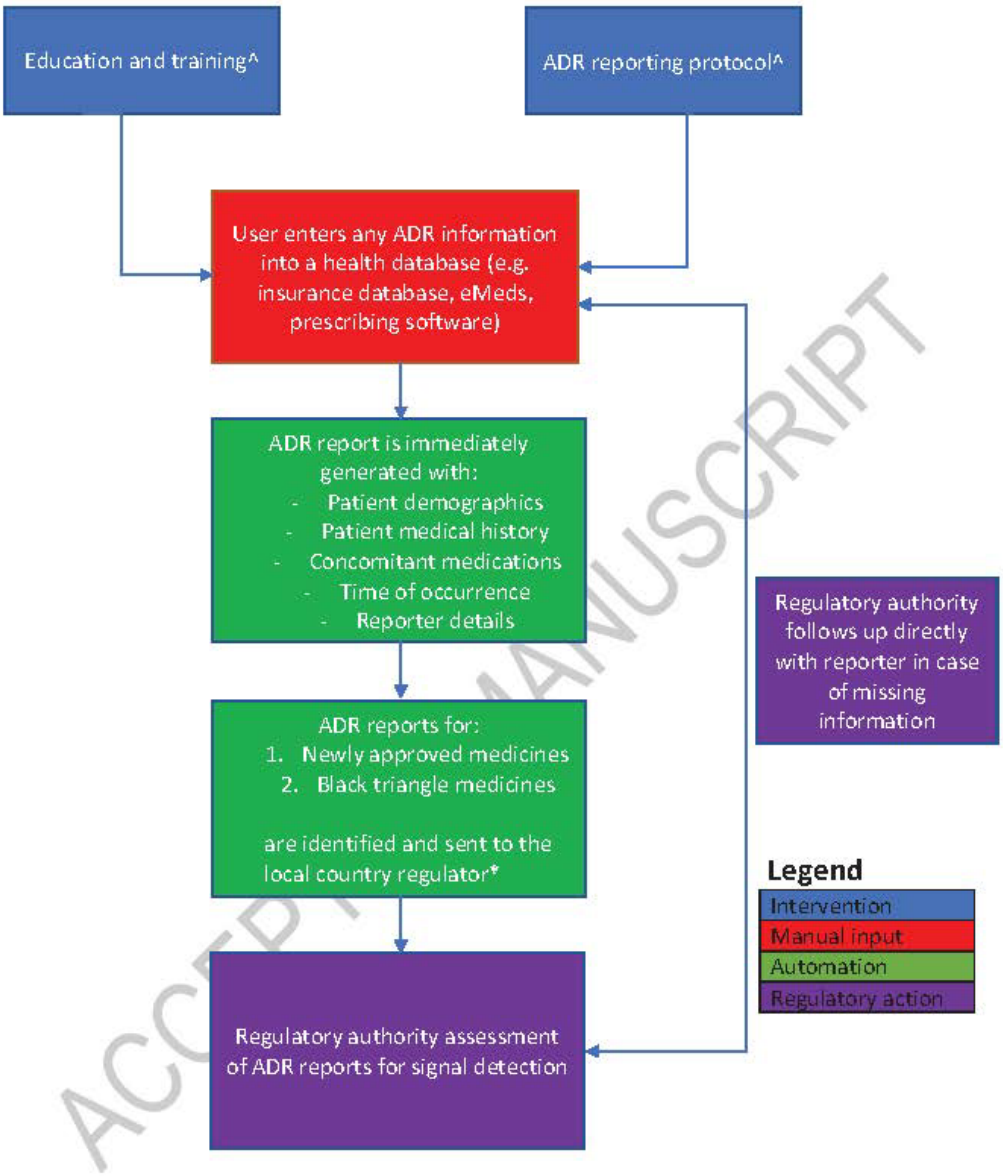


Figure 1: Comparison of the effect of different types of interventions to improve ADR reporting
*Mann Whitney U test used to compare multiple interventions vs single intervention.
Results reported as median point estimate. Error bars denote 95% confidence interval



^Education and training are mandatory as part of onboarding for all new healthcare employees. ADR reporting protocol should be mandatory for all healthcare settings. These should address the domains of knowledge and social influence as well as creating the capability, opportunity and motivation to report ADRs.
*Regulatory authority may request additional ADR reports of special interest to be built into the automation model

Figure 2: A framework for leveraging automation as part of ADR reporting

5.3 Summary

In this chapter, the integration of the quantitative and qualitative data identified that a digital tool incorporating automation will be required to address the significant ADR under-reporting, which can be as high as over 99%. While current interventions have been somewhat effective in improving the quantity and quality of ADR reporting, these have been only temporary in nature and their continued success depends significantly on ongoing activities that require human interventions (e.g. reminders, education etc.). The qualitative results identified several factors that are relevant to ADR reporting, and when mapped to the TDF provides a basis for future intervention development. In conclusion, a comprehensive multifaceted approach leveraging the features discussed above is required to improve the quantity and quality of ADR reporting. The final chapter below presents the key findings of this research, including recommendations for clinical practice, future research directions, as well as the key strengths and limitations of this project.

6 Key findings, recommendations, and future research

6.1 Introduction

This final chapter presents the key findings generated from this mixed methods research around the topic of improving the reporting of ADRs by HCPs in Australia. It also presents the recommendations for how the evidence generated from this research can be applied to change clinical practice in the area of ADR reporting. Finally, the strengths and limitations of this research are discussed, along with suggestions for future research directions that may further enhance the process for ADR reporting.

All research objectives have been met as this research has:

1. Identified the prevalence of ADR related hospitalisations and their characteristics.
2. Identified the proportion of ADR related hospitalisations that are reported to the hospital safety committee and/or the Australian regulator.
3. Quantified the success of the regulatory initiative 'black triangle scheme' on improving the quantity and quality of ADR reporting and identified further opportunities to enhance the effectiveness of this intervention.
4. Explored and identified the perspectives, facilitators and barriers of HCPs working in the hospital environment towards the reporting of ADRs.
5. Generated the evidence required to inform the design of a strategy to improve the quality and quantity of ADR reporting in Australia.

6.2 Key findings

There are five key findings generated from this research and these are described below.

6.2.1 Key Finding 1 – Current interventions for improving ADR reporting are only temporarily successful

Our systematic review of the literature showed that there were many initiatives implemented to improve ADR reporting. The majority of these interventions were

traditional in nature such as a providing education sessions, reminders, availability of reporting forms, or providing an incentive. The results showed that while these interventions were effective at improving ADR reporting rates, these were only temporary in nature with reporting rates returning to pre-intervention levels shortly after the conclusion of the intervention. Therefore, there is a clear need for interventions that will deliver more long-term improvements in ADR reporting. In addition, digital transformation in the healthcare setting in the areas of eMEDs, ePrescribing, and eMedical Records provides an opportunity to leverage these technologies to support the development of a digital tool that enables ADR reporting. Our systematic review identified some exploratory evidence of the effectiveness of these digital tools implemented overseas. These initiatives were found to be more effective than traditional interventions, however the quality of evidence to support this is poor to moderate. Therefore, generating the evidence to support the adoption of new and innovative tools to enhance ADR reporting is required and this research has contributed to addressing this evidence gap.

6.2.2 Key finding 2 – There is significant under-reporting of ADR related hospitalisations to the Australian regulator, and these involve a significant proportion of medicines that cause preventable ADRs

Our research showed that ADR related hospitalisations represented approximately 9% of all hospitalisations, with older patients and those taking a higher number of medicines more likely to experience an ADR related hospitalisation. Patients admitted for ADR related reasons also had a longer length of stay adding to higher economic costs in their management. Medicines affecting the nervous system were responsible for the highest proportion of these ADR related hospitalisations and they were also more likely to cause preventable ADRs. Over 99% of the identified ADR related hospitalisations were not reported to the national regulator highlighting the significant magnitude of ADR under-reporting in Australia. This key finding underpinned additional research into understanding the specific factors associated with ADR reporting by HCPs in a hospital setting. Understanding these factors is

critical to help inform the design of an intervention to improve the quantity and quality of ADR reporting.

6.2.3 Key finding 3 – Additional interventions to improve the quantity and quality of ADR reporting are needed despite regulatory interventions such as the black triangle scheme

The introduction of the black triangle scheme in Australia was strongly promoted by the TGA to increase awareness around the importance of ADR reporting and to encourage both patient and HCP reporting of ADRs. This promotional campaign was highly successful as it resulted in a 100-fold increase in visits to the TGA black triangle website. Our research showed that while there was an increase in the quantity of ADR reporting post-intervention, this was not clinically significant. Similarly, while the quality of ADR reporting improved post-intervention, the proportion of high-quality reports overall was low. The vast majority of ADR reports came from the pharmaceutical industry highlighting a need to improve the quantity of reporting from HCPs. From these results, it is clear that additional strategies are required to complement the black triangle scheme as part of a multifaceted approach to improve the quantity and quality of ADR reporting in Australia.

6.2.4 Key finding 4 – Improving HCP knowledge about ADR reporting, creating a better environment/providing resources to encourage ADR reporting, and changing HCP beliefs about ADR reporting should be key components of any future intervention

To understand the specific factors associated with ADR reporting, we deployed a mixed methods survey to hospital-based HCPs. These factors were then mapped to a behavioural change framework, the TDF, to help inform the design of future interventions to improve ADR reporting. The quantitative results showed that HCPs

who know how to report ADRs and those who encounter ADRs as part of their clinical practice are more likely to report them. Qualitative results identified three categories associated with ADR reporting namely modifying the ADR reporting process, enabling clinicians to report ADRs, and creating a positive ADR reporting culture. After integrating the quantitative and qualitative results, they were mapped to three domains within the TDF: knowledge, beliefs about consequences, and environment context/resource. Therefore, these areas should form the key considerations in the design of future interventions to improve ADR reporting.

6.2.5 Key finding 5 – Deploying automation within a digital tool as part of a multifaceted approach will help improve the quality and quantity of ADR reporting in Australia

After integrating all the evidence generated from this research, it was found that digital technologies leveraging automation and artificial intelligence should be deployed to facilitate HCP reporting of ADRs. Digital tools should be incorporated with existing electronic health datasets so that the appropriate information (e.g. patient demographics, concomitant medications, medical history etc.) can be retrieved and automatically populated into an ADR report. In addition, the rollout of the digital tool should be complemented by additional interventions that address the three domains within the TDF that were identified as part of the mixed methods survey. Examples may include implementing mandatory ADR reporting educational sessions that address the importance of ADR reporting, the ADR reporting process, and HCP beliefs about the consequence of ADR reporting. This multifaceted approach is essential for improving the quantity and quality of ADR reporting in a longer-term capacity.

6.3 Recommendations for clinical practice

Based on the key findings discussed above, the following five recommendations for clinical practice are suggested. These are as follows:

1. Mandate an educational and training module on ADR reporting for all new hospital-based HCPs and graduates with annual refresher training thereafter

This educational and training module should be delivered in conjunction with other mandatory onboarding training modules such as hand hygiene, personal protective equipment use, handling cytotoxic medications etc. as part of all new starter orientation. The module should cover topics such as the importance of ADR reporting, the process of ADR reporting, and build understanding around the regulatory actions taken/consequences of their ADR report. An annual refresher training should also be delivered to all hospital-based HCPs so they can be updated on the latest information/process for ADR reporting at the specific hospital. Currently, ADR reporting training is mandatory for all employees working in the pharmaceutical industry to comply with TGA pharmacovigilance requirements. It is also recommended that ADR training form part of the undergraduate and postgraduate curriculum of health-related degrees at university, as well as professional bodies that offer CPD accredited training sessions. It is also important that this recommendation is not implemented in isolation, but should be part of a multifaceted approach that enables and motivates HCPs to report ADRs.

2. Implement a formal hospital ADR reporting protocol and review process for ADRs at specific timepoints of the patient journey in hospital

It is recommended that all hospitals should have a protocol or standard operating procedure on ADR reporting that employees are trained on. This document should clearly outline the roles and responsibilities, the ADR reporting process workflow, and a process for monitoring compliance with the protocol. In addition, the process should include proactive screening for ADRs in patients at specific timepoints. It is recommended that this take place immediately at the time of patient admission to verify if it is an ADR related hospitalisation, and during patient discharge.

3. Create a digital ADR reporting tool that integrates with existing hospital software such as eMEDs

A digital ADR reporting tool should be created as an add on module that integrates with the existing eMEDs system that records patient medication details. This tool should automatically populate an ADR report when an HCP enters any ADR details into the eMEDs system by pulling out information such as the patient demographics, medical history, concomitant medications etc. and prepare the report ready for submission. This 'one click' approach will save significant time for HCPs to report ADRs and will simplify the process without the need for completing forms. This digital tool has already been developed and deployed at our study site at Blacktown Hospital. Data collection is underway to measure whether the implementation is associated with an increase in the quantity and quality of ADR reporting.

4. Create a dedicated resource within the existing hospital safety and quality committee to focus on ADR reporting

It is recommended that there should be a dedicated person within each hospital who is responsible for the oversight of all aspects of ADR reporting. Responsibilities would include but are not limited to: managing the initial ADR orientation training and the subsequent refresher trainings for HCPs, approving and maintaining the hospital ADR reporting protocol, identifying ways to improve the end-to-end user experience when reporting ADRs within the hospital, and analysing reported ADRs for trends and new safety signals which can bereported to the TGA. Having this dedicated resource will help to create a culture of ADR reporting within the hospital and ensure accountability for all facets of ADR reporting, which will help improve the quantity and quality of ADR reporting.

5. Mandate the reporting of ADRs for black triangle medicines

Black triangle medicines are newly approved medicines in Australia that have been on the market for less than 5 years. As such, the safety profile of these medicines are not well characterised by real world data and therefore require additional post-marketing safety surveillance. Mandatory reporting of ADRs for black triangle medicines will help address this gap by collecting ADR information to help with earlier identification of potential safety issues. This will result in faster regulatory action taken to mitigate these safety risks which

will improve patient safety and the quality use of medicines. It is recommended that when black triangle medicines are added to the hospital formulary or approved in an individual patient use application, they are marked in as such in eMEDs. When HCPs enter any ADR information into eMEDS for these medicines, a pop up should be displayed to alert HCPs that the ADR will need to be reported.

6.4 Study strengths and limitations

There are several important limitations for this research as follows:

1. This was a single centre study and the key factors associated with ADR reporting identified from this research may not be generalisable to other hospitals which may operate with different processes.
2. Our sample size of 133 HCPs was limited and our recruitment was impacted by COVID-19 lockdowns in Australia. Therefore, the results may not be representative of the perspectives and practices of other Australian HCPs in the area of ADR reporting.
3. Social desirability bias is an important limitation as some HCPs may feel guilty for not reporting ADRs and therefore are unlikely to admit this.(123) They may also provide 'socially desirable' responses about their perspectives towards ADR reporting resulting in higher scores in this area. However, the use of anonymisation in the completion of the survey may reduce the impact of this bias.
4. The quantitative analysis of ADR related hospitalisations was undertaken retrospectively for a period of 3 months at a single centre, and this may not be representative of all ADR related hospitalisations in Australia.
5. There is seasonal variability in the reporting of ADRs and limiting the period of analysis to 3 months may have underestimated the magnitude of ADR under-reporting.(124)
6. The time series analysis undertaken to evaluate the impact of the black triangle scheme on ADR reporting was limited to a duration of 24 months. Extending the duration of analysis beyond this time period would allow for a better estimation of

the ADR reporting trends prior to the intervention to better validate the effect size of any improvement in ADR reporting post intervention.

7. Using a time series analysis instead of a randomized controlled methodology makes it difficult to attribute the improvement in ADR reporting solely to the black triangle intervention as it is not possible to exclude other factors that may have influenced reporting rates during this period (e.g. media reports or publications of ADRs in literature)

There are also key strengths of this research described below:

1. The embedded mixed methods approach helped to provide a comprehensive understanding of the key factors associated with ADR reporting by HCPs. A single quantitative or qualitative approach would not be sufficient to achieve the objectives of this research.
2. Using an established behavioural change framework such as the TDF helped to inform an evidence-based intervention to improve ADR reporting, and this intervention is likely to be more successful than other interventions that have not utilised a behavioural change framework.
3. This is the first research undertaken in Australia to address the problem of ADR under-reporting. It has generated the evidence to inform the design of a future intervention for improving ADR reporting and provides evidence-based recommendations on the implementation of this intervention into hospital practice.
4. The survey tool that was deployed in this research was informed by the TDF and previous research undertaken on the topic of ADR reporting by HCPs in Australia. This tool was reviewed and piloted by a panel of experts in the area of ADR reporting.

6.5 Future research directions

This thesis has generated opportunities for further research into the following areas. Firstly, as the evidence has been generated to inform the design of an intervention to improve ADR reporting, an integrative ADR reporting tool should be created and deployed within a

hospital environment in conjunction with a comprehensive educational campaign targeting the three TDF domains as part of a multifaceted approach. The effectiveness of this intervention in improving both the quantity and quality of reporting should be investigated. Information around the type of ADRs reported and for what type of medicines should be captured and analysed. If the intervention is successful, it should be deployed across all hospital networks in NSW.

Secondly, a mixed methods approach can be undertaken to investigate the behavioural factors associated with ADR reporting for HCPs working in the primary care setting (e.g. general practitioners, community pharmacists etc.). A similar digital ADR reporting tool can then be developed and integrated with existing prescribing and/or dispensing software to facilitate the reporting process. The success of this intervention can then be evaluated by measuring the magnitude of any improvement in the quantity and quality of reporting.

Thirdly, research could be undertaken to explore the role of artificial intelligence in the detection of ADRs from large Australian health datasets such as the Pharmaceutical Benefits Scheme (PBS) reimbursement data, Medicare health records, NPS MedicineInsight, and the AIHW dataset. In addition, natural language processing tools can be utilized to data mine ADR information from social media sources. This automation in ADR detection should focus on identifying previously unknown ADRs and be integrated with an existing digital ADR reporting tool so that they are automatically reported to the TGA. The success of this initiative can be measured by investigating the magnitude of any reduction in time taken to identify new ADRs.

6.6 Conclusion

ADR under-reporting is highly prevalent internationally and multiple types of interventions have been implemented to address this problem, but these have only been marginally successful in improving ADR reporting rates over a limited timeframe. This mixed methods research informed by a behavioural change framework has contributed new knowledge to help address ADR under reporting by generating the evidence required to facilitate the design of a multifaceted intervention to improve ADR reporting. Specifically, the findings

suggest that providing education to improve HCP knowledge about the importance and process of ADR reporting, instigating a change in the beliefs about consequences of ADR reporting, and adjusting the allocation of resources to create a positive ADR reporting environment will help to improve ADR reporting. In addition, it is important to leverage the significant uptake of digital initiatives within the healthcare setting to create an electronic ADR reporting tool that features automation and integration with existing health datasets. All of these interventions as part of a multifaceted approach will help to improve the quantity and quality of ADR reporting by HCPs in Australia.

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8 Appendix 1 – Data Collection Form

Data collection form

Location of unit	Emergency ☐	Short Stay ☐	Intensive care ☐
Date of hospitalization		**Reporter**	Physician
	Patient age	**Gender**	**Onset date of adverse reaction**
		Not reporte	
Adverse reaction description			
Cost of managing ADR			
ADR outcome	Completely recovered		
Suspect medicine (generic name)	**Drug start and end date**	**Dosage (Strength)**	**Dosing frequency (How often)**
Concomitant medications (Generic Name)	**Drug start and end date**	**Dosage (Strength)**	**Dosing frequency (How often)**

Relevant medical history

- ☐ Congestive heart failure
- ☐ Myocardial infarction
- ☐ Peripheral vascular disease
- ☐ Transient ischaemic attack
- ☐ Dementia
- ☐ Chronic obstructive pulmonary disease
- ☐ Peptic ulcer disease
- ☐ Connective tissue disorder
- ☐ Diabetes mellitus
- ☐ Liver disease
- ☐ Renal impairment
- ☐ **Hemiplegia**
- ☐ Thyroid disease
- ☐ Leukemia
- ☐ Solid tumour
- ☐ Other:

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9 Appendix 2 – Survey Tool

Demographics

1. Pleases select your profession: (drop down)
   a) Physician
   b) Nurse
   c) Pharmacist

2. How many years have you been registered to practice in Australia? (numerical dropdown)

3. What is your highest level of qualification? (drop down)
   a) Undergraduate
   b) Postgraduate

4. How many hours are you employed to work (on average) at the hospital per week? (numerical dropdown)

Knowledge and skills

5. Can you define an adverse drug reaction? (K)
   a) Yes
   b) No

6. Please provide the definition of an adverse drug reaction (if answer yes to Q5) (K)

7. Does your hospital have a protocol or procedure for reporting adverse drug reactions? (K)
   a) Yes
   b) No
   c) Don't know
8. I know how to report adverse drug reactions within the hospital (S)
   a) Yes
   b) No
9. I know how to report adverse drug reactions to the Therapeutic Goods Administration (S)
   a) Yes
   b) No
10. I have received training on how to report adverse drug reactions (S)
    a) Yes

b) No

11. I am aware of the black triangle scheme that was introduced to Australia in January 2018. (K)
    a) Yes
    b) No
12. Define the black triangle scheme (free text) – skipped if answer 'no' to previous question (K)

13. Are you subscribed to receive safety alerts from the Therapeutic Goods Administration? (R)
    a) Yes
    b) No

ADR reporting practices

14. I have encountered adverse drug reactions in patients as part of my clinical practice
    a) Yes
    b) No

15. I have reported adverse drug reactions
    a) Yes
    b) No

16. If you were to report an ADR, who would you report it to? Tick all that apply (multiple tickbox)
    a) Australian regulator – Therapeutic Goods Administration
    b) Hospital drug safety committee
    c) State and territory health network
    d) Pharmaceutical manufacturer
    e) Other:
    f) Not sure

17. If you were to make an ADR report, what is the maximum time you would be willing to spend to complete and submit this report?

    a) <1 minute
    b) 1-5 minutes
    c) 6-10 minutes
    d) >10 minutes

Perspectives (5 point Likert scale strongly disagree to strongly agree)

18. Reporting adverse drug reactions is important for patient care (G)

19. Reporting adverse drug reactions should be mandatory for healthcare professionals (SI)

20. I have a professional obligation to report adverse drug reactions (SP)

21. The safety profile of medicines is well characterised by the time it is marketed (O)

22. I'm interested in reading about ADRs that are published in the medical literature (SP)

23. I'm more likely to report adverse drug reactions if:

    a) There was an incentive (e.g. monetary, CPD points etc.) (R)
    b) An electronic tool was available that automatically populates ADR information from existing health datasets such as eMEDs (EC)
    c) I am mandated to report and there is a consequence if I don't (BC)
    d) There is a hospital protocol mandating the reporting of adverse drug reactions (EC)
    e) I see that there are other healthcare professionals reporting adverse drug reactions (SI)
    f) There was a reminder alerting me to report adverse drug reactions (M)
    g) It was serious and unexpected (I)
    h) It was for a new medicine (I)
    i) It has a strong causal association with the medicine (I)
    j) There is someone monitoring our ADR reporting (BR)
    k) I receive an acknowledgement from the hospital or the Australian regulator thanking me for my report (R)

24. I don't report adverse drug reactions because:
    a) I don't have the time (EC)
    b) I fear there may be legal repercussions (BC)
    c) There are no results or actions taken based on the adverse drug reactions I report (BC)
    d) I forget to report at the time of the reaction (M)
    e) It was non-serious and expected (I)
    f) I usually don't have enough information to warrant a report (EC)
    g) I don't know how to report (S)
    h) I'm uncertain of the causal relationship (K)
    i) I would rather have it published in the medical literature (G)
    j) I don't know when I am supposed to (I)
    k) It won't make a difference (O)
    l) My colleagues don't (SI)

m) It would cause stress and burnout in my workload (E)
n) I have been encouraged not to (SI)

25. What do you think can be done to increase ADR reporting in hospitals? (free text)

26. What are the most important factors that prevent you from reporting ADRs? (free text)

27. Do you have any further comments?

KEY:

K: knowledge	BC: beliefs about consequences	EC: environmental context
S: skills	R: reinforcement	SI: social influences
SP: social/professional role	I: intentions	E: emotion
B: beliefs about capabilities	G: goals	BR: behavioural regulation
O: optimism	M: memory	

Version 1.0 16 April 2020

10 Appendix 3 – Ethics approval letter 2019/ETH13102

Health
Western Sydney
Local Health District

Research Office File No: **(6265)**

Project ID:	2019/PID14671
Ethics Ref:	2019/ETH13102
Governance Ref:	2019/STE16917

9 March 2020

Dr Ronald Castelino
Department of Pharmacy
Blacktown Hospital

Dear Dr Castelino

LNR Research Project: Retrospective analysis of hospitalisations due to adverse drug reactions (ADRs) related admissions and in-hospital ADRs at Blacktown hospital

Your request to undertake the above protocol as a Low or Negligible Risk (LNR) research project was reviewed by a subcommittee of members of the Scientific Advisory Committee (SAC) and the Human Research Ethics Committee (HREC). We are satisfied that your protocol meets the criteria for an LNR research project and does not require review by the full HREC.

The WSLHD HREC has been accredited by the NSW Ministry of Health as a lead HREC to provide the single ethical and scientific review of proposals to conduct research within the NSW public health system. This lead HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and the *CPMP/ICH Note for Guidance on Good Clinical Practice.*

This proposal meets the requirements of the National Statement and I am pleased to advise that the HREC has granted ethical approval of this LNR research project to be conducted by you at:

- Blacktown Mt Druitt Hospital

The following documentation has been reviewed and approved by the HREC:

- HREA 2019/ETH13102, version 4, dated 10 February 2020
- Protocol, version 3 dated 21 February 2020
- Data Collection Sheet version 2 dated 31 January 2020

Please note the following conditions of approval:

- The chief investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project.

HUMAN RESEARCH ETHICS COMMITTEE

Research Office, Level 2, REN Building
Westmead Hospital, Hawkesbury & Darcy Roads, Westmead NSW 2145
Telephone 02 8890 9007 Facsimile 02 9845 9636
Email: WSLHD-ResearchOffice@health.nsw.gov.au

WESTERN SYDNEY LOCAL HEALTH DISTRICT
ABN 48 702 394 764
WSLHD Office, Westmead Hospital Campus
Institute Road, Westmead NSW 2145
PO Box 533, Wentworthville NSW 2145
Telephone 02 8890 5555

- The chief investigator will immediately report any protocol deviation / violation, together with details of the procedure put in place to ensure the deviation / violation does not recur.
- Proposed amendments to the protocol or conduct of the research which may affect the ethical acceptability of the project, must be provided to the HREC to review via REGIS.
- The HREC must be notified, giving reasons, if the project is discontinued at a site before the expected date of completion.
- The Coordinating Chief Investigator must provide an annual report to the HREC and a final report at completion of the study, in the specified format.
- HREC approval is granted for a period of 5 years contingent upon submission of an annual report via REGIS.
- It should be noted that compliance with the ethical guidelines is entirely the responsibility of the investigators.

You are reminded that this letter constitutes *ethical approval only*. You must not commence this research project until separate authorisation from the Chief Executive or delegate has been obtained.

In all future correspondence concerning this study, please quote Research Office File number ***(6265)***
The HREC wishes you every success in your research.

Yours sincerely

Mrs Patricia Fa
Secretary
WSLHD Human Research Ethics Committee

cc: Research Governance Officer

11 Appendix 4 – Site approval letter 2019/STE16917

Health
Western Sydney
Local Health District

18 March 2020

Dr Ronald Castelino
Department of Pharmacy
Blacktown Mt Druitt Hospital

Dear Dr Castelino

WSLHD Research Office number: 6265
HREC reference number: 2019/ETH13102
SSA reference number: 2019/STE16917
Project title: Retrospective analysis of hospitalisations due to adverse drug reactions (ADRs) related admissions and in-hospital ADRs at Blacktown hospital
Protocol number: Version 3, dated 21 February 2020.

Thank you for submitting an application for site authorisation of this project. I am pleased to inform you that site authorisation has been granted for this study to take place at the following site:

- Blacktown Mt Druitt Hospital

The following conditions apply to this research project. These are additional to those conditions imposed by the Human Research Ethics Committee that granted ethical approval:

1. Non WSLHD research team members who will be conducting study visits within WSLHD are to be accredited as an external researcher through the WSLHD Research and Education Network; Mr Raymond Li is not authorised to work on this project within WSLHD until his contingent worker status has been approved by the WSLHD Research & Education Network.

2. Proposed amendments to the research protocol or conduct of the research, which may affect the ethical acceptability of the project, and are submitted to the lead HREC for review, are copied to the research governance officer;

3. Proposed amendments to the research protocol or conduct of the research which may affect the ongoing site acceptability of the project, are to be submitted to the research governance officer.

Yours faithfully

[REDACTION]

Lani Attwood
WSLHD Research Governance Officer

WESTERN SYDNEY LOCAL HEALTH DISTRICT
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WSLHD Executive Office Level 1, Education Block Westmead Hospital
PO Box 574, Wentworthville NSW 2145
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12 Appendix 5 – Study Protocol

Protocol

For Investigator-Initiated Clinical Research, LNR or QA projects

Study Title: Retrospective analysis of adverse drug reaction (ADR) related admissions and in-hospital ADRs at Blacktown hospital

Short Title: Retrospective analysis of drug-related admissions and in-hospital ADRs

Investigators:
Role: Principal Investigator
Dr Ronald Castelino
Renal Pharmacist
Pharmacy Department, Blacktown Hospital
WSLHD
Senior Lecturer in Pharmacology and Clinical Pharmacy,
University of Sydney
Ronald.Castelino@health.nsw.gov.au; Ronald.Castelino@sydney.edu.au;

Blacktown, NSW 2148
Telephone: +61[REDACTION]
Qualifications: *PhD, MPharm, BPharm, PDCR (Professional Diploma in Clinical Research), BCGP*

Other Co-Investigators

- Raymond Li – PhD candidate, University of Sydney
- Dr Connie Van, Lecturer in Pharmacology, University of Sydney
- Professor Kate Curtis, Professor and Principal Research Fellow, University of Sydney

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Background/Introduction

The problem

Under-reporting of adverse drug reactions (ADRs) is significant around the world with a systematic review showing that over 94% of ADRs are not reported.(1) This was even higher in the hospital setting at 96%. (2, 3) Under-reporting is a healthcare problem because this can delay regulatory actions taken to remove medicines with an unacceptable safety profile from the market causing further harm to patients. This was shown in a 2016 systematic review which reported that the median time from drug launch to drug withdrawal for safety reasons was 10 years.(4)

The quality of ADR reports are also reported to be very poor. Less than 5% contain adequate information to allow for a comprehensive assessment of the causal relationship between the suspect

medicine and the ADR. (5, 6) This significantly hampers signal detection activities used to identify new safety issues, particularly for new medicines with an incomplete safety profile. Furthermore, a high volume of poor-quality ADR reports may confound the trending analysis by generating false signals. Therefore, it is critical that both the quality and quantity parameters of ADR reporting are considered.

Review of literature

A literature search was conducted in August 2019 to identify studies that investigated the degree of ADR under-reporting in hospitals. A 2004 Swedish study showed that only 15 out of 107 serious ADRs that occurred in hospitals were reported, giving an overall under-reporting rate of 86%. (7) A 2000 study in France showed that 95% of ADR related hospital admissions were not reported to the national pharmacovigilance centre. Similar results were reported for studies conducted in the US, Denmark, Italy, and Hong Kong with rates of under-reporting ranging from 59% to 100% in the hospital setting. (8-11)

This situation is similar in Australia where the latest pharmacovigilance statistics for 2017 reveal that there were 1,879 cases of ADRs reported by hospital networks representing only 10% of the total number of ADRs received by the Australian regulatory agency Therapeutic Goods Administration (TGA). (12) With an estimated 230,000 medication related hospital admissions each year, this suggests that the rate of under-reporting in Australian hospitals is over 99%. (13) The TGA has recognised this problem in Australia and has implemented the black triangle scheme in January 2018 to encourage healthcare professionals to report ADRs, especially for newly approved medicines.(14) However, a recent analysis has shown that this scheme was not successful in improving the quantity of ADR reports, and that the vast majority of ADR reports in the current Australian adverse events database are of poor quality. Furthermore, an unpublished but provisionally accepted systematic review has shown that interventions used to improve ADR reporting are only temporarily successful and improvements in reporting rates are diminished once the intervention is ceased.

What will this project contribute?

There are no published studies investigating the magnitude of ADR under-reporting in an Australian hospital setting. Therefore, this project will contribute the following:

1. Identify the proportion of hospitalisations due to ADR in an Australian hospital
2. Quantify the degree of ADR under-reporting in an Australian hospital.
3. Determine the quality of information available to clinicians at an Australian hospital to make a high quality ADR report.
4. Identify factors that may be associated with not reporting an ADR (e.g. type of reaction, type of medicine, strength of causal relationship)

Aim: The main objectives of this study are to determine the quantity of ADR related hospital admissions and the rate of reporting these ADRs to the TGA over a period of 12 months. We will also look at the quality of information available on the admission records and the type of ADR to determine whether this impacts on the reporting of an ADR. The results from this study will determine future interventions aimed at improving the rate of ADR reporting by healthcare professionals.

Hypothesis

1. ADR reporting rates Blacktown hospital will be extremely low
2. ADR reporting rates will be higher for new medicines compared to older medicines
3. ADR reporting rate will be higher for unexpected adverse drug reactions

Methods

Study design: Retrospective analysis of electronic medical records

Where will the study be conducted? Blacktown hospital emergency department, short stay unit, and intensive care unit

Length of study/total number of patient records: All medical admission records for a period of 12 months from January 2019-December 2019

Recruitment methodology: All hospital admission records will be reviewed by the primary investigator and co-investigator (Raymond Li) to assess whether a hospital admission was due to an ADR. The criteria for assessment of a hospital admission record is provided in the section Inclusion/ Exclusion criteria. Each record will be reviewed once by each reviewer. For the records that meet the inclusion criteria, the second reviewer will verify this to ensure it meets the inclusion criteria. In case of disagreement, a third investigator will review the record and an agreement will be reached with the previous 2 reviewers for the final decision.

Visit schedules: Not applicable

Randomization: Not applicable

What do you plan on collecting and how are you going to do that:
Patient characteristics, medicine information and ADR related information will be extracted from the electronic medical record (see table 1)

Table 1:

Source	What will be extracted?
Electronic Record for Intensive Care (ERIC)	Patient characteristics, medicine information and ADRs related information from ICU
FIRSTNET	Patient characteristics, medicine information and ADR related information from hospital admissions in emergency and short stay units
POWERCHART	Patient characteristics, medicine information and ADR related information from clinical notes, observations, and discharge summaries

TGA Database of Adverse Event Notifications	ADRs reported to the TGA. This will be retrieved from the publicly available Database of Adverse Event Notifications.

.

The following information will be evaluated during data analysis:

1. Quality of information in the data collection form based on the minimum information required to apply the Karch and Lasagna algorithm for causality analysis:(15) a record will be classified as poor quality if one or more of the following is missing: (1) onset date of ADR; (2) suspect medicine details (start and end date, drug name, strength); (3) concomitant medication details (start and end date, drug name, strength). Otherwise, the record will be classified as good quality.

2. Completeness of information in the data collection form: a record will be classified as incomplete if there is any information missing from the data collection form.

3. Strength of causal relationship: the strength of causal relationship will be classified using the Karch and Lasagna algorithm into one of the five categories (definite, probable, possible, conditional, or not related). (15)

4. Expectedness of ADR: this will be evaluated by checking whether the ADR is listed in the Australian Product Information for the suspect medicine.

5. Type of medicine: the therapeutic area for the indication of the medicine will be classified using the MedDRA dictionary. (16) Medicines will also be classified as new if it was approved in Australia within the last 5 years, otherwise it will be classified as established. The year the medicine was approved in Australia will be retrieved from the Australian Product Information for that medicine.

6. ADRs reported to the TGA: We will search the TGA Database of Adverse Event Notifications using a combination of patient characteristics, adverse reaction terms, reporter type, and date of report to determine whether the ADR related admission was reported to the TGA.

Equipment required: Blacktown hospital computer

Consent: See ethical considerations

Inclusion/exclusion criteria:

Inclusion criteria:

1. The clinician suspects an ADR related event on the admission record; or
2. Any known ADR to the medicine is listed on the admission record
3. An unknown ADR to the medicine is listed on the admission record that must have a:

- Plausible temporal relationship between the onset of the event and start of the medicine; AND
- The ADR cannot be explained by the patient's existing medical conditions
- Note: this includes reactions that may not be documented as an ADR, but occurred in the patient

Exclusion criteria

1. No plausible temporal relationship between the ADR and any medicine

Data Collection

The following information will be collected:

Data	Source	Why is it needed?
Patient characteristics (gender, age)	ERIC, FIRSTNET, POWERCHART, discharge summary	To assist with identifying ADRs that have/have not been reported to the TGA
Date of hospitalization	ERIC, FIRSTNET, discharge summary	To assist with determining a temporal relationship between the ADR and suspect medicine
Description of ADR	ERIC, FIRSTNET, POWERCHART, discharge summary	To assist with determining a temporal relationship between the ADR and suspect medicine and for data analysis
Suspect medicine details (drug name, start date, dose, frequency, end date)	ERIC, FIRSTNET, POWERCHART, discharge summary	To assist with determining a temporal relationship between the ADR and suspect medicine
Concomitant medication details (drug name, start date, dose, frequency, end date)	ERIC, FIRSTNET, POWERCHART, discharge summary	To assist with determining the causal relationship between the ADR and suspect medicine
Relevant medical history	ERIC, FIRSTNET, POWERCHART, discharge summary	To assist with determining the causal relationship between the ADR and suspect medicine
Location of unit (emergency, short stay, ICU)	ERIC, FIRSTNET	For data analysis

The data above will be obtained by examining the hospital admission records. All data will be de-identified with a study code assigned. Please refer to ethical considerations section for more details

Statistical Analysis

There are 51481 number of presentations to the Blacktown hospital emergency department each year. (17)The literature suggests that 2-3% of hospital admissions are due to medication related problems and therefore, we are intending to include at least 1030 records based on our inclusion criteria. (18) This does not include ADRs that were not documented but identified as such by the

investigators. Based on this information, we believe that there are enough numbers to achieve our proposed study outcomes.

The following analyses will be conducted:

1. Descriptive statistics will be used to report patient characteristics type of medications, type of ADRs, and the frequency of hospital admissions due to ADRs.
2. Chi squared tests will be used to determine whether there is any difference between the quality of information based on type of hospital unit (emergency vs short stay vs ICU)
3. Logistic regression will be used to determine whether certain variables (e.g. expectedness of ADR, strength of causal relationship of ADR, type of medicine, quality of admission record) predicts whether an ADR was reported or not.

Ethical considerations

We seek a waiver of consent as all data extraction will occur from existing routinely collected sources. We seek a waiver of consent for the study as getting consent from up to 1100 health consumers for their health information to be included in the study is impracticable, an incomplete data set will substantially impair the research by introducing bias and reducing the validity and generalisability of the research.. Furthermore, this part of the study is not invasive, the research involves no more than low risk to participants, there will be sufficient protection of their privacy, and there is an adequate plan to protect the confidentiality of data. At the conclusion of this study, the authors will provide a report of all ADR related hospital admissions to the Blacktown Hospital Safety and Quality committee.

Privacy

Once all data are collected a unique identifier will be allocated to each participant. Any identifying information will be removed from the dataset. Reasonable steps to de-identify per the NSW State Privacy Commissioner's Guidelines for Research that the investigators will undertake include omitting the participant name and medical record in data collection. Further, the sample size is large (>1000 records) and re-identification from only health data will not be possible, in particular because only aggregate level data will be reported (ie. cell sizes ≥5).

We will assign a 4 digit study code in chronological order for each record that meets the inclusion criteria. The study code key will be stored on a password protected University of Sydney computer. No identifiable information will leave Blacktown hospital. The source key document will be held separately and securely on a password protected Blacktown hospital computer within the hospital facility that is only accessible to the study team.

Data storage, retention and destruction

Data will be stored on a password protected Blacktown hospital, pharmacy computer hard drive and will not be taken out of the hospital premises on external drives. The primary investigator will have access to all data as part of their usual role. Only de-identified data will be used for the final analysis and this will be stored on a Sydney University password protected computer. This will be transferred to Sydney University using the Cloudster portal, which is hosted on a secure university server allowing for secure data transfer. All records will be retained for 5 years. Once the retention period has passed, the study information will be destroyed by using secure methods that will ensure that the data is completely over written and the storage medium is physically destroyed and there is no possibility that the records can be retrieved.

Data will be entered into a secure electronic based database by the researchers accessible only with a password. The electronic database will be stored on a secure, password protected, central network server at Blacktown Hospital. Security measures include password-protected databases and restricted access to servers. All data will be destroyed within 5 years in accordance with the NHMRC Australian code for the responsible conduct of research.

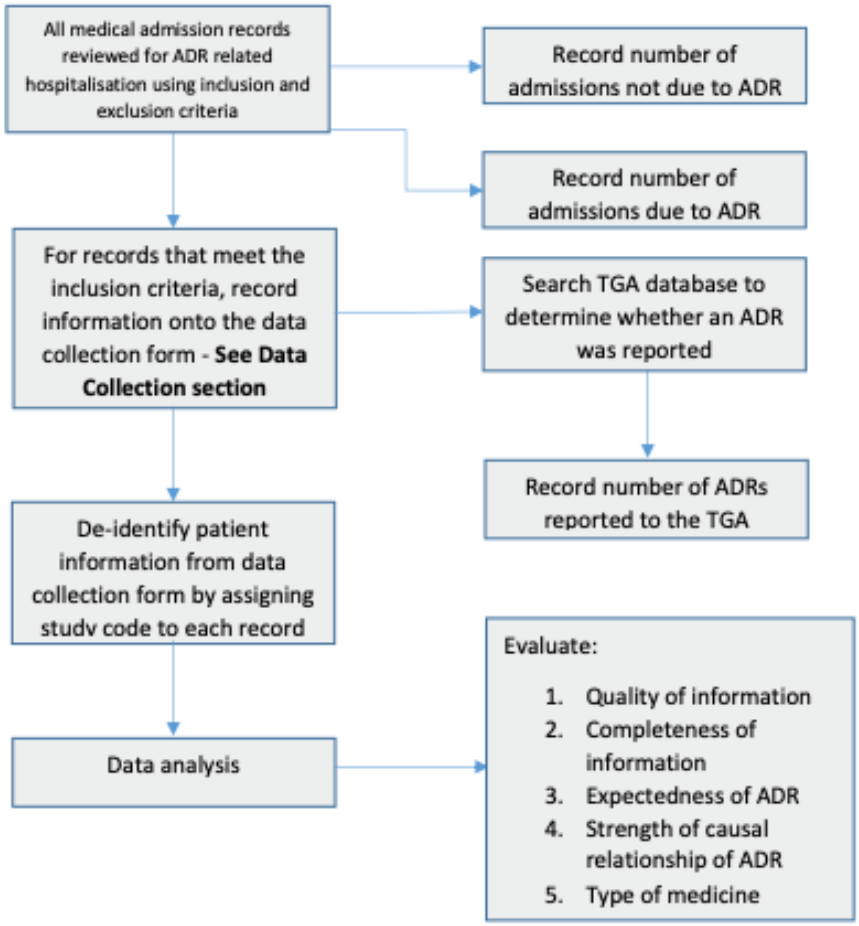
Data access

The primary investigator will have access to all data as part of their usual role at the Western Sydney Local Health District. All other researchers can access the data at Blacktown hospital only. Once data has been de-identified and stored on a Sydney University computer, only the investigators will have access.

Conclusion/Outcomes

The purpose of this study is to quantify the magnitude of ADR underreporting in a hospital environment. By doing so, we hope to draw awareness to the significance of this problem, which will then support the development of additional research to investigate the barriers towards ADR reporting. This will then inform the design of strategies to address this problem and improve the ADR reporting rates in Australian hospitals.

Flow chart – Figure 1



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13 Appendix 6 – University of Sydney HREC ethics exemption letter

THE UNIVERSITY OF SYDNEY

Research Integrity & Ethics Administration
Human Research Ethics Committee

Wednesday, 24 April 2019

Mr Raymond Li
Faculty of Nursing & Midwifery
Faculty of Medicine and Health
Email: rali3062@uni.sydney.edu.au

Dear Raymond,

Project Title: Impact of the black triangle scheme on the quantity and quality of adverse drug reaction reporting in Australia one year after implementation

The NHMRC National Statement on Ethical Conduct in Human Research ("The National Statement") outlines circumstances where research that carries only negligible risk may be exempted from ethical review.

The National Statement defines negligible risk: *"The expression 'negligible risk research' describes research in which there is no foreseeable risk of harm or discomfort; and any foreseeable risk is no more than inconvenience." (National Statement 2.1.7)*

Further, the National Statement states that institutions may choose to exempt research from ethical review which meets the following criteria:

(a) is negligible risk research (as defined in paragraph 2.1.7); and
(b) involves the use of existing collections of data or records that contain only non-identifiable data about human beings." (*National Statement 5.1.22*)

Based on what you have described in email communications to the Ethics Office, your project is considered negligible risk as it meets both of the above criteria.

Should any future work not comply with any of the above criteria, the project must be submitted for ethical review prior to commencing research. Please note that retrospective ethical approval of research cannot be given by the HREC.

Please contact the Ethics Office should you require further information or clarification.

Sincerely,

[REDACTION]

Kate Lowrie
Human Ethics Officer

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F23 Administration Building
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ABN 15 211 513 464
CRICOS 00026A

14 Appendix 7 – Ethics approval 2020/ETH00597

Health
Western Sydney
Local Health District

Research Office File No: **(6465)**

Project ID:	2020/PID00648
Ethics Ref:	2020ETH00597
Governance Ref:	2020/STE00981

20 August 2020

Dr Ronald Castelino
Department of Sydney Nursing School
University of Sydney

Dear Castelino

LNR Research Project: Knowledge, perspectives and practices of healthcare professionals towards adverse drug reaction reporting at Blacktown Hospital: a mixed methods study

Your request to undertake the above protocol as a Low or Negligible Risk (LNR) research project was reviewed by a subcommittee of members of the Scientific Advisory Committee (SAC) and the Human Research Ethics Committee (HREC). We are satisfied that your protocol meets the criteria for an LNR research project and does not require review by the full HREC.

The WSLHD HREC has been accredited by the NSW Ministry of Health as a lead HREC to provide the single ethical and scientific review of proposals to conduct research within the NSW public health system. This lead HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and the *CPMP/ICH Note for Guidance on Good Clinical Practice.*

This proposal meets the requirements of the National Statement and I am pleased to advise that the HREC has granted ethical approval of this LNR research project to be conducted by you at:

- Blacktown Mount Druitt Hospital

The following documentation has been reviewed and approved by the HREC:

- HREA 2020/ETH00597, version 3, dated 22 May 2020
- Protocol, version 2 dated 12 June 2020
- Blacktown Hospital - Participant Information Sheet and Consent Form - version 3, dated 24 July 2020
- Poster, version 2 dated 12 June 2020
- Email Communication, version 1 dated 16 April 2020
- Survey Questions, version 1 dated 16 April 2020

HUMAN RESEARCH ETHICS COMMITTEE

Research Office, Level 2, REN Building
Westmead Hospital, Hawkesbury & Darcy Roads, Westmead NSW 2145
Telephone 02 8890 9007 Facsimile 02 9845 9636
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WESTERN SYDNEY LOCAL HEALTH DISTRICT
ABN 48 702 394 764
WSLHD Office, Westmead Hospital Campus
Institute Road, Westmead NSW 2145
PO Box 533, Wentworthville NSW 2145
Telephone 02 8890 5555

Please note the following conditions of approval:

- The chief investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project.
- The chief investigator will immediately report any protocol deviation / violation, together with details of the procedure put in place to ensure the deviation / violation does not recur.
- Proposed amendments to the protocol or conduct of the research which may affect the ethical acceptability of the project, must be provided to the HREC to review via REGIS.
- The HREC must be notified, giving reasons, if the project is discontinued at a site before the expected date of completion.
- The Coordinating Chief Investigator must provide an annual report to the HREC and a final report at completion of the study, in the specified format.
- HREC approval is granted for a period of 5 years contingent upon submission of an annual report via REGIS.
- It should be noted that compliance with the ethical guidelines is entirely the responsibility of the investigators.

You are reminded that this letter constitutes *ethical approval only*. You must not commence this research project until separate authorisation from the Chief Executive or delegate has been obtained.

In all future correspondence concerning this study, please quote Research Office File number ***(6465).***
The HREC wishes you every success in your research.

Yours sincerely

[REDACTIO

Mrs Patricia Fa
Secretary
WSLHD Human Research Ethics Committee

cc: Research Governance Officer

15 Appendix 8 – Site approval 2020/STE00981

Health
Western Sydney
Local Health District

19th October 2020

Dr Ronald Castelino
Pharmacy Department
Blacktown Hospital

Dear Dr Ronald Castelino

WSLHD Research Office number: 6465
HREC reference number: 2020/ETH00597
SSA reference number: **2020/STE00981**
Project title: Knowledge, perspectives and practices of healthcare professionals towards adverse drug reaction reporting at Blacktown Hospital: a mixed methods study
Protocol number: version 2 dated 12 June 2020

Thank you for submitting an application for site authorisation of this project. I am pleased to inform you that site authorisation has been granted for this study to take place at the following site:

- Blacktown Mt Druitt

The approved information and consent documents for use at this site are:

- Blacktown Hospital - Participant Information Sheet and Consent Form - version 3 dated 24 July 2020

The following conditions apply to this research project. These are additional to those conditions imposed by the Human Research Ethics Committee that granted ethical approval:

1. Non WSLHD research team members who will be conducting study visits within WSLHD are to be accredited as an external researcher through the WSLHD Research and Education Network;

2. Proposed amendments to the research protocol or conduct of the research, which may affect the ethical acceptability of the project, and are submitted to the lead HREC for review, are copied to the research governance officer;

WESTERN SYDNEY LOCAL HEALTH DISTRICT
ABN 48 702 394 764
WSLHD Executive Office Level 1, Education Block Westmead Hospital
PO Box 574, Wentworthville NSW 2145
Telephone 02 8890 5555

Health
Western Sydney
Local Health District

3. Proposed amendments to the research protocol or conduct of the research which may affect the ongoing site acceptability of the project, are to be submitted to the research governance officer.

Yours faithfully

[REDACTION]

Pauline Geale
WSLHD Research Governance Officer

WESTERN SYDNEY LOCAL HEALTH DISTRICT
ABN 48 702 394 764

WSLHD Executive Office Level 1, Education Block Westmead Hospital
PO Box 574, Wentworthville NSW 2145
Telephone 02 8890 5555

16 Appendix 9 – Study Protocol

Protocol Guidance

For Investigator-Initiated Clinical Research, LNR or QA projects

Study Title: The knowledge, perspectives and practices of healthcare professionals towards adverse drug reaction reporting at Blacktown Hospital: a mixed method survey

Short Title: The knowledge, perspectives and practices of healthcare professionals towards adverse drug reaction reporting

Investigators:

Mr Raymond Li

University of Sydney
Email: rali3062@uni.sydney.edu.au
Phone: +61 4[REDACTION]

Professor Kate Curtis

University of Sydney
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Dr Ronald Castelino

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Email: Ronald.castelino@sydney.edu.au
Phone: +61 2 9351 0609

Background/Introduction:

A 2006 systematic review demonstrated that the global rate of under-reporting by healthcare professionals is 94%.(1) In 2017, only 10% of the 18,600 ADR reports received by the Therapeutic Goods Administration (TGA) were from hospitals, 7% from consumers, 6% from community pharmacists, and 3% from general practitioners versus 54% from pharmaceutical companies.(2) Furthermore, the quality of ADR reports have been reported

to be poor, with only 4.4% to 11.5% of reports containing adequate information to allow for an analysis of the causal relationship between the suspect medicine and ADR.(3, 4) This severely impedes the ability of regulators to identify and validate new safety signals and delay regulatory actions taken to remove medicines with unacceptable safety profiles from the market. A worldwide review of 462 medicines removed from the market for safety reasons showed that the median time from drug launch to drug withdrawal was 10 years.(5) These delays contribute significantly to increased healthcare costs as ADRs are a major cause of hospitalisations, morbidity and mortality with a literature review estimating that ADRs contribute to 2-12% of hospital admissions in Australia.(6)

Literature review

The biggest issue for ADR detection and monitoring is the substantial under reporting by healthcare professionals and consumers. The main barriers to reporting ADRs have been studied extensively in the international literature with lack of time, different care priorities, uncertainty about drug causing the ADR, difficulty in accessing reporting forms, and lack of awareness of the requirements for reporting being the key concerns.(7-9) Their perspectives also play a significant role in the under-reporting of ADRs with one survey showing that physicians believed that all serious reactions will be well documented by the time a drug is marketed and that a single case report will not contribute to medical knowledge.(10) All of these barriers contribute to the substantial under reporting of ADRs with studies showing that 50-97% of healthcare professionals admit they have not reported any ADRs in the last 12 months.(11)

International studies have also shown that healthcare professionals have very limited knowledge of pharmacovigilance and their perspectives towards ADRs play a strong role in influencing their reporting rates.(12-14) This relationship is clearly detailed in Suyagh et al and Xu et al which showed that perspectives of indifference, lack of remuneration, competing workplace priorities and dissatisfaction with reporting methods strongly impacted the ADR reporting rates.(12, 14) There is also evidence to show a relationship between ADR knowledge and reporting rates, with Herdeiro et al identifying a 5.9 fold increase in ADR reporting after pharmacists were provided with a one hour educational session on pharmacovigilance.(15) Despite the wealth of international literature, limited data exist on the practice of ADR reporting by Australian healthcare professionals.

Aims:

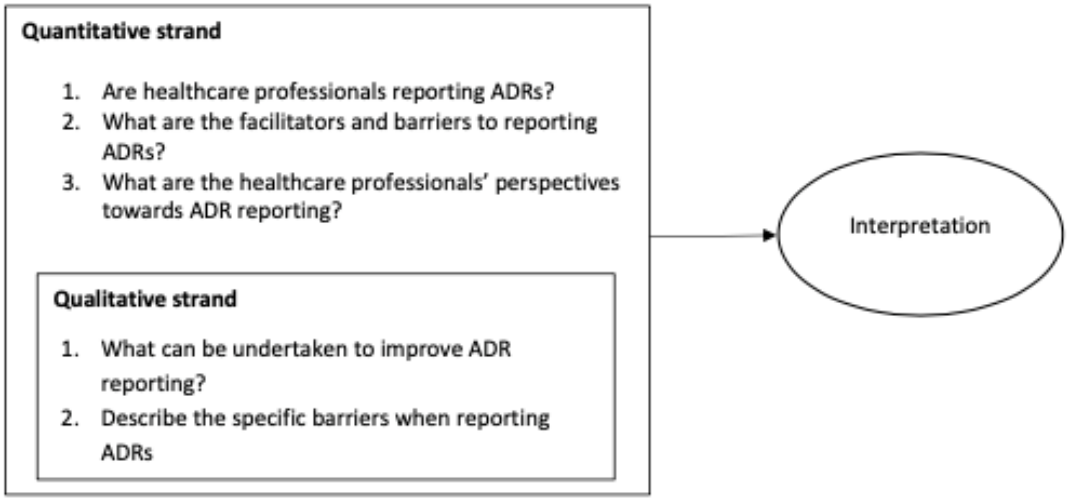
1. To investigate the ADR reporting practices of physicians, nurses, and pharmacists at Blacktown hospital.
2. To investigate their perspectives towards reporting ADRs.
3. To identify the facilitators and barriers towards reporting ADRs at Blacktown hospital.

Methods:

Design

This is an exploratory embedded mixed methods study where a qualitative strand is added to the quantitative strand and the data is collected and analysed together within the same study.

Figure 1



Location: Blacktown Hospital

Duration: 6 months

Survey tool development

We were interested in 3 specific domains namely, knowledge, perspectives, and practices of ADR reporting based on a previous survey tool conducted for community pharmacists practising in Australia.(16) An item pool for each of these domains was generated based on the theoretical domains framework of behaviour change, with the question selection based on consultations with senior clinicians from the investigators' network who were known to have an interest in this topic and practising in various settings. The theoretical domains framework was selected as it identifies a wide range of barriers and facilitators and can be used with the Behaviour Change Wheel to identify strategies for improving ADR reporting.(17)

Recruitment

All registered physicians, nurses and pharmacists practising at Blacktown Hospital will be eligible for participation in this survey. Participants will be sent an invitation to participate in this study by email from the director of each department. This email correspondence will contain the participant information sheet and an electronic link to the survey. Posters will

also be placed in the hospital inviting physicians, nurses and pharmacists to participate in the survey. This poster will contain a QR code that can be scanned by a mobile device to access the survey.

Reminders

Participants will be provided with 6 weeks to complete the survey. During this 6-week period, the invitation email will be sent every 2 weeks to all invited participants.

Consent

A participant information sheet will be accessible to all participants and participation is voluntary. Completion of the survey will be considered as implied consent.

Inclusion criteria

All registered physicians, nurses, and pharmacists practising at Blacktown Hospital.

Data Collection:

The survey will be conducted electronically using the Research Electronic Data Capture (REDCap) tool, which is a secure web-based database application maintained by the University of Sydney.

The following information regarding the survey participants will be collected:

- Profession
- Number of years registered to practice in Australia
- Highest level of educational qualification
- Hours employed at the hospital per week

This information will assist with identifying whether these variables affect the knowledge, perspectives and practices of reporting adverse drug reactions. The questionnaire will also include multiple choice questions, Likert scale questions on a 5-point scale from strongly disagree to strongly agree, and open ended questions to collect the participants' knowledge, perspectives and practices of reporting adverse drug reactions. The collected information will then be mapped to the theoretical domains framework and the behaviour change wheel to identify specific behavioural change strategies.(17)

Statistical Analysis:

Statistical analyses of the main survey data will be performed using IBM SPSS (version 26.0) with significance levels set at $p \leq 0.05$. Non-parametric tests will be used for comparing knowledge scores, perspectives, and ADR reporting practices across the different participant

demographics (Mann-Whitney U test for 2 groups and Kruskal Wallis for more than 2 groups).

Qualitative data will be analysed using NViVO software. Inductive thematic analysis will be conducted using the Braun Clarke six step method.(18) We will familiarize ourselves with the data by reviewing it several times and then breaking it down into small units. We will then identify the meaning units after applying initial coding and sorting into first order themes. This process will create second and higher order themes using the Constant Comparison method of analysis. This entire process will be conducted by 2 researchers (RL and RC).

Ethical considerations:

Confidentiality and privacy

No personal identifiers will be collected within the survey, each participant will be assigned a unique ID when completing the survey.

Data storage, retention and destruction

Data will be stored on a password protected University of Sydney computer hard drive and will not be taken out of the hospital premises on external drives. The primary investigator will have access to all data as part of their usual role. Only de-identified data will be used for the final analysis and this will be stored on a Sydney University password protected computer. All records will be retained for 5 years. Once the retention period has passed, the study information will be destroyed by using secure methods that will ensure that the data is completely over written and the storage medium is physically destroyed and there is no possibility that the records can be retrieved.

Data will be entered into a secure electronic based database by the researchers accessible only with a password. The electronic database will be stored on a secure, password protected, central network server at the University of Sydney. Security measures include password-protected databases and restricted access to servers. All data will be destroyed within 5 years in accordance with the NHMRC Australian code for the responsible conduct of research.

Data access

The primary investigator will have access to all data as part of their usual role at the University of Sydney. Once data has been de-identified and stored on a Sydney University computer, only the investigators will have access.

Conclusion/Outcomes:

This study will identify facilitators and barriers to ADR reporting, which will then inform the design of strategies to improve ADR reporting at Blacktown Hospital.

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17 Appendix 10 – Patient Information Sheet/Consent form

Health
NSW GOVERNMENT | Western Sydney Local Health District

Participant Information Sheet/Consent Form

Health/Social Science Research - *Adult providing own consent*

Blacktown Hospital

Title	Knowledge, perspectives and practices of healthcare professionals towards adverse drug reaction reporting at Blacktown Hospital: a mixed methods study
Short Title	Knowledge, perspectives and practices of reporting adverse drug reactions
Project Sponsor	University of Sydney
Coordinating Principal Investigator/ Principal Investigator	Dr Ronald Castelino
Associate Investigator(s)	Raymond Li Dr Connie Van Professor Kate Curtis
Location	*Blacktown Hospital*

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project, which is called 'Knowledge, perspectives and practices of healthcare professionals towards adverse drug reaction reporting at Blacktown Hospital: a mixed methods study'. You have been invited because you are practising as a registered physician, nurse or pharmacist at Blacktown Hospital.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the processes involved with taking part. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. Completion of the survey will be deemed to be consent to participate.

This Participant Information Form is for you to keep.

2 What is the purpose of this research?

Under-reporting of adverse drug reactions is highly prevalent and your opinions will assist with identifying strategies to improve the reporting of adverse drug reactions at Blacktown Hospital. The results of this research will be used by the researcher Raymond Li to obtain a Doctor of Philosophy degree. This research has been funded by The Faculty of Medicine and Health, The University of Sydney.

3 What does participation in this research involve?

You will be invited to participate in an online survey, which can be assessed through a link in an email from your head of department. You have six weeks to complete the survey and can complete it at a time convenient to you. This survey is anonymous, the research team will not know your details and they will be unaware whether or not you complete the survey.

The survey will ask you about what you know about reporting adverse drug reactions, and what your perspectives are towards the process. We will also ask you about your practices of reporting adverse drug reactions and your suggestions for overcoming barriers towards reporting adverse drug reactions.

There are no costs associated with participating in this research project, nor will you be paid.

It is anticipated that the survey will take up to 10 minutes to complete.

4 Other relevant information about the research project

This study will only be conducted at Blacktown hospital and we are anticipating that at least 150 participants will be included.

5 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to.

Your decision whether to take part or not to take part will not affect your relationship with professional staff or your relationship with Blacktown Hospital.

6 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research; however, possible benefits may include improved knowledge about the importance of reporting adverse drug reactions, and reporting more adverse reactions to improve patient care.

7 What are the possible risks and disadvantages of taking part?

Aside from giving up your time, we do not expect that there will be any risks or costs associated with taking part in this study.

8 What if I withdraw from this research project?

If you do consent to participate, you may withdraw at any time before you have submitted the survey. Once you have submitted it, your responses cannot be withdrawn because they are anonymous and therefore we will not be able to tell which one is yours.

If you decide to leave the research project, the researchers will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected up to the time you withdraw will form part of the research project results.

9 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as lack of response rate.

10 What happens when the research project ends?

Participants will find out about the outcomes of this study once the results are published in a peer reviewed journal.

Part 2 How is the research project being conducted?

11 What will happen to information about me?

By participating, you consent to the research team collecting and using personal information about you for the research project. We will not collect information that can identify you. Survey data will be collected using Research Electronic Data Capture (REDCap) and de-identified within REDCap by assignment of a unique ID, generated when you complete the survey. The information you provide will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law. The information will be stored securely in the Research Data Store (RDS) for 5 years, except as required by law, and then securely destroyed.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified.

In accordance with relevant Australian and/or NSW privacy and other relevant laws, you have the right to request access to the information about you that is collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please inform the research team member named at the end of this document if you would like to access your information.

12 Complaints and compensation

If you suffer any distress or psychological injury as a result of this research project, you should contact the research team as soon as possible. You will be assisted with arranging appropriate treatment and support.

13 Who is organising and funding the research?

This research project is being conducted by Dr Ronald Castelino. It is being funded by The Faculty of Medicine and Health, The University of Sydney.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

14 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC).
The ethical aspects of this research project have been approved by the HREC of Western Sydney Local Health District.
This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

15 Further information and who to contact

The person you may need to contact will depend on the nature of your query. If you want any further information concerning this project or if you have any problems which may be related to your involvement in the project, you can contact the researcher, Raymond Li on 0434503042 or any of the following people:

Research contact person

Name	Raymond Li
Position	PhD candidate
Telephone	[REDACTION]
Email	rali3062@uni.sydney.edu.au

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	HREC secretary
Position	HREC secretary
Telephone	02 8890 9007
Email	wslhd-researchoffice@health.nsw.gov.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	*WSLHD Human Research Ethics Committee*
Telephone	*02 8890 9007*
Email	*Wslhd-researchoffice@health.nsw.gov.au*

Local HREC Office contact

Name	Governance Manager
Position	Governance Manager
Telephone	02 8890 9007
Email	wslhd-researchoffice@health.nsw.gov.au

18 Appendix 11 – Email communication to clinicians

Email communication script

Dear colleagues

You are invited to contribute to an important initiative to identify strategies to improve the reporting of adverse drug reactions at Blacktown hospital. This study is designed to collect your perspectives and practices of reporting adverse drug reactions through an online survey, which will take approximately **10 minutes** to complete. The results will help to inform strategies to improve the quantity and quality of adverse drug reaction reporting at Blacktown hospital. Details of this project are set out in the accompanying Participant Information Statement, available for you to keep.

Project summary

If you agree to participate in this work, we will ask you to complete an online survey. In this survey, you will be asked about your knowledge of reporting adverse drug reactions, your perspectives towards this process, and whether you have undertaken any reporting. You will also be asked about any strategies that may help with improving the reporting of adverse drug reactions at Blacktown hospital.

This project has been approved by the Human Research and Ethics Committee at the Western Sydney Local Health District. The results of this project may be published or presented in professional forums. All results will be presented in aggregate form. Should you have any questions about this study please contact Mr. Raymond Li rali3062@uni.sydney.edu.au

The survey can be accessed through this link:

https://redcap.sydney.edu.au/surveys/?s=J3TFNR4LME

Alternatively, you can complete the survey on your mobile device by scanning this QR code

Kind regards,

Dr Ronald Castelino

19 Appendix 12 – Advertising brochure with QR code

All physicians, nurses, and pharmacists are invited to participate in research about the reporting of adverse drug reactions at Blacktown Hospital

The aims of this research are:

- Investigate the ADR reporting practices of physicians, nurses, and pharmacists at Blacktown hospital
- Investigate their perspectives towards reporting ADRs
- Identify the facilitators and barriers towards reporting ADRs at Blacktown hospital

This online survey will only take about 10 minutes to complete.

This project has been approved by the Western Sydney Local Health District Human Research and Ethics Committee REF: **2020/ETH00597**

Should you have any questions, please contact Mr. Raymond Li at: rali3062@uni.sydney.edu.au

To start, scan this QR code on your phone!

Version 3.0 24 Jul 2020