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**Estimated effects on unplanned hospitalisations of  
exposure to high-risk and potentially inappropriate  
medications in elderly Western Australians:  
a cross-jurisdictional data linkage approach**

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# SUMMARY

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The harmful effects of therapeutic drugs, including unplanned hospitalisations, are a significant health problem, especially in the elderly. Older people are major consumers of medication and are more susceptible to adverse drug events (ADEs) due to physiological deterioration and other age-related factors. To address this problem, various lists of medications considered potentially inappropriate in older people have been developed. Among them, the Beers Criteria are by far the most commonly referenced.

Until recently, most Australian statistics on ADE-related hospitalisations have been based on the analysis of external cause codes from the International Classification of Diseases (ICD) found on inpatient discharge summaries. Not only does this classification system lack sufficient detail to permit the identification of individual drugs as causal agents but, given the ambiguous symptoms associated with some adverse drug reactions, it is suspected that a number of patients hospitalised due to harmful drug effects may not be identified as such in hospital records.

The linkage of records from the Australian Pharmaceutical Benefits Scheme (PBS), Medicare Benefits Scheme (MBS) and System for the Payment of Aged Residential Care (SPARC) databases with Western Australian inpatient, death and electoral roll records provided the opportunity to explore alternative methods for estimating the ADE-related hospital admission burden in elderly Western Australians, and to assess the impact of exposure to potentially inappropriate medications (PIMs) from the general Beers list in this population in terms of unplanned hospitalisations.

## OBJECTIVES/METHODS

This study used the linked health data of 251,305 Western Australian residents aged  $\geq 65$  years over a 13-year period (1993-2005) to:

- Assess the impact on hospital burden of medications thought to be the leading causes of ADE-related hospitalisation in this population (i.e. high-risk drugs) by applying an enhanced case-time-control design and conditional logistic regression to the data, from which were derived odds ratios (ORs), attributable fractions (AFs), and the number and proportion of unplanned

hospitalisations associated with exposure to each high-risk drug group. The results were then compared with those obtained from more conventional methods, which involved the analysis of external cause codes on inpatient records. The broad drug groups investigated included anticoagulants, antirheumatics, opioids, corticosteroids, and four sub-groups of cardiovascular agents.

- Examine the prevalence over time of exposure to general PIMs from the 2003 Beers Criteria in elderly Western Australians, estimating not only the number and proportion of people exposed, but also daily doses/1000 person-years (both overall and for individual PIMs), and identifying associated risk factors through logistic regression analysis.
- Estimate the effects of exposure to Beers' general PIMs on unplanned hospitalisations in this population (overall and for each individual PIM), adopting similar methods to those applied in the analysis of high-risk drug groups.
- Evaluate the roles of general practitioner (GP) monitoring and high-level residential aged care in modifying the effects of exposure to Beers' general PIMs on unplanned hospitalisations, by applying a case-time-control design to relevant population sub-groups.
- Determine whether risk estimates of drug-related hospitalisations are altered in elderly patients taking medications from high-risk drug groups when specific Beers' medications are taken into consideration.

## **MAJOR FINDINGS**

A number of interesting results were uncovered during the course of this research project. The most noteworthy are highlighted below:

### ***UNPLANNED HOSPITALISATIONS ASSOCIATED WITH EXPOSURE TO HIGH-RISK DRUGS***

- The estimated number of hospitalisations attributed to medications from high-risk drug groups in the exposed was two to 31-fold higher when derived from the case-time-control design compared with identification from ICD external cause codes.

- Six of the eight high-risk drug groups were associated with an increased risk of unplanned hospitalisation, opioids (adjusted OR = 1.81, 95% confidence interval (CI) 1.75-1.88; AF = 44.9%) and corticosteroids (1.48, 1.42-1.54; 32.2%) linked with the highest risks. However, hypertension and serum lipid-reducing drugs (two of the cardiovascular sub-groups), appeared to have a protective effect against unplanned hospitalisations.

#### ***PREVALENCE OF GENERAL PIMS FROM THE BEERS CRITERIA***

- Three-quarters of study participants took  $\geq 1$  PIM during 1993-2005, the cohort consuming 109,415 PIM daily doses/1000 person-years (109 daily doses per person per year). Annual exposure decreased from 45-47% to 40%, and annual consumption rate declined from 117,836 to 90,364 daily doses/1000 person-years during that time.
- Temazepam was by far the most commonly used PIM; it was dispensed to 35% of the study cohort during 1993-2005 (14% in 2005), and was consumed at a rate of  $>17,000$  daily doses/1000 person-years. Other commonly used PIMs included digoxin, oxazepam, diazepam, naproxen, nifedipine, amitriptyline and piroxicam.
- Number of medications taken (OR 35.03; 95% CI 34.37-35.71 for  $\geq 10$  vs. 0-2 drugs), annual drug intake (2.08; 2.04-2.12 for highest vs. lowest quartile), and high-level residential aged care (1.96; 1.91-2.01) were most predictive of PIM exposure.

#### ***UNPLANNED HOSPITALISATIONS ASSOCIATED WITH PIM EXPOSURE***

- Based on the health profiles of 383,150 hospitalised index subjects, overall PIM exposure was associated with an elevated risk of unplanned hospitalisation (adjusted OR 1.18; 95% CI 1.15-1.21), this estimated risk increasing with the number of different PIMs and PIM quantity taken. Fifteen percent of unplanned admissions in exposed index subjects (1,980 per year) were attributed to PIM exposure.
- Patients taking meperidine (pethidine), nitrofurantoin, promethazine, indomethacin, and thioridazine appeared to be at particularly high risk of unplanned hospitalisation, whereas temazepam, oxazepam, diazepam, digoxin, amiodarone, ferrous sulphate, and naproxen were attributed the greatest numbers of unplanned admissions.

### **GP CARE EFFECT MODIFICATION**

- Participants were allocated to one of four groups according to their level of ongoing GP care. PIM exposure was associated with a similar relative risk of unplanned hospitalisation in elderly people receiving the lowest and highest levels of ongoing GP care, but with a decreasing risk in the three highest tiers; adjusted ORs (95% CIs; AFs) were 1.15 (1.09-1.21; 12.9%), 1.36 (1.27-1.46; 26.6%), 1.20 (1.15-1.26; 16.9%) and 1.13 (1.09-1.17; 11.4%), for groups from the lowest to highest levels. However, those with higher levels of GP care had higher rates of PIM-related hospitalisation.
- Similar patterns were demonstrated for commonly used high-risk PIMs (temazepam, diazepam, oxazepam, naproxen and digoxin).
- It is possible that patients from the lowest tier of ongoing GP care consisted of a heterogeneous population, one possibly involving both very healthy people with little need for ongoing GP care and unhealthy patients with restricted access to GP services. Alternatively, a form of misclassification may have been introduced, as some of these patients may have been seeing medical specialists, as opposed to GPs. These factors could explain the discrepant pattern identified in this group. If so, overall results suggest that the increased requirement for ongoing GP contact in less healthy elderly people may help minimise their risk of unplanned hospitalisation due to PIM-related harm.

### **HIGH-LEVEL RESIDENTIAL AGED CARE EFFECT MODIFICATION**

- PIM exposure was associated with a similar proportional increase in unplanned hospitalisations in high-care nursing home residents as in other older people; adjusted OR 1.21 (95% CI 1.10-1.34; AF 17.5%) vs. 1.19 (1.16-1.21; 15.7%). However, high-care nursing home residents had much higher estimated rates of hospitalisations attributed to Beers medications than other elderly (3,951 vs. 1,394 per 100,000 person-years).
- The relative risk of unplanned hospitalisation rose similarly in both groups with increasing numbers of different PIMs taken (OR 5.1 for 10 vs. 0 PIMs), but was affected more markedly by three-month PIM consumption in nursing home residents (OR 4.85 (2.40-9.83) for 900 vs. 0 PIM daily doses) than in other seniors (2.10 (1.73-2.55)).

### ***EFFECTS OF SPECIFIC PIMS IN PATIENTS TAKING HIGH-RISK DRUGS***

- PIMs included in the analysis (indomethacin, naproxen, temazepam, oxazepam, diazepam, digoxin, amiodarone and ferrous sulphate) all tended to increase ORs, AFs and drug-related hospitalisation estimates in high-risk drug combinations, although this was less evident for opioids and corticosteroids.
- Indomethacin had the greatest overall impact on the relative measures of drug-related unplanned hospitalisations in patients taking high-risk drugs (i.e. ORs, AFs), whereas temazepam yielded the greatest absolute increases in drug-related hospitalisation estimates, especially with hypertension drugs.
- Indomethacin (OR 1.40; 95% CI 1.27-1.54) and naproxen (OR 1.22; 1.14-1.31) were associated with higher risks of unplanned hospitalisation than other antirheumatics (overall OR 1.09; 1.06-1.12). Similarly, among cardiac rhythm regulators, amiodarone (OR 1.22; 1.13-1.32) was riskier than digoxin (OR 1.08; 1.04-1.13).

## **CONCLUSIONS**

### ***RESEARCH SIGNIFICANCE***

This study demonstrated the use of Australian cross-jurisdictional linked health data in drug safety research, with a focus on pharmaceutical claims and unplanned hospital admissions. In the process, it established an Australian pharmaceutical reference database, defined major drug groups and Beers medications using an international drug classification, created a set of computer programs, and developed an approach for identifying potentially harmful medications that shows great promise as part of a pharmacovigilance monitoring system.

Through better understanding of which potentially inappropriate medications are being prescribed to older Western Australians, of the patient characteristics and circumstances that lead to risky prescribing, and of which drugs and drug combinations are associated with the greatest risk of unplanned hospitalisation, this study may help better inform drug prescribing policies and guidelines in Australia and elsewhere.

In particular, given the high prevalence of Beers medication intake in elderly Western Australians and the apparent increased risk of unplanned

hospitalisation in older people taking these drugs, it may be beneficial to use the results of this study and the updated Beers Criteria as a starting point to establish an Australia-specific list of medications to be avoided in the elderly. The latter would complement the prescribing appropriateness indicators and other tools available in Australia to guide clinicians and measure the quality of prescribing practices in this country.

#### ***FUTURE DIRECTIONS***

This study has also identified other avenues to explore in pharmaco-epidemiological research. Refinements of the analytical methods are still possible and could be investigated and validated further. It would also be beneficial to repeat the high-risk drug component in settings with greater access to extended patient information, especially in relation to opioids and corticosteroids, to confirm that research findings did not result from uncontrolled time-dependent confounding and to identify specific medications that are associated with the greatest risk of serious harm. Furthermore, there is a need to delve more deeply into the role of ongoing GP care in the prevention of PIM-related hospitalisations, especially in relation to the characteristics of patients with the least regular contact with their GPs. Similarly, it would be useful to know with greater certainty why high-care nursing home residents seem more susceptible to PIM-related hospitalisations than other elderly people when taking increased quantities of Beers medications.

Finally, it is worth highlighting that the methods adopted in this study could be applied to an unlimited number of therapeutic drugs and drug combinations. The study's broad scope and constraints of the administrative health data may have restricted the researcher's ability to perform the analysis with the same level of control as would be expected from a randomised clinical trial, for instance. However, a greater focus on specific drugs should ensure that subsequent work in this area is more targeted and better adapted to the specific requirements of the medications of interest, guided by the findings of this study and other results presented in the literature. This is where the true value of this research will become apparent. The present study has simply opened the door to more in-depth exploration of the potential harm of certain medications in elderly Australians and possibly other populations.



# DEDICATION

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To my loving parents, who valued education despite not having the chance to pursue it very far.

Dad, unlike the doctor's son who squandered every opportunity, not realising how fortunate he was, I followed this venture to the end. I thought of you often along the journey, especially when I came across what seemed to be insurmountable obstacles.

This achievement may not be much in the broad scheme of things, but I know it would have meant the world to you both.

And to my caring husband, without whom this endeavour would never have been possible. You supported me in every way, worked around my research commitments throughout the project, endured the trials and tribulations, and made sure I took the time to smell the roses every now and then to maintain my sanity. For this, I am eternally grateful.

Sincerely,

*Sylvie*



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- Winthrop Professor D’Arcy Holman, my principal supervisor, who devised the original study protocol; secured funding for the project; reviewed all of my work with great insight and timeliness; provided epidemiological and intellectual support; and continued to encourage me throughout the project through his infectious enthusiasm, great respect for my thoughts and opinions, and ongoing praise of even the smallest of my achievements.
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- Winthrop Professor Jon Emery, research collaborator and co-author of all papers emanating from this research project, whose extensive experience with both clinical and research aspects of general practice were greatly appreciated, especially in the early stages of the study, when definitions were being established, and towards the end, in the interpretation of results from a clinical perspective.
- Dr John Bass, who worked tirelessly to establish the cross-jurisdictional linkage of health data from the Australian Department of Health and Ageing and the Department of Health of Western Australia, and without whose efforts the project’s linked data may never have been extracted.
- The Data Linkage Branch within the Department of Health of Western Australia for undertaking the record linkage and facilitating communication with the data custodians - Diana Rosman, Carol Garfield, Geoff Davis, Melinda Burmas, Brooke Baxter, April Rutkay, and undoubtedly many others who worked tirelessly in the background, especially in the early days of the project.

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- Last, but not least, my husband, whose vital support has already been highlighted, his family here in Perth, and my own family in Canada, all of whom have shown compassion, understanding and encouragement throughout this long journey.

# STATEMENT OF CANDIDATE CONTRIBUTION

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This thesis presents the original work undertaken by the postgraduate student during her PhD candidature at The University of Western Australia. This work has not been submitted or accepted for a degree at any other institution.

Winthrop Professor D'Arcy Holman (principal supervisor) developed the initial study protocol and, with the collaboration of Associate Professor Frank Sanfilippo (co-supervisor), Winthrop Professor Jon Emery and others, sought funding for the research. Thereafter, under the guidance of her supervisors, the candidate led significant and detailed theoretical and technical development of the original broad conception of the study and implemented all research components outlined in the objectives, managing the project, refining several aspects of the design, establishing the data sets, and conducting all data analyses. Thesis writing was also the candidate's full responsibility, with minor input from supervisors upon review.

This thesis contains a number of co-authored manuscripts, which have been submitted for publication (as listed on pages xiii-xiv). For each of these manuscripts, the candidate prepared the first draft, all co-authors making further (usually minor) amendments to its contents as necessary, until submission of the final draft. All co-authors have given their written permission for inclusion of these manuscripts within this document.

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Sylvie D Price  
(PhD Candidate)

17 / 01 / 2014

Date signed

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Prof C D'Arcy J Holman  
(Principal Supervisor)

17 / 01 / 2014

Date signed



# MANUSCRIPTS FOR PUBLICATION

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During her PhD candidature, the postgraduate student produced the following manuscripts for journal publication.<sup>†</sup> Her contribution was  $\geq 90\%$  for all manuscripts directly resulting from the candidate's research project, and  $\sim 10\%$  for the published paper that was indirectly related.

<sup>†</sup> Publication status updated on 9 June 2014, upon final thesis submission.

## MANUSCRIPTS DIRECTLY RESULTING FROM CANDIDATE'S RESEARCH PROJECT

- Price SD, Holman CDJ, Sanfilippo FM, Emery JD. Use of case-time-control design in pharmacovigilance applications: exploration with high-risk medications and unplanned hospital admissions in the Western Australian elderly. *Pharmacoepidemiology and Drug Safety* 2013; 22(11):1159-1170. doi: 10.1002/pds.3469. (Presented in chapter 4.)
- Price SD, Holman CDJ, Sanfilippo FM, Emery JD. Are older Western Australians exposed to potentially inappropriate medications according to the Beers Criteria? A 13-year prevalence study. Accepted by the *Australasian Journal on Ageing* on 03/12/2013; released online for early view on 20/03/2014. doi: 10.1111/ajag.12136. (Presented in chapter 5.)
- Price SD, Holman CDJ, Sanfilippo FM, Emery JD. Association between potentially inappropriate medications from the Beers Criteria and the risk of unplanned hospitalization in elderly patients. *The Annals of Pharmacotherapy* 2014; 48(1):6-16. doi: 10.1177/1060028013504904. (Presented in chapter 6.)
- Price SD, Holman CDJ, Sanfilippo FM, Emery JD. Does ongoing GP care in elderly patients help reduce the risk of unplanned hospitalisation related to Beers potentially inappropriate medications? Under review; submitted to *Geriatrics and Gerontology International* on 06/04/2014. (Presented in chapter 7.)
- Price SD, Holman CDJ, Sanfilippo FM, Emery JD. Are high-care nursing home residents at greater risk of unplanned hospital admission than other elderly patients when exposed to Beers potentially inappropriate medications? Accepted by *Geriatrics and Gerontology International* on 21/10/2013; released online for early view on 03/12/2013. doi: 10.1111/ggi.12200. (Presented in chapter 8.)

- Price SD, Holman CDJ, Sanfilippo FM, Emery JD. Impact of specific Beers Criteria medications on associations between drug exposure and unplanned hospitalisation in elderly patients taking high-risk drugs: a case-time-control study in Western Australia. *Drugs and Aging* 2014; 31(4):311-325. doi: 10.1007/s40266-014-0164-6. (Presented in chapter 9.)

**PUBLISHED PAPER RELATED TO CANDIDATE'S RESEARCH PROJECT**

- Zhang M, Holman CDJ, Price SD, Sanfilippo FM, Preen, DB, Bulsara MK. Comorbidity and repeat admission to hospital for adverse drug reactions in older adults: retrospective cohort study. *British Medical Journal* 2009; 338:a2752. doi: 10.1136/bmj.a2752.



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# ABBREVIATIONS

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ABS	Australian Bureau of Statistics
ACC	Aged and Community Care (data prefix)
ACOVE	Assessing Care of Vulnerable Elders (quality assessment tool)
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
AF	Attributable Fraction
AIHW	Australian Institute of Health and Welfare
ARIA	Accessibility/Remoteness Index of Australia; ARIA+ is the measure of remoteness endorsed by the Australian Bureau of Statistics
ASCII	American Standard Code for Information Interchange; ASCII files are often referenced as 'text' files
AsPEN	Asian PharmacoEpidemiology Network
ATC	Anatomical Therapeutic Chemical (drug classification)
BEACH	Bettering the Evaluation and Care of Health Program (source of general practice drug prescribing data)
CAPS	Coding Atlas for Pharmaceutical Substances (used in the BEACH database)
CD	Collector's District (in reference to geographical boundaries)
CI	Confidence Interval
CNODES	Canadian Network for Observational Drug Effect Studies
COVS	Covariance Sandwich option for robust analysis of variance (SAS)
COX-2	Cyclooxygenase-2
CRIME	CRIteria to assess appropriate Medication use among Elderly complex patients; Italian appropriate prescribing criteria
CRR	Cardiac Rhythm Regulator
DDD	Defined Daily Dose

DoH/DoHWA	Department of Health of Western Australia
DTH	Death (data prefix)
DURG	Drug Utilisation Research Group
Ecode	External Cause Code (from ICD clinical coding scheme)
ED	Emergency Department
ELR	Electoral Roll (data prefix)
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EPhMRA	European Pharmaceutical Market Research Association
GENMOD	Generalised Linear Models procedure (SAS); used to perform Poisson regression analysis
GORD	Gastro-Oesophageal Reflux Disease
GP	General Practitioner
HEDIS	Healthcare Effectiveness Data and Information Set (US healthcare performance tool)
HMD	Hospital Morbidity Data (data prefix)
HRD	High-Risk Drug
HRPIMS	High-Risk and Potentially Inappropriate Medications in Seniors
ICD	International Classification of Diseases
ICD-9-CM	International Classification of Diseases, 9 <sup>th</sup> Revision, Clinical Modification
ICD-10-AM	International Classification of Diseases, 10 <sup>th</sup> Revision, Australian Modification
ID	Identifier
IPET	Improving Prescribing in the Elderly Tool
LOGISTIC	Logistic Regression procedure (SAS)
MAI	Medication Appropriateness Index; implicit criteria for assessing prescribing appropriateness in older people
MBS	Medicare Benefits Scheme



MIMS	Monthly Index of Medical Specialities; MIMS Australia is the primary source of information for registered therapeutic drugs in Australia
MS	Microsoft (prefix; e.g. MS-Excel)
N/A	Not Applicable
NC	North Carolina
NEC	Not Elsewhere Classified
NHMRC	National Health and Medical Research Council
NORGEF	NORwegian GEneral Practice criteria for assessing potentially inappropriate prescribing in older people
NPS	National Prescribing Service
NSAID	Non-Steroidal Antiinflammatory Drug
NY	New York State
OR	Odds Ratio
PBS	Pharmaceutical Benefits Scheme
PDD	Prescribed Daily Dose
PhD	Doctor of Philosophy
PHREG	Proportional Hazard Regression procedure (SAS); can also be used to perform conditional logistic regression analysis
PID	Person Identifier
PIM	Potentially Inappropriate Medication
PRISCUS	Latin for “old and venerable”; German list of potentially inappropriate medications in older people
PY	Person-Years
RANUNI	Statistical function that returns a RANdom number from a UNIform distribution (SAS)
SAS	Statistical Analysis Software

SEIFA	Socio-Economic Indexes for Areas (includes a measure of socio-economic disadvantage); developed by the Australian Bureau of Statistics
SLA	Statistical Local Area (in reference to geographical boundaries)
SPARC	System for the Payment of Aged Residential Care
START	Screening Tool to Alert doctors to Right Treatment
STOPP	Screening Tool of Older Peoples' Prescriptions
US/USA	United States of America
WA	Western Australia(n); Washington State (if in USA)
WADLS	Western Australian Data Linkage System
WHO	World Health Organization

# CHAPTER 1 INTRODUCTION

---

## 1.1 OVERVIEW

The harmful effects of therapeutic drugs are an important cause of hospitalisation, especially in the elderly.<sup>1-3</sup> Older people are major consumers of medication and, due to physiological deterioration and other age-related factors, are more susceptible to adverse drug events (ADEs).<sup>4-8</sup> To address this problem, various lists of medications considered potentially inappropriate in older people have been developed.<sup>9-12</sup> Among them, the Beers Criteria<sup>13-16</sup> are by far the most commonly referenced.

Until recent years, most Australian statistics on ADE-related hospitalisations have been based on the analysis of external cause codes from the International Classification of Diseases (ICD) recorded on inpatient discharge summaries. Not only does this coding scheme lack sufficient detail to permit the identification of individual drugs as causal agents but, given the ambiguous symptoms associated with some adverse drug reactions, it is suspected that many patients hospitalised due to ADEs may not be identified as such in hospital records.<sup>17-20</sup>

The linkage of data from the Australian Pharmaceutical Benefits Scheme (PBS),<sup>21,22</sup> Medicare Benefits Scheme (MBS)<sup>23,24</sup> and System for the Payment of Aged Residential Care (SPARC)<sup>25</sup> databases with Western Australian (WA) inpatient, death and electoral roll records provided the opportunity to explore alternative methods for estimating the ADE-related hospitalisation burden in elderly Western Australians. Using the linked data, it was also possible to assess the impact of exposure to potentially inappropriate medications (PIMs) from the 2003 general Beers list<sup>15</sup> in this population in terms of unplanned hospitalisations.

## 1.2 RESEARCH OBJECTIVES

This major 'proof of concept' pharmacoepidemiological study aimed to explore the use of these linked health records from Australian and WA Government sources in potential pharmacovigilance and medication prevalence applications. More specifically, the study sought to establish the infrastructure, develop protocols and statistical programs, and perform the analyses required to meet

the following objectives, based upon the health data of WA residents aged  $\geq 65$  years over a 13-year period (1993-2005):

- 1) To assess the impact on hospitalisation burden of medications thought to be the leading causes of ADE-related hospitalisation in older Western Australians (i.e. 'high-risk drugs') by applying an enhanced case-time-control design<sup>26,27</sup> and conditional logistic regression to the data, from which the following measures would be derived: odds ratios (ORs), attributable fractions (AFs), and the number and proportion of unplanned hospitalisations associated with exposure to each high-risk drug group. Furthermore, to compare the results obtained using this approach with those derived from more conventional methods involving the analysis of external cause codes found on inpatient records.
- 2) To examine the prevalence over time of exposure to general PIMs from the 2003 Beers Criteria<sup>15</sup> in elderly Western Australians, estimating not only the number and proportion of people exposed, but also daily doses/1000 person-years (both overall and for individual PIMs), and to identify associated risk factors through logistic regression analysis.
- 3) To estimate the effects of exposure to Beers' general PIMs<sup>15</sup> on unplanned hospitalisations in this population (i.e. determine the strength of associations), overall and for each individual PIM, adopting similar methods to those applied in the analysis of high-risk drug groups.
- 4) To assess the role of ongoing general practitioner (GP) monitoring in modifying the effects of exposure to Beers' general PIMs<sup>15</sup> on unplanned hospitalisations, by applying a case-time-control design<sup>26,27</sup> to the data of relevant population sub-groups and comparing the results.
- 5) To evaluate the role of high-level residential aged care in modifying the effects of exposure to Beers' general PIMs<sup>15</sup> on unplanned hospitalisations, by applying a case-time-control design<sup>26,27</sup> to the health data of high-care nursing home residents and of all other WA residents aged  $\geq 65$  years (separately), and comparing the results obtained for each sub-group.
- 6) To determine whether risk estimates of drug-related hospitalisations are altered in elderly patients taking medications from high-risk drug groups when specific Beers' medications are taken into consideration.

### **1.3 ETHICS APPROVAL**

The study protocol was approved by The University of Western Australia's Human Research Ethics Committee. Since details that would reveal a person's identity were not released with the data extracts, patients were not required to provide informed consent. Copies of the ethics approval confirmation documents are provided in Appendix A.

### **1.4 THESIS STRUCTURE**

This thesis consists of ten chapters. Chapter 1 introduces the work undertaken during the PhD candidature, providing a brief overview of the research topic and specifying the study's primary objectives. This introductory chapter is then followed by a concise review of background literature (chapter 2) and a general outline of the research methodology (chapter 3). The core of the thesis (chapters 4-9) brings together the contents of six manuscripts submitted to medical journals for peer review and publication of study results. Each manuscript addresses one of the study objectives outlined in chapter 1. A short preface introduces each core chapter, providing the context and rationale for the study component being presented. Finally, the last chapter (chapter 10) discusses the key findings, issues and implications emanating from the study as a whole, highlighting the research significance and future directions.



# CHAPTER 2 BACKGROUND LITERATURE

---

This chapter examines key components of the literature related to this project. It concentrates on major concepts and issues as they apply within the context of this study, seeking to provide general background information for the research that was undertaken rather than provide an extensive account of each literature component.

## 2.1 ADVERSE DRUG EVENTS AND RISK OF HOSPITALISATION IN THE ELDERLY

### 2.1.1 DEFINING ADVERSE DRUG EVENTS

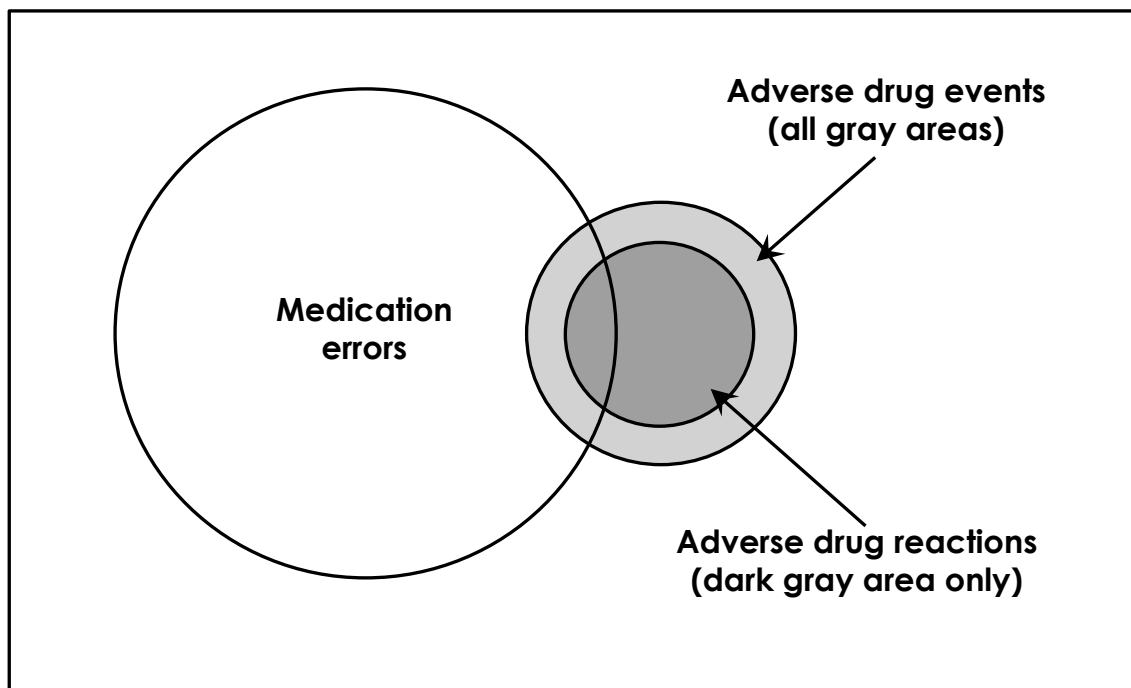
Much of the research presented in this thesis relates to the association between medication exposure and unplanned hospitalisations in older adults, potentially due to adverse drug events. But what do we mean by 'adverse drug events'? The term is used inconsistently in the literature. Medication use is associated with a broad range of drug-related problems, which relate to appropriate and inappropriate prescribing (including over- and under-prescribing), medication errors, non-adherence and other factors.<sup>28,29</sup> All of these issues can lead to patient harm. In an attempt to clarify related terminology, Nebeker et al. have proposed the following definitions:

**Adverse drug reactions** are injuries caused by drugs administered at usual doses; they are the primary focus of regulatory agencies and postmarketing surveillance. **Adverse drug events** are injuries caused by drug use that encompass adverse drug reactions and harm resulting from medication errors; they are the targets of broader efforts to improve patient safety.<sup>30</sup>

As illustrated in Figure 2-1, only a small proportion of medication errors result in ADEs. Conversely, the majority of ADEs do not involve a medication error.

This study has adopted these definitions, with the understanding that 'injuries' refer to any type of harm inflicted on a person as a result of medication use, including symptoms of a more ambiguous nature (e.g. cognitive impairment, sleep disruption, loss of appetite), but recognises that, in situations where ADEs are identified explicitly, ambiguous symptoms are more likely to be under-reported. Furthermore, the term 'medication errors' is interpreted quite broadly, encompassing both prescribing errors and drug administration problems,

including patient non-adherence. However, it should be acknowledged that, given the study design, ADEs that involve the non-use of a recommended medication will generally not be detected in the analysis.



**Figure 2-1 Relationship between adverse drug events, adverse drug reactions and medication errors<sup>a</sup>**

<sup>a</sup> Diagram adapted from Nebeker et al., 2004.<sup>30</sup>

### **2.1.2 INCREASED RISK OF ADE-RELATED HOSPITALISATION IN THE ELDERLY**

ADE-related hospitalisations are a major problem in the elderly.<sup>1-3</sup> Older adults become more susceptible to ADEs due to physiological deterioration (e.g. decline in renal and liver function; cognitive, sensory and motor function impairment); increasing comorbidities; greater complexity of medication therapy, including polypharmacy; and other age-related factors. This can lead to pharmacokinetic and pharmacodynamic complications, a rise in the likelihood of drug-drug and drug-disease interactions, and difficulties remembering and adhering to prescribed medication regimens, all of which are associated with drug-related problems.<sup>4-8,17,29</sup>

A recent review<sup>29</sup> has suggested that ADEs may be involved in up to 31% of hospital admissions in the elderly, this proportion increasing with age and over time. It concluded that the odds of being hospitalised due to drug-related problems were 4-7 times greater in older age groups than in younger people, conceding that there was a high level of heterogeneity between studies. In the



United States, ADEs may account for nearly 100,000 emergency hospitalisations each year in people aged  $\geq 65$  years.<sup>31</sup> In Australia, it is estimated that 15-22% of unplanned hospital admissions are drug-related in this age group.<sup>32</sup> Most importantly, according to a recent study of older Australian war veteran beneficiaries (median age of 80 years), ~20% of medication-related hospitalisations may be preventable.<sup>33</sup>

### **2.1.3 WESTERN AUSTRALIAN RESEARCH INITIATIVES**

In the early 1990s, a research study investigated the burden of hospital morbidity and mortality due to 'poisoning' in WA over the period 1980-1991.<sup>20</sup> The study estimated the cost of WA hospitalisations due to poisoning (which included all adverse effects from therapeutic drugs, as well as poisoning due to medications and other substances) to be around \$10.5 million in 1991, of which 57% involved ADE-related hospital separations. Moreover, the rate of ADE-related hospitalisations, most of which occurred in elderly patients, doubled during the study period.

This same research project also conducted a validation study of ADE-related hospitalisations in elderly patients, determining that rates were much higher when cases were ascertained from patient notes than from external cause codes on inpatient records from the WA Hospital Morbidity Data System (a centralised state repository of hospital inpatient summary records).

A subsequent study, which concentrated on ADE-related hospitalisations in Western Australians aged  $\geq 60$  years during 1981-2002, reported an increase in rate from 2.5 to 12.9 per 1000 person-years over the study period. As a broad medication group, cardiovascular agents accounted for the greatest proportion (17.5%) of these hospitalisations. A more refined categorisation identified anticoagulants, cytotoxics, antirheumatics, corticosteroids, opioids and antihypertensives as the most common therapeutic drugs involved.<sup>18</sup>

These same drug groups were found to be responsible for repeat hospitalisations due to the harmful effects of medications in yet another study of WA elderly (1980-2003), although not quite in the same order of relative importance.<sup>34</sup>

Several reviews of study results involving ADE-related hospitalisations in various Australian populations have provided further support to the WA findings, also suggesting that these particular drug classes were associated with high

rates of hospital admissions due to therapeutic drug harm.<sup>3,32,35</sup> Admittedly, a broader review of the literature now suggests that a few other drug classes (e.g. antidiabetic and psychotropic medications), may also have merited some consideration, at least from an international perspective.<sup>29</sup>

In any event, these previous observational studies, which involved older adults, were useful in assessing the ADE burden on the WA and Australian health care system, and in describing trends in related hospitalisation rates. However, under-ascertainment of cases<sup>18,20</sup> and lack of specificity of the inpatient clinical coding scheme in identifying the particular drugs responsible for the harmful effects<sup>34</sup> have been suggested as important limitations in these studies.

Some of the research presented in this thesis builds upon the previous Western Australian studies by further investigating the 'high-risk' drug groups, through the use of alternative methods that address these particular shortcomings.

## **2.2 THE BEERS CRITERIA AND INAPPROPRIATE PRESCRIBING IN THE ELDERLY**

### **2.2.1 DEVELOPMENT OF THE BEERS CRITERIA**

Given the increased susceptibility of older people to experience ADEs, much effort has been devoted to the identification of factors responsible for their occurrence, with the view to prevent them.<sup>17</sup> One such factor is inappropriate prescribing. In general terms, 'inappropriate prescribing' does include the prescribing of a medication that is not indicated; the omission of one that would clearly be beneficial; the prescribing of drug combinations with known negative interactions; dosages that are either too high or too low; and perhaps a few other more complex scenarios.<sup>4,12,36,37</sup> However, in the elderly, the focus has been on the prescribing of specific medications for which the risk of harm likely outweighs the potential benefit (especially when there is a safer or more effective alternative), in light of general age-related physiological decline and of particular concerns associated with common health conditions in this age group.<sup>4,9,36</sup>

In 1991, Mark Beers and his research colleagues from the University of California published a list of criteria, which identified medications considered inappropriate for use in nursing home dwellers.<sup>13</sup> These criteria were intended for use in the absence of extensive diagnostic information among the most frail elderly. The list was subsequently refined and adapted to the broader elderly

population through a rigorous process involving literature searches and the input of six American geriatric and pharmacology experts.<sup>14</sup>

A further update of the criteria was released in 2003, following a similar process to Beers' (i.e. a modified Delphi method).<sup>15</sup> The American Medical Directors Association and American Society of Consultant Pharmacists issued a joint position statement on the "Beers List", acknowledging it as a "helpful general guide regarding potentially inappropriate medication use ... for older adults" but emphasising that "it must be used in conjunction with a patient-centered [sic] care process".<sup>38</sup>

The 2003 Beers Criteria identified 49 general medication groups that should be avoided in all older people and a further 19 that should not be prescribed to those who have specific health conditions. Unconditional avoidance was recommended for most of these drugs, but a few were considered to be of concern if prescribed above a specified dosage level, for an extended period of time, or in a particular form. This version of the Beers Criteria has provided the framework for defining PIMs in this study, with a particular focus on medications to be avoided in all people aged  $\geq 65$  years (i.e. 'general' list).

In 2012, another version of the Beers Criteria was published, which was developed and endorsed by the American Geriatrics Society.<sup>16</sup> The latter provides a better structured and more explicit list of PIMs, quantifies the strength of the evidence associated with their inclusion, and is based on medications that were available in the United States (US) in 2011. Although this latest edition is obviously more current than the one used in this study, it does not differ substantially from its predecessor. At any rate, since it was not available for most of the period in which this research project was undertaken, it could not be used in the analysis.

### **2.2.2 DEVELOPMENT OF OTHER INAPPROPRIATE PRESCRIBING CRITERIA**

Although the Beers list may have been at the forefront in the development of inappropriate prescribing criteria in the elderly, many other sets of related criteria have been established since.<sup>9-12</sup> The majority are 'explicit' criteria, which are derived from agreed prescribing standards (usually lists of medications to be avoided, generally or under specific conditions), most often involving reviews of current evidence, expert opinions and consensus techniques. However, some are 'implicit', requiring clinical judgment and

individual assessment of each patient in the determination of inappropriateness. Explicit criteria are usually more straight-forward to implement, but may not take account of individual patient circumstances. In contrast, implicit criteria are more patient-focused, but are less clear-cut, more time-consuming to apply and, since they depend on clinicians' knowledge and attitudes, may be less reliable.<sup>10-12</sup>

In the US, around the time the first set of Beers Criteria were published in the early 1990s, Hanlon et al. produced the Medication Appropriateness Index (MAI), a set of implicit criteria in the form of ten questions, which led the clinician to assess drug indication, effectiveness, dosage, duration, duplication, cost, appropriateness and practicality of directions, as well as drug-drug and drug-disease interactions.<sup>39</sup> Similarly, in 1993, Lipton et al. produced a set of prescribing appropriateness criteria for geriatric outpatients that also required implicit judgment.<sup>40</sup>

Over time, additional sets of explicit criteria were implemented in the US as well, mostly derived from the Beers Criteria. For instance, in 2001, Zhan et al. published a validated subset of 33 PIMs from the 1997 Beers Criteria to be avoided in community-dwelling elderly irrespective of dose, duration or frequency of use, classifying them as follows: always avoid, rarely appropriate, and some indication for use in the elderly.<sup>41</sup> Moreover, the Healthcare Effectiveness Data and Information Set (HEDIS), a tool used by >90% of America's health plans to measure health care performance, incorporated a subset of the Beers Criteria in its 2007 update to be used as medication prescribing quality indicators.<sup>42</sup> Likewise, a subset of the indicators from the American Assessing Care of Vulnerable Elders (ACOVE) quality assessment tool pertains to inappropriate medications.<sup>42</sup>

In Canada, the 1991 Beers Criteria inspired McLeod et al. to produce a set of 38 criteria adapted to the Canadian national drug formulary (including four drug-drug interactions) to identify inappropriate prescribing in the elderly.<sup>43</sup> This PIM list, initially published in 1997, was subsequently condensed into a succinct set of 14 explicit criteria and validated in a hospital setting to form the basis of the Improving Prescribing in the Elderly Tool (IPET).<sup>44</sup>

The Beers Criteria have also influenced the development of PIM lists outside North America, especially since the release of the 2003 update. In Europe, the

French published explicit inappropriate prescribing criteria in 2007,<sup>45</sup> quickly followed by Ireland (STOPP),<sup>46</sup> Norway (NORGE),<sup>47</sup> Italy (CRIME),<sup>48,49</sup> Germany (PRISCUS),<sup>50</sup> Austria,<sup>51</sup> Croatia,<sup>52</sup> Finland,<sup>53</sup> and others. Most sets of criteria are Beers adaptations, at least to some extent, although differences in national medication formularies, incorporation of local drug prescribing guidelines, and input from additional sources have affected the end result, such that most of these PIM lists are not directly comparable. Additionally, one should mention the Swedish criteria, a succinct set of four broad prescribing rules, used as quality indicators in this country to assess inappropriate prescribing in patients aged  $\geq 75$  years.<sup>54,55</sup> PIM lists have also been published for Asian nations (e.g. Thailand,<sup>56</sup> Japan<sup>57</sup> and Taiwan<sup>58</sup>). The latter seem to closely mirror the 2003 Beers Criteria, but reflect medication availability in these countries.

In recent years, the Irish STOPP criteria<sup>46</sup> appear to have gained some attention, especially in Europe, as they have been shown to better reflect the availability of medications in this part of the world, and may possibly be better predictors of ADEs.<sup>10,59</sup> STOPP or “Screening Tool of Older Peoples’ Prescriptions” consists of 65 explicit rules for identifying inappropriate prescribing in the elderly, similar in nature to those from the Beers Criteria. What makes it stand out is its companion tool named START (Screening Tool to Alert doctors to Right Treatment),<sup>46,60</sup> which lists medications that should be prescribed to older adults with specific health conditions, thus permitting the identification of under-prescribing issues. These two screening tools combined provide a more comprehensive means of assessing inappropriate prescribing practices in the elderly.<sup>10,46</sup>

In Australia, a set of indicators for assessing prescribing appropriateness in the elderly was first published in 2008, but has since been refined and validated.<sup>61,62</sup> However, these indicators are not based on the Beers Criteria. They are essentially measures to evaluate prescribing guidelines rather than a list of medications that are potentially inappropriate in older people. They predominantly relate to optimal treatment for patients with specific health profiles. By-and-large, they are too complex to be applied readily to administrative health data, many indicators requiring a clinical assessment of patient circumstances, including knowledge of patients’ medical history, current

health and medication profile, and behaviour (e.g. smoking). Whilst these indicators may be a valuable set of rules to use in individual patients or to assess the quality of Australian prescribing practices in small clinical settings, they would be almost impossible to apply in a large population-based study that involves electronic records only, such as this one. In any case, the Australian indicators were not available at the time this study was initiated.

### **2.2.3 RESEARCH INVOLVING THE 2003 BEERS CRITERIA**

The Beers Criteria have been highly influential worldwide, especially since the release of the 2003 revision. Their impact can best be summarised by a quote from the co-chairpersons of the committee responsible for the 2012 Beers list update:

The Beers Criteria remain simultaneously one of the most used and most controversial sets of medication criteria in the world. Although not without limitations, the Beers Criteria have done more than any other tool in the past decade to improve the awareness of and clinical outcomes for older adults with polypharmacy and for the most vulnerable older adults at risk of adverse drug events. They have accomplished this because of their explicit nature, simple application for non-pharmacy experts, and wide dissemination. The continued development of explicit lists of medications to avoid in older adults, such as the Beers Criteria, is a critical component, albeit not the only one, in the public health imperative to decrease drug-related problems and improve the health of older adults.<sup>63</sup>

Not surprisingly, the literature related to the 2003 Beers Criteria is rather extensive and somewhat overwhelming. For instance, the journal article that presents these criteria<sup>15</sup> had been cited nearly 1000 times by the end of 2013 (Web of Knowledge, Thomson Reuters Corporation, New York NY, USA). Since most of the relevant literature is already referenced in the manuscripts presented in other chapters of this thesis, a detailed review in this section would be somewhat repetitious and does not seem warranted. Nonetheless, a very brief summary of research initiatives involving the 2003 Beers list and of associated findings is provided below.

Beyond reporting on the development of other PIM lists, the bulk of the literature related to the 2003 Beers Criteria<sup>15</sup> pertains to the ascertainment of PIM

prevalence in various populations, and of associated risk factors. Overall, research studies indicate that around 10-40% of older people are exposed to Beers medications, depending upon PIM definitions, settings, and duration of follow-up,<sup>36,64-66</sup> although figures as low as 6% and as high as 88% have been reported, in a Danish<sup>67</sup> and American<sup>68</sup> elderly home care setting, respectively. It is important to note, however, that the Danish study assessed PIM prevalence based on a seven-day period only, whereas its American counterpart followed patients for up to 2-3 years (depending upon the duration of home care) and restricted follow-up to home care periods that were immediately preceded by a hospital stay.

The prevalence of individual PIMs has also been reported in the literature, but is highly dependent upon availability, which varies from country to country. In an Australian setting, the Beers PIMs most consistently reported as being highly prevalent in the elderly include benzodiazepines (e.g. temazepam, diazepam), amitriptyline (antidepressant) and amiodarone (cardiac rhythm regulator).<sup>69-75</sup>

In terms of risk factors, polypharmacy (i.e. number of drugs taken concurrently)<sup>64,67,75-103</sup> and female gender<sup>84-86,95,103-105</sup> have been most frequently reported to be significant predictors of exposure to Beers medications. Age has also been linked with PIM exposure, although not consistently, and not always in the same direction.<sup>64,67,77-79,84,87-90,95,103-105</sup> Other possible predictors reported in the literature include increased level of comorbidity,<sup>79,90,101,104,106</sup> number of health care visits,<sup>85</sup> socio-economic factors,<sup>67,79,84</sup> and others.

A pivotal yet controversial aspect of the Beers Criteria is whether exposure to listed PIMs increases the risk of ADEs in the elderly. Early reviews assessing the association between Beers medications and adverse health outcomes in older people were inconclusive, although most of the studies included were based on older versions of the Beers list (1991/97).<sup>36,107,108</sup> A number of more recent studies involving Beers 2003 have helped strengthen the evidence in this regard,<sup>90,106,109-118</sup> although this is far from universal. The issue may not necessarily be that Beers medications are unlikely to increase the risk of harmful outcomes in older people, but that other prescribing factors may be of greater importance in the quest to prevent ADEs in this age group. A recent study by Budnitz et al., for instance, has suggested that, in the US, a number of

therapeutic drugs that are not on the Beers list may be responsible for the majority of ADE-related hospitalisations in the elderly following an Emergency Department visit.<sup>31</sup> Thus, more research in this area and perhaps further refinements of the Beers list may be justified. Furthermore, the sparsity of studies reporting on interventions involving the Beers list make it difficult to assess its effectiveness in the prevention of inappropriate prescribing and of associated adverse health outcomes in older people.<sup>119-121</sup>

Despite these controversies, it is estimated that the healthcare expenditures related to PIM use in older community-dwelling Americans was around US\$7.2 billion in 2001.<sup>122</sup> This estimate alone should be a sufficient reason to continue paying attention to Beers medications, avoiding them in the elderly whenever possible.

### **2.3 PHARMACOVIGILANCE AND THE USE OF LARGE HEALTH DATABASES**

The primary aim of this study was to develop a protocol involving the use of linked pharmaceutical claims data that could help identify individual medications likely associated with a high risk of serious harm. Although the approach could be used to investigate any prescribed drug, it seemed particularly relevant in post-marketing pharmacovigilance applications. Thus, it is important to examine pharmacovigilance concepts and initiatives worldwide, to place this study into its appropriate context.

Although randomised controlled trials have long been considered the gold standard in providing evidence of the efficacy and safety of therapeutic products within pre-market regulatory systems, their limited sample sizes and study durations, restricted populations, and controlled settings are not always adequate in detecting potential adverse effects.<sup>123-125</sup> This is particularly true in relation to medication safety in older adults, who tend to be under-represented in these trials due to age and comorbidity exclusion criteria.<sup>125</sup> The need to balance adequate drug safety assessment with the timely release of efficient and apparently beneficial medications has led to the establishment of mechanisms to continue monitoring the safety of medications once they are released onto the market.<sup>123</sup>

The World Health Organization (WHO) has defined pharmacovigilance as “the science and activities relating to the detection, assessment, understanding and



prevention of adverse effects or any other possible drug-related problems”.<sup>126</sup> Several different ADE detection mechanisms have been established over time, of which spontaneous reporting has been used most extensively. This approach, which involves the voluntary reporting of suspected adverse drug reactions to a national coordinating centre by health professionals, manufacturers and, in some instances, patients, is simple and cost-effective, but may lead to under-reporting and potential selection biases.<sup>123,125,127,128</sup> In fact, estimates suggest that periodic drug safety reports from pharmacovigilance databases may only capture around 1-10% of adverse drug reactions.<sup>129,130</sup>

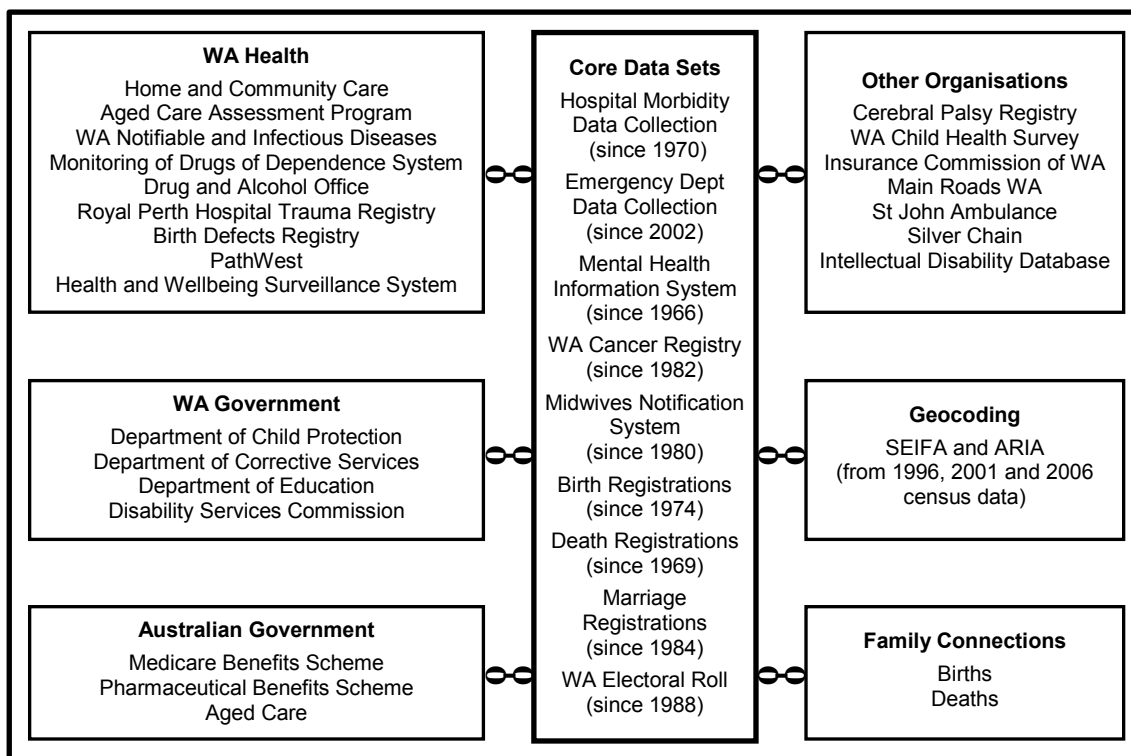
Other forms of ADE detection mechanisms include intensive ADE monitoring and chart reviews, both of which are rather labour-intensive, costly and usually of short duration, although more comprehensive and accurate than most other approaches;<sup>127,128</sup> automated ‘signal detection’ techniques applied to computerised health administration systems, which require rules and algorithms of high specificity to identify ADE scenarios of interest and are most effective with structured data (as opposed to narrative notes) and standard definitions;<sup>128,131-133</sup> and the use of administrative health data to conduct non-interventional observational studies (e.g. pharmacoepidemiological research).<sup>124,125</sup>

Observational studies used in post-marketing pharmacovigilance applications have become increasingly popular in recent years,<sup>124</sup> with the establishment of major pharmacoepidemiological data networks in Europe (e.g. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance - ENCePP),<sup>134</sup> North America (e.g. Canadian Network for Observational Drug Effect Studies - CNODES)<sup>135</sup> and Asia (e.g. Asian Pharmacoepidemiology Network - AsPEN).<sup>136</sup> These studies, which analyse administrative health data using a variety of epidemiological designs, more closely reflect the ‘real-life’ situation (as opposed to clinical trials), are not restricted to patients who experience ADEs and, although often dismissed for providing less compelling evidence than randomised controlled trials, have been shown to be far more useful than generally acknowledged, providing important drug safety information when properly conducted.<sup>124,137</sup>

The research presented in this thesis falls into this latter category of ADE detection mechanisms, analysing administrative health data to identify medications associated with a high risk of serious adverse effects. Although not commissioned as a post-marketing pharmacovigilance initiative per se, it does seek to demonstrate how broad population-based observational studies involving linked health data could be used as such in an Australian setting.

## 2.4 LINKAGE OF HEALTH DATA - WESTERN AUSTRALIAN PERSPECTIVE

The Western Australian Data Linkage System (WADLS), which was established in 1995, uses computerised probabilistic matching involving full names and addresses, phonetic compression and other identifiers to link together more than 30 administrative and research health databases (Figure 2-2).<sup>138-140</sup> This linkage process maintains chains of links for each individual within the system (around four million chains linking nearly 40 million records in 2013).<sup>141</sup> An evaluation of linked chains has estimated that fewer than 0.3% contain incorrect links.<sup>138</sup>



**Figure 2-2 Western Australian Data Linkage System - core data sets (linked regularly) and other sources of linked data<sup>a</sup>**

<sup>a</sup> Diagram adapted from Data Linkage Western Australia, 2013.<sup>140</sup>

WA - Western Australia(n)

SEIFA - Socio-economic indexes for areas (Australian socio-economic indicators)

ARIA - Accessibility/remoteness index of Australia

The WADLS is one of only a handful of well-established data linkage systems worldwide. It brings together person-level information from different sources without compromising the privacy of individuals and is particularly useful in the research of health-related issues in the Western Australian population.<sup>138,139</sup>

Initially, the WADLS concentrated on linking data from Western Australian sources, including birth and death registrations; public and private hospital discharge summary records; mental health data; and information from a number of health-related state registries. However, this restriction imposed a number of limitations on health services research, as primary care and other services from the MBS, prescriptions from the PBS, and residential aged care services data were excluded. In Australia, these services are under the jurisdiction of the Commonwealth Government.<sup>138,142</sup>

However, in June 2001, an important agreement allowed the linkage of health data held by the Western Australian and Australian Commonwealth jurisdictions for a pilot study of nearly 150,000 WA diabetics over the period 1990-1999.<sup>142,143</sup> The success of this project led to a formal agreement between the two jurisdictions for a more comprehensive linkage of health records involving the entire WA population. Although the agreement was executed in 2003, various processes prevented the extraction of cross-jurisdictional linked health data until early 2007.<sup>142</sup> Fortunately, investigators associated with this pharmacoepidemiological study were among the initial recipients of data from these combined cross-jurisdictional sources. As such, they were very keen to ensure the successful completion of this research.

## **2.5 THERAPEUTIC DRUG UTILISATION RESEARCH**

Development of drug utilisation research stems from early work in northern Europe and the United Kingdom in the mid-1960s. The pioneers recognised the need to compare drug utilisation patterns between countries and the difficulties in doing so due to differences in methodology. This led to the establishment of the World Health Organization's European Drug Utilization Research Group (DURG) in 1969.<sup>144</sup>

At the centre of drug utilisation research are the Anatomical Therapeutic Chemical (ATC) classification and the Defined Daily Dose (DDD), which have been used in Norway since the early 1970s, and continue to be maintained by

the WHO Collaborating Centre for Drug Statistics Methodology in Oslo since 1982. The former provides a framework for classifying generic pharmaceutical products, originating from an expansion and refinement of the European Pharmaceutical Market Research Association (EPHRA) classification system. The latter is defined as “the assumed average maintenance dose per day for a drug used for its main indication in adults”. It is the preferred unit of measure for computing drug consumption statistics, which are usually presented in terms of DDDs per person-time or, in hospital settings, per number of bed-days.<sup>145,146</sup>

Drug utilisation research has expanded quickly over the last few decades, the ATC/DDD methodology also being adopted in Australia.<sup>144</sup> For instance, it is used by the Australian Institute of Health and Welfare (AIHW) to report on national drug prescription figures. Using this approach, the AIHW has identified various blood lipid-reducing and anti-hypertensive medications among the top ten most frequently consumed therapeutic drugs in the Australian population.<sup>147</sup>

In this study, the ATC/DDD methodology has been used to identify and classify medications, to calculate daily dose rates, and to ascertain the likely drug exposure duration associated with individual prescriptions. However, daily dose allocations for each generic drug have been refined, based on comparisons between several available sources, to better reflect Australian prescribing practices. Furthermore, daily dose figures have been applied to individual drug strengths for each generic drug, such that rates identify the estimated number of days of drug exposure for a given medication rather than a specific drug quantity. These variations were desirable in this study, as the main reason for using daily dose measures was not to compare population-level drug consumption patterns with other countries, but to determine, as accurately as possible, the period of medication exposure in individual patients.

## **2.6 CASE-CROSSOVER AND CASE-TIME-CONTROL DESIGNS**

Difficulties in identifying appropriate controls using a conventional case-control design to study some of the transient effects associated with the incidence of myocardial infarction led Maclure in the early 1990s to introduce the “case-crossover” design.<sup>148</sup> This approach made use of cases as their own controls, measuring the exposures of interest immediately prior to an infarct (the ‘case time’) and during an interval of equal length at some other point in time (the ‘control time’). Using the case subject as its own control eliminated the need to

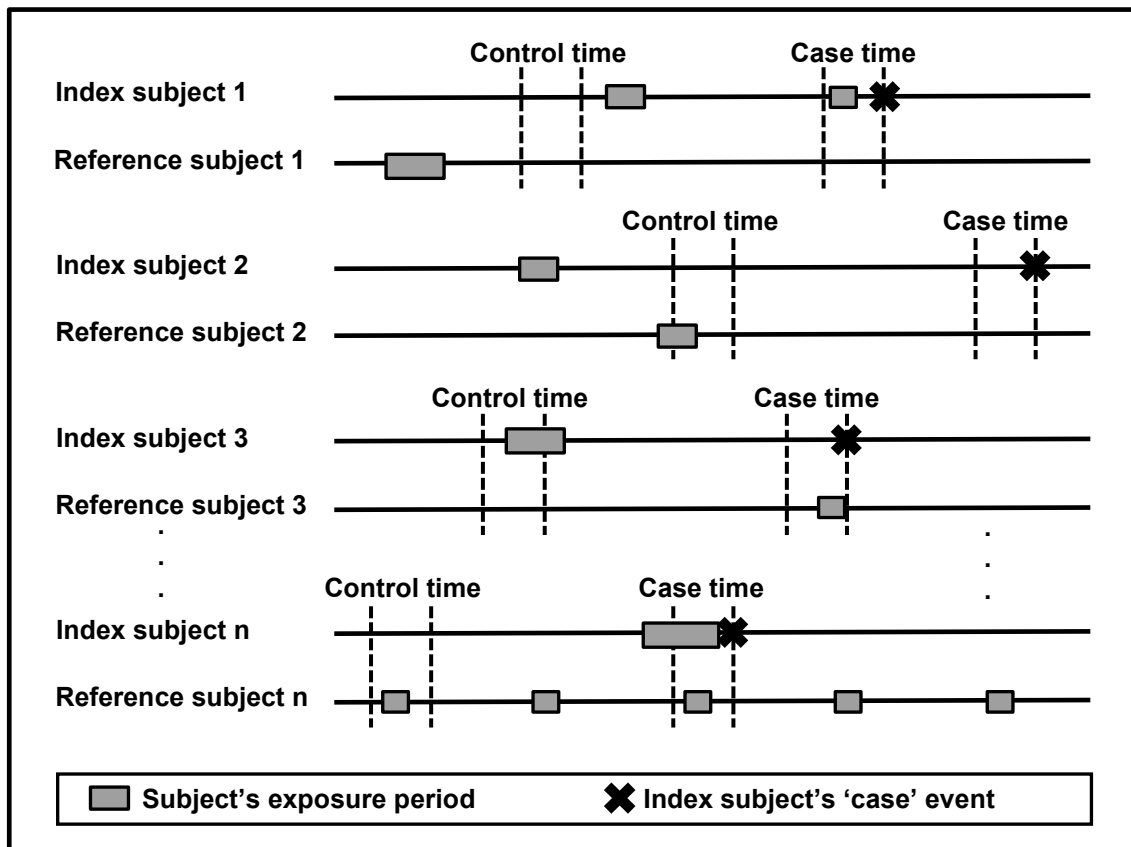
adjust for potential confounding effects associated with constant characteristics within individuals. This, it was argued, was useful in situations where information about these characteristics is not available or difficult to obtain. A review of the use of the case-crossover design about a decade later concluded that this design was best suited to studies where “the exposure is intermittent, the effect on risk is immediate and transient, and the outcome is abrupt”.<sup>149</sup> These conclusions were re-iterated in a very recent review, which also emphasised the need for caution, given the design’s inability to control for time-varying confounding.<sup>150</sup>

In 1995, Suissa proposed the “case-time-control” design, an extension of the case-crossover approach, which introduces a matched reference group to the ‘case time’ and ‘control time’ concept used in the case-crossover design.<sup>26</sup> In the case-time-control design, each case (i.e. index subject) is matched to a reference subject from an appropriate population at risk. Operationally, this appears similar to a standard matched case-control study with different subjects as cases and controls; however, the theoretical purpose of the matched reference group in a case-time-control design is different. Exposure status is ascertained in index subjects for the ‘case time’ and ‘control time’ in the same way as in the case-crossover design. However, exposure status is also established in the reference subjects for each of the same time periods as in the index subjects (Figure 2-3).

The strength of association between exposure and the outcome of interest can then be estimated in a conditional logistic regression model by concentrating on the apparent effect in the index subjects, over and above the general time trend that also applies in the reference group. This estimate is obtained from the odds ratio derived from the interaction term between the dichotomous index/reference indicator and the binary exposure variable in a basic model that also includes exposure as a separate variable.

Suissa referred to the two groups as “cases” and “controls” (as opposed to index and reference subjects), and identified the control time period in each subject as the “reference period”. A revised terminology has been adopted in this study to emphasise the fact that subjects in both the index and reference groups are used as their own controls, analogous to Maclure’s original case-crossover design. The reference group may be viewed as a surrogate for

performing a case-crossover on the index subjects under the counterfactual of absence of the outcome that made them an index subject. We also prefer to use the term ‘control’ to refer consistently to the source of information on the distribution of exposure in the underlying study base from which the outcomes derive, a concept central to modern epidemiologic thinking on the nature of case-control and other case-distribution sampling strategies.



**Figure 2-3 The case-time-control design<sup>26</sup>**

As per the case-crossover design, the case-time-control approach eliminates the need to control for the effects of potential confounding factors that do not vary over time within individuals. However, the case-time-control design also permits adjustments associated with temporal changes, especially in relation to protopathic bias and confounding by indication (forms of bias related to variations in medication prescribing over time as a result of disease progression or manifestation of a new health condition).<sup>26,27,151,152</sup>

Although the case-time-control design may be unable to control confounding in all situations, as suggested by both Greenland<sup>153</sup> and Suissa,<sup>27</sup> it seemed suitable in this pharmacoepidemiological application, which involved the use of administrative health data (from which information related to some potential

confounders is not readily available) to examine the association between medication use (intermittent exposures and transient effects) on unplanned hospitalisations (acute events). Adoption of the case-time-control design would also permit adjustments associated with potential time-related bias, through the use of reference subjects (for unknown variables) and the introduction of additional factors in the multivariate conditional logistic regression models (for known and measurable time-dependent variables).

## **2.7 CONCLUSION**

The outline presented in this chapter has brought together background information for the various components of this research project. Together they set the scene for a study that makes use of the linked health data of older Western Australians to examine the association between unplanned hospitalisations and exposure to specific medications (i.e. broad 'high-risk' drug groups and potentially inappropriate medications from the general Beers list), in an attempt to identify therapeutic drugs that may cause serious patient harm in this population. Concepts of pharmacovigilance, drug utilisation and relevant pharmacoepidemiological self-control designs were also reviewed, to provide a rationale for the study and the approach used for data analysis. This information will hopefully give some context to the rest of the material presented in this thesis.





## CHAPTER 3 METHODOLOGY

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Since this research project aimed to develop mechanisms for analysing Australian linked health data in medication safety applications, it is particularly important to document the methods used. Some of this information is included in the manuscripts presented in chapters 4-9 of this thesis. However, given publication constraints, the manuscripts were generally restricted to presenting an abridged version of the applicable methodology. Hence, this chapter provides a detailed outline of the approach taken to establish the research infrastructure and conduct the data analysis for this study.

### 3.1 GENERAL DATA PREPARATION

Manipulation of the project's data sets in preparation for data analysis proved to be a rather complex process. As depicted in Figure 3-1, the task consisted of nine sub-processes, as follows:

- One to process the data files from each of the six data sources (1-6)
- One to identify patients with records post-death (7)
- One to reconcile demographic details across the various data sources (8)
- One to bring together information derived from most other sub-processes into a patient master file for the study cohort (9).

The six sub-processes responsible for the handling of data files from the individual data sources converted the ASCII files received from the data providers into SAS data sets;<sup>154</sup> applied various sequence numbers, flags and person ID mappings to the converted data sets to produce a master data file from each source; and eventually cleaned up the master files to retain a final data set from each source, which strictly contained records for individuals included in the study cohort. As indicated in Figure 3-2, this cohort was defined as all people who:

- Were born prior to 1940 (i.e. aged at least 65 years by the end of 2004)
- Continuously lived in Western Australia throughout 1993-2005
- Had at least one PBS prescription filled during that period
- Did not have any post-death health records
- Had at least one record (from any source) with a specified gender.

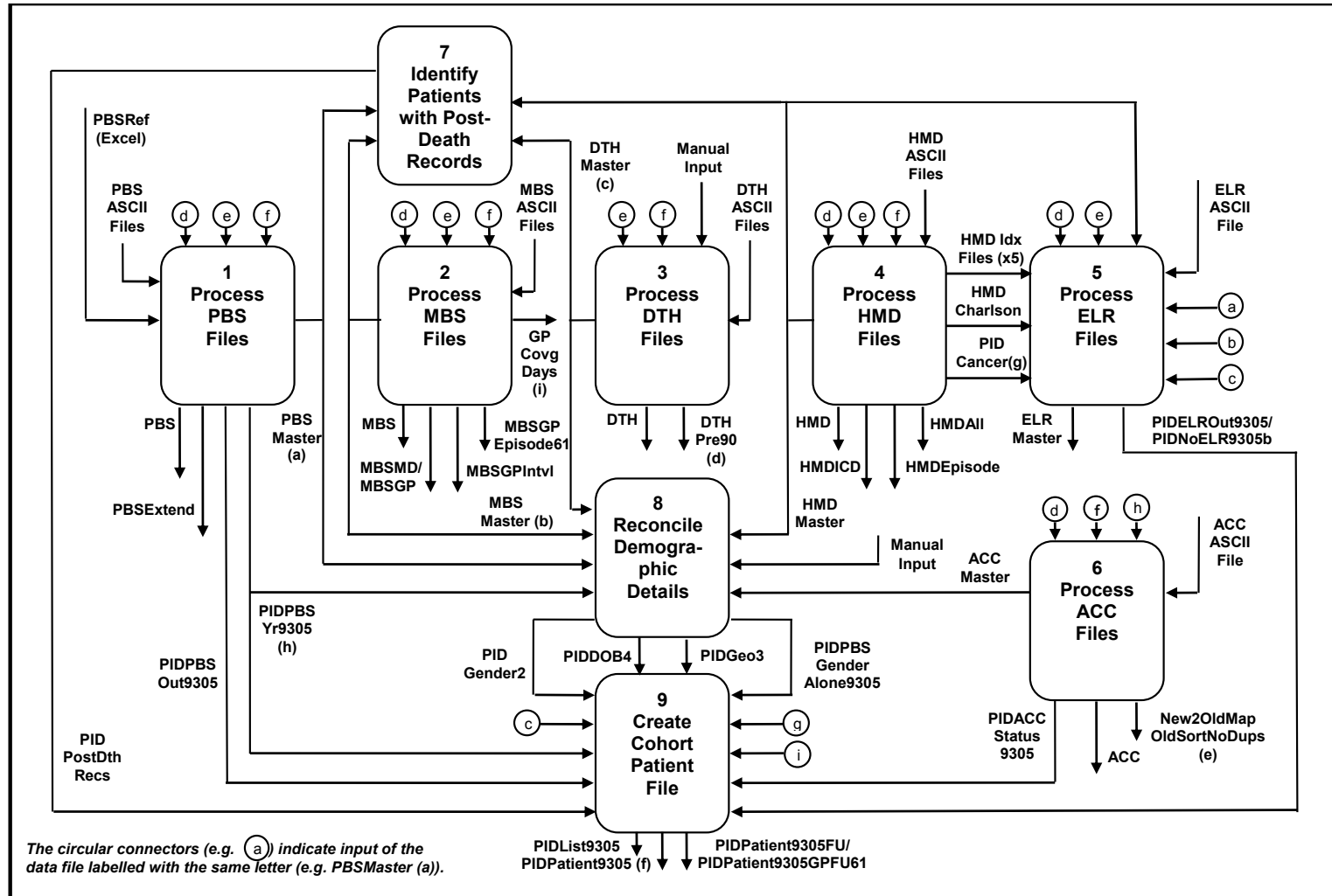
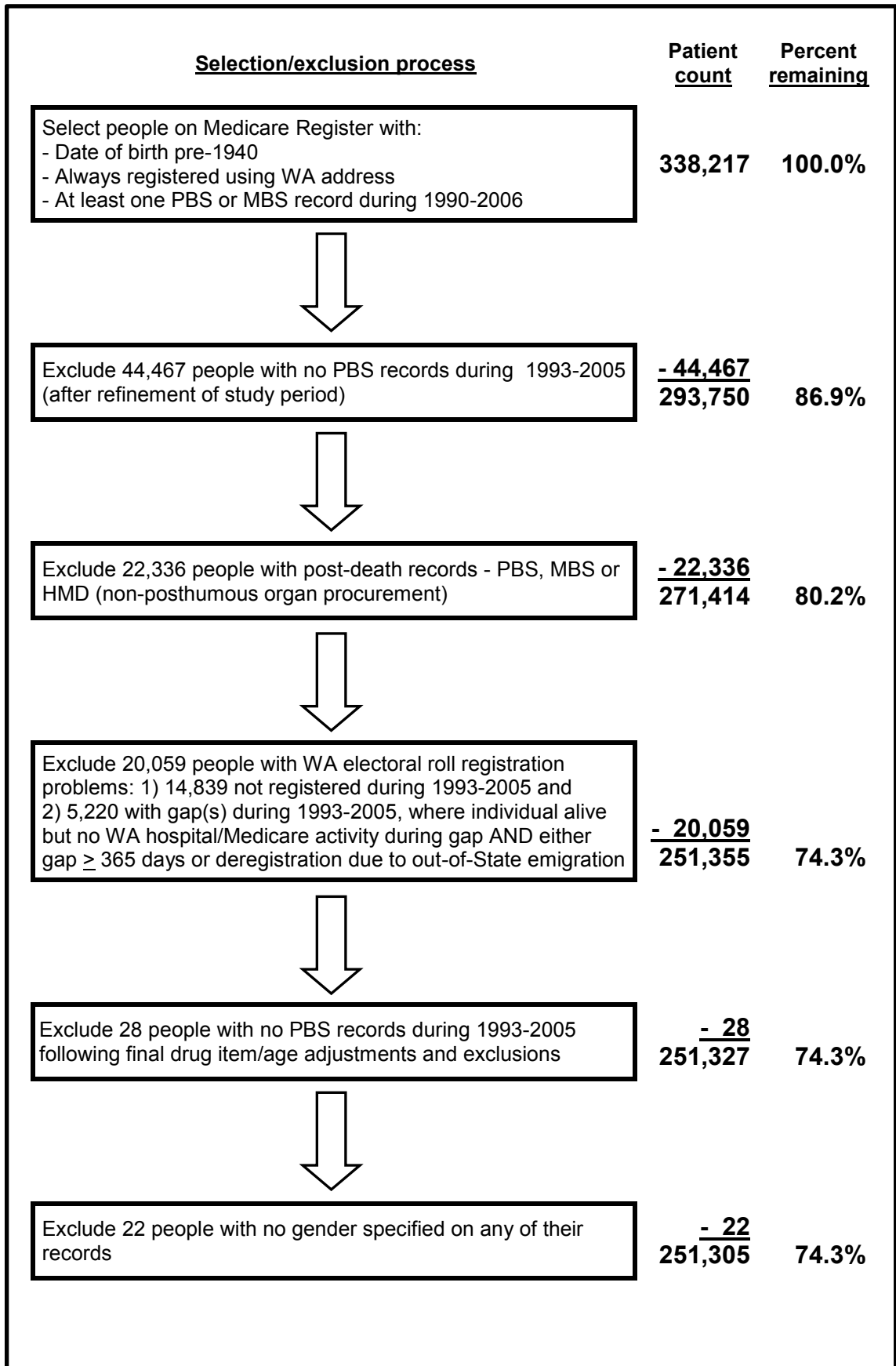


Figure 3-1 Overview of data preparation processes



**Figure 3-2 Selection of cohort participants and associated records**

For particular data sources, some additional file processing was required, which was dependent upon the specific information received from these sources.

Once the master data files were generated, it was possible to merge the date of death to each record and to identify the people with records post-death; 22,336 individuals (7.6% of the study cohort) were eliminated for this reason. Two main scenarios appear to be responsible for these unexpected occurrences. Firstly, in some instances, more than one member of a given household may have shared the same Medicare card number. This practice was particularly prevalent during the period 1996-2001. Secondly, a few incorrect links may have been formed during the data linkage process, bringing together the records of two separate individuals. Although incorrect links are infrequent, they cannot be eliminated altogether due to data quality issues related to the linkage fields. Regardless of the cause, the records for person identifiers with records post-death were deemed unreliable and were excluded from the study.

Using the master data files, it was also possible to cross-check the demographic details for each individual and to reconcile this information between records from all sources. This involved both automated and manual procedures. From this sub-process, overall gender, estimated date of birth, socio-economic disadvantage level, remoteness of residence category, and 'living alone' status were generated for each patient.

Finally, once all reconciliations were complete, a preliminary patient master file for all individuals included in the study cohort was created, assembling all static information for each one, as derived from the various data sources. This sub-process also applied relevant exclusion flags to generate an ultimate patient master file for the study cohort.

More details of the data preparation process applicable to each specific data source are provided in the following pages (including Figures 3-3 to 3-11). File specifications for data extracted from each source are presented in Appendix B.

### **3.1.1 PROCESS PHARMACEUTICAL BENEFITS SCHEME (PBS) FILES**

Processing of the PBS data files involved the conversion of three ASCII files to SAS format,<sup>154</sup> each containing a subset of the PBS records extracted for this project. Once converted, the files were amalgamated, and the records were allocated sequence numbers and sorted by person ID, supply date and PBS item number.

At a later date, once the aged care data set was received, revised person identifiers were applied to each PBS record to ensure consistency across all data sets, and flags to identify records for patients who died prior to 1990 (as supplied by the WA Data Linkage Branch) were added. The re-sorted and re-sequenced output was labelled “HRPIMS\_PBSMaster”.

From this PBS master file, a list of person IDs was created for all patients with  $\geq 1$  PBS record during the period 1993-2005. This was achieved by selecting all records with a year of supply in the range 1993-2005, retaining their person ID only and sorting the resulting output with elimination of duplicate entries. This preliminary list was required for input into various sub-processes that were executed prior to the creation of the final patient list for the study cohort.

An additional pass of the PBS master file was also performed after reconciliation of demographic details to further refine the selection of patients for the study cohort. This pass used the subset of all records with a supply date during 1993-2005 and calculated the age at date of supply for each record, as derived from the patient’s estimated date of birth. It then flagged all records with a calculated age outside the range 65-114 years, as well as those with a PBS item number below 1000 (i.e. extemporaneous preparations). Patients with no PBS records left for the period 1993-2005 after exclusion of these flagged records were marked for further exclusion from the study cohort.

Upon creation of the ultimate patient list for the study cohort, the PBS master file was once again accessed to create a PBS data file that strictly included records for the study cohort. This process only retained records for patients on the ultimate cohort patient list, and only if these records had a year of supply in the range 1993-2005, a calculated age of at least 65 years and an item number of at least 1000 (i.e. not extemporaneous preparation). The resulting output was labelled “HRPIMS\_PBS”.

Once the study cohort’s PBS file was output, it was possible to merge key fields from the PBS reference file, which was in MS-Excel® 2003 format ((Microsoft Corporation, Redmond WA, USA), onto its records. These fields included the ATC code (to identify the generic drug type), the strength, the number of units, the average prescribed daily dose, and other related parameters commonly used in the analysis. The resulting file was named “HRPIMS\_PBSExtend”.

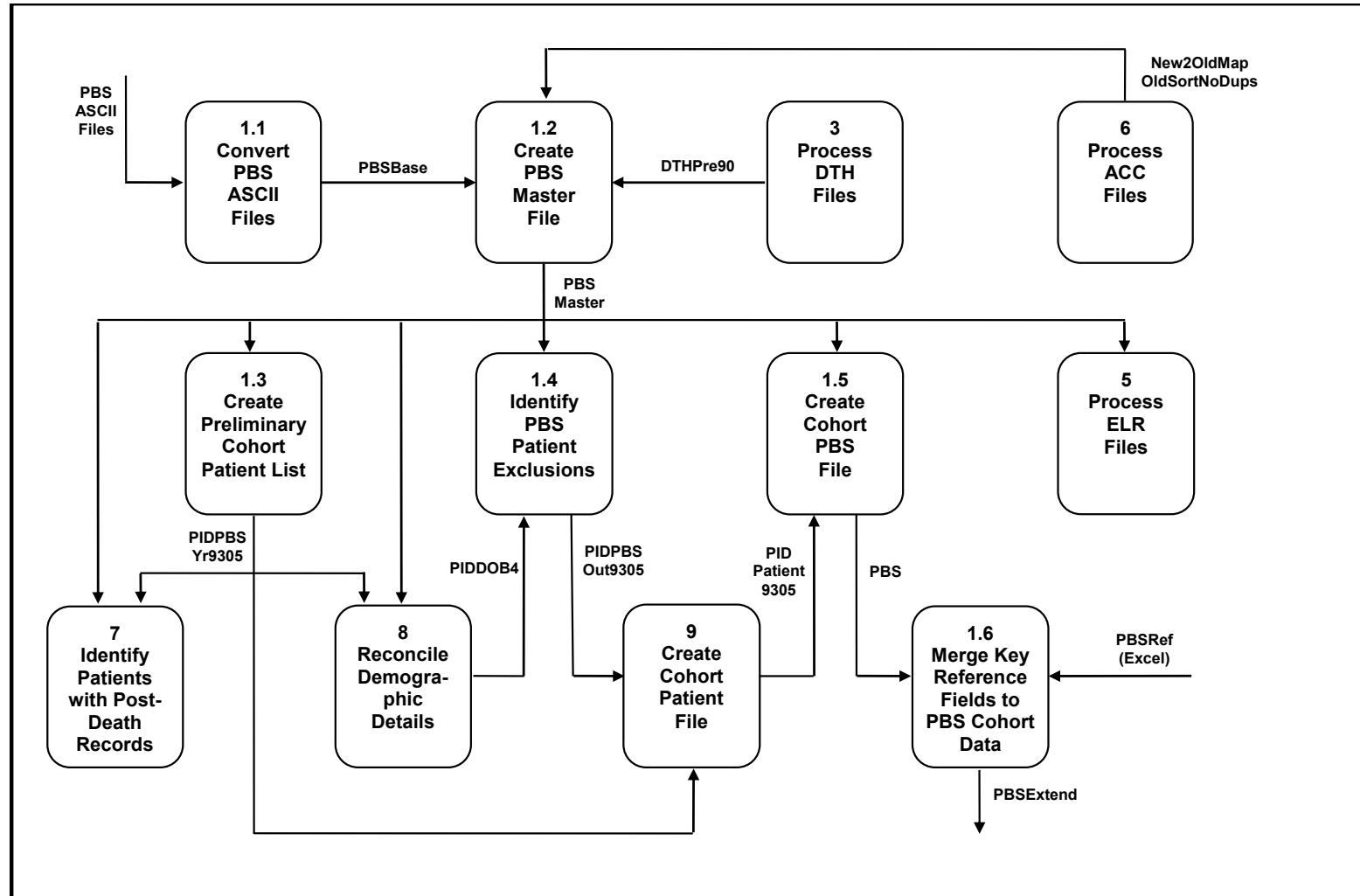


Figure 3-3 Pharmaceutical Benefits Scheme (PBS) file processing

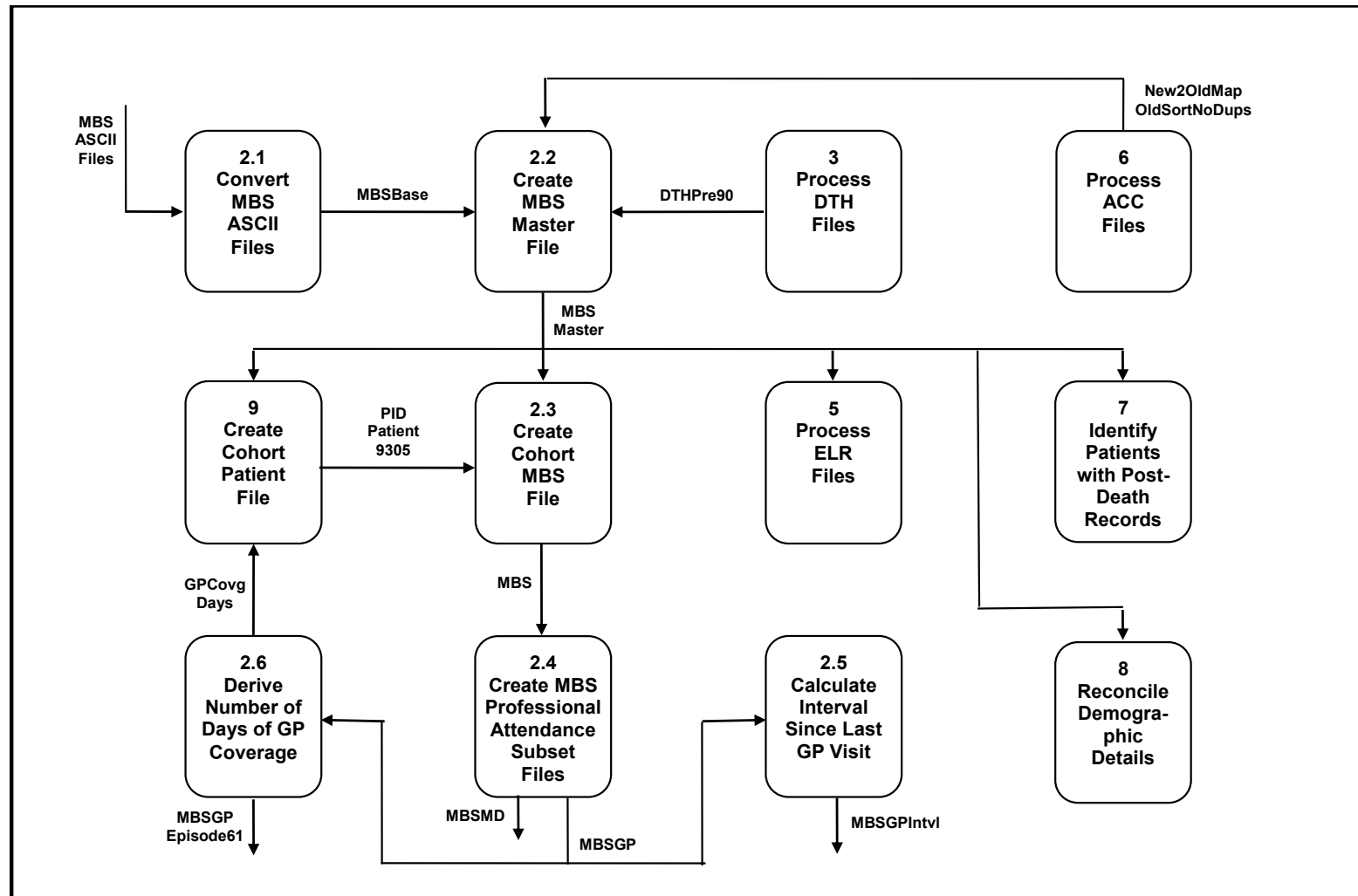


Figure 3-4 Medicare Benefits Scheme (MBS) file processing

### **3.1.2 PROCESS MEDICARE BENEFITS SCHEME (MBS) FILES**

As per the PBS data, processing of the MBS data files involved the conversion of three ASCII files to SAS format,<sup>154</sup> each containing a subset of the MBS records extracted for this project. Once converted, the files were brought together into a single file, and the records were allocated sequence numbers and sorted by person ID, service date and MBS item number.

At a later date, once the aged care data set was received, revised person IDs were applied to each MBS record, and flags to identify records for patients who died prior to 1990 (as supplied by the WA Data Linkage Branch) were incorporated. The re-sorted and re-sequenced output was labelled “HRPIMS\_MBSMaster”.

Once the ultimate patient list for the study cohort was generated, a subset of the MBS master file was created, which strictly included MBS records for the study cohort. This process first eliminated records flagged for deletion through the ‘number of services’ field. All MBS records with a code of 0 (which identified a duplicate bulk billing incentive record for miscellaneous services) or -1 (negative adjustment) were excluded, as well as a matching pair for records flagged with -1, since the latter code indicated the reversal of a previous entry. Thereafter, only records for patients on the cohort patient list were retained, and only if these records had a year of service in the range 1992-2005 and a calculated age (based on estimated date of birth)  $\geq 65$  years. The resulting output was labelled “HRPIMS\_MBS”.

Subsequently, using the study cohort’s MBS file, a subset of all records for MBS ‘professional attendances’ was created (i.e. visits to any medical doctor) and another strictly restricted to general practitioner (GP) visits. These files were named “HRPIMS\_MBSMD” and “HRPIMS\_MBSGP” respectively. The latter file was then used to derive the number of days (interval) since the last GP visit for each record, setting the value to ‘missing’ on the first available record for each person. This information was saved in a file called “HRPIMS\_MBSGPIntvl” and would later be used to determine GP visit intervals at specific points in time.

At a later date still, a further set of variables was extracted from the “HRPIMS\_MBSGP” data, this time in relation to patient ‘GP coverage’ over time. Different measures of GP access had initially been considered for inclusion in the study’s regression analysis models, but eventually this



'coverage' measure was adopted as the preferred option. Thus, upon examination of previously generated annual counts of GP visits and associated follow-up times, it was determined that, on average, older patients would likely have adequate GP coverage if they visited their GP at least once every two months. In other words, every GP visit would have a coverage period of 61 days.

To obtain the patients' GP coverage figures, the GP coverage end date was first calculated for each record on the MBS GP master file, based on a 61-day coverage period per GP visit. In a second pass, the date of the GP visit and the GP coverage end date were used to aggregate periods of overlapping GP coverage into one record. The resulting file ("HRPIMS\_MBSGPEpisode61") contained one record for each period of uninterrupted GP coverage for each patient.

The file of GP 'episodes' was then used to accumulate the count of GP coverage days for each patient by calendar year (for 1992-2005) and overall for the period 1993-2005. For 1992, the first two months of the year were excluded from the coverage calculations, as part of the GP coverage for that year would involve GP visits that took place in late 1991 (i.e. not part of the study's MBS GP master file). This information would subsequently be added to the patient master file for further processing.

### **3.1.3 PROCESS DEATH REGISTRATION (DTH) FILES**

The project's death registration (DTH) records were received in two ASCII files, one containing the bulk of the requested death registration fields and another consisting of information derived from the patients' place of residence (i.e. Socio-Economic Indexes for Areas (SEIFA)<sup>155,156</sup> scores and Accessibility/Remoteness Index of Australia (ARIA+)<sup>157</sup> categories). These two files were first converted to SAS format.<sup>154</sup> Records from the main file were then allocated sequence numbers and sorted by person ID and date of death.

The main death file was also checked for duplicate entries. The records for the ten cases with duplicates were first examined manually to ascertain what information to retain for each death. Resolution of duplicates was then applied through an automated process.

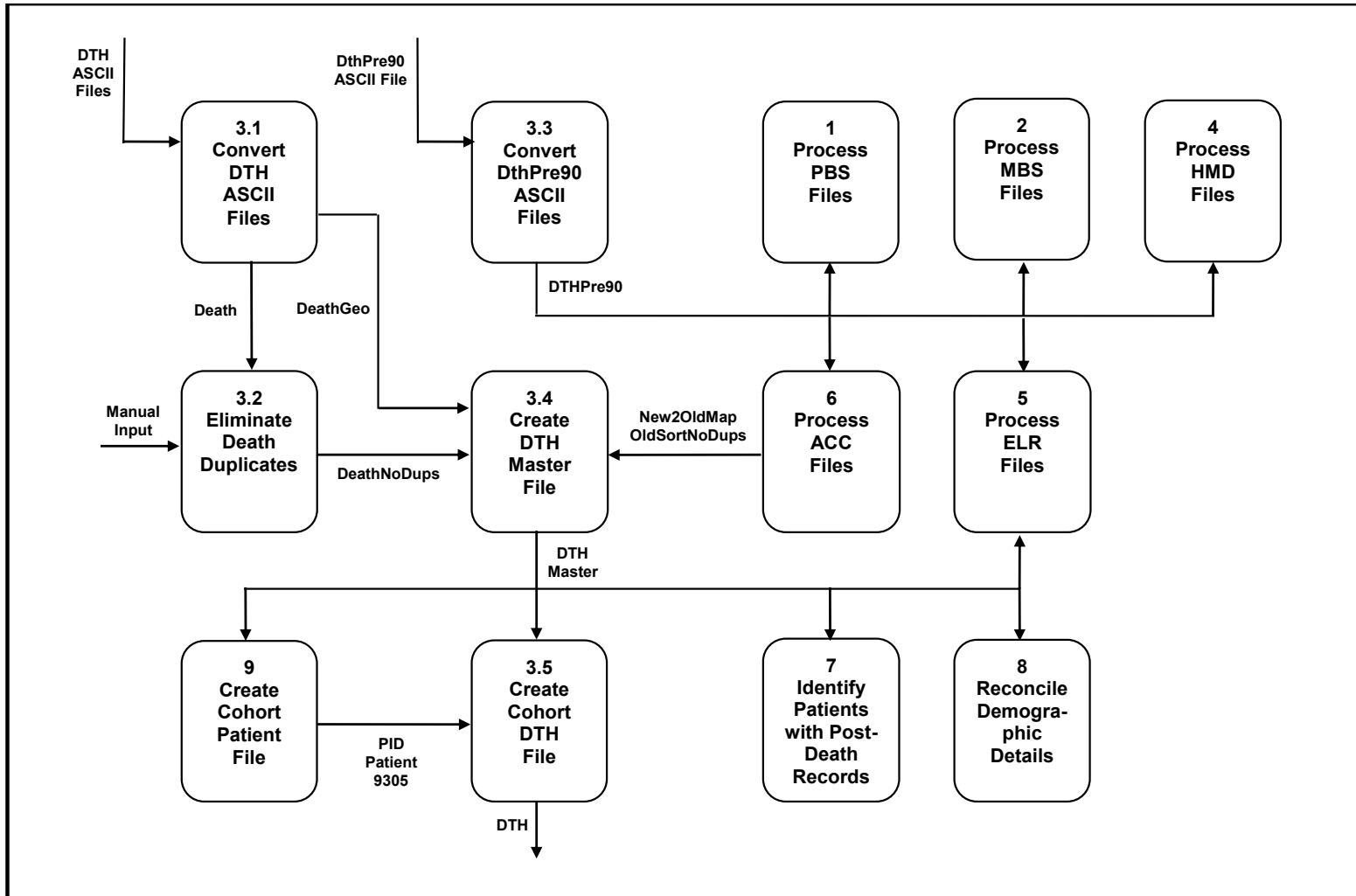


Figure 3-5 Death (DTH) file processing

In addition to the death records for the period 1990-2006, the WA Data Linkage Branch supplied a list of person IDs for people on the Medicare Register who met the selection criteria for the project but had died prior to 1990. Initially, this list seemed unnecessary as no health records were expected to exist beyond each patient's death. However, given that some post-death PBS and MBS records had been found in the project's data sets, it seemed prudent to obtain this additional information. The list was supplied in an ASCII file, which strictly contained the relevant person IDs. The file was converted to SAS format<sup>154</sup> and a flag field was added to each record. The output file, which was named "HRPIMS\_DTHPre90", would later be merged to the preliminary data files from each source in the creation of the project's master data files. The "dthpre90" flag field, combined with the actual date of death for those who died from 1990 onwards, would then facilitate the elimination of patients with records post-death from the study cohort.

Upon receipt of the aged care data set, revised person IDs were applied to each death record, and both the main death file (duplicates excluded) and the file containing the geographic information (i.e. SEIFA/ARIA data) were brought together into a master file. The re-sorted and re-sequenced output was labelled "HRPIMS\_DTHMaster".

Once the ultimate patient list for the study cohort was generated, a subset of the death master file was created, which strictly included death records for the study cohort. Only records for patients on the cohort patient list were retained, and only if these records had a year of death prior to 2006. Age, calculated from each patient's estimated date of birth, was added to each record for future reference. Conversely, geographic details were dropped, as they had been superseded by the overall SEIFA and ARIA categories recorded on the master patient file for the study cohort. The resulting output was labelled "HRPIMS\_DTH".

#### **3.1.4 PROCESS HOSPITAL MORBIDITY DATA (HMD) FILES**

Like the death registration records, the project's hospital morbidity data (HMD) were initially provided in two ASCII files, one containing the bulk of the requested inpatient summary fields (including clinical codes) and another consisting of information derived from the patients' place of residence (i.e. SEIFA<sup>155,156</sup> scores and ARIA+<sup>157</sup> categories). These two files were first

converted to SAS format<sup>154</sup> and sequence numbers were allocated to the main one. At a later date, two additional hospital morbidity variables were requested: patient type (client status) and marital status. Separate ASCII files were supplied for each field, which were also converted to SAS.

Once all files were converted, they were sorted by linkage project record number (lpno) and merged together into a preliminary master data set. The resulting output was sorted by person ID, admission date and separation date and additional sequence numbers were allocated to each record. Later on, upon receipt of the aged care data, revised person IDs were applied to each HMD record, and flags to identify records for patients who died prior to 1990 (as supplied by the WA Data Linkage Branch) were added. The re-sorted and re-sequenced output was labelled "HRPIMS\_HMDMaster".

Subsequently, following the generation of an ultimate patient list for the study cohort, a subset of the hospital morbidity data master file was created, which strictly included inpatient records for the study cohort. Only records for patients on the cohort patient list were retained, and only if these records had an admission date prior to 2006, a calculated age (based on estimated date of birth)  $\geq 65$  years, and a patient type of 'admitted client', 'contracted service' or 'nursing home type' (i.e. boarders, duplicate 'funding hospital' records and posthumous organ procurement cases were excluded). Geographic details were dropped, as they had been superseded by the overall SEIFA and ARIA categories recorded on the master patient file for the study cohort. The resulting output was split into two files, one containing demographic and administrative hospitalisation details ("HRPIMS\_HMD") and another restricted to clinical coding fields (i.e. ICD-9-CM<sup>158</sup> and ICD-10-AM<sup>159</sup> diagnoses, procedures and external causes), labelled "HRPIMS\_HMDICD".

Using the HRPIMS\_HMD file, a file of hospital episode records was derived. Each record on this file identified an uninterrupted period of hospitalisation for a given person, bringing together overlapping hospital admissions and hospital transfers. Information in this format would make it easier to identify if a patient was hospitalised at any given time.

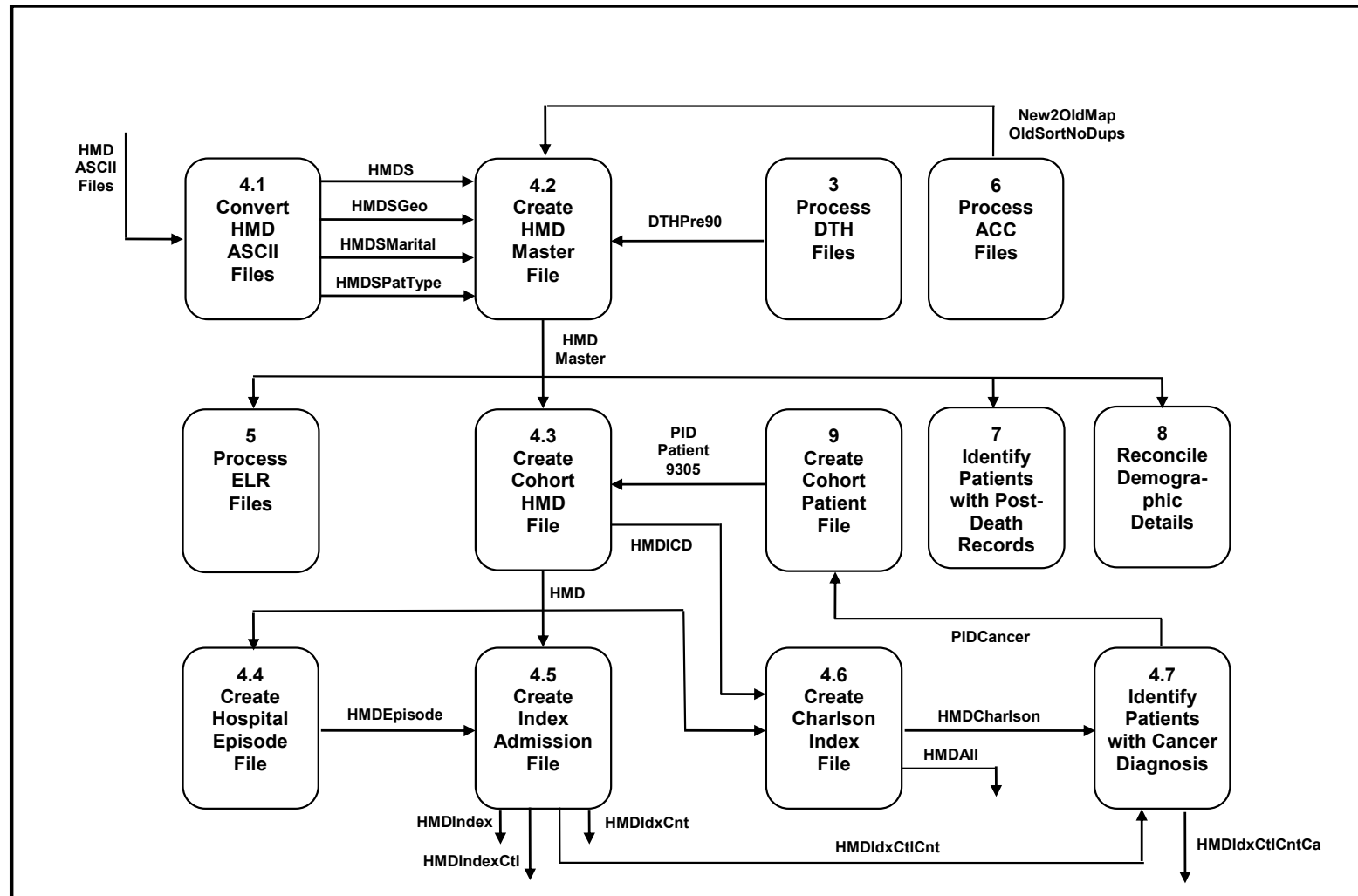


Figure 3-6 Hospital Morbidity Data (HMD) file processing

The HRPIMS\_HMD file was also processed to identify the study's index hospital admissions. These included hospitalisations with an admission type of 'emergency' to flag unplanned hospitalisations (as opposed to 'elective'); an admission date between 1 July 1994 and 31 December 2005; and for which the patient's admission age was  $\geq 67$  years. These latter constraints were required to ensure that details of interest at both the subject's case and control times (one year prior) were available, keeping in mind that some parameters required a one-year look-back period. Additionally, the selection of index admissions excluded admissions that occurred while the patient was already hospitalised. Once the relevant admissions were identified, additional parameters were appended to each record for use during the analysis phase. These included the control times associated with the admission and the patient's overall count of index admissions during the study period.

The two components of the study's hospital morbidity data (HRPIMS\_HMD and HRPIMS\_HMDICD) were also accessed to derive Charlson index comorbidity scores. To achieve this, the diagnostic variables on each record were first searched for ICD codes associated with 17 different health conditions. A weight was then applied to each condition, from which the admission's overall Charlson index score was calculated. Relevant disease definitions for this process were obtained from Quan et al.<sup>160</sup>

From the Charlson index data (HRPIMS\_HMDCharlson), a cancer flag was derived for each person, to indicate whether any of the person's inpatient records included a cancer diagnosis (as per Charlson index definitions). Identification of cancer patients had been identified as a requirement, as it was felt that the effects of medication exposure on the risk of unplanned hospitalisations might be different in cancer patients compared to other older people, especially in relation to pain management drugs. This flag, kept in file HRPIMS\_PIDCancer, was then merged to each index admission record. The resulting output, which was the final version of the index admission file, was named HRPIMS\_HMDIdxCtlCntCa. The cancer flag would also be included on each patient record upon creation of the master cohort patient file. Refer to section 3.1.9 for more details.

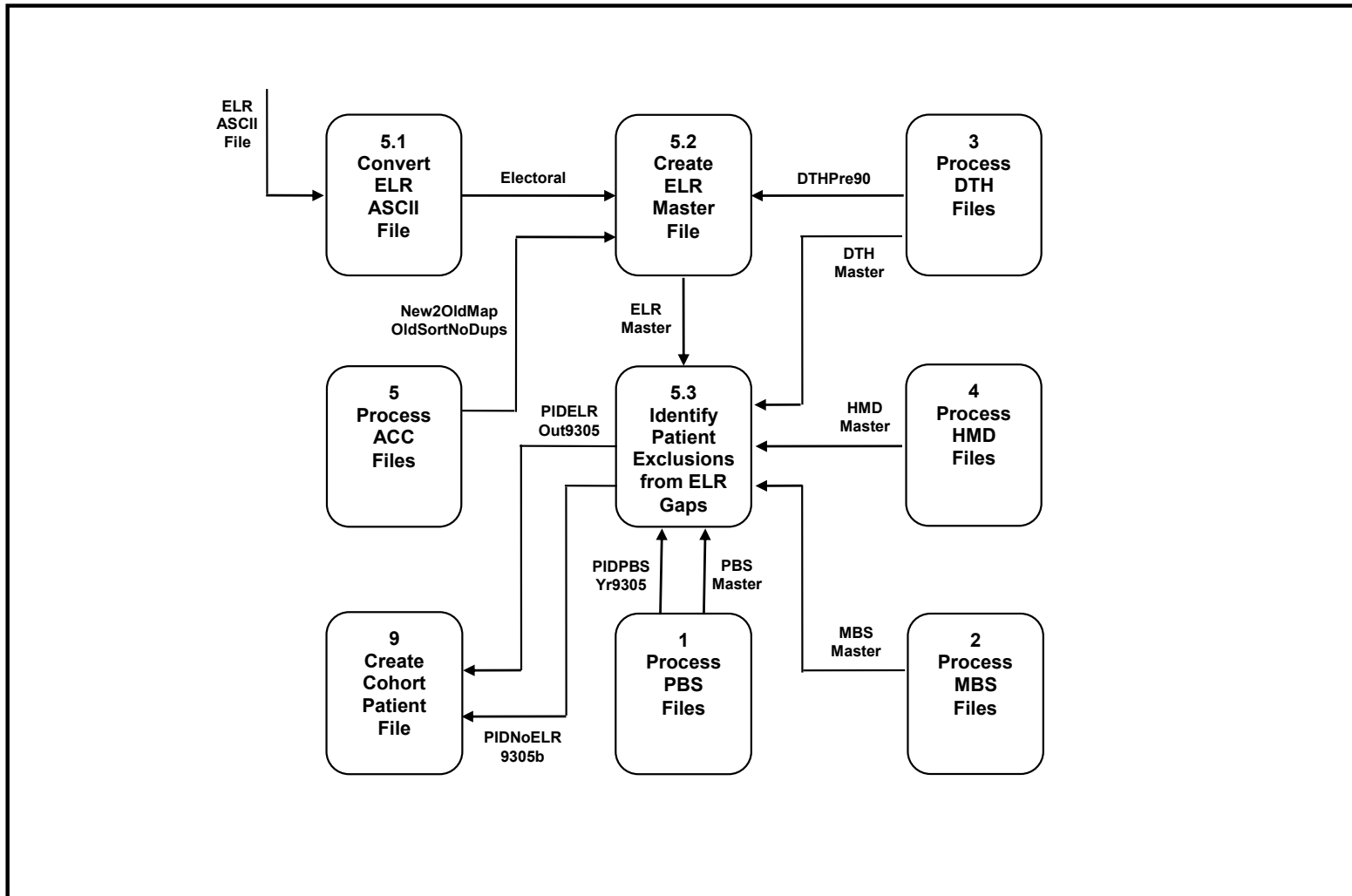


Figure 3-7 Electoral Roll (ELR) file processing

### **3.1.5 PROCESS ELECTORAL ROLL (ELR) FILES**

Electoral Roll (ELR) unit records contain information about additions, deletions and amendments to the Western Australian electoral roll. As this project was specifically interested in identifying gaps in individuals' electoral roll registration over the study period, it was decided to supply a summary file to the research team (as opposed to unit records) to simplify this task. Thus, the file received contained one or more records for each person who met the project's selection criteria, each record containing details of a registration 'episode'. The fields supplied included the person ID, the start and end date of the registration episode and the end type, which indicated one of the following: registration still current, deregistration due to interstate/overseas emigration or 'other deletion' (i.e. deregistration for other reason). The earliest registration start date was 18 November 1988 (i.e. prior to the study's start date) and the latest end date (for registrations that were still current at the time of data extraction) was 10 September 2007. The file received was first converted from ASCII to SAS format.<sup>154</sup> The records were then allocated sequence numbers and sorted by person ID, start date and end date to obtain a chronologically ordered list of WA electoral roll registration periods for each patient.

At a later date, once the aged care data set was received, revised person IDs were applied to each ELR record, and flags to identify records for patients who died prior to 1990 (as supplied by the WA Data Linkage Branch) were incorporated. The re-sorted and re-sequenced output was labelled "HRPIMS\_ELRMaster".

Subsequently, using the ELR master file, a series of steps were performed to identify patients with electoral roll gaps during the study period (i.e. 1993-2005) and to determine if any of these gaps met the criteria for exclusion of the person from the study cohort. To achieve this, the list of person IDs for patients with at least one PBS record during 1993-2005, and the date of death were first merged to the ELR master file to select records for patients of interest. From this subset a file was created to record the start and end date of each registration gap and the reason for deregistration (where applicable).

Using the 'gap' file, a list of person IDs for people with gaps was generated and used to extract death, PBS, MBS and hospitalisation records for these people. All extracted records were then brought together with the ELR gap file and



sorted by person ID, event date and source (starting with the ELR record for each date). The resulting output was then processed to identify if any WA health care activity (PBS script, Medicare service or hospitalisation) had occurred during the gap period or if the patient had died. (Note that inpatient records were only available for WA hospitalisations and that the PBS/MBS data supplied only involved people who strictly had Medicare registrations with WA addresses. Therefore, all activity from these sources was assumed to have occurred in WA.)

A summary file of gap records, which consisted of the relevant person ID, gap start and end dates, reason for deregistration, number of gap days, death flag and number of WA 'health activity' records encountered during the gap was subsequently generated, from which a list of patients to exclude from the study due to electoral roll deregistration issues ("HRPIMS\_PIDELROut9305") could be derived. All patients with at least one gap of 365+ days or of any length but due to interstate/overseas emigration were flagged for exclusion, but only if no WA 'health activity' occurred during these gaps and the patient had not died.

In a separate pass, the list of person IDs for people with PBS records during the study period was merged to the ELR master file to identify patients with no electoral roll registrations at all on this master data set. A list of these patients was output to a file labelled "HRPIMS\_PIDNoELR9305b" to flag additional exclusions from the study cohort.

### **3.1.6 PROCESS AGED AND COMMUNITY CARE (ACC) FILES**

Due to data linkage issues, it was not possible for the Commonwealth Department of Health and Ageing to extract the Aged and Community Care (ACC) data from the "System for Payment of Aged Residential Care" (SPARC) database at the same time as other project data. Consequently, there was a delay of more than two years between the acquisition of the project's first few data sets and receipt of data from this source. Nonetheless, upon receipt, the aged care data set was first converted from an ASCII file to SAS format,<sup>154</sup> as per other data sources.

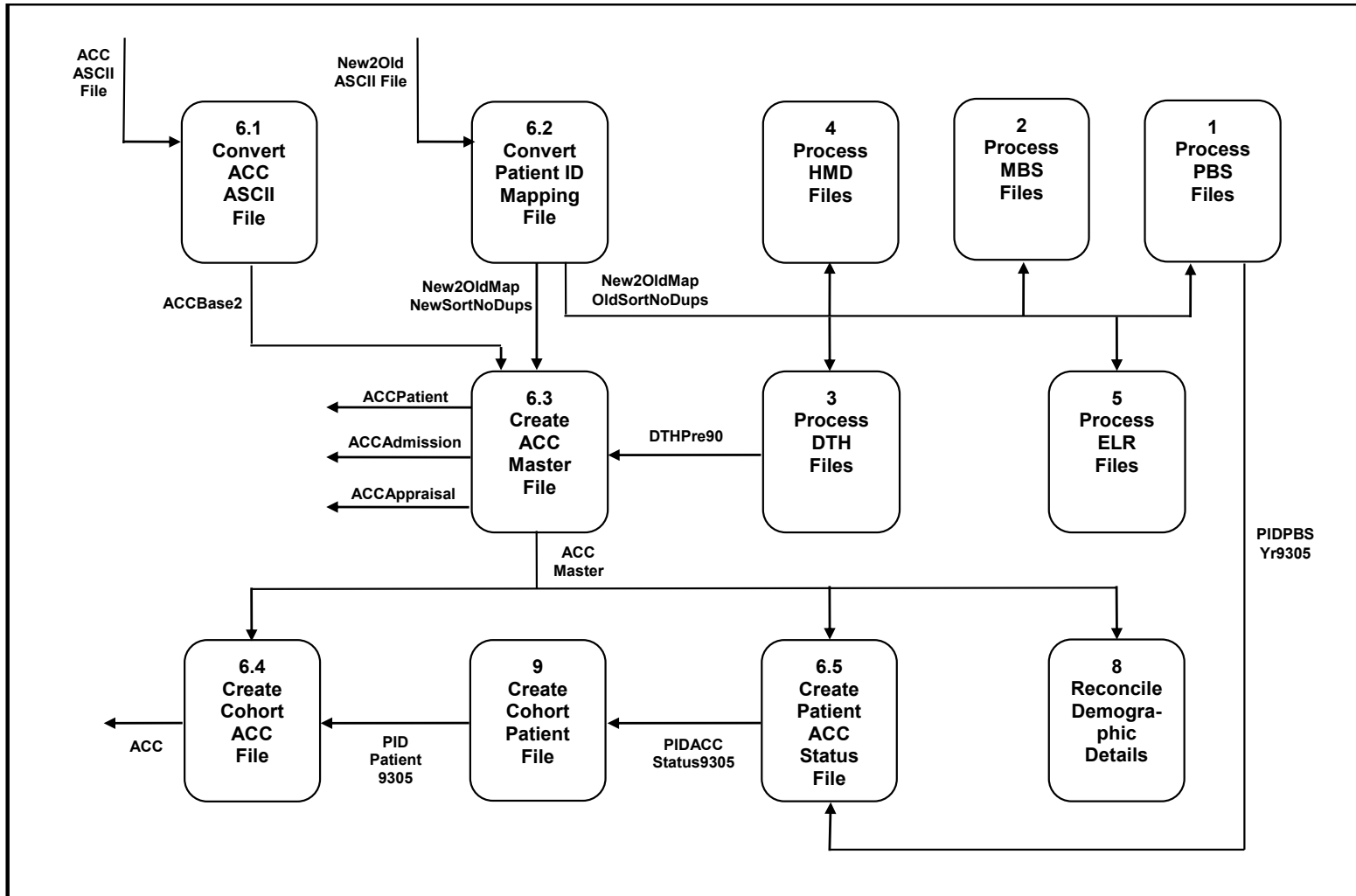


Figure 3-8 Aged and Community Care (ACC) file processing

Thereafter, it was possible to interweave the ACC admission and appraisal records in a chronological order by patient to create an output file from which the aged care level of each patient could readily be determined from first admission onwards. Only admissions to permanent residential care were retained in this process (i.e. respite care and admissions to community or transitional care programs were excluded). For admission records, the level of care from the last appraisal prior to admission was recorded (including appraisals on the same day as the admission). If no such information was available, the appraisal details were sought from the first appraisal record post-admission. The resulting output (appropriate sequence numbers included) was named "HRPIMS\_ACCMaster".

As per other data sets, once the ultimate patient list for the study cohort was generated, a subset of the ACC master file was created, which strictly included aged care records for the study cohort. Only records for patients on the cohort patient list were retained, and only if these records had a year of admission or appraisal prior to 2006. Age, calculated from each patient's estimated date of birth, was added to each record for future reference. The resulting output was labelled "HRPIMS\_ACC".

One additional step was required in the processing of the aged care data. To match index subjects to their reference counterparts in some of the logistic regression analyses, it was decided to use patients' aged care status at the midpoint of the calendar year associated with 'case' hospital admission dates. A summary patient file was therefore generated by merging the list of patients with at least one PBS record during 1993-2005 and the patients' date of death (where applicable) to the ACC master file, and searching the aged care records to determine each patient's care status at 30 June for each calendar year during this period. 'No care' was assumed until the first admission to a residential aged care facility. Thereafter, the care level from the record currently being processed was applied to the remaining period until it was superseded by a more recent appraisal outcome on a subsequent record. Once all care level allocations were completed, one last pass of the patient summary data was performed to replace the aged care status with a missing value for all mid-year points occurring after the patient's death.

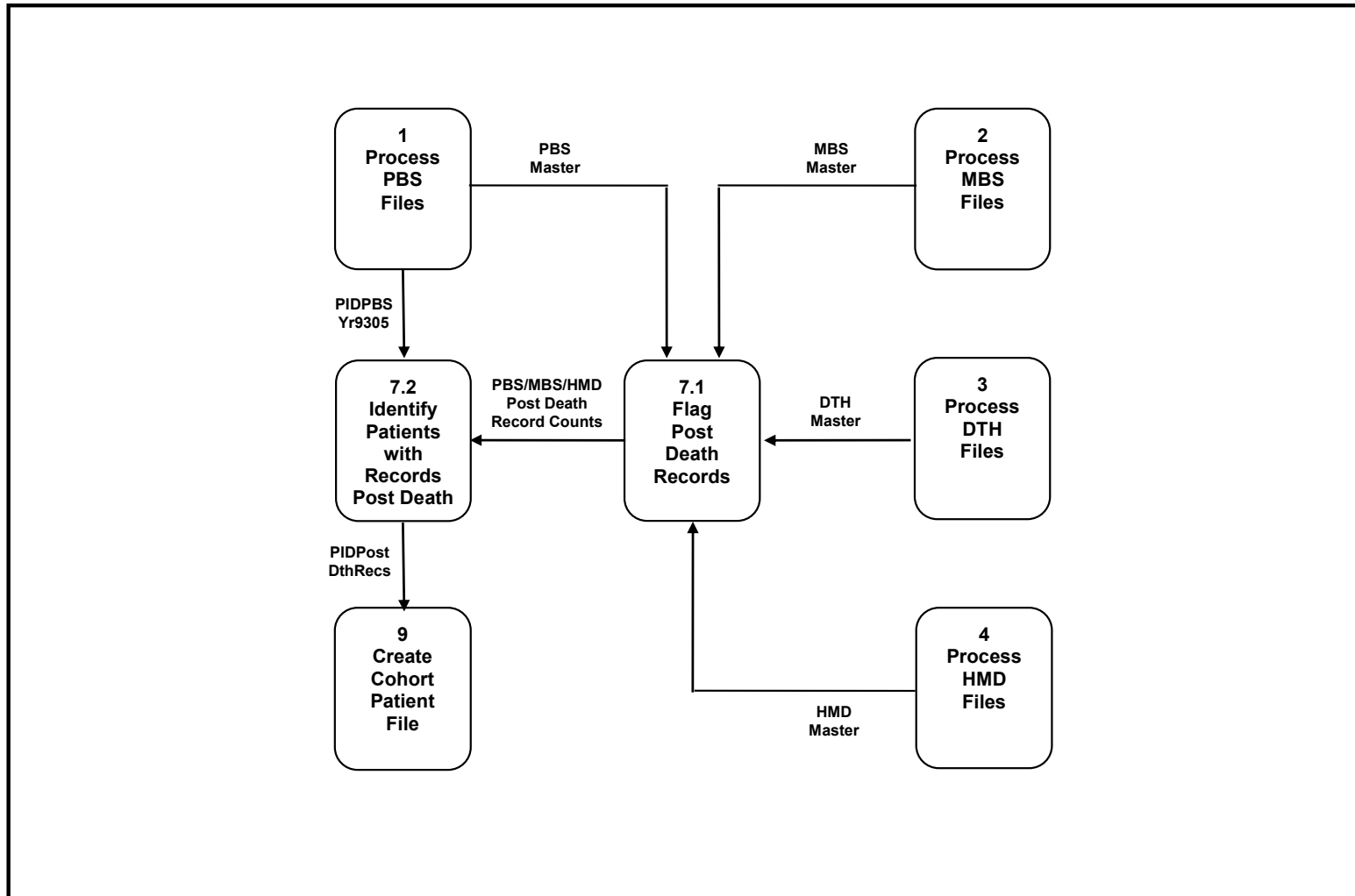


Figure 3-9 Process to identify patients with post-death records

### **3.1.7 IDENTIFY PATIENTS WITH POST-DEATH RECORDS**

As previously mentioned, preliminary statistics using the project's health data identified a few unexpected problems, one of which was the presence of health care records (mainly from Medicare sources) after death. Further investigations strongly suggested that use of Medicare cards by more than one family member (in some situations) was the main reason for this phenomenon, which was especially prominent during the period 1996-2001. Although it was not possible to identify all person IDs associated with this issue, Medicare records post-death were a good indicator of those who had continued this practice following their spouse's death. Incorrect linkage of records belonging to more than one person may also have accounted for at least some instances of records post-death. In any event, it seemed appropriate to exclude person IDs with such problematic records from the study cohort.

Once the project's data sets from all available sources had been processed, health care data files (PBS, MBS and HMD) were searched for occurrences of records post-death. ELR records were excluded from this search as it is not uncommon for electoral roll deregistration to occur some time after death. Similarly, the aged care data set was not searched, as post-death appraisal records are not really problematic. They likely occur when an annual appraisal takes place shortly before a set anniversary date and the anniversary date is recorded as the appraisal date. If the person dies before reaching the anniversary date, the appraisal appears to have occurred post-death. Most of these post-death records are eventually flagged as 'rejects' in the aged care system.

To perform the desired search, the patients' date of death was first merged to records from each master data set of interest (i.e. PBS, MBS and HMD). Records with a date of death prior to the event date or with a 'dthpre90' flag set to 1 were then flagged and a count of records post-death was accumulated at the person level for each source. For post-death hospital morbidity records, an additional check was made to ensure that the inpatient summary did not relate to a posthumous organ procurement case.

Upon completion of the search, the post-death record counts from each source were merged to the list of person IDs for patients with at least one PBS record during the period 1993-2005. A count of post-death records from all three

sources was calculated for each person and an overall indicator derived to flag patients with records post-death. The resulting output was named “HRPIMS\_PIDPostDthRecs”.

### **3.1.8 RECONCILE DEMOGRAPHIC DETAILS**

Availability of linked data from multiple sources permits the cross-validation of patients’ demographic details both within and between sources. Given that the PBS data set, for which demographic details seemed less complete and reliable than some of the other data sets, was the primary source for defining the study cohort, this cross-validation process was particularly important in this project. The process consisted of four main tasks (see Figure 3-10), which determined the most appropriate demographic details for individuals within the study cohort. These tasks, which are described in more detail below, were responsible for:

- Reconciling the gender allocation for each individual
- Estimating patients’ date of birth from the age specified on their records
- Reconciling SEIFA and ARIA+ categories using inpatient and death records
- Determining each person’s overall ‘living alone’ status for the study period.

#### **Reconcile Gender**

To determine the gender of each person within the study cohort, all records that contained a gender variable were brought together into one file and sorted by person ID and event date. These records were extracted from the PBS, MBS, HMD and ACC master data files. (Gender was not supplied on records from other sources.) Male and female counts were then accumulated at the person level for each source and overall.

Thereafter, an automated process allocated a gender to each person by source and overall, based on the most common value. If equal male and female counts were found, the gender was flagged as ‘undetermined’. Similarly, if no gender was specified on any record, the gender was shown as ‘missing’.

Once this initial allocation was completed, gender values from each source were compared to the overall gender allocation and a count of matching sources was accumulated. Subsequently, an overall gender status was assigned to each person to help determine whether there was a need for manual review. If the overall gender was either missing or undetermined, the person’s gender allocation was immediately marked for review. If the overall

allocation was either male or female, it was considered acceptable if one of the following scenarios was encountered: the gender was the same on all records with a specified value; at least 20 records specified a valid gender and 70% or more of these matched the overall allocated gender; at least 20 records specified a valid gender, 60-69.9% of these matched the overall allocated gender and at least three data sources agreed with the overall gender assignment. All other cases with an overall allocation of male or female were flagged for manual review.

Of the 338,217 people in the preliminary patient cohort, the gender allocation for 337,899 (99.9%) was considered acceptable. Of these, 310,643 (91.9%) had complete agreement on all records with a specified gender; all but six of the others had at least 70% agreement.

This left 318 cases flagged for manual review, of which no gender information was available at all in 180 cases (i.e. 'missing' overall gender). After some consideration, it was decided not to assign a male or female gender to any of the latter; a number of them would likely be omitted from the final study cohort for other reasons and the remaining ones could be excluded explicitly due to their missing gender. A manual review was undertaken for the other 138 cases though, taking into consideration both overall and source-specific gender counts, and giving greater significance to hospital morbidity and aged care data sources due to the better quality of information expected from these sources. As a result of this review, 40 gender changes were made among the 134 cases with a tentative gender assignment, and the four instances of 'undetermined' gender (i.e. equal overall male and female counts) were resolved. The final output was saved in a file labelled "HRPIMS\_PIDGender2".

### **Estimate Date of Birth**

Some aspects of the project required subjects to be followed up from the time they turned 65 years of age. Achieving this requires knowledge of each person's date of birth. Although this date was not supplied to the research team, age was available on patient records from most of the project's data sources.

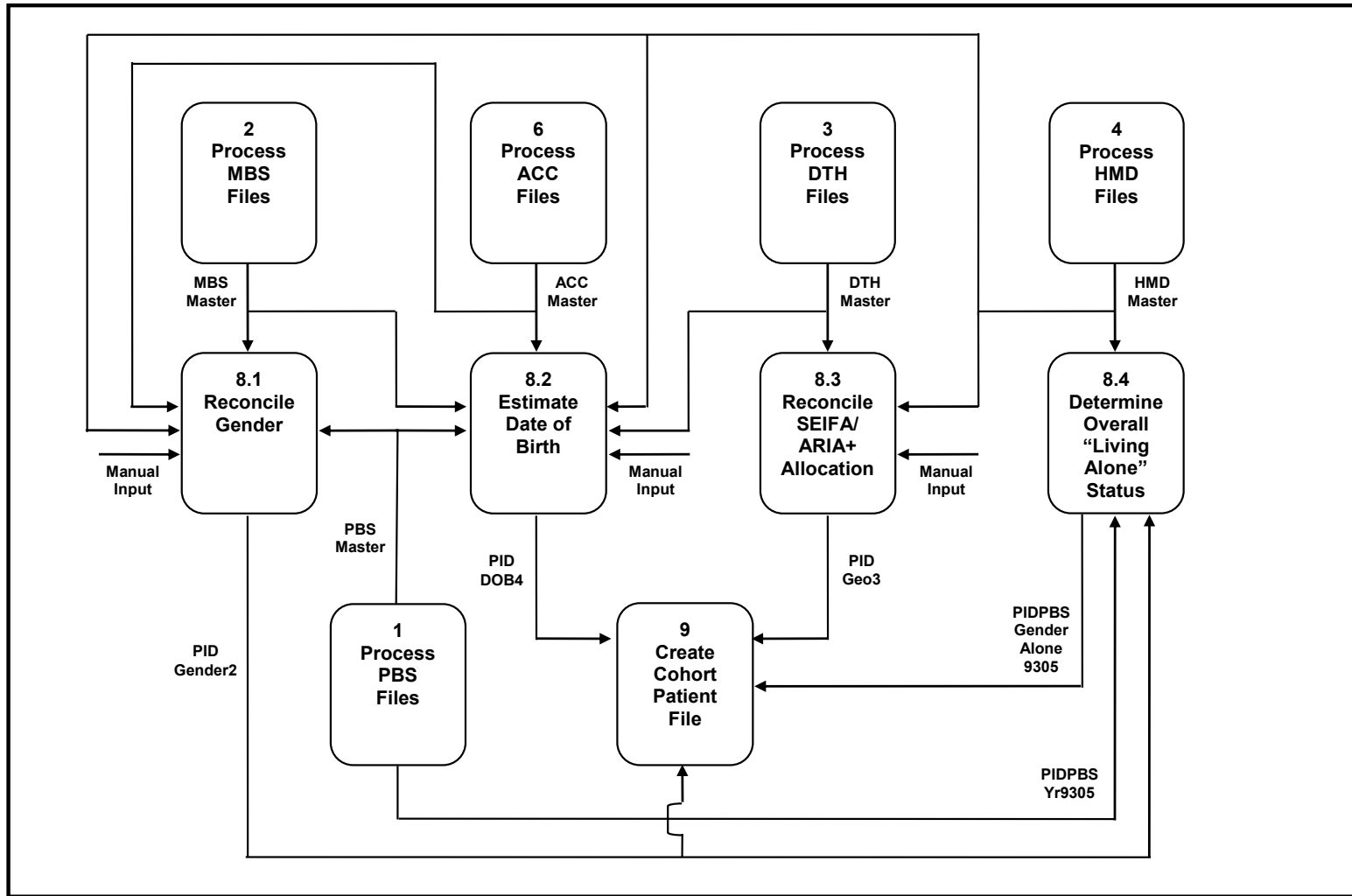


Figure 3-10 Process to reconcile demographic details



Thus, a SAS program<sup>154</sup> was developed to derive the best estimate of each patient's date of birth from available age data. This program brought together records from all sources for which age was supplied as a variable (i.e. HMD, DTH, ACC, MBS and PBS master files). These records were sorted by person ID, source sequence and descending event date, giving precedence to sources expected to have more reliable age data and to the more recent information recorded from each source.

Using the sorted file, a date of birth estimate was derived for each patient. This was achieved by calculating the minimum and maximum date of birth possible based on age and event date on the first record, and gradually refining this date of birth range by overlapping the initial estimate with date of birth ranges derived from subsequent records for each person. Once all records for a given person had been processed, the mid-point of the refined date of birth 'window' was calculated and assigned as the person's preliminary date of birth estimate.

The preliminary estimates were then applied to all patient records. A revised age was derived from the preliminary date of birth and compared with the age supplied on the record. Manual checks were made of a few date estimates that were clearly out of range (i.e. birth year <1876 or >1939). This led to the correction of the year of birth for two specific cases with obvious typographical errors (i.e. 1836 and 1839 rather than 1936 and 1939, respectively). Additionally, as it was known that the cohort consisted of people born prior to 1940, date estimates beyond 1939 were re-calculated using 31 December 1939 as an upper limit.

A further refinement was also applied to correct another recurrent problem. Several patients had a date of birth estimate that was just slightly inaccurate but that resulted in a few records with a derived age of 64 years. All records with such a problem were identified and the date of the first event (chronologically) associated with an age of 64 years was used to change the date of birth estimate to 65 years prior.

Once all of these adjustments had been applied, revised ages were again derived for all patient records and statistics were generated to identify records with an estimated age that was still out of range or that did not match the recorded age. Of the 152,600,417 patient records with a specified age, the age derived from the estimated date of birth was an exact match to the recorded

age in 70.0% of entries and was within one year of the recorded age in most others (i.e. 29.2%).

Despite this high level of accuracy, it was decided to extract the records of patients who had a major problem with their date of birth estimate for further assessment. This involved 1,493 patients, of which 641 (42.9%) had entries with an absolute age difference (estimated age less recorded age) greater than 5 years; 528 (35.4%) had records with an estimated age outside the range 65-114 years; and the remaining 324 (21.7%) had a mix of records involving either one of these problems or both. Most of the problem date of birth estimates resulted from at least one age specification that was clearly incorrect or from ages based on different dates of birth for different sources. Giving priority to ages from sources expected to have better quality of demographic details and taking into consideration some of the data extraction criteria, all of these issues were resolved through a very thorough manual review of all records for each 'problem' patient. Not only was the year of birth assessed more accurately through this process, but the day and month of birth was estimated as closely as possible by examining changes in age from one event to the other. Due to large numbers of PBS and MBS records for most of these patients, it was even possible to derive an exact date of birth in a number of cases.

Upon completion of the manual review, the master file of patients' dates of birth was updated with the corrected estimates from the review. Thereafter, a final check was made of ages derived from the latest set of date of birth estimates. Records for patients who had at least one entry with a derived age greater than 109 years were then identified and examined more closely. Of the four cases involved, two seemed feasible but the other two were judged to have an erroneous date of birth, which was increased by twenty years. The final output was saved in a file labelled "HRPIMS\_PIDDOB4".

### **Reconcile SEIFA/ARIA+ Allocation**

Other demographic details of interest in this study were those derived from a person's place of residence. For this project, no address details were provided explicitly (e.g. suburb, postcode, Collector's District (CD), Statistical Local Area (SLA)). However, a number of variables derived from the CD and SLA of residence were supplied for addresses on hospital morbidity and death records. They included SEIFA<sup>155,156</sup> scores and ARIA+<sup>157</sup> categories. This information

was supplied as derived from the 1996 and 2001 Australian Census, based on CD and SLA address allocations (when CD/SLA could be ascertained from the address on the inpatient summary). The index values are averages for all residents in the specified geographical area at a specific point in time rather than specific allocated values for each individual. Of course, a person may also move to different areas over time, which creates additional complications. Despite these constraints, it seemed appropriate to derive an overall SEIFA disadvantage level and ARIA+ category for each patient, to get some indication of their socio-economic status and of their ability to access health services over the study period.

To achieve this, all records from the HMD and DTH master files with available SEIFA and ARIA+ details were brought together and the most appropriate SEIFA disadvantage level and ARIA+ category was allocated to each one. If the hospital separation or death date on the record occurred prior to 1999, then the information derived from the 1996 Census was used; otherwise, the equivalent details from the 2001 Census were retained. (Note that geographical index details from the 2006 Census had not been released at the time the project data sets were extracted.) Furthermore, if the CD-derived details were available, they were used in preference to the equivalent SLA information, as CDs cover a smaller area than SLAs.

For SEIFA, the appropriate disadvantage score was assigned to a quantile from the relevant Census (i.e. 0-10%, >10-25%, >25-50%, >50-75%, >75-90% or >90%, with values 0-5, respectively), as defined by the Australian Bureau of Statistics (ABS) for the Western Australian population.<sup>155,156</sup> For the ARIA+ category, which consisted of a label for the appropriate remoteness group,<sup>157</sup> the label was simply translated into a numerical value (1-6) for ease of use. On each record, a flag was set to indicate whether the SEIFA/ARIA+ categories had been derived from CD or SLA details.

Upon completion of the SEIFA and ARIA+ allocations at the record level, the resulting file was sorted by person ID and event date (i.e. hospital separation or death date), and counts of occurrences for each SEIFA level and ARIA+ category were accumulated at the patient level, distinguishing between CD and SLA derivations. The SEIFA and ARIA+ category with the most counts was then determined (for both CD and SLA derivations and overall) and various

parameters required to calculate related percentages were generated. Once the preliminary overall allocations were determined, SEIFA and ARIA+ status indicators were generated for each patient based on the level of agreement between records, the sources of derivation and the number of entries involved, to give some indication of the 'strength' of the value assigned.

Initially, these indicators were used to identify patients whose overall allocation needed to be reviewed manually. However, after reviewing more than 600 'problem' SEIFA cases, a more appropriate allocation mechanism was devised, which eliminated the need for further manual review. The revised approach first allocated the overall SEIFA and ARIA category based on the category with the greatest overall count, disregarding the source of derivation (i.e. CD or SLA). Corresponding status indicators were then derived based on the percentage of patient records in agreement with the overall allocation and the derivation sources (CD/both or SLA only).

Thereafter, a final allocation was applied, which assigned the overall SEIFA or ARIA+ category to the most common value if at least 70% of records were in agreement or to the CD-derived value if only two records supplied information and one was CD-derived and the other based on SLA derivation. Otherwise, the overall category was calculated from an average of the allocations from all records for a given patient. Obviously, if no information was available at all to derive the overall category, the latter was assigned a 'missing' value. For the overall ARIA+ category, only the first five categories were used in the average as category 6 represents a 'migratory' status rather than an ordinal level of accessibility to services. In fact, this was only a precautionary measure as none of the records supplied specified this 'migratory' category.

### **Determine Overall 'Living Alone' Status**

To complete the set of static demographic details for the people included in the study, one additional status field was generated. This field would indicate whether a person likely lived alone 'always', 'sometimes' or 'never' during the period 1993-2005 and was derived from the marital status on the person's hospital morbidity records. To produce this variable, the HMD master data file was sorted by person ID, admission date and separation date and all records were allocated an 'alone' status based on the specified marital status. All entries with a valid marital status other than 'married/de facto' (i.e. never

married, widow, divorced or separated) were assumed to relate to people who lived alone at the time of admission. Entries with an 'unknown' marital status were assigned a 'missing' alone status.

Using this data set, a file of records representing episodes of 'living alone' status for each patient was created by checking the alone status on each record for a given person. If the patient's first HMD record was being processed, a new episode record was set up with a start date, end date and alone status matching the current HMD record's admission date, separation date and alone status, respectively. For subsequent records with no change in 'living alone' status, the end date of the current episode was adjusted to match the separation date on the current HMD record. Upon detection of a change in 'alone status', the duration of the current episode was calculated, the episode record was output and a new episode record was initiated, as per the first record for a given patient. The algorithm for processing the HMD records also ensured that the last episode record was output once all entries for a patient had been processed.

Using the resulting episode file, each episode's start and end dates were adjusted to cover the entire period from 1 January 1990 to 31 December 2006. This was achieved in two passes. In the first pass, all episode start dates and the end date on the last record for each patient were revised. The start date on the first record for a given patient was set to 1 January 1990 and the end date on the last record was set to 31 December 2006. The start date for other episodes was set to the mid-point of the gap between the end of the previous episode and the start of the current one. In the second pass, the episode file was sorted in reverse chronological order for each patient and the end date for each episode was set to the day prior to the start date of the next episode (i.e. previous record in the inverted file), thus eliminating any gaps between episodes. The duration of each episode was then recalculated and the output was re-sorted in chronological order by person ID.

From this revised episode file, a summary file was created to accumulate 'living alone' statistics for each patient, including the number of 'alone' and 'not alone' HMD records and episodes, and the overall duration for each status. This summary file was then used to derive the overall 'living alone' status of all patients with at least one PBS record over the study period (i.e. 1993-2005). As

the patient's gender is quite relevant when examining the 'living alone' status of older people, the overall gender allocated to each patient was also accessed in this final process. Thus, the list of person IDs for patients who had at least one PBS record during 1993-2005 and the file of overall gender allocations were merged to the 'living alone' summary file, and one record was retained for each entry in the person ID list. If none of the patient's HMD records had a marital status suggesting that the patient was living alone, the patient's overall 'living alone' status was set to 'never'. Conversely, if all of the patient's HMD records suggested that the patient was living alone, the overall 'living alone' status was set to 'always'. If the patient didn't have any HMD records or if none of these records specified a marital status, the status of interest was set to 'unknown'. Otherwise the patient's 'living alone' status was set to 'sometimes'. The final output from this process was saved in a file that was labelled "HRPIMS\_PIDPBSGenderAlone9305".

### **3.1.9 CREATE COHORT PATIENT FILE**

Once the overall demographic details for each patient were reconciled and various other patient exclusion flags were generated, it was possible to bring all of this information together into a preliminary master patient file (see Figure 3-11). This file was assembled by merging fields from the following data sets to the list of person IDs for patients with at least one PBS record during 1993-2005:

HRPIMS\_PIDGender2 - Overall gender

HRPIMS\_PIDDOB4 - Date of birth estimate

HRPIMS\_PIDGeo3 - Overall SEIFA and ARIA+ categories

HRPIMS\_PIDPBSGenderAlone9305 - Overall "living alone" status

HRPIMS\_DTHMaster - Date and cause of death

HRPIMS\_PIDACCStatus9305 - Aged care status at 30 June for 1993-2005

HRPIMS\_PIDCancer - Indicator of cancer diagnosis on inpatient records

HRPIMS\_PIDELROut9305 - Electoral roll exclusion flag (from gap checks)

HRPIMS\_PIDNoELR9305b - List of people with no electoral roll registrations

HRPIMS\_PIDPostDthRecs - Exclusion flag indicating records post-death

HRPIMS\_PIDPBSOut9305 - PBS exclusion flag (from age/item adjustments).

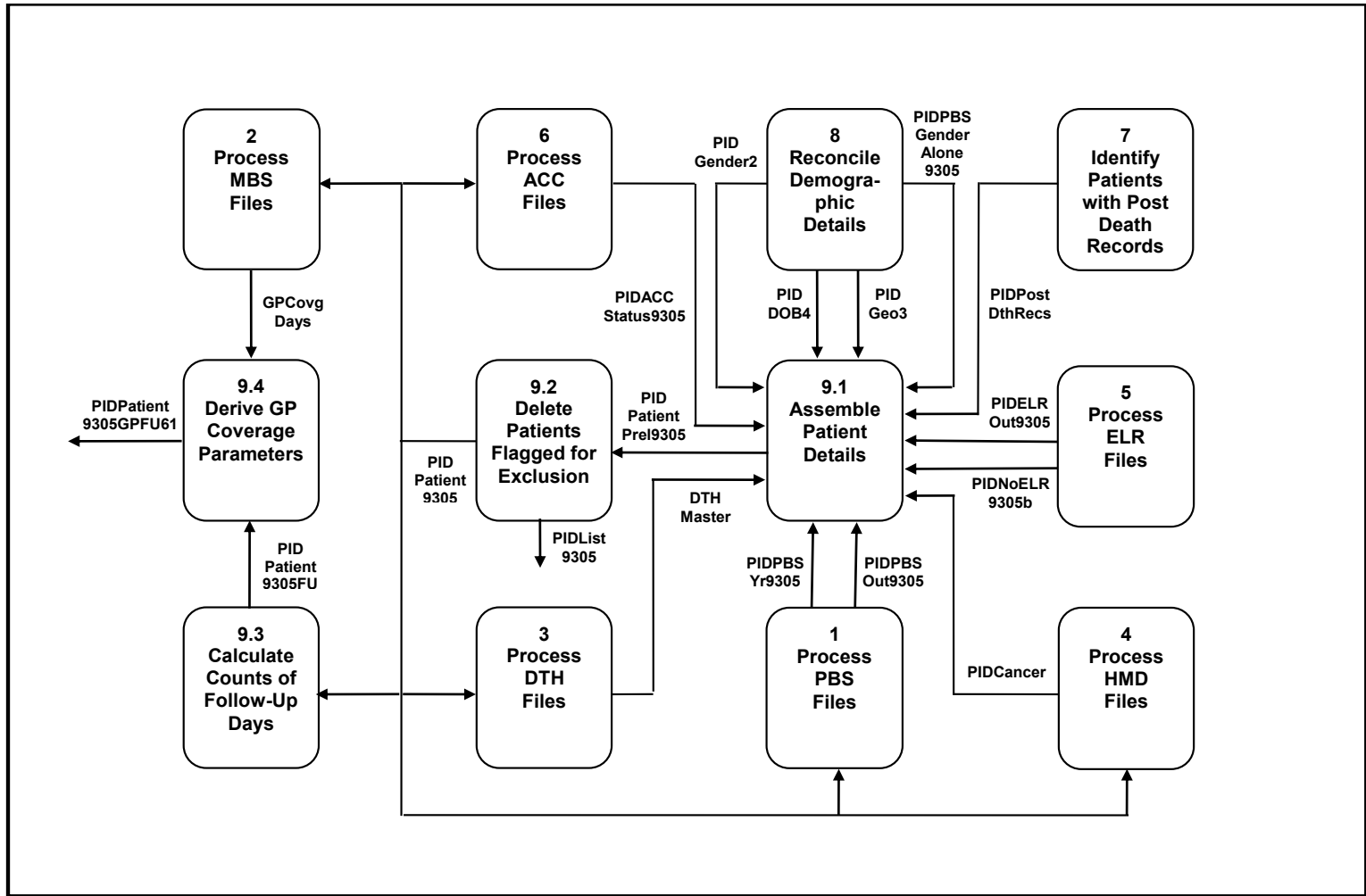


Figure 3-11 Process to create cohort patient file

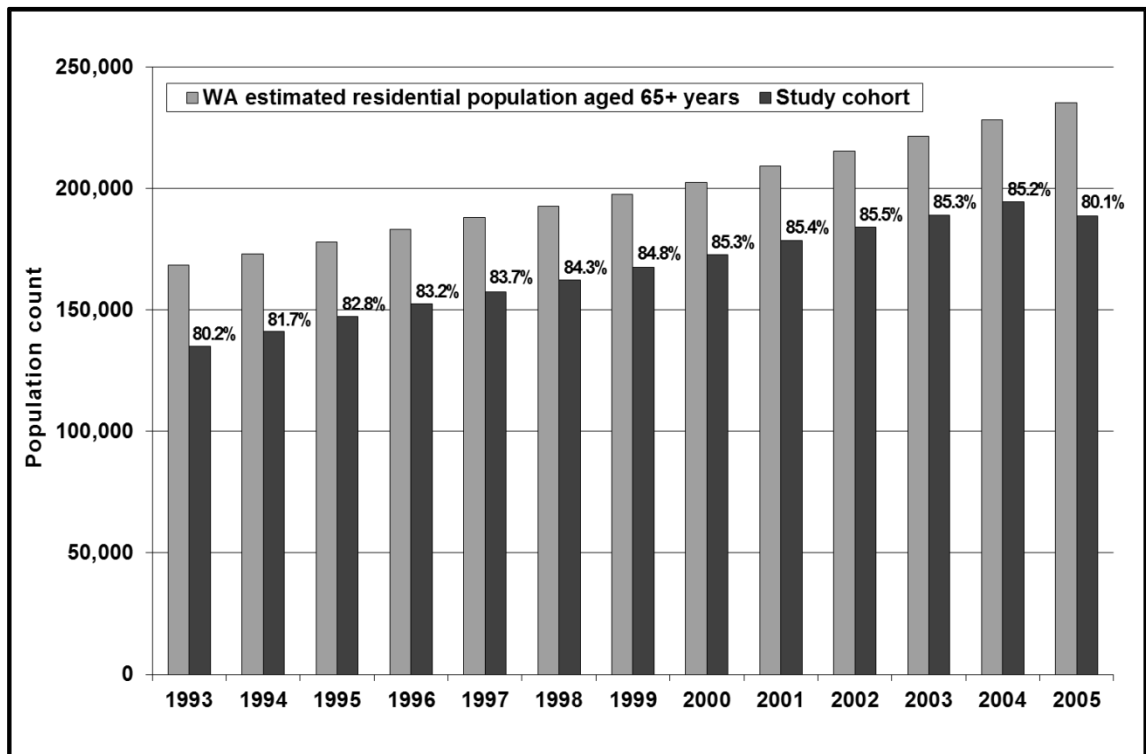
Upon amalgamation of the above data, the 'elrout' flag generated when checking for electoral roll registration gaps was set to three (3) for person IDs on the list of people with no electoral roll registrations at all, to reflect this additional electoral roll exclusion requirement.

From the preliminary file described above, an ultimate patient master file was created, which retained the same format as its predecessor but omitted entries for patients flagged for exclusion in the initial file (including those with no specified gender) and dropped the exclusion flags. A corresponding master list of person IDs was also generated to identify all patients in the study cohort. The two resulting files were named "HRPIMS\_PIDPatient9305" and "HRPIMS\_PIDList9305", respectively. As previously mentioned (Figure 3-2), the final cohort consisted of 251,305 individuals (i.e. 74.3% of the older people initially selected, before refinement of the study period and application of exclusion criteria). However, comparing the study's annual patient counts for 1993-2005 with official statistics of the WA estimated residential population aged  $\geq 65$  years<sup>161</sup> suggests that the study's ultimate cohort captured 80-85% of WA elderly residents over that period (Figure 3-12).

At a later date, upon initiation of the PIM prevalence study, fields related to patient follow-up duration were added to the original patient master file. To derive this information, the overall follow-up time was calculated for each patient record as the count of days from the follow-up start date (i.e. study period's start date (01/01/1993) or date on which the patient turned 65 years if within the study period) to the follow-up end date (i.e. study period's end date (31/12/2005) or date of death if within the study period). This overall follow-up period was then superimposed against calendar year periods to determine patient follow-up days for each calendar year during 1993-2005.

Additionally, counts of follow-up days were calculated for each patient by five-year age group, both overall and for each calendar year within the study period. This was derived by allocating counts of follow-up days in each calendar year as two components - one for days prior to the person's birthday and another for all remaining days within the year. Pre and post-birthday follow-up days could then be allocated to the appropriate follow-up count according to the patient's age in each part of the year. The revised patient master file was labelled "HRPIMS\_PIDPatient9305FU".





**Figure 3-12 Comparison of study cohort’s annual patient counts against Western Australia’s estimated residential population aged ≥65 years (1993-2005)<sup>a</sup>**

<sup>a</sup> Western Australia’s estimated residential population counts obtained from Australian Bureau of Statistics, 2008.<sup>161</sup> Patient counts for 2005 are slightly lower than expected as those who turned 65 years old during 2005 could not be included in the cohort (for logistical reasons).

Subsequently, the GP coverage duration figures accumulated for each patient from the file of MBS GP episodes were also added to the patient master file. GP coverage percentages were then derived, using the counts of GP coverage days as numerator and corresponding patient follow-up days as denominator. If the count of follow-up days was less than 182 days for a given calendar year, the percentage field for that year was allocated a missing value. Additionally, a category number (0-3 or missing) was allocated to each coverage percentage, roughly based on quartile boundaries. From this process, a record containing all of these GP coverage fields, as well as all other fields already existing on the patient master file was generated for each person. The resulting file was saved as “HRPIMS\_PIDPatient9305GPFU61”.

### 3.2 ESTABLISHMENT OF MEDICATION REFERENCE DATABASE

The pharmaceutical claim records extracted from the PBS database for this project were restricted to a few variables only (see Appendix B.1). They provided a unique person identifier, the age and gender of the patient receiving the prescription, a PBS code for the pharmaceutical item being supplied, the

supply date, and the number of scripts involved (to flag instances where multiple repeats were supplied at once). The records contained no details at all about the specific medication supplied (e.g. generic drug name, medication class, drug strength, number of pills/units per pack, etc.). However, the PBS item code specified on each record could be used to access reference information available through the PBS schedules, which had been published periodically since August 1991 and contained all of these details.

Furthermore, our study needed to ascertain the likely daily dose prescribed to older Australian patients on average (given that dosage details from the prescriber were not available), as well as the likely period of drug effect. These additional details would facilitate estimation of the drug consumption period associated with each script and the expected duration of drug effect. All of this information was required in a format that could readily be merged to the PBS records, for use in analytical computations.

Thus, this section describes the processes involved in establishing a reference database that would serve as a repository for all of this drug information, from the creation of base medication reference files from published PBS schedules to the ultimate allocation of an average prescribed daily dose estimate and likely period of drug effect for each PBS item. An overview of these various processes is presented in Figure 3-13.

### **3.2.1 CREATE MASTER PBS REFERENCE FILES**

The first step in establishing the study's medication reference database was to obtain PBS schedule text files from the time schedules were first published to the current time (August 1991 - June 2007) and to check their record layout. Although this information can now be accessed from the PBS website<sup>162</sup> (in text format from April 2007 onwards), online access was only being established when the data were sought. Consequently, one had to rely on output generated from ad hoc requests to the Department of Health and Ageing at various points in time, which was not always supplied in the same format. The text files were then converted from ASCII to SAS,<sup>154</sup> ensuring the correct layout was applied.

All converted records were then brought together into a master PBS reference file and sorted by PBS item, schedule date and ATC code. This SAS file contained all PBS entries for that time period (i.e. from all schedules), including multiples per PBS item code.

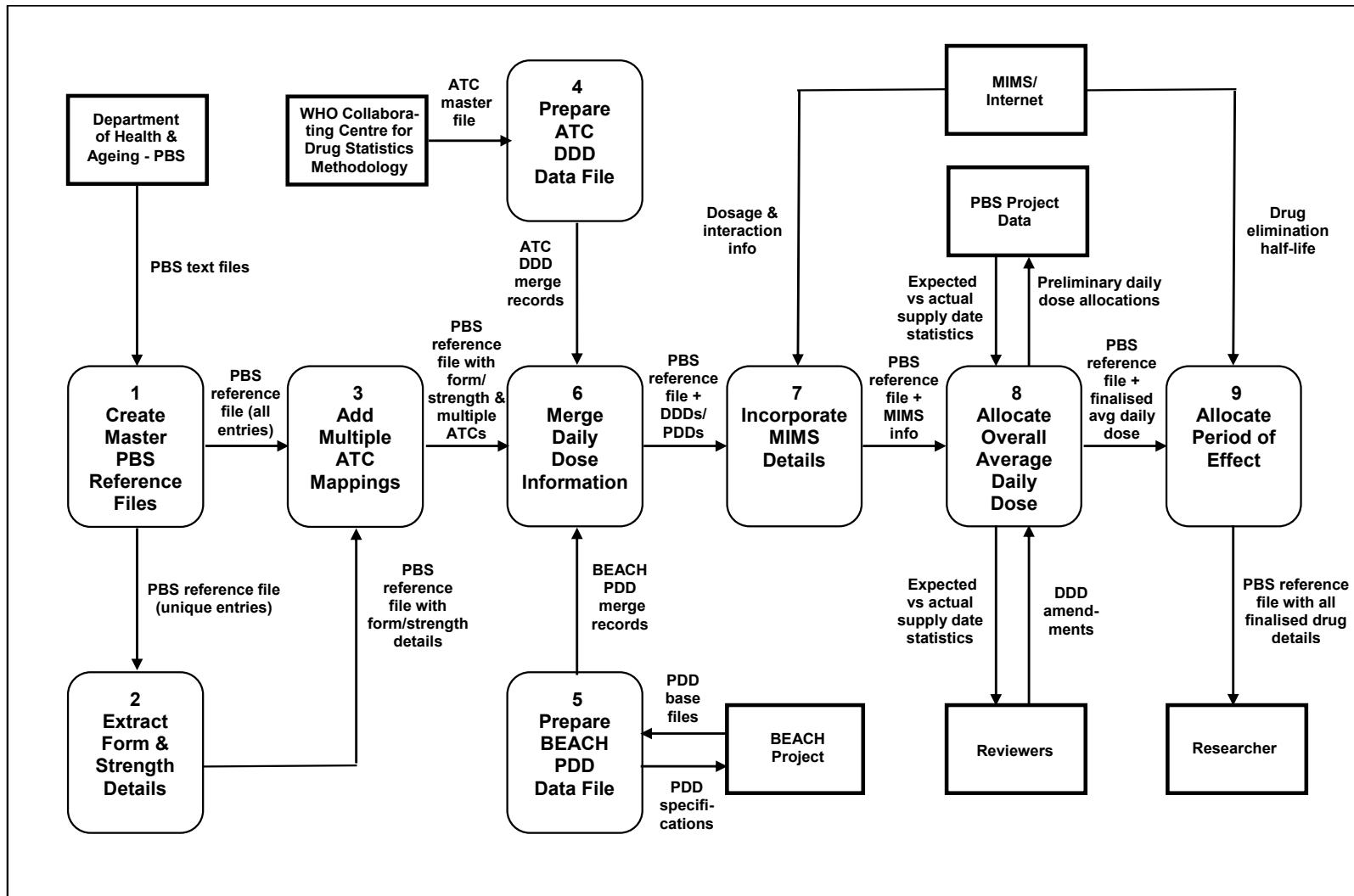


Figure 3-13 Overview of processes involved in establishing the medication reference database

Using the multiple-entry master PBS reference file, a file containing a unique record for each PBS item was created, retaining the most recent details for each item (up to June 2007) and the first and last schedule date.

### **3.2.2 EXTRACT FORM AND STRENGTH DETAILS**

A key field in the master PBS reference files is the FormStrength string variable. This field contains information about the route (oral, parenteral, inhalation, nasal, rectal, vaginal, dermal, etc.), form (capsule, tablet, liquid, powder, injection, etc.) and unit quantity (drug strength) associated with each specified PBS item. In some instances, it also includes the number of units per prescription pack, when the latter is not specified in the Packsize field.

This text variable was first examined manually to identify route, form and unit keywords, and to determine the relative position and format of strength and other related numeric values. Thereafter, a SAS program<sup>154</sup> was developed to extract all relevant keywords and values from the FormStrength string, to allocate the appropriate route and form categories to each PBS entry, to specify the drug strength as a numeric variable, and to calculate the total prescription dosage (and units) from the extracted numeric values and the Packsize variable. The resulting SAS output was converted to an MS-Excel file and then formatted and printed to facilitate verification of the contents.

Manual checks of all generated numeric values subsequently took place, with particular attention to the route, form, strength, script total dose and associated units. All identified errors were then corrected manually on both the MS-Excel and SAS master files.

### **3.2.3 ADD MULTIPLE ATC MAPPINGS**

To identify the specific drug associated with each item, PBS schedule entries specify the most appropriate code from the WHO ATC classification<sup>163</sup> applicable upon schedule publication. Although this code generally remained stable over time for a given PBS item, in some instances it changed as the ATC coding scheme evolved. Since the ultimate PBS reference database would only contain one entry per PBS item, it was important to ensure that these code variations were resolved and remained available for future reference.

Hence, the SAS file that contained all PBS reference entries was accessed once again and sorted by PBS item, ATC code and schedule date. Records were then aggregated by PBS item code and ATC code, retaining the most

recent details for each entry. The file containing these aggregated records was then sorted by PBS item, last schedule date (descending order), length of ATC code (descending order) and ATC code, thus ensuring that the most recent and full length codes were given priority in the mapping.

The resulting file was checked manually, ensuring that the output ATC priority sequence was appropriate. In a few instances, this sequence was reassigned, making sure that the most relevant mappings came first. The ATC mappings (and corresponding end dates) were then collapsed into unique entries per PBS item, sequencing ATC codes as per priority order.

Thereafter, the primary ATC code for each PBS entry was set to the first ATC code in the sequence (i.e. the most recent), which was also verified through a manual check, with appropriate reassignments made where necessary. Most required adjustments applied to PBS items with more than one possible ATC mapping, where the first one listed was not considered the most common, or to entries that had been deleted from the PBS schedule over time, but for which ATC classification changes had occurred since this deletion. The resulting list of ATC mappings and corresponding end dates was then merged to the master reference file with unique PBS entries, the primary mapping for each entry thus reflecting the 2007 WHO ATC classification.<sup>163</sup>

#### **3.2.4 PREPARE ATC DDD DATA FILE**

Although PBS schedule entries included ATC codes, they did not specify any information about average prescribed daily doses. These dosage details had to be obtained from other sources. In the first instance, DDD values from the WHO ATC classification were considered for this purpose.

Since the research team had already purchased an MS-Excel copy of the 2005 edition of the WHO ATC classification index with DDD assignments,<sup>164</sup> this file was used as a basis to derive the required dosage information. However, before proceeding with the extraction process, the file had to be updated and formatted accordingly.

To begin with, all of the 2006 and 2007 modifications advised by the WHO Collaborating Centre for Drug Statistics Methodology were applied to the 2005 edition. The 2008 amendments were also available by then but, since the ATC codes applied to the master PBS reference file reflected the 2007 edition, the 2008 ATC code updates were not applied to the project's ATC master file. The

2008 DDD amendments were incorporated, however, as they would provide additional DDD values for consideration and refinements to existing ones.

Upon completion of the ATC file updates, entries associated with the lowest level ATC codes (i.e. seven-character codes) were extracted from the master MS-Excel worksheet, ensuring that all such entries had an ATC code and, if a DDD was available, that a route identifier was specified. ATC codes were missing on the master worksheet for entries where DDDs were specified for more than one route of drug administration. Route text codes also needed to be refined and, with the help of MS-Excel functions, ATC codes with multiple entries per route were resolved by specifying a subroute where applicable, making use of the ATC notes in the process. Once the route information had been cleaned up, the route text codes were converted to numeric values to match those used in the master reference file with unique PBS entries.

### **3.2.5 PREPARE BEACH PDD DATA FILE**

A close examination of the DDD values available from the WHO ATC classification and conversations with Australian interstate drug utilisation experts suggested that relying exclusively on WHO DDD data to derive the average daily doses likely taken by elderly patients in this study would not be sufficient. Not only were there a number of missing DDD values on the ATC master file, but it seemed Australian prescribing practice varied from international practice in a number of instances. Furthermore, for some drugs, the daily quantities recommended by doctors were lower for older people than for other patients. It became very important to identify an Australian source that would give us a better indication of daily dose estimates for our target population. One such source was the general practice database maintained by the Bettering the Evaluation and Care of Health (BEACH) program.<sup>165</sup>

After extensive discussions with BEACH representatives, the project's research team specified the requirements and negotiated a contract to obtain prescribed daily dose (PDD) statistics from BEACH for April 2000 to March 2007. For all adults aged  $\geq 18$  years and for seniors aged  $\geq 65$  years, we obtained:

- The total number of prescriptions (including those with missing dosage information) for each medication, where the latter were identified using codes from the Coding Atlas for Pharmaceutical Substances (CAPS), as recorded on the BEACH database (Pass 0).

- Prescribed daily dose (PDD) statistics (i.e. number of valid cases, mean, median, minimum, maximum, 5<sup>th</sup> and 95<sup>th</sup> percentiles, and standard deviation) for each CAPS code, based on all relevant prescriptions with available dosage details (Pass 1).
- PDD statistics (as above) but excluding outlier prescriptions, i.e. those with PDDs less than the 5<sup>th</sup> percentile or greater than the 95<sup>th</sup> percentile (Pass 2).
- All of the statistics described in the above three points (i.e. repeat of Passes 0-2) with a further breakdown by drug form within CAPS drug code.

Upon receipt of the above data, the twelve related MS-Excel files were formatted, sorted and aggregated into a master worksheet sorted by ATC, CAPS code, form, age group and pass number. Records from Pass 2 were also extracted into a new worksheet and minor coding adjustments were made (mainly to ATC codes that were incomplete or incorrect according to the 2007 ATC classification).

From the 'clean' Pass 2 worksheet, two worksheets were created that could be merged to the master PBS reference file with unique PBS entries. The first contained unique entries at the ATC-CAPS code level for all Pass 2 entries with a form code of '\_All' (i.e. overall statistics at the generic drug level). The second contained unique entries at the form level within ATC-CAPS code for all Pass 2 entries with a specific form (i.e. Form is not '\_All'). For both worksheets, the corresponding statistics for all adults (≥18 years) and for seniors only (≥65 years) were placed side by side in the appropriate entry (as opposed to separate entries). All entries with multiple CAPS codes per ATC code were then allocated one-digit numbers (0-4) to distinguish them from one another, a process that was repeated for both the ATC-CAPS and the ATC-CAPS-Form worksheets. Finally, the form labels on the ATC-CAPS-Form worksheet were converted to numbers to match those used in the master PBS reference file.

### **3.2.6 MERGE DAILY DOSE INFORMATION**

Before merging the average daily dose information to the master PBS reference file with unique entries, a few checks and adjustments were required. Firstly, ATC codes used on both the ATC DDD worksheet and the BEACH PDD worksheets and on the master PBS reference file were cross-checked to make sure there were no discrepancies for any given drug. Furthermore, the form category codes in the master PBS reference file were checked to ensure they

matched those in the BEACH PDD worksheet that contained statistics at the form level within ATC-CAPS codes. Where multiple ATC-Route entries existed in the ATC-DDD worksheet, an appropriate 'RteSub' code was added to the corresponding master PBS reference entry to facilitate the correct merging. Similarly, where multiple CAPS codes existed in the BEACH PDD worksheets for a given ATC code, the relevant 'MultiCAPS' number was added to the corresponding PBS reference entries.

Once the files were ready, a SAS program<sup>154</sup> was created and executed to convert the relevant ATC DDD and BEACH PDD worksheets from MS-Excel to SAS, sort the resulting files and merge them onto the master PBS reference file. The ATC DDD entries were merged by ATC and RteSub code, the BEACH PDD worksheet at the generic drug level by ATC and MultiCAPS code, and the BEACH PDD worksheet at the form level within generic drug by ATC, MultiCAPS code and Form code. The resulting SAS file was then converted to MS-Excel for further review and processing.

### **3.2.7 INCORPORATE MIMS DETAILS**

Although the WHO DDD values and BEACH PDD statistics were helpful, it was felt that they could not be relied upon exclusively to determine the average prescribed daily dose associated with each PBS item in our data. In Australia, the primary source of information used by medical practitioners for advice on prescribing specific therapeutic drugs is MIMS. Originally developed as a paperback product known as the "Monthly Index of Medical Specialities" in the early 1960s (hence the acronym), MIMS provides full details of the composition, pharmacological properties, indications, contraindications, precautions, interactions, potential adverse reactions and other information for all medications currently available on the Australian market. Most importantly, it also provides recommended dosage and administration instructions for each item.<sup>166</sup>

Hence began an extensive search of the MIMS products (MIMS Online<sup>167</sup> and, for medications that were no longer available, several editions of the MIMS Annual<sup>166,168,169</sup> hard-copy publication) to ascertain more precisely the daily dose usually prescribed to elderly patients for each medication by drug strength (e.g. 50 mg vs. 100 mg tablet). For each item found in the master PBS reference file (MS-Excel format), MIMS Online<sup>167</sup> was first searched for the



relevant medication entries. The dosage information found was reviewed and summarised, and a very brief outline was inserted as a text string within the PBS reference file. A list of all interacting drugs specified in MIMS was also inserted, when possible.

If no information was available from MIMS Online, the MIMS hard-copies<sup>166,168,169</sup> were searched and relevant details were extracted accordingly, as per MIMS Online. This was usually required when the drug was no longer on the current PBS schedule.

In the few situations where the various MIMS sources yielded no dosage information, the Internet was searched for suggested dosages for the medication of interest. Although this information may not always have been from an Australian source, it was felt that it would still be of some relevance and better than no information at all. Nonetheless, to distinguish these dosage recommendations from those obtained directly from MIMS, they were prefixed with the word "Internet:" in the master PBS reference file.

### **3.2.8 ALLOCATE OVERALL AVERAGE DAILY DOSE**

With information from MIMS, BEACH and the WHO DDD allocations, it was possible to form a better judgment of the likely daily dose prescribed to most elderly patients. To facilitate this process, flags were first set in the master PBS reference file with unique PBS entries to identify available sources of daily dose information for each entry. Thereafter, an extensive manual review was undertaken, comparing the daily dose statistics from all available sources and allocating a preliminary overall average prescribed daily dose to all PBS entries where this information was relevant. A daily dose status flag was also set to indicate whether the daily dose value needed to be reviewed and to reflect the degree of confidence in the allocated value, based on available sources. If no daily dose sources were available but the item was not required as it was excluded from our study (e.g. dermal or dental preparations; irrigating solutions; eye, ear or nasal drops; treatment aids such as bandages, stoma bags and others), the daily dose status field was set to 9 and the overall daily dose field was left blank. Please refer to Appendix C for a full list of pharmaceutical products excluded from the study and to Appendix E for more extensive details of the daily dose allocation process.

Once this preliminary allocation was completed, the resulting daily dose values were applied to the project's PBS data, using them to determine the patients' expected dates of re-supply for each drug (at the generic drug name level). The actual supply dates were then compared with the corresponding expected dates calculated using average daily dose estimates, and summary statistics were generated for the difference between the two. For these statistics, patients' first prescription for a medication were excluded, as well as those with an actual re-supply date 90 days greater than the expected date, as these prescriptions were deemed to represent the start of new episodes of drug consumption (i.e. a valid expected date of supply could not be determined).

The 'expected vs. actual' supply date statistics were then reviewed, and PBS items with an absolute mean difference greater than 3-4 days were identified. All such items were examined more closely, assigning them a revised overall daily dose that reduced the average gap between expected and actual dates to the smallest possible value, but also taking into consideration realistic consumption patterns. Thus, daily dose allocations were generally restricted to increments of 0.5 of the unit strength. In a few instances, however, where the likely daily drug use was equally divided between a half and a whole unit dose, an average daily dose of 0.75 of the unit strength may have been allocated, if this was judged to be appropriate. Upon completion of this review process, revisions to the daily dose allocations were incorporated into the master PBS reference file.

### **3.2.9 ALLOCATE PERIOD OF EFFECT**

A good part of this research project revolved around the assessment of potential associations between exposure to specific medications and unplanned hospitalisations. Given the study design, it would not be possible to confirm whether these associations resulted from the causal effects of these medications. Nonetheless, it made sense to define medication exposure in such a way that it would at least be plausible for the unplanned hospitalisations to have resulted from the adverse effects of drug exposure. Consequently, it was decided that being 'exposed' to a drug on a given day would not simply mean that the patient had taken the drug on that day. Instead, the exposure definition was broadened to mean that the patient was still under the effects of

the drug on that day. It was therefore important to determine the likely period of effect for each PBS item.

To achieve this, the elimination half-life of the specified medication on each PBS entry used in the study was first extracted, mostly from MIMS but, where necessary, from other relevant Internet sources. This extracted information was entered onto the master PBS reference file. Where the elimination was multiphasic (usually represented as alpha ( $\alpha$ ), beta ( $\beta$ ) and gamma ( $\gamma$ )), the beta half-life figure was recorded where possible. The alpha phase is usually associated with drug distribution, whereas the gamma half-life (if reported) generally applies when metabolised drug components are stored in body tissues (e.g. bones), often in a semi-inactive state for extended periods of time, and eventually released from the body at a very slow rate. The beta half-life was of greatest interest as it either represents terminal body elimination (for biphasic elimination) or the excretion of the bulk of the active drug (for triphasic elimination).<sup>167</sup>

Based on the extracted information, the period of effect of each required PBS item was allocated (i.e. number of days of effect beyond the day of drug consumption). In most instances, this was achieved by calculating the number or hours of effect as five times the elimination half-life (in hours)<sup>170,171</sup> and converting this figure to whole number of days. If the fraction component of the number of days represented more than 1-2 hours beyond a whole day, the number of days figure was rounded up to the next integer (as opposed to the standard rounding process). For example, if the half-life was six hours, then the number of hours of effect was  $5 \times 6 = 30$  hours, which was converted to a period of effect of two days (i.e. one day plus a fraction becomes two). However, if the half-life was five hours, then the number of hours of effect was  $5 \times 5 = 25$  hours, which was converted to a period of effect of one day, since the fraction only represented one hour.

Once verification of the estimated period of effect values was completed, relevant fields from the medication reference database were ready to be integrated into the master pharmaceutical claims data set.

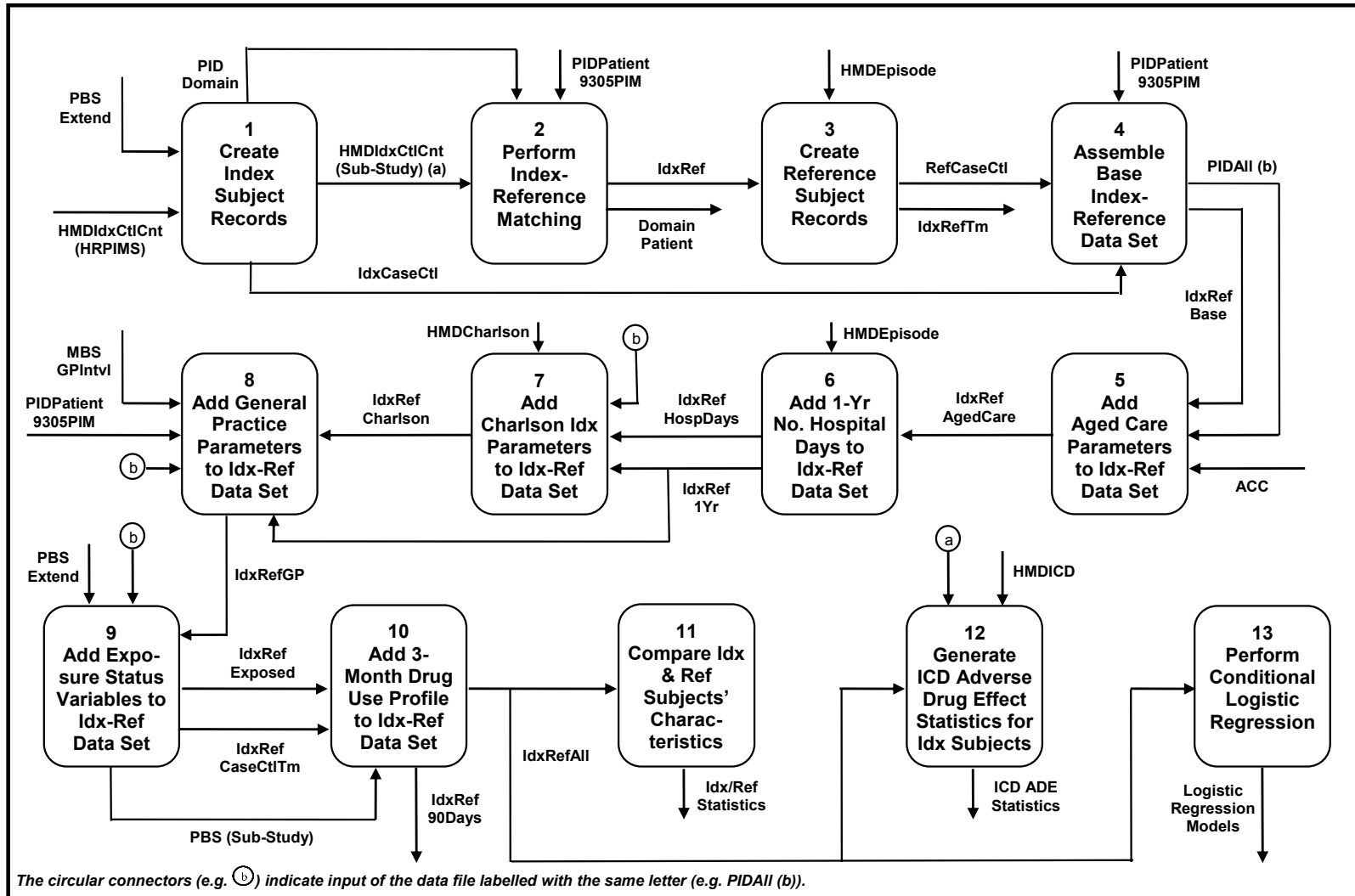


Figure 3-14 Exploration study using high-risk drugs - data preparation and analysis

### **3.3 EXPLORATION STUDY USING HIGH-RISK DRUGS**

Upon completion of the master data set clean-up, it was possible to initiate the data analysis phase, starting with the high-risk drug study. Processing for this phase consisted of the following steps, which were repeated for each of the eight high-risk drug groups:

- Identify index subjects/admissions (1)
- Match the index subjects to appropriate reference subjects (2-3)
- Assemble case and control time records for index and reference subjects (4)
- Add data analysis parameters to the base index-reference data set (5-10)
- Generate statistics to compare index and reference subjects' characteristics (11)
- Produce adverse drug effect statistics using ICD codes from index admissions (12)
- Perform conditional logistic regression (13).

Further details of each of these processing steps are outlined in the remainder of this section. A summary diagram is also presented in Figure 3-14.

#### **3.3.1 CREATE INDEX SUBJECT RECORDS**

To initiate the data analysis phase for a given high-risk drug group, all patients who had been prescribed a medication from the sub-study's 'drug domain' over the study period (i.e. 1993-2005) were identified. Each domain included drugs of the same class as the specific drug group being studied and/or used to treat similar health conditions. ATC definitions for each high-risk drug group and corresponding domain are presented in Appendix F. To identify these patients, the study's extended PBS data set was searched for relevant drug prescription records, from which a list of 'domain' person IDs (PIDs) was derived.

Using this patient list, the file of all potential index hospital admissions (i.e. admissions between 1 July 1994 and 31 December 2005 with an admission age  $\geq 67$  years) was searched and all records for 'domain' patients were extracted. These constraints were necessary to ensure that relevant information was available for all subjects during the look-back period preceding their control time, which was one year prior to the date of hospital admission (i.e. case time), keeping in mind that most patient records were only available from the time they

turned 65 years and were only considered complete enough to use from either 1992 or 1993, depending upon the data source. Index records for patients with >50 index admissions ( $\leq 0.1\%$ ) were subsequently excluded from the analysis, due to concerns of representativeness.

For each selected index admission, a record for the index case time and one for the corresponding control time were generated and saved into a separate file (IdxCaseCtl). For these records, the admission date was used as the case time and a previously calculated date found on the index admission record was used for the index control time. In most instances, the latter was 365 days prior to the admission date but, if the patient was in hospital at this preferred control time, the admission date of this earlier hospitalisation was used instead.

### **3.3.2 PERFORM INDEX-REFERENCE MATCHING**

Once the index subjects were identified, they were matched by gender, GP coverage category (based on proportion of adequate GP monitoring over the entire study period) and year of birth to randomly selected reference subjects from the sub-study's domain. Unit year of birth was used for matching in most cases but, due to their low number, subjects with a year of birth prior to 1900 were allocated a notional year of birth of 1900 for matching purposes only.

To perform the matching, all patient records with person IDs from the sub-study's domain were first extracted and allocated a random number (using the SAS RANUNI function).<sup>154</sup> A random number was also allocated to all of the sub-study's index admission records. Records from both sources were then brought together and sorted by gender, GP coverage category, year of birth and random number.

In the first pass of the matching process, domain records preceding each index record were examined and the closest match (in terms of gender, GP coverage, year of birth and random number) for which the potential candidate was still alive was selected as a tentative reference subject. The file was then inverted to check records that followed each index record in the initial sort. If a closer match was found, it superseded the tentative reference subject identified in the first pass (if one existed). Otherwise, the reference subject identified in the first pass was retained.

Relevant details from each identified reference subject were then appended to the corresponding index subject's record, which was subsequently output to a

file named IdxRef. This file was ultimately sorted by match ID to facilitate further processing.

### **3.3.3 CREATE REFERENCE SUBJECT RECORDS**

Using the file of index-reference matches output from the previous step (file IdxRef), this process verified the HMDEpisode file, which contained hospital episode records for study patients, to determine if each index subject's defined case and control times were appropriate for the corresponding reference subject. If the reference subject was in hospital on the date of the index admission, then the start date of the reference subject's overlapping hospital episode was used as the reference case time. Otherwise, the index admission date was used for the latter. Similarly, the date 365 days prior to the index admission date was used as the reference control time unless the reference subject was in hospital at that time. If so, the start date of the overlapping hospital episode was used as the reference control time.

Once the reference case and control times for each index-reference match were determined, a record for the reference case time and one for the corresponding control time were generated and saved into a separate file (RefCaseCtl).

### **3.3.4 ASSEMBLE BASE INDEX-REFERENCE DATA SET**

Once the index and reference case/control time records were generated, they were brought together into a single file, which was sorted by person ID and case/control time. A patient sequence number was allocated to all records for each given person for subsequent reference. A patient ID list (PIDAll) for the sub-study was also generated from this file.

The patient ID list was then used to extract the corresponding demographic details from the master patient file (i.e. PIDPatient9305PIM). These demographic details were merged to the file of all index and reference case/control records. The resulting output (IdxRefBase) would serve as a basis in subsequent processes for accumulating additional parameters on each record to meet the requirements of the sub-study's data analysis.

### **3.3.5 ADD AGED CARE PARAMETERS TO INDEX-REFERENCE DATA SET**

To obtain relevant aged care parameters for the sub-study, all records for subjects included in the sub-study were extracted from the project's Aged Care (ACC) file and brought together with the base file of index and reference case/control records. The resulting output was sorted by person ID,

case/control time and data source, ensuring that aged care records for a given date occurred before case/control records for the same date.

This file was then used to determine the aged care status at the case or control time on each case/control record. Through this process, the aged care category, high care indicator, date first admitted to a high care facility, and number of days in high care were added to each case/control record, as appropriate.

### **3.3.6 ADD ONE-YEAR NUMBER OF HOSPITAL DAYS TO INDEX-REFERENCE DATA SET**

To determine the number of days of hospitalisation in the one-year period prior to each case/control time, this process first created arrays for each person, which contained the start and end dates for all of their 'one-year periods'. The end date for each period was the case or control date specified on the record, whereas the start date was 365 days prior. The end date was retained as such as it would be required in other processes but, for the accumulation of hospital days (i.e. this process), the end date was adjusted to the day prior to the case or control time.

Thereafter, the start and end date arrays were merged to the subjects' hospital episode records (HMDEpisode), which were then processed to determine the number of days from each episode that overlapped with each of the patient's one-year time period (as defined by the start and end date arrays). These numbers of overlapping days were accumulated for each patient and output to a corresponding array record at the end of processing for that patient. In these calculations, the discharge date was not counted as a hospital day. However, same-day discharges were counted as one-day stays.

The array of accumulated number of hospital days for each person's one-year periods was subsequently merged back to the index and reference case/control data set. The appropriate count for each case or control record was then extracted from the array and retained as an additional parameter on the record. Upon termination of processing, the array itself was discarded as it was no longer required.

### **3.3.7 ADD CHARLSON INDEX PARAMETERS TO INDEX-REFERENCE DATA SET**

To determine the overall Charlson index parameters for the one-year period prior to each index or reference case/control time, this process first merged the one-year array records created in the previous step to the project's



HMDCharlson data set, retaining all array entries but only Charlson data for the patients of interest. It then checked all Charlson records for each patient to determine if the period bound by their admission and separation dates overlapped with any of the patient's defined one-year periods (from the patient's 'one-year' array). If so, the values of the Charlson parameters on the record being processed were accumulated in the appropriate array entries, ensuring that, once all records for a given patient were processed, the resulting Charlson arrays flagged all health conditions treated during hospital stays that occurred during each relevant one-year period. Charlson array records were output for each patient as part of this process.

The arrays of accumulated parameters were subsequently merged back to the index and reference case/control data set. The appropriate Charlson values for each case or control record were then extracted from the arrays and retained as additional parameters on the record. Using the extracted Charlson values and the appropriate weights, an overall Charlson index was then calculated for each record. Upon termination of processing, the Charlson arrays were discarded since they were no longer required.

### **3.3.8 ADD GENERAL PRACTICE PARAMETERS TO INDEX-REFERENCE DATA SET**

Like the previous two steps, this process accumulated parameter values in arrays, checking for events occurring during each patient's defined "one-year" periods. However, in this instance, the sub-study subjects' general practice records (derived from the project's Medicare data) were examined. In particular, the file containing records on GP visits, including the number of days (interval) since the last GP visit (MBSGPIntvl) was accessed.

This time, the 'one-year' array file was first merged to the patients' extracted MBSGPIntvl records. The count of GP visits occurring during each one-year period was then accumulated and the date of the last GP visit for the period determined. This information was retained in arrays for each one-year period (for each patient).

As per previous processes, the arrays of accumulated parameters were subsequently merged back to the index and reference case/control data set. The appropriate count of GP visits and date of the last GP visit for the one-year period immediately prior to each case or control record were extracted from the arrays and retained as additional parameters on the record. Finally, the number

of days since the last GP visit was derived for each record. The latter was calculated as the difference between the case/control date and the date of the last GP visit, up to a maximum of 365 days.

In addition to the derivations described above, this process also retrieved relevant calendar-year GP coverage parameters from the patient master file (PIDPatient9305PIM). To achieve this, it first merged the latter with the output file from the previous step, matching on patient identifier (PID). It then allocated the most appropriate GP coverage category and percentage value for each record. In most instances, these values were those associated with the calendar year immediately preceding the year of the case or control date found on each record. However, if this information was not available, the equivalent details from the case/control year itself or (if required) from the calendar year immediately after the case/control date were used instead. In the few instances where the patient's follow-up time was too short for any of these GP coverage values to be available, the GP coverage percentage value for the entire follow-up time was adopted as a proxy, and its value was applied to the GP coverage definitions used at the calendar year level to determine the appropriate GP coverage category.

### **3.3.9 ADD EXPOSURE STATUS VARIABLES TO INDEX-REFERENCE DATA SET**

This process determined the exposure status of index and reference subjects at their case and control times for drugs of interest in the sub-study. It first extracted all of the subjects' records from the PBS extended data file, merged an array of each patient's case/control times to each record and examined each one to determine if the ATC code was relevant. If so and if the drug form was appropriate, the process checked each case/control time point for the related patient to ascertain whether it was within the time period bound by the drug supply date and the exposure end date (previously calculated upon creation of the PBS extended data file). For each time point found to be within the 'exposure' window, the corresponding entry in an exposure flag array was set to 1. The exposure flag array was subsequently merged back to the index and reference case/control data set (as per other processes), in this instance creating an exposure status variable as a result.

The exposure-checking routine was first performed for the primary drug of interest in the sub-study, and then repeated for key potentially inappropriate

medications (PIMs). The PIM exposure details would be required for the study component that focused on the estimation of effects of specific PIMs on the risk of unplanned hospitalisations in patients taking high-risk drugs, the results of which are presented in chapter 9 of this thesis.

#### **3.3.10 ADD THREE-MONTH DRUG USE PROFILE TO INDEX-REFERENCE DATA SET**

This process derived the drug use profile of index and reference subjects for the three-month period prior to their case and control times (i.e. 90-days prior plus the case/control day itself). It achieved this by creating an array file of start and end dates for all defined three-month periods for each patient, merging this file to the PBS extended records for the sub-study's patients, and then determining if the drug item specified on the record (ATC code) was one of interest and if its associated consumption period overlapped with any of the patient's three-month periods. If so, the number of days of overlap was calculated for each three-month period and accumulated to the total number of days of drug consumption (i.e. number of 'daily doses') for each period.

This search process was repeated for the primary drug of interest in the study, for all drugs combined, and for 22 major drug groups (as defined in Appendix G). For each drug pass, the resulting count of daily doses was extracted from the patient's three-month array and stored in an appropriately named variable on the index and reference case/control data set (as per other processes).

Once all of the three-month daily dose counts were determined, the file of case and control records was processed in one final pass to derive 0/1 flag values that would correspond with each daily dose parameter. If the daily dose count for a given drug group was found to be greater than zero, its corresponding flag value was set to 1. Using these flags, the number of drug categories contributing to the patient's three-month drug consumption profile was also derived, as were the 3-month daily dose count for all drugs except the exposure drug of interest, the cross-product between the 'exposed' variable and the index/reference status, and the cross product between the three-month daily dose count for the drug of primary interest and the index/reference status. Cross-products involving the main drug and PIM exposure variables were also generated (required for the study component pertaining to the estimation of effects of specific PIMs on the risk of unplanned hospitalisations in patients taking high-risk drugs).

The resulting output was sorted by GP coverage status for the entire study period, match ID, index/reference status (descending order) and case/control time indicator (descending order) and saved in a file labelled "IdxRefAll" for data analysis.

### **3.3.11 COMPARE INDEX AND REFERENCE SUBJECTS' CHARACTERISTICS**

Once the data analysis file was assembled, it was possible to compare the demographic and time-dependent characteristics of index and reference subjects. The demographic details were examined based on the contents of case time records, whereas both the case and control time statistics were compared for time-dependent parameters. Cross-tabulations, summary statistics (minimum, maximum, mean, standard deviation, etc.) and T-tests were produced in this process. These statistics were required to determine whether reference subjects were similar to their index counterparts and to assess whether their differing characteristics might impact on the study results.

### **3.3.12 GENERATE ICD ADVERSE DRUG EFFECT STATISTICS FOR INDEX SUBJECTS**

This process examined the file of all unplanned hospitalisations for index subjects from the sub-study domain, comparing the diagnosis and external cause codes for exposed and unexposed subjects, as well as other patient characteristics. This was achieved by bringing together the index case time records from the file output from step 10 (section 3.3.10) with the index subject case records generated in step 1 (section 3.3.1) and the file containing all inpatient summary diagnoses (HMDICD). Diagnostic and external cause categories were derived from the ICD codes for the index admission records, whereas the exposure status variable on the index case time records identified whether or not patients were exposed to the drug of interest at the time of each unplanned hospitalisation. Cross-tabulations, summary statistics and T-tests by exposure status and/or adverse drug effect status were generated from the resulting file.

One statistic of particular interest in the output was the count of exposed index subjects with an adverse drug effect (including accidental drug poisoning) flagged on their index admission record (as external cause). This count would later be used to compare against the number of drug-related hospitalisations derived from the logistic regression analysis and odds ratio/attribution fraction

method. For most drugs, it was expected that the drug-related external cause counts would be lower than those derived from regression analysis.

### **3.3.13 PERFORM CONDITIONAL LOGISTIC REGRESSION**

The main reason for assembling the data analysis file for each sub-study was to perform conditional logistic regression analysis. This was achieved using the SAS PHREG procedure.<sup>154</sup> Each model used:

- The covariance sandwich option (COVS) to ensure the generation of robust sandwich covariance estimates,<sup>172</sup> thus accounting for the potential within-cluster correlation associated with multiple hospitalisations per person
- A dummy time variable with value 1 for case time and 2 for control time records
- The case/control status as the censoring variable (with 0 as the censor value)
- The match ID and index/reference status as stratification variables (to uniquely match case/control pairs for the identification of discordant pairs in the conditional regression analysis)
- The match ID and index/reference status as “ID” variables, to meet the requirements of the covariance sandwich option.

The base model included the main drug exposure status (i.e. ‘exposed’ variable) as well as the cross-product between the ‘exposed’ variable and the index/reference status indicator (i.e. *expidx*). Adjusted models also included most of the time-dependent variables assembled into the sub-study’s main data analysis file, including the three-month daily dose counts for all major drug groups. This is an enhancement to the basic case-time-control design initially proposed by Suissa,<sup>26</sup> which did not control explicitly for time-variant potential confounding factors in the analysis. Static demographic characteristics and the three-month drug consumption flags were excluded, however. For the adjusted model, stepwise analysis was requested. The main parameter of interest in the final model was the odds ratio (OR) associated with the ‘*expidx*’ variable as it represented the estimated effect of drug exposure on unplanned hospital admissions in the index subjects, over and above the general time trend expected in all subjects included in the sub-study.<sup>26</sup> Using this OR, it was possible to calculate the proportion of unplanned hospitalisations attributable to drug exposure (among the exposed) as: attributable fraction (AF) = (OR – 1) / OR. An estimate of the corresponding count of unplanned hospitalisations

attributed to drug exposure was then derived as AF times the number of exposed index subjects.<sup>173-175</sup>

Variations of this main conditional logistic regression process were also performed for comparison, including a dose-response model (adding the primary drug's daily dose variable (DDDexp) and its cross-product with the index/reference status (DDDexpidx) to the models); a GP effect modification model (including a "BY" statement to repeat the modelling separately for each GP coverage category); a case-crossover model (excluding the reference subjects and the variables required to identify them from the analysis); and models to estimate the impact of selected PIMs on the risk of unplanned hospitalisations in patients taking the high-risk drugs of interest (adding PIM exposure status and its cross-products with the 'exposed' and 'expidx' variables to the models).

At a later date, once all results had been collated for the high-risk drug study, other model variations were introduced to explore the possibility of potential time bias in the study results, especially in relation to the opioid and corticosteroid sub-studies. Details of these additional models are provided in the manuscript presented in chapter 4.

### **3.4 PREVALENCE STUDY OF BEERS MEDICATIONS**

Before undertaking the main study on associations between exposure to Beers medications (PIMs) and unplanned hospitalisations, it was important to ascertain which of these medications were available from the Australian PBS over the study period; to what extent these drugs were consumed by the study population; and which factors were associated with PIM exposure. The approach used to derive this information is described below. It consists of the following steps, as depicted in Figure 3-15:

- Identify PIMs with prescriptions recorded on the study's PBS data set (1)
- Derive the number of days of PIM consumption for the study population (2)
- Generate statistics from the counts of patient follow-up days (3)
- Aggregate PIM consumption days at the patient level (4)
- Assemble PIM prevalence statistics for the study population (5)
- Perform Poisson regression to determine significant differences in PIM consumption rates between study population sub-groups (6)

- Derive patient-level consumption statistics for all prescribed drugs, as potential factors predicting PIM exposure (7)
- Identify predictors of PIM exposure through logistic regression analysis (8).

#### **3.4.1 IDENTIFY PIMs RECORDED ON STUDY'S PBS MASTER DATA SET**

As a first step in this prevalence study, a SAS program<sup>154</sup> was written to generate the counts of PBS records with a supply date within the study period (1993-2005) for each ATC/PBS code combination. Using the ATC definitions specified for each PIM (as per Appendix H), and the drug form constraints established for the study (Appendix D), it was possible to determine which PIMs from the general Beers list (i.e. drugs to be avoided in all people aged  $\geq 65$  years) were recorded on the PBS data set for the study cohort.

All such drugs were included in the PIM prevalence study, except for five individual drugs with very low overall counts and no records at all for the core years of the study (i.e. none other than in the first or last few calendar years). It was felt that the consumption of these excluded drugs was insufficient to justify further investigation of their effects. Overall, 43 drugs were selected, which involved 31 PIM categories, one of which (diphenhydramine) was embedded within a broader PIM category (anticholinergics/antihistamines).

#### **3.4.2 DERIVE COUNTS OF PIM CONSUMPTION DAYS**

Using the ATC definitions for the PIM study's drug domains (Appendix H), a file containing all related records for the study population was created from the master PBS data file. Patient details were merged to the extracted data as part of this process. The patient's aged care status at the midpoint of the calendar year associated with the drug supply date was isolated for subsequent generation of statistics. Similarly, the GP coverage status for the year of drug supply was selected for use in calendar year statistics, if available. If not, the GP coverage status for the year immediately before or after the year of supply was selected as a proxy. Average daily dose counts were determined for each record by calendar year and overall, ensuring prescription days after the patient's date of death or beyond the end of the study period (i.e. 31 December 2005) were omitted from these counts.

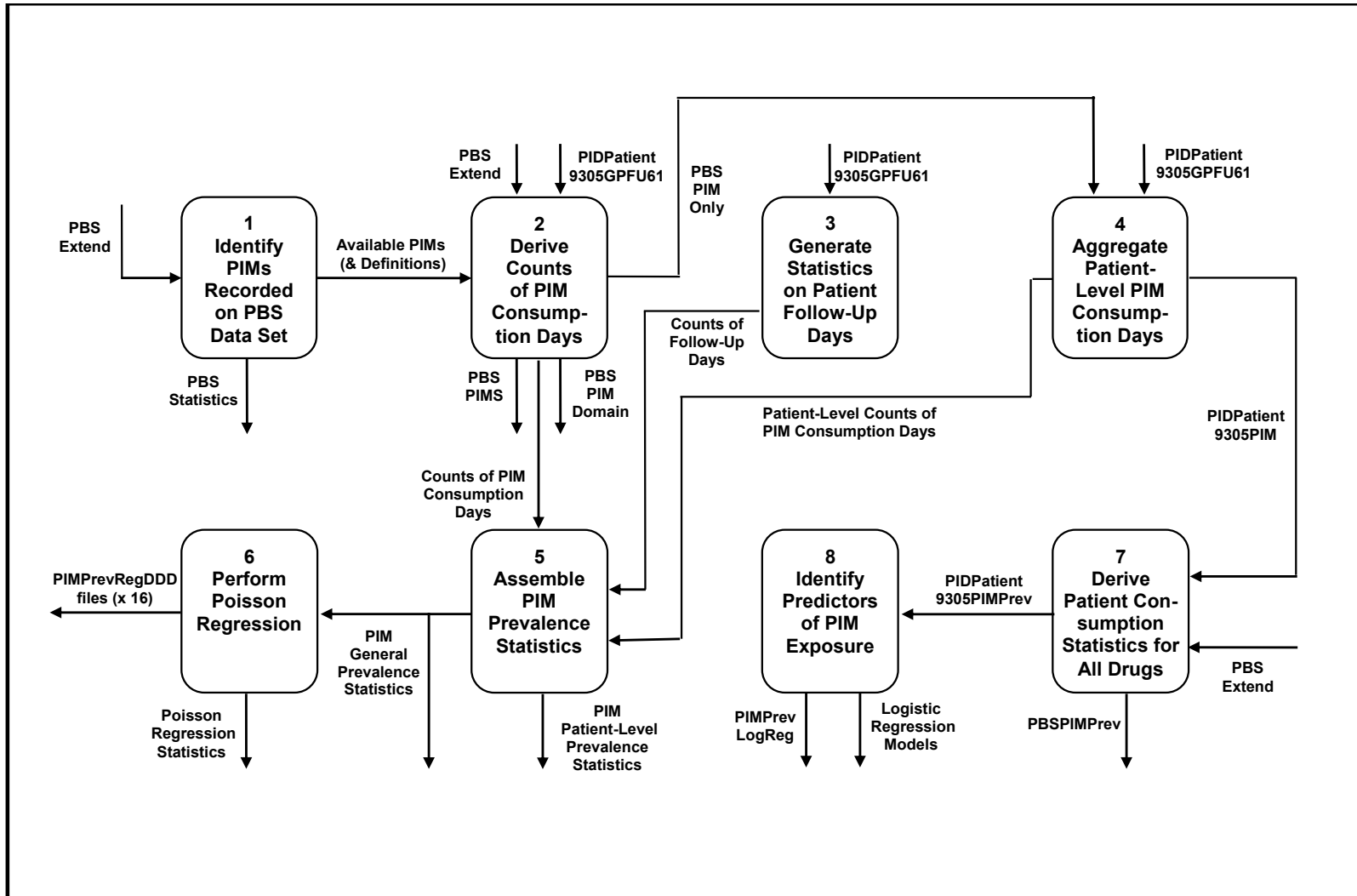


Figure 3-15 Prevalence study of Beers potentially inappropriate medications - data preparation and analysis



The resulting file was saved as “HRPIMS\_PBSPIMDOMAIN”, and a subset file that strictly contained records for PIM prescriptions was also retained as “HRPIMS\_PBSPIMONLY”. Once the daily dose counts were derived, the PIM subset data file was used to generate drug consumption summary statistics overall and by various patient characteristics, for all PIMs combined and for each individual PIM. These statistics were obtained for the entire study period (i.e. 1993-2005 overall) and for each calendar year within this period.

### **3.4.3 GENERATE STATISTICS ON PATIENT FOLLOW-UP DAYS**

Producing drug prevalence statistics not only requires counts of days of drug consumption (numerator), but also counts of days of follow-up in the study population (denominator). These counts were calculated using information found on the patient master file and retained in a revised copy labelled “HRPIMS\_PIDPatient9305GPFU61”. (Refer to the methods for the general data preparation process in section 3.1.9 for more details.)

Using the follow-up counts found on this patient master file, follow-up summary statistics were generated by various patient characteristics, overall, for each calendar year within the study period (i.e. 1993-2005) and for five-year age groups (overall and by calendar year). For aged care status, the statistics were based on status at 30 June for each calendar year.

### **3.4.4 AGGREGATE PIM CONSUMPTION DAYS AT PATIENT LEVEL**

Using the subset file containing PBS records for PIMs only, this process first aggregated daily dose totals by patient, for each PIM and calendar year combination. These patient-level totals were output to a temporary file, which was then merged to the patient master file that contained follow-up counts.

As part of this merge, additional drug consumption variables were derived, including the number of consumption days (daily dose counts) per patient for each PIM over the entire study period (1993-2005); the number of consumption days per patient for all PIMs combined by calendar year and overall; flag fields (0/1) to indicate whether the patient consumed a specified PIM during the time period of interest for all daily dose count variables; and counts for the number of different PIMs consumed in each calendar year and overall. All patient-level drug consumption fields for calendar years in which the patient had no follow-up time were set to missing values during this process to ensure that they were not included in the patient-level statistics for these years.

The resulting output was saved in a final version of the patient master file labelled “HRPIMS\_PIDPATIENT9305PIM”. From this file, patient-level drug consumption statistics were generated overall and by various patient characteristics, for all PIMs combined and for individual PIMs. These statistics related to the period 1993-2005 (overall) and to each individual calendar year within this period. Both summary statistics (e.g. sum, minimum, maximum, mean, etc.) and cross-tabulations were generated, the latter primarily for drug consumption flags and for counts of different PIMs consumed over specified periods.

Note that, for age-related statistics by calendar year, patients were assigned their predominant age for that year. Thus, if patients had more follow-up days within a calendar year from their birthday onwards than prior to their birthday, their assigned age was their unit age from their birthday onwards for that year, whereas if they had more follow-up days before their birthday than after (i.e. their birthday was later in the year), their assigned age was the unit age prior to their birthday.

#### **3.4.5 ASSEMBLE PIM PREVALENCE STATISTICS**

Once the counts of PIM consumption days (i.e. daily dose counts) and of follow-up days were generated, they were entered onto MS-Excel worksheets. All follow-up figures were entered onto one worksheet, with patient characteristics identified in the leftmost column and the time period specified as a header for all other columns (i.e. specific calendar year or 1993-2005 for the entire study period).

For daily dose counts, multiple worksheets were created, each pertaining to a particular patient characteristic (e.g. male, female, specific age group, etc.). On each drug consumption worksheet, the PIM categories and the specific drugs associated with each one were specified on the left-hand side, followed by columns for the daily dose counts in each calendar year and overall for the period 1993-2005.

The daily dose count worksheets were then duplicated to derive the prevalence statistics (i.e. number of days of drug consumption per 1000 person-years of follow-up) for each set of patient characteristics. However, in the prevalence worksheets, the appropriate formula was inserted in each cell (rather than a daily dose count) to calculate the required prevalence figure. This formula

applied the corresponding daily dose count (numerator) and follow-up number of person-days (denominator) to the cell, multiplying the quotient by the number of days per year (exact for calendar years but averaged for 1993-2005 as a whole) times 1000. Further adjustments were made to the follow-up number of days to account for drugs that were only available on the Pharmaceutical Benefits Scheme (PBS) for a fraction of a time period of interest.

For overall prevalence statistics involving the entire study period, one set of figures was first calculated based on the complete period of drug availability on the PBS during 1993-2005 (including the addition of an estimated number of days of drug consumption per script beyond PBS removal, where applicable). However, since follow-up time was only approximate for these calculations, a second set of figures was derived, the latter restricted to complete years of PBS drug availability only.

In terms of patient-level statistics, counts of people consuming each PIM for each calendar year were also imported into MS-Excel worksheets according to various patient characteristics. For these worksheets, a calculation was derived for the proportion (%) of people who consumed the drug of interest during each time period in patients who had at least some follow-up time over that period. Additionally, some person counts were imported into MS-Excel based on the number of different PIMs they consumed in each calendar year and overall.

#### **3.4.6 PERFORM PIM PREVALENCE POISSON REGRESSION ANALYSIS**

The PIM consumption statistics generated from the MS-Excel worksheets were interesting, but did not indicate whether differences between the various population sub-groups or time trends in PIM consumption were statistically significant. To generate these statistics for overall PIM consumption, Poisson regression analysis was required.

This was achieved by first creating MS-Excel worksheets derived from information available on worksheets generated in the previous step. These new worksheets specified the daily dose counts, total number of person follow-up days and number of days per calendar year aggregated by various person characteristics (e.g. gender, age group, etc.) or calendar year (for time trends). These worksheets were imported and converted into SAS<sup>154</sup> and values for follow-up person-years and for their natural logarithm (ln) were computed.

Using this information, results from Poisson regression models were generated for daily dose counts using the SAS procedure GENMOD,<sup>176</sup> with categories for person characteristics as class variables and an offset of ln(follow-up person-years). For models involving calendar years, the latter were represented by an ordinal rather than a class variable to examine time trends. From the output model coefficients, rate ratios and 95% confidence intervals were derived.

#### **3.4.7 DERIVE PATIENT-LEVEL CONSUMPTION STATISTICS FOR ALL DRUGS**

Although this prevalence study had generated overall PIM exposure statistics for a number of patient characteristics that could potentially predict the likelihood of PIM exposure, one other factor frequently linked with exposure to Beers medications in the literature had not been assessed. This factor was polypharmacy (i.e. the number of different medications taken concurrently). It was also felt that the overall quantity of drugs consumed might be associated with the intake of Beers medications. Thus, before undertaking further analysis to identify predictors of PIM exposure, patient-level statistics on overall drug exposure were sought.

To obtain these statistics, the daily dose counts for all prescribed PBS medications combined (as opposed to PIMs only) were accumulated for each patient in the study cohort (overall and by calendar year), based on the pharmaceutical claims recorded on the PBS master data set. During this process, a count of different ATC codes recorded was computed for each patient (also overall and by calendar year). This information was then merged to each record in the study's patient master file.

#### **3.4.8 IDENTIFY PREDICTORS OF PIM EXPOSURE**

The final component of the PIM prevalence study involved logistic regression analysis to identify the factors associated with exposure to Beers medications in the study cohort. Before proceeding with this analysis, records from the updated patient master file generated in the previous step (section 3.4.7) were broken down by calendar year. This was necessary given the time-varying nature of medication consumption and the study period's long duration (1993-2005). General statistics by calendar year were generated from the output file.

Upon completion of this file preparation process, univariate and multivariate logistic regression analyses were undertaken using the SAS LOGISTIC procedure.<sup>176</sup> Potential predictors under consideration were declared as class

variables in the models, overall PIM exposure (as a binary indicator) being the primary outcome of interest. However, additional models were also generated with calendar year as an ordinal variable to assess time trends for each gender and age group.

### **3.5 CASE-TIME-CONTROL STUDY OF BEERS MEDICATIONS**

Upon completion of the drug prevalence analysis for Beers medications (i.e. PIMs), it was possible to initiate the analysis to examine associations between PIM exposure and unplanned hospitalisations. Based upon the PIM prevalence statistics, 43 individual drugs from the general Beers list were identified for which there was sufficient consumption in the study population to justify further investigation in terms of a relationship with unplanned hospitalisations.

These PIMs were first organised into groups of related drugs from which drug 'domains' were defined (refer to Appendix H). As per the high-risk drug study, each domain consisted of medications of the same class as the specific drugs being studied and/or used to treat similar health conditions. Twenty PIM domains were specified, each one incorporating between one and six PIMs.

As per the high-risk drug study, processing for the Beers medications case-time-control sub-studies consisted of 13 steps, which performed the following:

- Identify index subjects/admissions (1)
- Match the index subjects to appropriate reference subjects (2-3)
- Assemble case and control time records for index and reference subjects (4)
- Add data analysis parameters to the base index-reference data set (5-10)
- Compare index and reference subjects' characteristics (11)
- Produce adverse drug effect statistics using ICD codes from index admissions (12)
- Perform conditional logistic regression (13).

A summary diagram of these 13 processing steps is presented in Figure 3-16. However, since processing for the PIM sub-studies was almost identical to that of the high-risk drug study, a description of each step has not been repeated here.

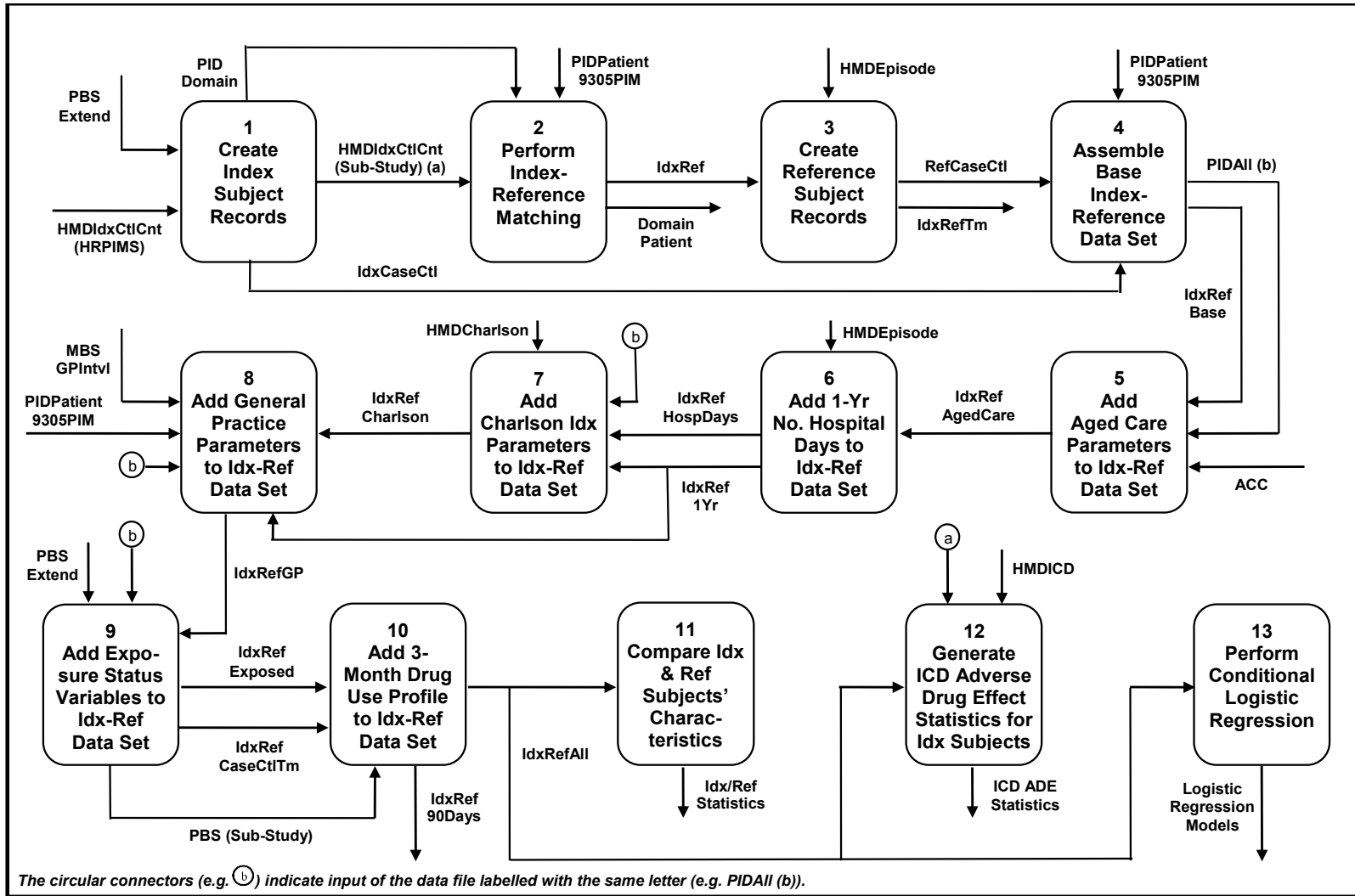


Figure 3-16 Case-time-control study of Beers potentially inappropriate medications - data preparation and analysis

In the Beers medication sub-studies, domain and drug definitions were based on specifications from Appendix H, and processing involving the main exposure variable was often repeated multiple times (once for each PIM within the sub-study drug domain), including the regression models. Conversely, in these sub-studies, there was no need to generate additional models that involved interaction terms between the main exposure of interest and specific PIMs, nor was it necessary to create the related variables.

Moreover, for the Beers medication study, an additional processing pass was undertaken to examine the potential effects of all PIMs combined. The drug domain for that sub-study consisted of all medications included in any of the 20 drug domains specified for the PIM-specific sub-studies (Appendix H).

Furthermore, to examine potential effect modification associated with high-level residential aged care, a separate pass was required in which reference subjects were matched by high-level aged care status at the mid-point of each index subject's hospital admission year rather than GP coverage category.





# CHAPTER 4 HIGH-RISK DRUGS AND UNPLANNED HOSPITALISATIONS - EXPLORATION OF STUDY DESIGN

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This research project involved the analysis of pharmaceutical claims and other data maintained by Australian Government agencies (i.e. data that had not been used previously in a WA context) linked with more familiar WA health records. The study also adopted the case-time-control design, which had not been applied before in the analysis of WA health data. Making use of new data sets and methodologies is always a challenge. Although much of this research project would concentrate on medications from the Beers Criteria, it was decided that, in the first instance, the proposed design should be applied to more readily recognised 'high-risk' drugs. Such drugs had been identified in previous studies involving elderly Western Australians, using external cause codes from the International Classification of Diseases (ICD-9-CM/ICD-10-AM) found on inpatient discharge records. Constraints of the ICD clinical coding scheme necessarily restricted the analysis to broad drug classes. However, the use of these well-established definitions would permit the comparison of study results against those obtained using more conventional methods.

This chapter summarises the investigations into the application of a case-time-control design to the project's linked health data. Ultimately, it compares estimates of unplanned hospitalisations attributable to exposure to these high-risk drugs with those identified from external cause codes on the inpatient records of exposed patients. It also applies different variations of case distribution designs to the data, in a bid to better understand the case-time-control design's strengths and limitations.

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Supplementary statistics related to the study component presented in this chapter are presented in Appendix I.1.



## **Use of case-time-control design in pharmacovigilance applications: exploration with high-risk medications and unplanned hospital admissions in the Western Australian elderly**

### **ABSTRACT**

**Purpose:** To use a case-time-control design to derive preliminary estimates of unplanned hospitalisations attributable to suspected high-risk medications in elderly Western Australians.

**Methods:** Using pharmaceutical claims linked to inpatient and other health records, the study applied a case-time-control design and conditional logistic regression to estimate odds ratios (ORs) for unplanned hospital admissions associated with anticoagulants, antirheumatics, opioids, corticosteroids and four major groups of cardiovascular drugs. Attributable fractions (AFs) were derived from the ORs to estimate the number and proportion of admissions associated with drug exposure. Results were compared with those obtained from a more conventional method using International Classification of Diseases (ICD) external cause codes to identify admissions related to adverse drug events.

**Results:** The study involved 1,899,699 index hospital admissions. Six of the eight drug groups were associated with an increased risk of unplanned hospitalisation, opioids (adjusted OR=1.81, 95% CI 1.75-1.88; AF=44.9%) and corticosteroids (1.48, 1.42-1.54; 32.2%) linked with the highest risks. For all six, the estimated number of hospitalisations attributed to the medication in the exposed was higher (two to 31-fold) when derived from the case-time-control design compared with identification from ICD codes.

**Conclusions:** This study provides an alternative approach for identifying potentially harmful medications and suggests that the use of ICD external causes may underestimate adverse drug events. It takes drug exposure into account, can be applied to individual medications and may overcome under-reporting issues associated with conventional methods. The approach shows great potential as part of a post-marketing pharmacovigilance monitoring system in Australia and elsewhere.

**Keywords:** Adverse drug events, hospitalisation, pharmaceutical claims, data linkage, Australian elderly, case-time-control design, pharmacovigilance

## Key points:

- The linkage of pharmaceutical claims with inpatient and other health records has allowed this study to assess the strength of association between exposure to high-risk medications and unplanned hospitalisations using a case-time-control design and to derive preliminary estimates of hospitalisations attributable to this exposure.
- Previous studies using ICD external cause codes on inpatient summaries appear to have underestimated hospitalisations due to adverse drug effects when compared with results based on our methodological approach, especially for opioids and corticosteroids.
- Although our method also has its limitations, in combination with other established mechanisms, it shows great potential in helping to identify individual ‘problem’ drugs as part of a post-marketing pharmacovigilance monitoring system in Australia and elsewhere.

## 4.1 INTRODUCTION

Adverse drug events (ADEs) are a major cause of hospitalisation, especially in the elderly.<sup>1-3</sup> In Australia, some 15-22% of unplanned hospital admissions in people aged  $\geq 65$  years are drug-related.<sup>32</sup> In the United States, ADEs account for nearly 100,000 emergency hospitalisations each year in this age group.<sup>31</sup>

Different approaches exist for estimating medication harm resulting in hospitalisation, such as medical record reviews,<sup>35,177-182</sup> analysis of spontaneous reporting data,<sup>183-189</sup> and identification of ADE-related codes from the International Classification of Diseases (ICD) on inpatient records.<sup>18,19,190-194</sup> Some of these methods are labour-intensive while others are subject to under-reporting and selection bias.<sup>19,35,194-199</sup>

Ideally, assessment of ADE-related hospitalisation needs to consider drug exposure upon admission and the likelihood that exposure effects may have contributed to the cause of hospitalisation. Until recent years, it has been difficult to achieve this in Australia at a population level due to the segregation of pharmaceutical claims data from hospital inpatient records. Linkage of records from these and other sources through the Western Australian Data Linkage System (WADLS)<sup>138,142</sup> has facilitated this process, permitting the

development of an alternative approach for obtaining preliminary estimates of unplanned hospitalisations attributable to drug exposure.

This paper describes the use of this approach applied to medication groups previously reported to be associated with a high rate of ADE-related hospitalisations in Western Australian (WA) elderly people.<sup>18,20,34</sup> The results are compared with those obtained from the identification of ADE-related ICD codes on inpatient summary records.

## **4.2 METHODS**

### **4.2.1 DATA LINKAGE AND STUDY COHORT SELECTION**

This study linked Australian Pharmaceutical Benefits Scheme (PBS),<sup>21,22</sup> Medicare Benefits Scheme (MBS)<sup>23,24</sup> and System for Payment of Aged Residential Care (SPARC)<sup>25</sup> data with inpatient, death and electoral roll records from the WADLS<sup>138,142</sup> through probabilistic linkage. The research protocol was approved by The University of Western Australia's Human Research Ethics Committee.

The selection of participants is outlined in Figure 4-1. The cohort was restricted to people who were  $\geq 65$  years old by the end of 2004, continuously lived in WA during 1993-2005 (until death) and had at least one PBS prescription dispensed during that time. These criteria ensured that those included in the study had ascertainable drug exposures. People with problem data (e.g. records post-death, no gender on any record) were excluded, following an extensive cross-validation process. The final study group comprised 74.3% of the source population.

### **4.2.2 ESTABLISHMENT OF DRUG REFERENCE DATABASE**

Details of all PBS items were assembled into a reference database from schedules published between August 1991 and June 2007.<sup>200</sup> Relevant prescription information was extracted from the last published entry for each item. Anatomical Therapeutic Chemical (ATC) codes were reconciled with the 2007 World Health Organization (WHO) ATC classification.<sup>163,201</sup>

Because PBS claims did not include the prescribed dose, average daily doses for each item were determined from comparisons between average prescribed daily doses obtained from the Australian Bettering the Evaluation and Care of Health (BEACH)<sup>165,202,203</sup> data, the Australian MIMS<sup>166,167,169</sup> registered drug

information and the 2008 WHO ATC Defined Daily Doses (DDDs)<sup>146,204</sup> corresponding to the drug form and route. Precedence was given to the most appropriate information applicable to older Australians. Furthermore, each drug's elimination half-life was obtained (predominantly from MIMS),<sup>166,167,169</sup> from which the period of drug effect, defined as five times the drug's half-life,<sup>170,171</sup> was estimated.

Once finalised, drug reference variables were merged to PBS records to facilitate data analysis.

#### **4.2.3 DEFINITION OF HIGH-RISK DRUG GROUPS AND DOMAINS**

Previous studies of the WA elderly,<sup>18,20,34</sup> which used ICD external cause codes (ecodes) from inpatient records, associated the following drugs with a high rate of ADE-related hospitalisation: anticoagulants, cytotoxics, antirheumatics, corticosteroids, opioids and cardiovascular agents. All were included in this study except cytotoxics, which are predominantly administered in WA public hospitals for which prescriptions were not recorded in the PBS data. Cardiovascular agents were further expanded to include hypertension drugs, cardiac rhythm regulators, beta-blockers and serum lipid-reducing agents.

ATC code definitions for each of these high-risk medication groups are presented in Table 4-1. The table also includes ATC definitions for associated study domains, which consisted of broad classes of medications used to treat similar conditions to those treated by each high-risk drug group.

#### **4.2.4 CASE-TIME-CONTROL DESIGN**

Associations between high-risk medications and unplanned hospitalisations were expressed as odds ratios (ORs) estimated from a case-time-control design.<sup>26,27</sup> This approach involved case distribution analysis in which index subjects acted both as cases and as their own historical controls, while background time trends in predisposition to exposure due to ageing, natural disease progression and treatment patterns were adjusted using similarly constructed case and control observation windows in a reference group drawn from the same general domain of patients as the index subjects. The reference subjects essentially played the role of 'negative controls' in this design. In this instance, the patient domain for each drug group included everyone in the study cohort who had ever been prescribed a medication from the associated list under "ATC domain definition" in Table 4-1 during 1993-2005.

Index subjects were patients within the drug domain who had experienced an unplanned hospital admission between 1 July 1994 and 31 December 2005 whilst aged  $\geq 67$  years, thus ensuring sufficient lead-up time for the control observation period. Many individuals were included in the analysis as multiple index subjects, although those with  $>50$  index admissions were excluded due to concerns about representativeness. Two records were created for each index subject, one representing the 'case time' (i.e. the admission date) and the other the 'control time' (usually 365 days prior). In 2-3% of subjects, where the patient was in hospital at this preferred control time, the admission date of that earlier hospitalisation was used as control time instead.

Each index subject was matched by gender, general practitioner (GP) coverage category (based on the proportion of days with GP coverage over the entire study period), and year of birth to a randomly selected reference subject from the sub-study's domain. Each GP visit identified in the MBS data set was allocated a 'coverage' period of 61 days, overlapping and adjacent periods for each patient being merged together. Subjects born prior to 1900 were allocated a notional year of birth of 1900 for matching purposes only. 'Case time' and 'control time' records were created for each reference subject as per the index subjects, matching the case and control dates of corresponding index subjects as closely as possible.

Once created, the case and control time records for index and reference subjects were populated with the variables required for analysis, including nursing home status at the time specified on the record (i.e. case or control time); number of hospital days, overall Charlson comorbidity index<sup>160</sup> and GP coverage percentage, all based on the one-year period prior to the specified time; and a drug consumption profile for the period covering the 90 days preceding the specified time (plus the specified date itself), which included the number of broad medication categories involved, the overall number of daily doses consumed (for any drug) and a count of daily doses for each broad drug category. For the Charlson index and GP coverage percentage, the one-year period included the case or control date, but that day was excluded from calculations of hospital days.

Additionally, PBS records were checked to ascertain exposure status at each case and control date. If a prescription was found for a relevant high-risk drug

and if the time period bound by its supply date and exposure effect end date overlapped with the case or control time, the exposure status was set to 'exposed'. The end date was calculated by adding the number of drug consumption days associated with the script to the supply date (-1) plus the period of drug effect (up to seven days) and a seven-day latency period. Thus, the exposure status indicated the potential for a hospital admission at the case or control time to have resulted from the effects of high-risk drug exposure.

For each high-risk drug sub-study, conditional logistic regression models with robust analysis of variance were applied using the SAS PHREG procedure (i.e. stratified Cox proportional hazard regression), with the COVS option and stratification based on a unique identifier for each subject.<sup>154</sup> The baseline model included the binary exposure variable and the cross-product between exposure and the binary index/reference indicator. The OR of primary interest was derived from the coefficient of this interaction term, which represented the association between exposure and unplanned hospitalisation in the index subjects, over and above apparent time-trend effects that applied to both index and reference subjects.<sup>26</sup> The adjusted model controlled for all health and drug consumption indicators mentioned earlier, except for the three-month count of daily doses for the drug group of interest.

#### **4.2.5 ESTIMATION OF UNPLANNED HOSPITALISATIONS RELATED TO DRUG GROUP**

Using the OR derived from the interaction term in the adjusted model described above, it was possible to calculate the attributable fraction (AF) of unplanned hospitalisations associated with each high-risk drug group within the exposed, where  $AF = (OR - 1) / OR$ . The estimate of unplanned hospital admissions attributed to each drug group was then derived as AF times the number of exposed index subjects.<sup>173-175</sup>

#### **4.2.6 IDENTIFICATION OF ADE-RELATED HOSPITALISATIONS FROM ICD ECODES**

For comparison, the count of ADE-related unplanned hospitalisations in cohort members considered exposed to each high-risk drug group was determined based on relevant ICD ecodes for accidental drug poisoning and adverse drug reactions<sup>158,159</sup> recorded on inpatient summaries, as per Table 4-2. These derivations more closely reflected the conventional approach for identifying ADE-related hospitalisations using inpatient data. However, other studies



would not usually restrict their admission counts to exposed patients as most often exposure status is not readily available.

### **4.3 RESULTS**

Table 4-3 presents results for each high-risk drug group under investigation. The number of people involved from each sub-study domain ranged between 39,596 (cardiac rhythm regulators) and 193,196 (opioids). Overall, 1,899,699 unplanned admissions ('index subjects') were included, each sub-study yielding 128,241-358,570 admissions, which were associated with 29,919-108,513 patients. Around 45-46% of index subjects were male and the mean age was 78-79 years. The proportion of index subjects considered exposed to a medication of interest at the time of admission ranged from 12-13% (anticoagulants and opioids) to 57% (hypertension drugs).

Both the unadjusted and adjusted ORs were below one for hypertension and serum lipid-reducing medications, suggesting that these drugs may have had an overall protective effect against unplanned hospitalisations. The corresponding ORs for the other high-risk drug groups (after adjustment for health indicators and medication use) ranged between 1.08 (95% CI 1.05-1.11) for beta-blockers and 1.81 (1.75-1.88) for opioids. Most adjusted ORs were lower than the corresponding unadjusted ORs.

For high-risk drug groups with  $OR > 1$ , the proportion of unplanned admissions attributed to the medication in exposed subjects ranged from 7.4% (beta-blockers) to 32.2% (corticosteroids) and 44.9% (opioids). This represented 20,539 (19,572-21,477) unplanned admissions associated with opioids alone, an average of 1,786 per year.

By contrast, for drug groups with  $OR > 1$ , the number and proportion of unplanned ADE-related hospitalisations in exposed index subjects were lower when determined from ICD ecodes than corresponding values derived using the OR/AF approach (Figure 4-2). For corticosteroids and opioids they were 19- and 31-fold lower, respectively. Obviously, this did not apply to the two medication groups that appeared to have an overall protective effect against unplanned hospitalisations.

Given the magnitude of our ORs for opioids and corticosteroids, we sought to investigate further whether residual confounding effects might partially explain

our results for these two drug groups. This involved the decomposition of our case-time-control design into its various components; inclusion of more explicit Charlson index covariates in our models; stratification by cancer status; and sensitivity analysis using other medications. The decomposition process showed the independent effects on our results of each confounding control measure already included in our adjusted models, whereas model variations attempted to isolate potential confounding effects due to drug indication (e.g. reverse causation bias). Results of our investigations (Table 4-4) were unable to demonstrate any substantial residual confounding due to indication.

#### **4.4 DISCUSSION**

This study applied an alternative approach for deriving estimates of unplanned hospital admissions attributable to medication exposure, using existing methodologies and linked health data. Unlike the more conventional method, which relies on the presence of ICD codes on inpatient summaries, this approach took patients' drug exposure status upon admission into account. Although applied to broad ICD categories in this instance for comparative purposes, the methods presented are intended for use with individual medications.

A strength of the study is its large sample sizes and thus narrow confidence intervals. Nearly two million index admissions were included, each sub-study comprising well over 100,000. This is considerably more than is generally reported from ADE studies involving medical record reviews, for instance.<sup>35,177-182</sup>

Most ORs derived from the case-time-control models without adjustment for health indicators were higher than corresponding adjusted ORs. Furthermore, adjusted ORs obtained from the equivalent case-crossover design<sup>148</sup> involving only the index subjects (not shown) were also generally higher than those from the case-time-control design. This was expected, as both the health status adjustments and the use of case-time-control reference subjects sought to adjust for increasing disease severity and other sources of time trend bias, which became associated with drug exposure whilst independently predicting the effect (i.e. unplanned hospitalisation).<sup>26</sup>

The attributable fractions in the exposed (7.4%-44.9%) from our analysis of high-risk drug groups seem plausible given that several previous studies based on medical record reviews have produced overall estimates of 15-22% for the proportion of unplanned hospitalisations that were drug-related in Australians aged  $\geq 65$  years.<sup>32</sup> Similarly, a meta-analysis involving 17 studies of elderly patients from various countries (all but two involving people aged  $\geq 65$  years) estimated that 16.6% were hospitalised due to adverse drug reactions.<sup>2</sup>

We expected that, in general, results based on the OR/AF method would yield higher estimates than corresponding statistics derived from ICD ecodes, mainly because ADEs may not always be recorded on inpatient summaries.<sup>18-20</sup> This may occur because presenting symptoms are not readily linked to harmful drug effects or, even when identified as ADEs by clinicians, due to incomplete patient notes or omissions by clinical coders. Our results support this hypothesis.

However, in some instances, the difference between the two methods was not as pronounced as anticipated. The likely explanations are two-fold. Firstly, the ADE counts obtained from ICD ecodes included ADEs that occurred during the hospital stay. Restriction of index admissions to unplanned hospitalisations minimised this to some extent but not entirely. Consequently, despite the likely under-reporting of ADEs through ecodes, our ICD results were inflated by a number of hospitalisations for which the ADE was not the actual cause of admission. Although recent clinical coding amendments in WA now distinguish between pre- and post-admission ADEs,<sup>205</sup> these were not in place during the study period.

Conversely, the figures obtained using the OR/AF method were net estimates of unplanned hospitalisations attributable to ADEs, over and above beneficial therapeutic effects that may have prevented some hospitalisations. In other words, for drugs that also have preventive effects, the OR/AF approach may yield lower counts than the true number of ADE-caused hospitalisations. In fact, for hypertension and lipid-reducing medications, it appears that, for the study period at least, the prevention of unplanned hospital admissions may possibly have outweighed the corresponding harm associated with ADEs, highlighting the likely strong preventive value of these drugs. However, it is possible that, in some instances, these medications were purposely discontinued with the development of a serious illness that eventually resulted

in an unplanned hospitalisation, giving the false impression that the withdrawn medication was the cause of the subsequent hospital stay. Study limitations prevented us from examining this issue in any more detail.

Our findings also indicate that corticosteroids and opioids are associated with a particularly high risk of unplanned hospitalisations in the WA elderly. We sought to identify whether our estimates for these two drug groups might be affected by unadjusted confounding (especially in relation to reverse causation bias), but were unable to find any strong evidence in support of this premise. However, we acknowledge that our investigations were constrained by study limitations, and suspect that some of the apparent hospitalisation burden attributed to opioid and corticosteroid exposure was likely due to the condition being treated rather than the drug itself.

For these two drug groups, the risk derived from our OR/AF approach appears substantially (19- and 31-fold) higher than that suggested by the identification of ADE-related hospitalisations from ICD ecodes. Corticosteroids and opioids have a wide range of side effects with multiple causes, making it difficult to establish a connection between drug use and presenting symptoms. Consequently, ADEs are less likely to be recorded for resulting hospitalisations. Corticosteroid ADEs may manifest as mental disturbances, infections, hypertension-related conditions and endocrine disorders (potentially leading to fractures and diabetes), whereas common opioid side effects include dizziness and drowsiness (which may cause falls and injuries), as well as nausea, constipation and other gastrointestinal complaints.<sup>166</sup> Our results suggest that clinicians need to be more aware of the potential for these drugs to increase unplanned hospital admissions for a range of seemingly obtuse reasons.

In comparison, the gap between corresponding ADE hospitalisation estimates for anticoagulants was considerably smaller (only two-fold). This is possibly due to the more conspicuous nature of ADE symptoms for this drug group (e.g. bleeding) or to clinicians' greater awareness of associated risks, not least because anticoagulant activity has been routinely monitored and 'overdose' readily confirmed from laboratory tests.<sup>206,207</sup>

The adopted case-time-control design seems appropriate for our study in which drug exposures varied over time and related outcomes (i.e. unplanned hospitalisations) were acute in nature. However, one should be mindful of the

inherent assumptions and conditions associated with this design,<sup>26,27,153</sup> especially in relation to potential time trend bias. To minimise this source of error, we adjusted for each subject's health status and overall drug consumption over time using a number of relevant variables. This was facilitated by the availability of a fairly comprehensive health profile for each individual, made possible through record linkage. The reference subjects' inclusion further controlled for time-dependent confounders for which adequate measures were unavailable. These measures are not perfect though. In particular, they are unable to fully control for reverse causation bias, which may have affected our results. Additionally, for drugs recently introduced on the market, it may be more difficult to control for exposure trends using reference subjects, as uptake may be faster in patients with more severe conditions (i.e. index subjects who are hospitalised) than in a general reference group.

The study results were also constrained by limitations of the administrative health data. Difficulties in the ascertainment of drug exposure at the specific times of interest were of particular concern. No data were available on the daily dose prescribed for each dispensed drug or on patient compliance. Much attention was devoted to the derivation of exposure status from average recommended daily doses but this could not have been completely accurate for every subject. Nonetheless, given the study size, we expect that sufficient numbers abided by average drug consumption patterns to yield adequate results. In any event, since there is no reason to suspect that exposure misclassification would have been different at 'case time' compared with 'control time' for a given subject (i.e. non-differential measurement error), estimated ORs would likely have been attenuated (i.e. pushed towards null) should exposure measurement issues have affected the outcome.<sup>208</sup>

Additionally, results may have been affected by the accuracy, completeness and coverage of the data from each source, the quality of the record linkage, and the availability of relevant data items. Every effort was made to improve data quality through extensive cross-validations between sources, to exclude subjects for whom information appeared problematic and to obtain appropriate proxy measures where necessary for data items of particular interest. The WADLS is a well-established record linkage facility.<sup>138,142</sup> Thus, the quality of the record links was likely very good. Nonetheless, our findings should be

considered suggestive rather than conclusive until supported by other high-quality studies, especially ones that can more adequately control for potential confounding associated with reverse causation bias.

The prototype developed through this research, assisted by continued improvements in the quality, coverage and linkage of related data sources, should help guide the development of ongoing pharmacovigilance initiatives in Australia and potentially elsewhere. Such a system on its own may not provide full details of medication harm, but should be a valuable tool for monitoring potentially serious ADEs, in combination with other existing mechanisms. In particular, the demonstrated approach could help identify ADE 'hot spots', ensuring that more extensive post-marketing investigations are better targeted towards medications of greatest concern.

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**Conflicts of interest:** None declared

**Table 4-1 Definition of high-risk drug groups and associated domains based on the 2007 WHO ATC classification<sup>a</sup>**

High-risk drug group		ATC drug group definition		ATC domain definition <sup>b</sup>
Anticoagulants	B01AA	Vitamin K antagonists (including warfarin)	B01	Antithrombotic agents
	B01AB	Heparin group		
Antirheumatic/antiinflammatory drugs (excluding corticosteroids and salicylates)	M01	Antiinflammatory and antirheumatic products	M01	Antiinflammatory and antirheumatic products
Opioids and related narcotics (excluding methadone and heroin)	N02A	Opioids (excluding methadone; including therapeutic heroin (i.e. diamorphine), but drug is not available in Australia)	N02	Analgesics
Corticosteroids (systemic)	H02A	Corticosteroids for systemic use, plain	H02A	Corticosteroids for systemic use, plain
	M01BA	Antirheumatics with corticosteroids	M01BA	Antirheumatics with corticosteroids
Hypertension medications (excluding diuretics other than low-ceiling, beta-blocking agents and peripheral vasodilators)	C01D	Vasodilators used in cardiac diseases	C01D	Vasodilators used in cardiac diseases
	C02	Antihypertensives	C02	Antihypertensives
	C03A/B/EA	Low-ceiling diuretics, including thiazides	C03A/B/EA	Low-ceiling diuretics, including thiazides
	C08	Calcium channel blockers	C08	Calcium channel blockers
	C09	Agents acting on the renin-angiotensin system	C09	Agents acting on the renin-angiotensin system
Cardiac rhythm regulators (including cardiac glycosides, excluding beta-blockers)			C07B-E	Beta-blocking agents with antihypertensives
	C01A	Cardiac glycosides	C01A	Cardiac glycosides
	C01B	Antiarrhythmics, Class I & III	C01B	Antiarrhythmics, Class I & III
Beta-blockers	C07	Beta-blocking agents	C07	Beta-blocking agents
Serum lipid-reducing agents	C10	Lipid modifying agents	C10	Lipid modifying agents

<sup>a</sup> Code definitions are based on the World Health Organization's Anatomical Therapeutic Chemical classification of therapeutic drugs (2007 edition).<sup>163,201</sup>

<sup>b</sup> Drugs within each domain definition are those used to treat similar conditions to those included in the definition for the corresponding high-risk drug group; individuals from the study cohort who were prescribed medications from a given domain definition were considered part of the 'domain' (sub-study cohort) for the related high-risk drug sub-study (i.e. they were considered to be part of the sub-study's population at risk).

**Table 4-2 International Classification of Diseases codes (Australian ICD-9-CM<sup>158</sup> and ICD-10-AM<sup>159</sup> editions) for all causes that could potentially identify accidental poisoning or ADR due to medications within each high-risk drug group**

High-risk drug group	ICD-9-CM external cause (accidental poisoning or ADR)		ICD-10-AM external cause (accidental poisoning or ADR)	
Anticoagulants	E858.2	Poisoning - Agents primarily affecting blood	X44	Poisoning - Other and unspecified drugs/medicaments
	E934.2	ADR - Anticoagulants	Y44.2	ADR - Anticoagulants
Antirheumatic/antiinflammatory drugs (excluding corticosteroids and salicylates)	E850.6	Poisoning - Antirheumatics	X40	Poisoning - Nonopioid analgesics, antipyretics, antirheumatics
	E935.6	ADR - Antirheumatics	Y45.2	ADR - Propionic acid derivatives
			Y45.3	ADR - Other nonsteroidal antiinflammatory drugs
			Y45.4	ADR - Antirheumatics
Opioids and related narcotics (excluding methadone and heroin)	E850.2	Poisoning - Other opiates and related narcotics	X42	Poisoning - Narcotics and psychodysleptics, NEC
	E935.2	ADR - Other opiates and related narcotics (both codes exclude methadone and heroin)	Y45.0	ADR - Opioids and related analgesics (both codes include methadone and heroin)
Corticosteroids (systemic)	E858.0	Poisoning - Hormones and synthetic substitutes	X44	Poisoning - Other and unspecified drugs/medicaments
	E932.0	ADR - Adrenal cortical steroids	Y42.0	ADR - Glucocorticoids and synthetic analogues
Hypertension medications (excluding diuretics other than low-ceiling, beta-blockers and peripheral vasodilators)	E858.3	Poisoning - Agents affecting cardiovascular system	X43	Poisoning - Other autonomic nervous system drugs
	E858.5	Poisoning - Water, mineral, uric acid metabolism drugs	X44	Poisoning - Other and unspecified drugs/medicaments
	E942.0	ADR - Cardiac rhythm regulators	Y51.2	ADR - Ganglionic blocking drugs, NEC
	E942.3	ADR - Ganglion-blocking agents	Y52.1	ADR - Calcium channel blockers
	E942.4	ADR - Coronary vasodilators	Y52.2	ADR - Other antidysrhythmic drugs, NEC
	E942.6	ADR - Other antihypertensive agents	Y52.3	ADR - Coronary vasodilators, NEC
	E944.3	ADR - Saluretics	Y52.4	ADR - Angiotensin-converting enzyme (ACE) inhibitors
	E944.4	ADR - Other diuretics	Y52.5	ADR - Other antihypertensive drugs, NEC
			Y54.3	ADR - Benzothiadiazine derivatives
			Y54.5	ADR - Other diuretics
Cardiac rhythm regulators (including cardiac glycosides, excluding beta-blockers)	E858.3	Poisoning - Agents affecting cardiovascular system	X44	Poisoning - Other and unspecified drugs/medicaments
	E942.0	ADR - Cardiac rhythm regulators	Y52.0	ADR - Cardiac-stimulant glycosides (and similar)
	E942.1	ADR - Cardiac glycosides (and similar)	Y52.2	ADR - Other antidysrhythmic drugs, NEC
Beta-blockers	E855.6	Poisoning - Sympatholytics [antiadrenergics]	X43	Poisoning - Other autonomic nervous system drugs
	E855.8	Poisoning - Other autonomic nervous system drugs	X44	Poisoning - Other and unspecified drugs/medicaments
	E855.9	Poisoning - Unspecified drug affecting nervous system	Y51.7	ADR - Beta-adrenoreceptor antagonists, NEC
	E858.3	Poisoning - Agents affecting cardiovascular system	Y52.2	ADR - Other antidysrhythmic drugs, NEC
	E941.3	ADR - Sympatholytics [antiadrenergics]	Y52.3	ADR - Coronary vasodilators, NEC
	E941.9	ADR - Unspecified autonomic nervous system drug	Y52.5	ADR - Other antihypertensive drugs, NEC
	E942.0	ADR - Cardiac rhythm regulators		
	E942.4	ADR - Coronary vasodilators		
E942.6	ADR - Other antihypertensive agents			
Serum lipid-reducing agents	E858.3	Poisoning - Agents affecting cardiovascular system	X44	Poisoning - Other and unspecified drugs/medicaments
	E942.2	ADR - Antilipemic and antiarteriosclerotic drugs	Y52.6	ADR - Antihyperlipidaemic and antiarteriosclerotic drugs

ADR - Adverse drug reaction; NEC - Not elsewhere classified



**Table 4-3 Associations and preliminary attribution estimates in relation to high-risk medications and unplanned hospital admissions in Western Australian elderly, 1993-2005 - summary results**

Statistics	Anticoagulants	Anti-rheumatic drugs	Opioids	Corticosteroids	Hypertension drugs	Cardiac rhythm regulators	Beta-blockers	Serum lipid-reducing agents
Domain (number of people in sub-study cohort)	90,124	174,585	193,196	84,960	180,539	39,596	89,017	100,787
Index subjects - number of people involved	57,609	92,903	108,513	53,369	99,635	29,919	55,179	50,295
Index subjects - number of index admissions	212,187	307,276	358,570	197,385	335,259	128,241	195,311	165,470
Index subjects - gender distribution (% males)	47.1%	45.0%	44.9%	45.7%	45.3%	45.5%	45.3%	49.8%
Index subjects - mean age at admission (years)	78.1	78.3	78.5	78.0	78.5	79.5	78.2	76.4
Exposed index subjects (Exp Idx)	26,088	61,595	45,772	30,740	192,674	44,730	60,755	69,286
% exposed index subjects	12.3%	20.0%	12.8%	15.6%	57.5%	34.9%	31.1%	41.9%
Unadjusted odds ratio (Unadj OR)	1.19	1.08	2.01	1.68	0.95	1.17	1.13	0.88
Unadjusted OR 95% confidence interval	1.14-1.25	1.06-1.11	1.94-2.08	1.62-1.75	0.93-0.97	1.13-1.21	1.10-1.16	0.86-0.91
Unadjusted OR p-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Adjusted odds ratio (OR)	1.13	1.09	1.81	1.48	0.92	1.11	1.08	0.85
Adjusted OR 95% confidence interval	1.07-1.19	1.06-1.12	1.75-1.88	1.42-1.54	0.90-0.94	1.07-1.15	1.05-1.11	0.82-0.88
Adjusted OR p-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Attributable fraction: AF = (OR-1) / OR (%)	11.3%	8.3%	44.9%	32.2%	-9.2%	9.7%	7.4%	-17.8%
AF 95% confidence interval (%)	6.5-15.9%	6.0-10.6%	42.8-46.9%	29.3-35.1%	-11.7--6.7%	6.3-13.0%	4.6-10.2%	-22.0--13.9%
Estimate of index admissions related to drug (AFxExp Idx) <sup>a</sup>	2,960	5,138	20,539	9,913	-17,669	4,360	4,500	-12,323
Exposed index subjects with relevant drug ecode <sup>b</sup>	1,514	793	658	524	2,987	1,051	1,175	147
% exposed index subjects with relevant drug ecode	5.8%	1.3%	1.4%	1.7%	1.6%	2.3%	1.9%	0.2%

<sup>a</sup> Estimates were derived from more precise AF figures than those displayed in this table.

<sup>b</sup> Exposed index subjects with relevant drug ecode refers to hospitalisations among index subjects who were exposed to a high-risk drug of interest at the time of admission and for which an ICD external cause code related to accidental poisoning or adverse drug reaction potentially from a medication in this high-risk drug group (i.e. codes listed in Table 4-2 for the drug group) was recorded on the corresponding inpatient summary.

**Table 4-4 Associations between opioid and corticosteroid exposure and unplanned hospital admissions in Western Australian elderly, 1993-2005 - odds ratios and 95% confidence intervals resulting from logistic regression model variations**






Regression model variations	Opioids	Corticosteroids
<b>Decomposed case-time-control model<sup>a</sup></b>		
Case-crossover - index subjects only (unadjusted)	2.57 (2.52-2.62)	2.03 (1.98-2.08)
Case-crossover - reference subjects (i.e. negative controls) only (unadjusted)	1.28 (1.25-1.31)	1.21 (1.17-1.24)
Case-time-control (unadjusted)	2.01 (1.94-2.08)	1.68 (1.62-1.75)
Case-time-control (adjusted with health status and drug consumption covariates)	1.81 (1.75-1.88)	1.48 (1.42-1.54)
<b>Case-time-control models with more explicit adjustment for indications<sup>b</sup></b>		
Case-time-control (+ Charlson index covariates re cancer)	1.85 (1.78-1.92)	1.49 (1.42-1.55)
Case-time-control (+ Charlson index re rheumatic/connective tissue disease)	No effect on model	No effect on model
Case-time-control (+ Charlson index re chronic pulmonary disease)	Not applicable	1.46 (1.40-1.52)
<b>Case-time-control models with cancer status matching and stratification<sup>c</sup></b>		
Case-time-control (cancer instead of GP status matching) - all	1.80 (1.73-1.87)	1.46 (1.40-1.52)
Case-time-control (cancer instead of GP status matching) - non-cancer group	1.81 (1.72-1.89)	1.45 (1.38-1.52)
Case-time-control (cancer instead of GP status matching) - cancer group	1.88 (1.75-2.02)	1.50 (1.38-1.62)
<b>Case-time-control models using other drugs for sensitivity analysis<sup>d</sup></b>		
Case-time-control (adjusted - with hypertension medications as main exposure)	0.93 (0.91-0.96)	0.90 (0.87-0.93)
Case-time-control (adjusted - with serum lipid-reducing agents as main exposure)	0.86 (0.83-0.89)	0.83 (0.79-0.86)

<sup>a</sup> Models in the first section show the independent effects on our results of each confounding control measure integrated into our adjusted case-time-control model, including the elimination of unmeasured time trends through the use of reference subjects (i.e. negative controls) and further adjustments through the inclusion of measurable time-varying factors as model covariates. Results from the adjusted case-time-control model shown above correspond with the 'adjusted odds ratios' reported in Table 4-3.

<sup>b</sup> Models in the second section included all covariates from our adjusted case-time-control model (including an overall Charlson comorbidity score), with the addition of the specified Charlson index variable(s) to adjust more explicitly for potential confounding due to drug indication. "No effect on model" indicates that, although listed as a covariate in the regression analysis, the specified Charlson index was not included in the final model in a stepwise selection process.

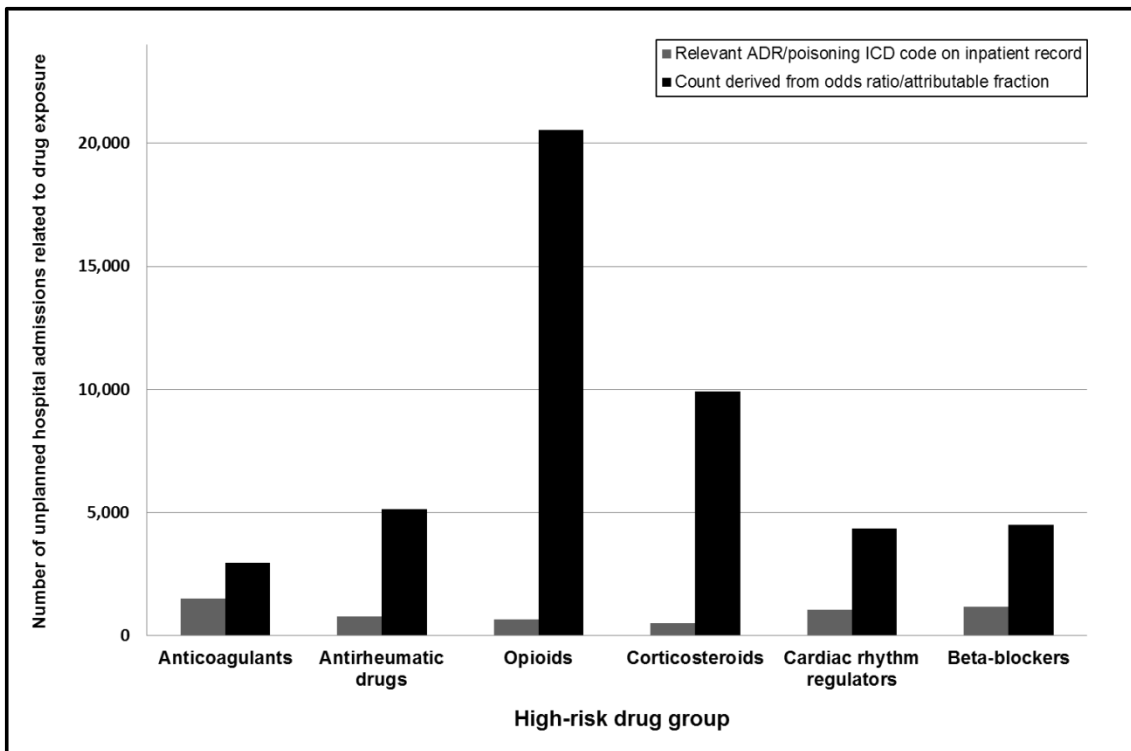
<sup>c</sup> Results shown in the third section were generated from models in which index and reference subjects were matched according to cancer status instead of General Practitioner (GP) coverage (as well as year of birth and gender). The regression analysis was first performed on the entire group to examine the effects of this different matching process, but then applied to the cancer and non-cancer groups independently in an attempt to isolate the effects of cancer (as a drug indication) on the results.

<sup>d</sup> Models from the last section included hypertension and serum lipid reducing drugs as primary exposure (instead of opioids or corticosteroids). These medications appeared to have a protective effect against unplanned hospitalisations in our sub-studies involving cardiovascular patients. Similar results to those obtained with opioids and corticosteroids as primary exposure would have suggested that the indications for opioids and corticosteroids might account for most of the apparent associations rather than drug exposure itself. As shown above, our results provide no evidence that this is the case.

<u>Selection/exclusion process</u>	<u>Person count</u>	<u>Percent remaining</u>
Select people on Australian Medicare Register with: - Date of birth pre-1940 - Always registered using Western Australian address - At least one PBS or MBS record during 1990-2006	338,217	100.0%
		
Exclude 44,467 people with no PBS records during 1993-2005 (after refinement of study period)	<u>- 44,467</u> 293,750	86.9%
		
Exclude 22,336 people with post-death records - PBS, MBS or inpatient (non-posthumous organ procurement)	<u>- 22,336</u> 271,414	80.2%
		
Exclude 20,059 people with WA electoral roll registration problems: 1) 14,839 not registered during 1993-2005 2) 5,220 with gap(s) during 1993-2005, where individual alive but no WA hospital/Medicare activity during gap AND either gap ≥365 days or deregistration due to out-of-State emigration	<u>- 20,059</u> 251,355	74.3%
		
Exclude 28 people with no PBS records during 1993-2005 following final drug item/age adjustments and exclusions	<u>- 28</u> 251,327	74.3%
		
Exclude 22 people with no gender specified on any of their records	<u>- 22</u> 251,305	74.3%

PBS - Pharmaceutical Benefits Scheme; MBS - Medicare Benefits Scheme; WA - Western Australian

**Figure 4-1 Selection of study cohort**



**Figure 4-2 Estimates of unplanned hospital admissions associated with exposure to medications in high-risk drug groups for which the odds ratio suggests an increased risk of hospitalisation**

The counts associated with the two columns for each high-risk drug group presented in this chart were derived as follows from hospitalisations for index subjects who were considered exposed to a medication in the specified high-risk drug group at the time of admission:

- 1) Number of these hospitalisations for which an ICD external cause code related to accidental poisoning or adverse drug reaction potentially from a medication within the specified high-risk drug group (i.e. codes listed in Table 4-2 for this drug group) was found on the inpatient summary record.
- 2) Number of these hospitalisations considered to be attributable to the exposure drug, calculated as  $\text{count} = \text{AF} \times \text{number of exposed index subjects}$ , where  $\text{AF} = (\text{OR}-1)/\text{OR}$  and is the attributable fraction derived from the primary adjusted OR in the corresponding regression analysis.

# CHAPTER 5 PREVALENCE OF POTENTIALLY INAPPROPRIATE MEDICATIONS

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Before analysing the project data in an attempt to estimate the adverse effects of exposure to medications from the Beers Criteria, it was important to assess the availability of these medications in Australia and their prevalence in elderly Western Australians over the study period. This would not only identify the PIMs to include in our subsequent analyses, but would also provide a useful profile of PIM exposure in this population. Also of interest were the determinants of PIM exposure (i.e. which factors are potential predictors of PIM use).

All of these issues are examined in this chapter, the contents of which were included in the following manuscript:

- Price SD, Holman CDJ, Sanfilippo FM, Emery JD. Are older Western Australians exposed to potentially inappropriate medications according to the Beers Criteria? A 13-year prevalence study. Accepted for publication by the *Australasian Journal on Ageing* on 03/12/2013; released online for early view on 20/03/2014. doi: 10.1111/ajag.12136.

Supplementary statistics related to PIM prevalence in elderly Western Australians are presented in Appendix I.2.



## **Are older Western Australians exposed to potentially inappropriate medications according to the Beers Criteria? A 13-year prevalence study**

### **ABSTRACT**

**Objective:** To examine time trends and factors associated with exposure to Beers potentially inappropriate medications (PIMs).

**Methods:** PIM consumption days accumulated from the pharmaceutical claims of 251,305 Western Australians aged  $\geq 65$  years (1993-2005) and person follow-up times produced counts/rates. Logistic/Poisson regression generated odds/rate ratios.

**Results:** 187,616 participants (74.7%) took  $\geq 1$  PIM (1993-2005), the cohort consuming 109,415 PIM daily doses/1000 person-years. Annual exposure decreased from 45-47% to 40%, and annual consumption rate declined from 117,836 to 90,364 daily doses/1000 person-years. Temazepam had the highest exposures ( $>17,000$  daily doses/1000 person-years). Number of medications taken (OR 35.03; 95% CI 34.37-35.71 for  $\geq 10$  vs. 0-2 drugs), annual drug intake (2.08; 2.04-2.12 for highest vs. lowest quartile), and high-level residential aged care (1.96; 1.91-2.01) were most predictive of PIM exposure.

**Conclusions:** PIM exposure remains high in older Western Australians. Our findings identify patients most at risk and medications to consider on Australia-specific PIM lists.

**Keywords:** Inappropriate prescribing, prevalence, risk factors, aged, Western Australia

## **Key Points:**

- Three-quarters of Western Australians aged  $\geq 65$  years (40-47% each year) were exposed to Beers potentially inappropriate medications (PIMs) to be avoided in older people during 1993-2005, annual consumption rate decreasing over that time.
- Temazepam was the most commonly prescribed PIM, whereas number of medications prescribed, annual drug intake and high-level residential aged care were factors associated with the highest risks of PIM exposure.
- Our findings identify Beers medications that are available and most frequently used in Australia for potential inclusion on Australia-specific PIM lists.

## **5.1 INTRODUCTION**

Adults generally become more susceptible to adverse drug events with advancing age due to physiological deterioration, increasing comorbidities and other age-related factors.<sup>4</sup> This has led to the development of lists of 'potentially inappropriate medications' (PIMs) to be avoided in older people. Among them, the Beers Criteria<sup>15</sup> are by far the most commonly used.

Beers medication prevalence studies have reported the number/proportion of exposed older patients, but not utilisation rates. Most have been restricted to short time periods and very few have involved Australians.

The aim of this comprehensive study was to examine time trends in exposure to Beers medications in older Western Australians over a 13-year period (1993-2005), by estimating not only the number/proportion of people exposed but also daily doses/1000 person-years (PY) for both overall and individual PIMs. Furthermore, this study identified factors associated with PIM exposure.

## **5.2 METHODS**

### **5.2.1 DATA PREPARATION**

The study protocol was approved by The University of Western Australia's Human Research Ethics Committee. As only de-identified records were accessed, participants' informed consent was not required.

People aged  $\geq 65$  years by 31 December 2004, who continuously lived in Western Australia (WA) and had  $\geq 1$  prescription claim during 1993-2005 were



included, thus ensuring all had ascertainable drug exposures. Further details of the cohort selection are presented elsewhere.<sup>209</sup> The ultimate cohort captured 80-85% of older WA residents.

Participants' Pharmaceutical Benefits Scheme (PBS), Medicare and residential aged care data were linked with their inpatient, death and electoral roll records from the WA Data Linkage System<sup>138</sup> through probabilistic linkage. For each person, a record registered reconciled demographic details, date of death, follow-up time estimates and other characteristics. Socio-economic disadvantage was derived based on place of residence from WA quartiles (1996/2001) for Socio-Economic Indexes for Areas (SEIFA).<sup>155,156</sup> Similarly, remoteness was determined using Accessibility/Remoteness Index of Australia (ARIA+) definitions.<sup>157</sup>

Overall follow-up time was calculated as the count of days from the start of follow-up (1 January 1993 or person's 65<sup>th</sup> birthday if within study period) to the follow-up end date (31 December 2005 or date of death). Follow-up days by calendar year and five-year age group were also computed.

Additionally, patients' general practitioner (GP) visits (identified from Medicare records) were each allocated a 'coverage' period of 61 days (merging overlapping periods together), from which overall and annual coverage proportions were calculated. Derived quartiles helped define GP coverage categories, providing a general indicator of ongoing GP monitoring for each patient. Using aged care records, participants' mid-year aged care status for each calendar year was also determined.

Furthermore, details of all PBS items from available schedules (August 1991-June 2007) were assembled, retaining the last published entry for each item and reconciling Anatomical Therapeutic Chemical (ATC) codes with the 2007 World Health Organization (WHO) ATC drug classification.<sup>201</sup> Average daily doses for each item were estimated using average prescribed daily doses from the BEACH<sup>165</sup> general practice data, MIMS<sup>167</sup> registered drug information, and 2008 WHO ATC Defined Daily Doses (DDD).<sup>146</sup> Estimates were allocated per drug strength, consumption statistics reflecting exposure days per medication rather than a specific drug quantity.

### **5.2.2 STATISTICAL ANALYSIS**

Each item from the 2003 Beers list<sup>15</sup> was defined according to the 2007 ATC classification.<sup>201</sup> Once patient and drug reference variables had been merged to the PBS master file, the ATC code list for 'general' PIMs (i.e. excluding disease-specific criteria but including PIMs with dosage or duration constraints irrespective of the dose/duration likely prescribed) was applied to identify relevant prescriptions supplied to participants.

For each selected PBS record, the drug consumption period was determined as follows: start date = supply date and end date = supply date + (quantity prescribed / drug item's average daily dose) - 1 (excluding time post-death and beyond 2005). Consumption days were then allocated for each record to the relevant calendar year(s) and overall. Thereafter, patient-level and population-level drug consumption statistics (overall and annual) were generated for each PIM and for all PIMs combined using SAS 9.2.

Subsequently, summary follow-up statistics derived from the patient master file and PIM consumption sums (daily doses) were imported into Microsoft Excel® 2003, from which corresponding drug consumption rates were calculated as follows: PIM daily doses/1000 PY = (total PIM daily doses consumed / total follow-up person-days) x 1000 persons x days per calendar year.

Rate ratios were computed using univariate Poisson regression on grouped data (SAS 9.3 GENMOD); ordinal analysis was used for time trends. To determine which factors predicted PIM exposure, univariate and multivariate logistic regressions were performed (SAS 9.3 LOGISTIC). All variables shown in Table 5-3 were included in the multivariate model. Since several covariates were time-dependent, multiple entries per participant were included, one for each calendar year in which the person contributed follow-up time. To obtain patients' overall drug intake, all PBS records were checked (i.e. not just PIMs), from which counts of consumption days by calendar year were accumulated for each person, as per computations for PIMs only. The number of different generic drugs contributing to each annual drug consumption count was also retained for each person, based on the number of different ATC codes involved.

### 5.3 RESULTS

The study involved 251,305 participants and 2,076,176 PY of follow-up (1993-2005). Annual follow-up time increased from 128,262 to 185,816 PY (1993-2004) before decreasing to 185,776 (2005). Exclusion of WA residents whose 65<sup>th</sup> birthday occurred in 2005 (for logistical reasons) predominantly explains the lower 2005 figure.

As indicated in Table 5-1, 187,616 participants (74.7%) were prescribed  $\geq 1$  general PIM during 1993-2005, the cohort taking 109,415 PIM daily doses/1000 PY. Older Western Australians who were female, born in earlier years, from more disadvantaged areas, living less remotely, and with more ongoing GP monitoring appeared more likely to have been exposed to PIMs and had higher PIM consumption rates than their counterparts. High-level aged care residents had a PIM consumption rate more than double that of other older people.

Until 2001, 45-47% of participants took  $\geq 1$  PIM annually, this proportion decreasing to 40% by 2005. The PIM consumption rate fluctuated during 1993-2000 between 117,836 and 110,477/1000 PY, but then declined to 90,364/1000 PY in 2005. Female figures were consistently higher than males' (Table 5-2).

Although PIM consumption rates remained higher in older age groups throughout 1993-2005, age-specific rates decreased more substantially over time in the oldest age groups. For example, in people aged  $\geq 90$  years, annual rates declined from 215,808 to 149,350 daily doses/1000 PY between 1993 and 2005 (3.4%/year,  $p < 0.0001$ ) compared with 84,133 to 65,238 daily doses (1.8%/year,  $p < 0.0001$ ) in 65-69 year-olds.

On average, each person took 2.2 different PIMs during 1993-2005 (males 2.0; females 2.5). Annually, participants initially averaged 0.8 different PIMs (1993-2000), this figure decreasing to 0.6 by 2005. The highest number of different PIMs taken by an individual over the 13-year study period was 20 (8-13 annually).

Table 5-3 shows the results of univariate and multivariate logistic regression performed on participants' annual data to determine PIM exposure risk factors. Regression models included 1,860,630 entries, after excluding 311,312 (14.3%) with missing SEIFA/ARIA+ details. Univariate findings reflected the relative proportions of exposed participants from Table 5-1. For time-dependent

characteristics, they also suggested that higher PIM use was associated with increasing age, high-level aged care, annual quantity of medications, number of different drugs taken, and year of death.

In multivariate results, many of these associations remained, but were generally weaker than those from the univariate model. PIM use still increased with age, although participants aged 65-69 years had higher odds of PIM exposure than 70-74 and 75-79 year-olds. A decreasing trend by calendar year became more apparent, whereas the association between PIM exposure and birth year virtually disappeared, and the effects of socio-economic status and remoteness of residence were reversed in direction. Moreover, only those in the highest tier of ongoing GP contact had higher PIM exposure than those with the lowest GP coverage. The annual count of different drugs taken had the strongest association with PIM exposure.

Table 5-4 presents counts of patients (1993-2005) taking each of the 43 individual drugs from the general PIMs list for which claims were recorded in our PBS data set. These relate to 31 of Beers' 49 general PIM categories (30 shown in table, as diphenhydramine applied to two categories). Table 5-5 provides corresponding rates of daily doses for each drug.

The medications consistently used by the most people and with the highest consumption rates, both overall and in 2005, included: temazepam, digoxin, nifedipine, oxazepam, diazepam, amitriptyline, naproxen and piroxicam. The consumption rate of these drugs generally decreased over time, especially for digoxin, piroxicam and naproxen. However, it increased for both amitriptyline and temazepam. Temazepam was by far the most commonly used (Figure 5-1).

Among other PIMs, indomethacin and bisacodyl were prescribed to a high number of participants throughout but this was not reflected in terms of daily doses consumed, suggesting that these drugs were usually not prescribed for long-term use. From a trend perspective, dipyridamole, amiodarone and oxybutynin intake increased over time, whereas cimetidine, oestrone, ferrous sulphate, methyl dopa, doxepin and indomethacin use declined.

## **5.4 DISCUSSION**

This comprehensive study assessed older Western Australians' exposure to Beers' medications over time (1993-2005) and identified predictors of PIM exposure. Our linked data improved the accuracy of demographic details and follow-up time estimates, and permitted the generation of person-level statistics for a broader range of characteristics. Furthermore, comparison of daily dosage information from three different sources (two of which were Australian) and the allocation of separate average daily dose estimates for different drug strengths ensured a more precise assessment of drug intake duration for each prescription.

### **5.4.1 OVERALL PREVALENCE**

Our results suggest a very high level of exposure to Beers' general PIMs in our cohort. Three-quarters of participants (nearly 80% of females) were prescribed  $\geq 1$  PIM over the study period, each exposed to an average of 2.2 (up to 20) different PIMs during that time. Annually,  $\geq 40\%$  of older patients were exposed, double the 21% reported by Roughead et al.<sup>69</sup> in Australian war veteran beneficiaries ( $\geq 70$  years) but similar to the 35-50% estimates from Australian nursing home<sup>72,75</sup> and retirement village sub-populations.<sup>74</sup> However, Roughead's study was based on a 6-month period only and excluded PIMs associated with dosage/duration criteria, whereas the other Australian results were based on drug use at a specific point in time and also had different Beers inclusions. Similar variations are noted in international studies, which have generally reported 10-40% PIM prevalence in older people.<sup>36,64</sup> Our study also estimated PIM consumption rates but comparable statistics were not available in the literature.

Despite remaining high, PIM exposure has decreased over time in older Western Australians, as per several other studies.<sup>84,86,88</sup> Hopefully this reflects a greater awareness of PIMs, and replacement of Beers medications with more appropriate treatment options. Nonetheless, we project from our data that  $\geq 30\%$  of WA residents aged  $\geq 65$  years were prescribed  $\geq 1$  PIM in 2012, which is still quite high as each PIM prescription could lead to potentially preventable adverse effects.

#### **5.4.2 PREDICTORS OF PIM EXPOSURE**

Medication intake was strongly associated with PIM exposure in our cohort. However, the number of different drugs taken was a much greater predictor than overall drug quantity, suggesting that polypharmacy predisposes to increased PIM use in older people.

Additionally, female gender was an independent predictor of PIM exposure, as per other studies.<sup>84-86,95,104,105</sup> Our multivariate results also linked increasing PIM exposure with advancing age, but only from  $\geq 70$  years. It is unclear why 70-79 year-olds were less likely to be exposed than those aged 65-69 years. Clinicians may perhaps consider their 'younger' aged patients still too healthy to concern themselves with possible adverse PIM effects. Mixed results are reported in the literature in relation to age as a predictor of PIM exposure.

Residing in a high-level aged care facility was also an independent factor predicting PIM exposure after adjustments. Two other studies initially identified living in residential care as a risk factor for PIMs, but this association no longer existed once other factors, including polypharmacy, were taken into account.<sup>84,95</sup>

The associations of socio-economic status and remoteness of residence with PIM exposure were reversed after confounding adjustments. Although varying demographic profiles in these sub-groups may have played a part, medication intake was likely the main confounder. If so, it is somewhat reassuring to find that the apparent increase in PIM exposure in the lower socio-economic tiers is probably due to a greater need for medications overall than to sub-standard prescribing practices. The increased likelihood of prescribing PIMs to those living in remote areas (all other factors being equal) is of greater concern, however, as potential GP monitoring restrictions would make these patients more vulnerable to PIM-related adverse events.

In our multivariate model, only those with extensive GP coverage had a higher level of PIM exposure than those with the least coverage, whilst those from intermediate levels were the least likely to be exposed to PIMs. It could be that many patients with little GP contact are generally very healthy, such that clinicians are less concerned about possible adverse PIM effects in this sub-group compared with those from the intermediate sub-groups. In contrast, patients receiving extensive GP coverage may be deliberately monitored very

closely due to their increased comorbidities and polypharmacy. Clinicians may feel it is justified to prescribe specific PIMs in some of these patients, but compensate through extensive monitoring in these circumstances.

Study participants were also 54% more likely to take PIMs during their year of death than at other times. Thus, palliative treatment may be a higher priority than potential harm from PIMs as patients approach death.

### **5.4.3 MOST COMMON PIMs**

Temazepam was by far the most common PIM in our study. This is particularly alarming as intake of this sedative, which was given a Beers 'high severity' rating, increased over time and was still >17,000 daily doses/1000 PY in 2005, whereas consumption of most other drugs of concern declined. Some may contest that these patients unlikely exceeded the Beers 2003 upper daily limit of 15 mg. However, since the latest Beers Criteria update<sup>16</sup> recommends avoidance of short-acting benzodiazepines in older people regardless of dosage, alternative treatment of insomnia is advised in this age group.

By comparison, digoxin, a cardiac glycoside with a 1993 consumption rate similar to temazepam's, saw its rate decrease to 11,000 daily doses/1000 PY by 2005. Similarly, consumption of naproxen and piroxicam, two non-steroidal antiinflammatory drugs (NSAIDs), decreased considerably during the study period. The NSAID decline likely related to increased prescribing of cyclooxygenase-2 inhibitors though, some of which were eventually withdrawn due to potential adverse effects.<sup>210</sup>

Diazepam, oxazepam and amitriptyline were also among the most commonly prescribed PIMs, which is not surprising given the high intake of anxiety and depression medication in older people,<sup>211</sup> as was nifedipine, an anti-hypertensive.

Although not highly prevalent during 1993-2005, dipyridamole, amiodarone and oxybutynin may require particular attention in future PIM prevalence studies, due to their upward consumption trends. Conversely, it is reassuring that exposure to cimetidine, oestrone, ferrous sulphate, methyldopa, doxepin, and indomethacin has declined considerably, likely due to safer alternatives becoming available. In the case of cimetidine, once the preferred drug for treating peptic ulcers and reflux, better understanding of disease aetiology has largely removed the need for this drug.<sup>212</sup> Similar developments from ongoing

medical research will hopefully promote the decline of other risky drug prescribing practices in older people.

#### **5.4.4 STUDY LIMITATIONS**

Despite extensive cross-validations between data sources, our results were constrained by some data limitations. For instance, no data were available on the daily dose specifically prescribed or on patient compliance. We used average recommended daily doses to estimate individual drug consumption, but this could not have been completely accurate in every case. Nevertheless, given our large cohort, average dosages likely yielded adequate population-level PIM consumption estimates.

Additionally, our PBS data set excluded drugs prescribed within public hospitals, over-the-counter medications, and prescriptions for which a PBS claim cannot be made. However, most PIMs prescribed in a community setting would have been recorded for our older cohort, which mostly involved concession cardholders with very low co-payment requirements. Moreover, our study excluded older people with no PBS record during 1993-2005 and only included those who resided in WA for the entire period (until death). As the excluded seniors were probably younger, healthier and wealthier than the study population average, our overall results may have slightly overestimated PIM exposure rates based on PBS scripts compared with those applicable to the entire population of older Western Australians.

#### **5.4.5 IMPACT OF RECENT DEVELOPMENTS**

An inventory of the latest Australian PBS schedule indicates that only five individual PIMs from our study have been removed from the PBS since 2005. Of those, propoxyphene and meperidine (pethidine) had extremely low consumption rates by 2005 and the other three were 'oestrogen only' medications, which could readily have been substituted with oestradiol, a PIM that remains on the current PBS. Consequently, it seems unlikely that current PIM consumption patterns would be much different from those suggested by time trends derived from our study.

Furthermore, five individual drugs from our study have been removed from the latest Beers Criteria update.<sup>16</sup> Two (propoxyphene and ethacrynic acid) are no longer or seldom prescribed (in America and Australia) and two others (ferrous sulphate and fluoxetine) were omitted because related concerns are not



restricted to older patients. Bisacodyl was the only one excluded due to insufficient evidence.<sup>213</sup> The revised Beers Criteria also include a number of new medications, although many are not yet available in Australia.

#### **5.4.6 CONCLUSIONS**

Our study has demonstrated a high level of exposure over time to temazepam and many other Beers medications in older WA residents, and identified patients at highest risk of exposure. Clinicians are urged to exert caution when treating vulnerable older patients, particularly those who require multiple drugs, have a high drug intake or reside in nursing homes, avoiding Beers medications when possible.

Given this high prevalence, it may be beneficial to use the Beers medications as a starting point to establish general lists of PIMs to be avoided in older Australians. Our research has identified which PIMs are on the Australian PBS and are most frequently prescribed in older Australians. Common Australian medications that are unavailable elsewhere and drugs appearing on non-Beers PIM lists should also be considered, as well as relevant medications from Basger's prescribing appropriateness criteria for older Australians.<sup>62</sup>

#### **ACKNOWLEDGMENTS**

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**Table 5-1 Potentially inappropriate medications in Western Australian residents aged ≥65 years (1993-2005) - cohort participants, number/proportion exposed and rate of consumption (daily doses/1000 person-years)**

Population	Cohort participants	Number/proportion taking PIMs (%) <sup>e</sup>	Daily doses/1000 PY <sup>f</sup>
Persons	251,305	187,616 (74.7%)	109,415
<b>Gender</b>			
Male	114,146	79,417 (69.6%)	88,381
Female	137,159	108,199 (78.9%)	125,745
<b>Year of birth</b>			
<1910	12,426	10,757 (86.6%)	198,115
1910-1919	41,852	36,957 (88.3%)	154,267
1920-1929	91,131	76,892 (84.4%)	106,354
1930-1939	105,896	63,010 (59.5%)	78,408
<b>Socio-economic disadvantage<sup>a</sup></b>			
Most disadvantaged	54,002	44,097 (81.7%)	126,629
Moderately disadvantaged	53,739	43,183 (80.4%)	118,460
Slightly disadvantaged	47,629	37,793 (79.3%)	115,579
Least disadvantaged	55,240	42,761 (77.4%)	106,724
Unknown	40,695	19,782 (48.6%)	56,438
<b>Remoteness of residence<sup>b</sup></b>			
Major city	152,169	122,467 (80.5%)	118,914
Inner regional area	29,448	23,494 (79.8%)	112,600
Outer regional area	18,165	14,033 (77.3%)	112,937
Remote/very remote area	5,496	4,062 (73.9%)	104,288
Unknown	46,027	23,560 (51.2%)	62,666
<b>Aged care status<sup>c</sup></b>			
High-level residential aged care	N/A	N/A	236,106
Other	N/A	N/A	106,324
<b>GP coverage (overall)<sup>d</sup></b>			
0-6 months/year (average)	71,864	42,973 (59.8%)	69,053
>6-8 months/year (average)	51,065	34,855 (68.3%)	65,113
>8-10 months/year (average)	60,004	48,245 (80.4%)	100,855
>10 months/year (average)	68,372	61,543 (90.0%)	197,073

<sup>a</sup> Derived based on place of residence from Western Australian quartiles (1996 and 2001) for Socio-Economic Indexes for Areas (SEIFA) - disadvantage component;<sup>155,156</sup> reflects most common quartile over time.

<sup>b</sup> Derived from place of residence using Accessibility/Remoteness Index of Australia (ARIA+) definitions;<sup>157</sup> reflects most common level of accessibility/remoteness over time.

<sup>c</sup> Identifies person's high-level residential aged care status at 30 June of calendar year associated with drug supply date; patient counts available by calendar year but not really relevant for 1993-2005 as a whole.

<sup>d</sup> Based on 61-day coverage per general practitioner visit and derived from proportion of coverage for 1993-2005.

<sup>e</sup> Corresponding overall  $\chi^2$  tests and univariate logistic regression analysis comparing proportions of people taking PIMs against first (reference) category defining each characteristic all yielded p-values <0.0001.

<sup>f</sup> Corresponding univariate Poisson regression analysis for all comparisons of daily dose rates against first (reference) category defining each characteristic yielded p-values <0.0001.

GP - General practitioner; PIMs - Potentially inappropriate medications; PY - Person-years;  
N/A - Not applicable

**Table 5-2 Potentially inappropriate medications in Western Australian residents aged ≥65 years (1993-2005) - cohort participants, number/proportion exposed and rate of consumption (daily doses/1000 person-years) by gender and calendar year**

Population	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	1993-2005
<b>Males</b>														
Cohort participants	57,123	60,206	63,215	66,053	68,624	71,154	73,678	76,447	79,518	82,217	84,716	87,250	84,262	114,146
Number taking PIMs	22,177	23,507	24,970	27,219	27,718	28,542	30,367	31,501	31,246	29,193	29,080	29,536	29,006	79,417
% taking PIMs <sup>a,c</sup>	38.8%	39.0%	39.5%	41.2%	40.4%	40.1%	41.2%	41.2%	39.3%	35.5%	34.3%	33.9%	34.4%	69.6%
Daily doses/1000 PY <sup>b,c</sup>	95,269	95,078	91,660	98,370	96,137	95,094	92,199	94,797	78,243	78,902	75,275	73,508	70,758	88,381
<b>Females</b>														
Cohort participants	78,013	81,131	84,103	86,564	88,884	91,237	93,819	96,366	99,264	101,906	104,471	107,323	104,398	137,159
Number taking PIMs	38,768	40,505	41,212	43,206	43,623	44,098	48,129	48,833	49,460	50,410	48,790	48,573	47,279	108,199
% taking PIMs <sup>a,c</sup>	49.7%	49.9%	49.0%	49.9%	49.1%	48.3%	51.3%	50.7%	49.8%	49.5%	46.7%	45.3%	45.3%	78.9%
Daily doses/1000 PY <sup>b,c</sup>	133,599	134,499	124,434	132,317	128,700	125,431	133,960	129,261	114,552	127,082	116,106	111,446	106,123	125,745
<b>Persons</b>														
Cohort participants	135,136	141,337	147,318	152,617	157,508	162,391	167,497	172,813	178,782	184,123	189,187	194,573	188,660	251,305
Number taking PIMs	60,945	64,012	66,182	70,425	71,341	72,640	78,496	80,334	80,706	79,603	77,870	78,109	76,285	187,616
% taking PIMs <sup>a,c</sup>	45.1%	45.3%	44.9%	46.1%	45.3%	44.7%	46.9%	46.5%	45.1%	43.2%	41.2%	40.1%	40.4%	74.7%
Daily doses/1000 PY <sup>b,c</sup>	117,520	117,836	110,477	117,725	114,594	112,208	115,661	114,088	98,474	105,664	97,910	94,515	90,364	109,415

<sup>a</sup> Estimated 1.1%, 0.2% and 0.7% decreases in proportions exposed per year for males, females and persons, respectively, based on univariate logistic regression.

<sup>b</sup> Estimated 2.7%, 1.6% and 2.1% decreases in daily dose rates per year for males, females and persons, respectively, based on univariate Poisson regression.

<sup>c</sup> All ordinal unadjusted time trend analysis (males, females, persons) for both proportions exposed and daily dose rates yielded  $p \leq 0.0001$ .

**Table 5-3 Factors associated with exposure to potentially inappropriate medications in Western Australian residents aged ≥65 years (1993-2005) - odds ratios**

Factor/characteristic	Unadjusted		Adjusted	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Male <sup>a</sup> - Gender	-	-	-	-
Female	1.54 (1.53, 1.55)	<0.01	1.36 (1.35, 1.37)	<0.01
<1910 <sup>a</sup> - Year of birth	-	-	-	-
1910-1919	0.75 (0.74, 0.77)	<0.01	1.02 (0.99, 1.04)	0.25
1920-1929	0.52 (0.51, 0.53)	<0.01	0.99 (0.96, 1.02)	0.49
1930-1939	0.39 (0.38, 0.40)	<0.01	1.03 (0.99, 1.07)	0.21
65-69 years <sup>a</sup> - Age group	-	-	-	-
70-74 years	1.27 (1.26, 1.28)	<0.01	0.93 (0.92, 0.94)	<0.01
75-79 years	1.55 (1.54, 1.56)	<0.01	0.95 (0.94, 0.97)	<0.01
80-84 years	1.88 (1.86, 1.90)	<0.01	1.02 (1.00, 1.05)	0.02
85-89 years	2.22 (2.19, 2.25)	<0.01	1.11 (1.08, 1.14)	<0.01
≥90 years	2.49 (2.45, 2.54)	<0.01	1.20 (1.16, 1.25)	<0.01
Most disadvantaged <sup>a</sup> - Disadvantage <sup>b</sup>	-	-	-	-
Moderately disadvantaged	0.94 (0.93, 0.95)	<0.01	1.00 (0.99, 1.01)	0.95
Slightly disadvantaged	0.91 (0.90, 0.92)	<0.01	1.03 (1.02, 1.04)	<0.01
Least disadvantaged	0.82 (0.82, 0.83)	<0.01	1.10 (1.09, 1.11)	<0.01
Major city <sup>a</sup> - Remoteness <sup>c</sup>	-	-	-	-
Inner regional area	0.95 (0.94, 0.96)	<0.01	1.06 (1.05, 1.07)	<0.01
Outer regional area	0.89 (0.88, 0.90)	<0.01	1.06 (1.05, 1.08)	<0.01
Remote/very remote area	0.79 (0.77, 0.80)	<0.01	1.10 (1.07, 1.12)	<0.01
Not high-level aged care <sup>a</sup> - Aged care <sup>d</sup>	-	-	-	-
High-level residential aged care	3.36 (3.29, 3.43)	<0.01	1.96 (1.91, 2.01)	<0.01
0-4 months/year <sup>a</sup> - Annual GP coverage <sup>e</sup>	-	-	-	-
>4-8 months/year	0.88 (0.87, 0.88)	<0.01	0.97 (0.96, 0.98)	<0.01
>8-11 months/year	1.69 (1.67, 1.70)	<0.01	0.96 (0.95, 0.97)	<0.01
>11 months/year	3.56 (3.53, 3.59)	<0.01	1.16 (1.15, 1.18)	<0.01
0-166 daily doses <sup>a</sup> - Annual drug intake <sup>f</sup>	-	-	-	-
>166-643 daily doses	5.99 (5.93, 6.06)	<0.01	1.79 (1.77, 1.82)	<0.01
>643-1330 daily doses	10.22 (10.12, 10.34)	<0.01	1.73 (1.71, 1.76)	<0.01
>1330 daily doses	21.88 (21.64, 22.12)	<0.01	2.08 (2.04, 2.12)	<0.01
0-2 drugs <sup>a</sup> - Annual drug count <sup>g</sup>	-	-	-	-
3-5 drugs	7.61 (7.51, 7.70)	<0.01	5.97 (5.88, 6.07)	<0.01
6-9 drugs	18.10 (17.87, 18.32)	<0.01	12.71 (12.50, 12.93)	<0.01
10+ drugs	54.05 (53.35, 54.77)	<0.01	35.03 (34.37, 35.71)	<0.01
Not year of death <sup>a</sup> - Death year	-	-	-	-
Year of death	2.13 (2.09, 2.16)	<0.01	1.54 (1.51, 1.58)	<0.01
1993 <sup>a</sup> - Calendar year	-	-	-	-
1994	1.02 (1.00, 1.03)	0.04	0.93 (0.91, 0.95)	<0.01
1995	1.01 (0.99, 1.02)	0.30	0.88 (0.86, 0.90)	<0.01
1996	1.07 (1.05, 1.08)	<0.01	0.81 (0.80, 0.83)	<0.01
1997	1.04 (1.02, 1.05)	<0.01	0.74 (0.73, 0.76)	<0.01
1998	1.02 (1.01, 1.04)	<0.01	0.67 (0.66, 0.68)	<0.01
1999	1.12 (1.11, 1.14)	<0.01	0.76 (0.75, 0.78)	<0.01
2000	1.12 (1.10, 1.14)	<0.01	0.66 (0.65, 0.68)	<0.01
2001	1.08 (1.06, 1.09)	<0.01	0.54 (0.53, 0.55)	<0.01
2002	1.01 (0.99, 1.02)	0.36	0.45 (0.44, 0.46)	<0.01
2003	0.94 (0.93, 0.96)	<0.01	0.40 (0.39, 0.41)	<0.01
2004	0.93 (0.92, 0.94)	<0.01	0.36 (0.35, 0.36)	<0.01
2005	0.94 (0.92, 0.95)	<0.01	0.35 (0.34, 0.36)	<0.01

<sup>a</sup> The first category listed for each factor was used as reference for odds ratio comparisons.

<sup>b</sup> Derived based on place of residence from Western Australian quartiles (1996 and 2001) for Socio-Economic Indexes for Areas (SEIFA) - disadvantage component;<sup>155,156</sup> reflects person's most common quartile over time.

<sup>c</sup> Derived from place of residence using Accessibility/Remoteness Index of Australia (ARIA+) definitions;<sup>157</sup> reflects most common level of accessibility/remoteness over time.

<sup>d</sup> Identifies person's high-level residential aged care status at 30 June of calendar year.

<sup>e</sup> Based on 61-day coverage per general practitioner (GP) visit and derived from proportion of coverage for calendar year.

<sup>f</sup> Derived from study population quartiles for the overall quantity of medication consumed annually; the daily dose units estimate the cumulative number of days of exposure per drug during the calendar year of interest.

<sup>g</sup> Number of different generic drugs taken during the calendar year of interest.

GP - General practitioner; CI - Confidence interval

**Table 5-4 Potentially inappropriate medications in Western Australian residents aged ≥65 years (1993-2005) - number of participants exposed by PIM and calendar year<sup>a</sup>**

Medication class	PIM	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	1993-2005 (%)
Antirheumatics	Indomethacin	4,212	4,534	4,538	4,841	4,796	4,743	4,821	4,266	3,476	3,385	3,445	3,384	3,376	24,846 (9.9%)
	Naproxen	8,808	9,302	9,544	10,243	10,188	10,395	10,848	9,264	6,900	6,530	5,539	5,695	6,341	48,513 (19.3%)
	Piroxicam	8,253	8,664	8,659	9,428	9,281	9,422	9,494	7,623	5,011	4,197	3,761	3,649	3,940	38,332 (15.3%)
Analgesics	Dextropropoxyphene	202	170	168	214	201	205	218	217	149	109	105	77	83	1,115 (0.4%)
	Meperidine/pethidine	132	144	152	170	175	173	150	118	125	113	113	100	68	1,180 (0.5%)
Anti-Parkinson drugs	Orphenadrine	79	73	70	75	63	49								171 (0.1%)
Antihistamines (systemic)	Diphenhydramine	22	23	21	33	32	<5								76 (0.0%)
	Hydroxyzine	30	24	26	38	71	57	64							206 (0.1%)
	Cyproheptadine	1,008	1,152	1,233	1,296	1,183	1,279	1,498	1,610	1,753	1,796	1,739	1,747	1,527	10,121 (4.0%)
	Promethazine	1,925	2,385	2,385	2,618	2,297	232	289	293	303	340	339	325	327	9,128 (3.6%)
Antipsychotics	Thioridazine	980	1,019	1,023	1,026	1,035	1,045	1,008	850	359	118	85	49	39	3,673 (1.5%)
Anxiolytics, hypnotics/sedatives (benzodiazepines)	Oxazepam	7,215	7,480	7,433	7,722	7,564	7,592	8,153	8,314	8,225	8,128	8,303	8,146	8,031	30,985 (12.3%)
	Alprazolam	<5	182	296	360	419	481	551	660	756	777	823	862	917	2,786 (1.1%)
	Diazepam	6,212	6,554	6,658	7,361	7,262	7,439	7,900	8,001	7,967	8,364	8,291	8,474	8,383	37,556 (14.9%)
	Temazepam	16,229	17,425	18,460	20,213	20,656	21,446	23,532	24,570	25,118	25,740	25,729	26,244	26,021	87,602 (34.9%)
Antidepressants	Amitriptyline	2,862	3,043	3,149	3,513	3,770	4,190	5,013	5,774	6,282	6,379	6,848	7,462	7,676	26,672 (10.6%)
	Doxepin	3,267	3,355	3,140	3,121	2,933	2,934	3,050	2,945	2,908	2,484	2,325	2,250	2,116	12,252 (4.9%)
	Fluoxetine	916	1,565	1,220	1,466	1,564	1,505	1,522	1,502	1,556	1,352	1,480	1,538	1,468	7,870 (3.1%)
Psychostimulants	Dexamphetamine	7	15	26	35	34	36	44	63	79	61	60	71	63	194 (0.1%)
Cardiac rhythm regulators	Disopyramide	162	152	135	125	113	104	90	89	84	79	57	49	42	297 (0.1%)
	Digoxin	9,288	10,040	9,913	10,175	10,127	10,289	10,625	10,555	10,391	9,676	9,426	9,343	9,048	32,302 (12.9%)
	Amiodarone	763	1,001	1,296	1,659	2,019	2,463	2,977	3,435	3,974	3,854	3,867	3,853	3,761	12,351 (4.9%)
Hypertension drugs	Methyldopa	2,505	2,276	1,919	1,711	1,539	1,408	1,303	1,108	1,013	841	749	703	690	4,738 (1.9%)
	Nifedipine	6,532	6,698	6,860	6,937	6,716	7,262	7,345	7,354	7,416	6,416	6,170	6,140	5,947	23,527 (9.4%)
	Clonidine	145	156	171	225	229	268	293	303	284	285	303	325	277	1,477 (0.6%)
High ceiling diuretics	Ethacrynic acid	104	111	102	81	83	82	93	84	84	78	94	9	21	467 (0.2%)
Antithrombotics	Dipyridamole							752	1,965	2,757	2,635	2,493	2,298	2,202	5,914 (2.4%)
	Ticlopidine	5	8	27	57	63	70	58	47	38	23	22	24	17	234 (0.1%)
Diabetes drugs	Chlorpropamide	204	206	174	152	135	87	<5							340 (0.1%)
Iron preparations	Ferrous sulphate	5,461	5,272	5,776	6,300	6,171	6,103	6,582	7,032	5,165	4,103	4,788	5,291	3,396	32,500 (12.9%)
Peptic ulcer/reflux drugs	Cimetidine	6,741	5,932	4,784	4,067	3,240	2,736	2,286	1,875	1,486	1,031	754	604	469	13,102 (5.2%)
Laxatives	Bisacodyl	2,227	2,546	2,798	2,998	3,037	3,028	3,195	3,264	3,175	3,371	3,314	3,178	3,123	18,657 (7.4%)
Bowel disorder drugs/belladonna & derivatives	Belladonna alkaloids	1,493	1,717	1,726	1,845	1,557	25	22	15	36	78	89	86	46	5,791 (2.3%)
	Dicyclomine	11	13	11	7	16	23	20	23	22	19	14	14	<5	97 (0.0%)
	Propantheline	781	865	792	915	896	884	958	972	779	686	576	508	530	5,649 (2.2%)
Urinary antispasmodics	Oxybutynin				345	759	1,067	1,447	2,052	2,517	2,848	2,989	3,194	3,279	9,798 (3.9%)
Urinary tract antibacterials	Nitrofurantoin	1,135	1,183	1,341	1,328	1,391	1,393	1,349	1,388	1,453	1,493	1,586	1,580	1,781	10,452 (4.2%)
	Ethinylloestradiol	426	450	436	510	214									874 (0.3%)
	Oestradiol	1,566	1,781	2,246	2,612	2,952	3,175	3,611	3,965	4,058	3,261	2,624	2,174	1,833	10,047 (4.0%)
	Oestriol	7	11	6	12	26	27	25	39	37	48	36	34	33	148 (0.1%)
	Oestrone	2,082	2,614	3,041	3,520	3,997	4,356	4,885	5,188	5,261	4,333	2,887	2,126	1,782	11,450 (4.6%)
	Oestrogens-conjugated	2,371	2,852	3,356	3,878	4,601	5,016	5,602	6,238	6,341	5,211	3,564	2,789	2,450	14,971 (6.0%)
	Fosfestrol sodium	57	45	29	25	48	62	74	73	72	67	29			258 (0.1%)

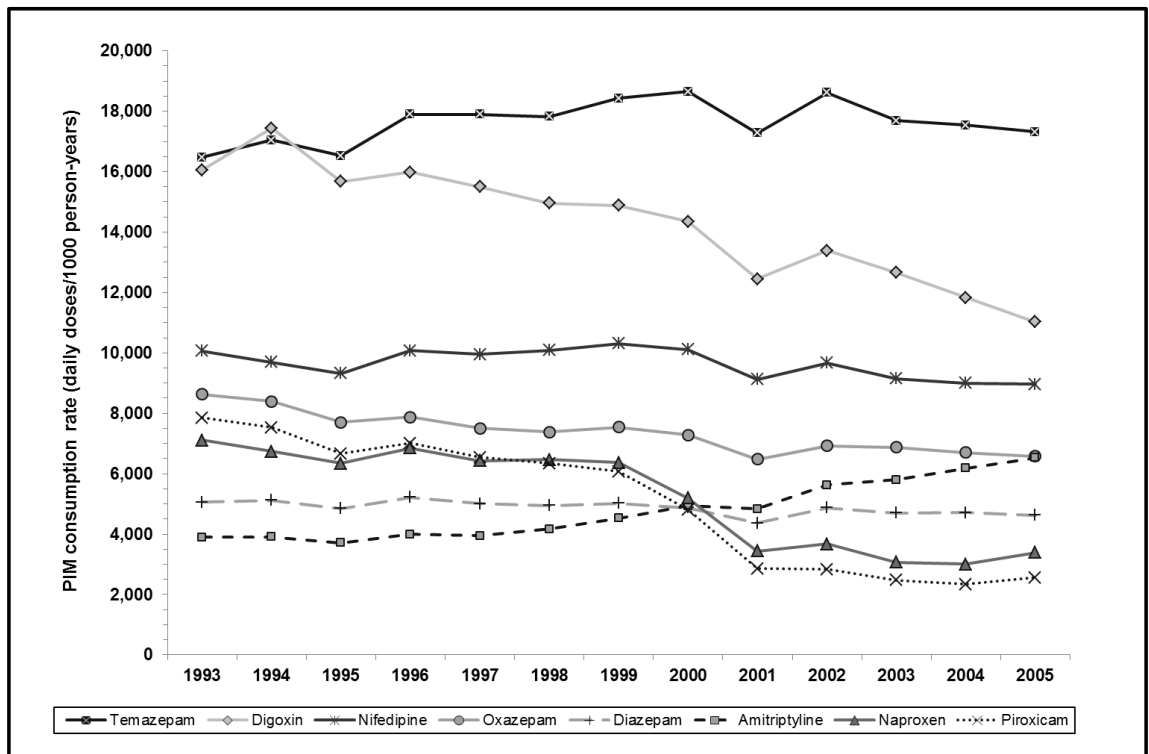
<sup>a</sup> To derive percentages of exposed participants for individual PIMs by calendar year, please use person counts (i.e. 'Cohort participants') from Table 5-2 as denominators.

PIM - Potentially inappropriate medication

**Table 5-5 Potentially inappropriate medications in Western Australian residents aged ≥65 years (1993-2005) - rate of consumption (daily doses/1000 person-years) by PIM and calendar year**

Medication class	PIM	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	1993-2005
Antirheumatics	Indomethacin	3,653	3,363	3,094	3,179	3,019	2,827	2,705	2,273	1,641	1,773	1,726	1,637	1,607	2,417
	Naproxen	7,110	6,743	6,345	6,847	6,431	6,462	6,365	5,199	3,437	3,668	3,065	3,012	3,395	5,065
	Piroxicam	7,853	7,525	6,666	7,012	6,535	6,342	6,072	4,809	2,857	2,832	2,469	2,337	2,563	4,834
Analgesics	Dextropropoxyphene	29	26	23	27	26	25	24	22	15	12	11	10	9	19
	Meperidine/pethidine	33	55	54	49	49	46	66	40	25	24	21	16	13	36
Anti-Parkinson drugs	Orphenadrine	109	97	73	71	66	55								77
Antihistamines (systemic)	Diphenhydramine	16	21	20	21	20	4								20
	Hydroxyzine	26	22	23	23	34	28	36							27
	Cyproheptadine	667	708	722	761	699	699	818	870	878	990	950	928	856	822
	Promethazine	977	1,108	1,133	1,307	1,085	122	134	136	136	147	136	140	146	469
Antipsychotics	Thioridazine	1,159	1,166	1,169	1,140	1,137	1,144	1,043	872	245	124	103	58	55	672
Anxiolytics, hypnotics/sedatives (benzodiazepines)	Oxazepam	8,625	8,398	7,700	7,874	7,509	7,375	7,539	7,284	6,475	6,924	6,872	6,699	6,573	7,302
	Alprazolam		119	264	374	444	499	535	606	631	794	842	902	932	604
	Diazepam	5,053	5,116	4,853	5,215	5,006	4,942	5,026	4,871	4,359	4,876	4,704	4,708	4,625	4,855
	Temazepam	16,474	17,048	16,528	17,891	17,901	17,821	18,426	18,651	17,273	18,615	17,680	17,542	17,321	17,664
Antidepressants	Amitriptyline	3,891	3,908	3,708	3,992	3,940	4,163	4,522	4,928	4,837	5,629	5,803	6,176	6,531	4,874
	Doxepin	4,879	4,604	4,060	4,099	3,838	3,725	3,666	3,476	2,986	3,079	2,823	2,654	2,504	3,486
	Fluoxetine	725	1,281	1,119	1,297	1,534	1,490	1,546	1,515	1,404	1,585	1,638	1,740	1,735	1,458
Psychostimulants	Dexamphetamine	11	19	31	51	50	48	53	63	65	70	72	83	79	56
Cardiac rhythm regulators	Disopyramide	264	232	187	174	160	138	125	114	102	104	91	76	57	134
	Digoxin	16,060	17,440	15,678	15,976	15,501	14,955	14,885	14,354	12,447	13,385	12,651	11,833	11,022	14,119
	Amiodarone	1,047	1,245	1,525	2,066	2,453	2,910	3,373	3,824	3,991	4,716	4,618	4,683	4,582	3,309
Hypertension drugs	Methyldopa	4,580	3,907	3,014	2,754	2,425	2,137	1,936	1,644	1,261	1,209	1,081	1,004	996	2,025
	Nifedipine	10,064	9,690	9,322	10,071	9,954	10,082	10,304	10,108	9,127	9,671	9,153	9,003	8,958	9,622
	Clonidine	177	186	175	207	206	209	231	241	204	216	235	235	223	213
High ceiling diuretics	Ethacrynic acid	136	149	121	75	68	59	69	69	58	56	63	5	11	68
Antithrombotics	Dipyridamole							711	1,513	2,393	3,099	3,029	2,886	2,708	2,622
	Ticlopidine	5	11	19	39	47	52	54	42	30	27	25	22	17	32
Diabetes drugs	Chlorpropamide	370	349	268	238	209	168								283
Iron preparations	Ferrous sulphate	4,935	4,362	4,597	4,997	4,750	4,670	4,791	4,999	2,329	2,868	3,275	3,706	1,077	3,851
Peptic ulcer/reflux drugs	Cimetidine	8,151	6,953	5,337	4,699	3,543	2,906	2,338	1,927	1,358	1,055	765	592	443	2,807
Laxatives	Bisacodyl	1,395	1,643	1,679	1,697	1,695	1,670	1,588	1,645	1,474	1,631	1,581	1,489	1,372	1,577
Bowel disorder drugs/belladonna & derivatives	Belladonna alkaloids	961	1,011	988	1,054	850	1	1	1	1	2	2	2	2	327
	Dicyclomine	12	11	7	8	10	14	12	12	13	11	11	7	1	11
	Propantheline	748	738	639	656	602	556	603	576	434	419	346	324	299	517
Urinary antispasmodics	Oxybutynin				282	534	796	1,079	1,488	1,653	2,109	2,199	2,328	2,496	1,680
Urinary tract antibacterials	Nitrofurantoin	759	711	750	804	763	726	736	778	714	818	823	732	878	771
Oestrogen-only medication	Ethinylloestradiol	265	264	238	280	126									262
	Oestradiol	1,791	2,104	2,386	3,037	3,297	3,624	4,186	4,462	4,047	4,110	3,200	2,566	2,355	3,205
	Oestriol	7	6	2	6	12	16	19	25	23	26	23	22	23	17
	Oestrone	2,702	3,429	3,726	4,601	4,950	5,319	6,148	6,456	5,704	5,381	3,408	2,479	2,202	4,343
	Oestrogens-coniugated	1,743	2,027	2,204	2,750	3,085	3,336	3,835	4,137	3,796	3,549	2,373	1,876	1,702	2,815
	Fosfestrol sodium	60	41	28	22	33	46	61	59	52	60	43			47

PIM - Potentially inappropriate medication



**Figure 5-1 Potentially inappropriate medications in Western Australian residents aged  $\geq 65$  years (1993-2005) - rate of consumption (daily doses/1000 person-years) by calendar year for most commonly prescribed PIMs**

PIM - Potentially inappropriate medication





# CHAPTER 6 POTENTIALLY INAPPROPRIATE MEDICATIONS AND UNPLANNED HOSPITALISATIONS

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The most important objective of this research project was to estimate the adverse effects of exposure to Beers PIMs in older Western Australians in terms of unplanned hospitalisations, both overall and for each individual PIM. Although the study design would only permit the identification of associations between PIM exposure and hospitalisation events, the ORs generated from the statistical analyses would allow the derivation of attributable fractions, which would in turn facilitate the estimation of the number of unplanned hospitalisations attributable to PIM use in exposed patients. Thus, both a relative measure of adverse drug effect and an absolute measure of public health burden would be estimated through this process, for all PIMs combined and for each individual PIM.

The results of our analyses in relation to this important objective are presented in this chapter, the contents of which were included in the following manuscript:

- Price SD, Holman CDJ, Sanfilippo FM, Emery JD. Association between potentially inappropriate medications from the Beers Criteria and the risk of unplanned hospitalization in elderly patients. *The Annals of Pharmacotherapy* 2014; 48(1):6-16. doi: 10.1177/1060028013504904.

A more extensive set of statistics for individual PIMs is presented in Appendix I.3.



## **Association between potentially inappropriate medications from the Beers Criteria and the risk of unplanned hospitalisation in elderly patients**

### **ABSTRACT**

**Background:** Predisposition to adverse drug events with advancing age has led to the development of lists of potentially inappropriate medications (PIMs) to be avoided in the elderly, such as the Beers Criteria. The prevalence of Beers medications has been studied widely, but it is still unclear whether PIM use is predictive of adverse events in older people

**Objectives:** To examine potential associations between exposure to PIMs from the general Beers list and unplanned hospitalisations in elderly Western Australians.

**Methods:** Using an enhanced case-time-control design and conditional logistic regression applied to the pharmaceutical claims and other linked health data of 251,305 Western Australians aged  $\geq 65$  years (1993-2005), odds ratios for unplanned hospitalisation were obtained, from which attributable fractions, number and proportion of hospitalisations associated with drug exposure were derived.

**Results:** Based on the health profiles of 383,150 hospitalised index subjects, overall PIM exposure was associated with an elevated risk of unplanned hospitalisation (adjusted OR 1.18; 95% CI 1.15-1.21), this estimated risk increasing with the number of different PIMs and PIM quantity taken. Fifteen percent of unplanned hospitalisations in exposed index subjects (1,980 per year) were attributed to PIM exposure. Patients taking meperidine (pethidine), nitrofurantoin, promethazine, indomethacin, and thioridazine appeared to be at particularly high risk of unplanned hospitalisation, whereas temazepam, oxazepam, diazepam, digoxin, amiodarone, ferrous sulphate, and naproxen were attributed the greatest numbers of unplanned hospitalisations.

**Conclusions:** Due caution prescribing Beers medications in the elderly seems justified, paying particular attention to PIMs listed above and to the concurrent use of multiple PIMs. Our results also support the retention of specific medications on PIM lists in future developments.

**Keywords:** Beers Criteria, inappropriate prescribing, unplanned hospitalisation, Australian elderly, case-time-control design, pharmaceutical claims, pharmacoepidemiology

## 6.1 INTRODUCTION

Due to physiological deterioration, increasing comorbidities, polypharmacy and other age-related factors, adults generally become more susceptible to adverse drug events (ADEs) with advancing age.<sup>4-6</sup> In America, ADEs account for nearly 100,000 emergency hospitalisations each year in people aged  $\geq 65$  years.<sup>31</sup> In Australia, 15-22% of unplanned hospitalisations are drug-related in this age group.<sup>32</sup> This has led to the development of lists of 'potentially inappropriate medications' (PIMs) to be avoided in the elderly. Among them, the Beers Criteria<sup>13-16</sup> are the most commonly referenced.

Numerous studies have examined the prevalence of medications from the Beers Criteria in elderly populations worldwide. However, it is still unclear whether the use of Beers medications is predictive of adverse events in older people. Earlier reviews<sup>36,107,108</sup> have concluded that the evidence linking medications from the Beers list with adverse health outcomes was generally weak and contradictory. Most of the reviewed studies used early versions (1991/97)<sup>13,14</sup> of the Beers Criteria though and had important limitations. More recently, additional research projects based on Beers 2003<sup>15</sup> have produced results supporting the association of PIM exposure with adverse outcomes in older people,<sup>90,106,109-118</sup> although these findings are far from universal. For example, research by Budnitz et al. estimated that only 6.6% of elderly Americans hospitalised due to ADEs following an Emergency Department visit were due to Beers medications.<sup>31</sup> Many studies are still limited in terms of participant numbers, duration of study period or ability to control for important confounding factors. Furthermore, most of this research has concentrated on the effects of overall PIM exposure, with few studies reporting on the adverse outcomes of individual medications from the Beers list.

This paper presents the results of a large population-based linked-data study (1993-2005), which sought to identify associations between exposure to PIMs from the 'general' Beers list (i.e. excluding disease-specific PIMs) and unplanned hospitalisations in Western Australian (WA) residents aged  $\geq 65$  years. The study not only examined associations related to overall exposure to

these medications, but also assessed the impact of concurrent exposure to multiple PIMs, and estimated unplanned hospitalisation outcomes for each individual PIM. Although PIM use was defined according to the 2003 Beers Criteria,<sup>15</sup> differences between the latter and the 2012 updated version<sup>16</sup> are examined briefly in the paper's Discussion, within the context of this study.

## **6.2 METHODS**

### **6.2.1 DATA LINKAGE AND COHORT SELECTION**

This study linked Australian Pharmaceutical Benefits Scheme (PBS),<sup>21,22</sup> Medicare<sup>23,24</sup> and System for Payment of Aged Residential Care (SPARC)<sup>25</sup> data with inpatient, death and electoral roll records from the WA Data Linkage System<sup>138</sup> through probabilistic linkage. The study protocol was approved by The University of WA's Human Research Ethics Committee.

The cohort was restricted to people who were  $\geq 65$  years old by the end of 2004, continuously lived in WA during 1993-2005 (until death) and had at least one PBS prescription filled during that time, thus ensuring that those included in the study had ascertainable drug exposures. Ninety-two percent of people who met these criteria participated in the study, the remainder excluded due to problem data (e.g. records post-death, no gender on any record). Our ultimate cohort captured 80-85% of WA residents aged  $\geq 65$  years.

### **6.2.2 ESTABLISHMENT OF DRUG REFERENCE DATABASE**

Details of all drug items from available PBS schedules (August 1991-June 2007)<sup>200</sup> were assembled into a large reference database. Relevant prescription details were extracted from the last published entry for each item. Anatomical Therapeutic Chemical (ATC) codes were reconciled with the 2007 World Health Organization (WHO) ATC classification.<sup>201</sup>

Since PBS claims did not include the prescribed dose, average daily doses for each item were determined from comparisons between average prescribed daily doses from the Australian Bettering the Evaluation and Care of Health (BEACH)<sup>165</sup> general practice data, the MIMS Australia<sup>167</sup> registered drug information and the 2008 WHO ATC Defined Daily Doses (DDDs),<sup>146</sup> according to drug form, route and strength. Furthermore, each drug's elimination half-life was obtained (predominantly from MIMS),<sup>167</sup> from which the period of drug effect, defined as five times the drug's half-life,<sup>170,171</sup> was estimated.

### **6.2.3 DEFINITION OF DRUG GROUPS AND DOMAINS**

To identify medications of interest, each item from the 2003 Beers list<sup>15</sup> was defined according to the 2007 ATC classification.<sup>201</sup> Once patient and drug reference variables had been merged to the PBS master data file for 1993-2005, the ATC code list for 'general' PIMs (i.e. excluding disease-specific criteria, but including PIMs with dosage or duration constraints irrespective of the dose/duration likely prescribed) was applied to determine which of these PIMs were supplied to WA residents aged  $\geq 65$  years during the study period. Forty of the 43 individual drugs identified through this process were included in the study and grouped into 20 broad drug classes (corresponding to 20 drug-defined domains of exposed patients) as per Table 6-2, each class consisting of medications used to treat similar conditions to those treated by related PIMs. Diphenhydramine, dicyclomine, and oestriol were omitted from the analysis due to very low prevalence.

### **6.2.4 CASE-TIME-CONTROL DESIGN**

Associations between PIMs and unplanned hospitalisations were expressed as odds ratios (ORs) obtained from a case-time-control design.<sup>26,27</sup> This approach involved index subjects that acted both as cases and as their own historical controls, while background time trends in exposure due to ageing, natural disease progression and treatment patterns were adjusted using similarly constructed case and control observation windows in a reference group drawn from the same drug-defined domain of patients as the index subjects. In this instance, the domain for each PIM included everyone in the study cohort who had ever been prescribed a drug from the PIM's broad medication class during 1993-2005. The motivation for restriction of reference group sampling to the same patient domain as each index subject was to achieve enhanced comparability between index and reference observations, thus reducing the potential for differential exposure time trends under the null hypothesis, a problem that may affect poorly constructed case-time-control designs.<sup>214,215</sup> Essentially, the approach conferred advantages similar to those of a case-case-time-control design,<sup>214,215</sup> but rather than conditioning on all patients sustaining observed outcomes, our design achieved a similar ends of a relatively homogenous study base by restricting each analysis to members of the same drug-defined patient domain.

Index subjects were patients within the drug-defined domain who had experienced an unplanned (i.e. emergency) hospital admission between 1 July 1994 and 31 December 2005 whilst aged  $\geq 67$  years, thus ensuring sufficient lead-up time for the control observation period. Many individuals were included in the analysis as multiple index subjects, although a few ( $\leq 0.1\%$ ) with  $>50$  index admissions were excluded due to concerns about representativeness. Two records were created for each index subject, one representing the 'case time' (i.e. the admission date) and the other the 'control time' (usually 365 days before the admission date but, if the patient was in hospital at this preferred control time, the admission date of that earlier hospitalisation was used instead).

Each index subject was matched by gender, general practitioner (GP) coverage category and year of birth to a randomly selected reference subject from the drug-defined domain. For GP coverage, each GP visit identified in the Medicare data set was allocated a 'coverage' period of 61 days (overlapping periods for each patient being merged together), from which patients' number and proportion of 'GP coverage' days over the study period was ascertained. Categories were then derived, loosely based on related quartiles. For year of birth, subjects born prior to 1900 were allocated a birth year of 1900 for matching purposes only. 'Case time' and 'control time' records were created for each reference subject as per the corresponding index subjects, matching the case and control dates as closely as possible.

Once created, the case and control time records for index and reference subjects were populated with the variables required to control for potential confounding, including nursing home status at the time specified on the record (i.e. case or control time); hospital days, overall Charlson comorbidity index<sup>160</sup> and GP coverage percentage, all for the previous year; and a drug consumption profile for the preceding 90 days (plus the case or control date), which included the number of broad medication categories involved, the overall number of 'daily doses' consumed (for any drug) and a count of 'daily doses' for each broad drug category.

Additionally, PBS records were checked to ascertain exposure status at each case and control date. If a prescription was found for a PIM of interest and if the time period bound by its supply date and exposure effect end date

overlapped with the case or control time, the PIM's exposure status was set to 'exposed'. The end date was calculated by adding the number of drug consumption days associated with the script (i.e. total drug quantity / average daily dose) to the supply date (-1) plus the period of drug effect (up to seven days) and a seven-day latency period. Thus, the exposure status indicated the potential for a hospital admission at the case or control time to have resulted from the effects of PIM exposure.

For each PIM sub-study, conditional logistic regression models with robust analysis of variance were applied using the SAS 9.2 PHREG procedure, with the COVS option and stratification based on a unique identifier for each subject. The baseline model included the binary exposure variable and the cross-product between exposure and the binary index/reference indicator, the OR of primary interest being derived from the coefficient of this interaction term.<sup>26</sup> The adjusted model controlled for all health and drug consumption indicators mentioned earlier, excluding the three-month count of 'daily doses' for the PIM of interest.

The analysis was repeated for each individual PIM and for all PIMs combined. For the latter, drug consumption adjustments covered all medications, including PIMs. Furthermore, additional regression models were applied to the overall PIM study, substituting the PIM exposure dichotomous variable with the number of different PIMs and the total number of PIM 'daily doses' taken in the three-month period prior to the case or control time. These model variations enabled the estimation of effects of PIM polypharmacy and dose-response, respectively.

#### **6.2.5 ESTIMATION OF UNPLANNED HOSPITALISATIONS ATTRIBUTED TO PIMS**

Using the OR derived from the interaction term in the adjusted model described above, it was possible to calculate the attributable fraction (AF), in the form of an incidence density fraction, of unplanned hospitalisations associated with each PIM within the exposed, where  $AF = (OR - 1) / OR$ . An estimate of the number of unplanned hospitalisations attributed to each medication was then derived as  $AF \times$  the number of exposed index subjects.<sup>174,216</sup>

#### **6.2.6 IDENTIFICATION OF ADE-RELATED HOSPITALISATIONS FROM ICD CODES**

For comparison, the count of ADE-related unplanned hospitalisations in cohort members considered exposed to each PIM was determined based on relevant ICD external cause codes for accidental drug poisoning and adverse drug



reactions<sup>158,159</sup> recorded on inpatient discharge summaries. These derivations more closely reflected the conventional approach for identifying ADE-related hospitalisations using inpatient data. However, other studies would not necessarily have restricted their hospitalisation counts to exposed patients as exposure status is not always readily available.

### **6.3 RESULTS**

Table 6-1 presents summary results for the overall study of associations between PIM exposure and unplanned hospitalisations. From an initial cohort of 251,305 participants, 245,436 (97.7%) had either taken a PIM from the 'general' Beers list during 1993-2005 or a drug used to treat conditions similar to the indications for prescribing these PIMs. They comprised the patient domain for this study. Of these, 187,616 (76.4%) had actually been prescribed a PIM. Overall, 383,150 unplanned hospitalisations ('index subjects') were included, which involved 120,332 patients. Index subjects were 45.5% males, their mean age was 78.4 years, and 149,289 (39.0%) were considered exposed to a PIM at the time of admission.

Exposure to a PIM was associated with a significant increase in unplanned hospitalisations - odds ratio (OR) 1.18; 95% confidence interval (CI) 1.15-1.21, after adjusting for general time trends (through the inclusion of reference subjects), and changes in patients' health profile and medication intake over time. Based on the derived attributable fraction, 15.3% (13.3-17.1%) of unplanned hospitalisations were attributed to PIMs in exposed subjects, yielding 22,773 (19,922-25,500) hospitalisations from July 1994 to December 2005 (1,980 per year). By comparison, only 9,172 of the exposed index subjects (6.1%) had an International Classification of Diseases (ICD) external cause code related to ADEs on their inpatient summary record over the same period.

The estimated risk of unplanned hospitalisation depended on both the number of different PIMs taken and the PIM quantity consumed. For instance, the OR increased progressively from 1.18 (95% CI 1.16-1.19) to 5.07 (4.42-5.81) as the number of different PIMs increased from one to ten in the three-month period preceding a potential hospital admission (Figure 6-1). Similarly, the OR rose from 1.00 (1.00-1.00) to 2.20 (1.83-2.63) when a total of one to 900 PIM 'daily doses' were taken over the same time period (Figure 6-2).

Table 6-2 provides summary results for all general PIMs prescribed in our cohort during 1993-2005 (excluding diphenhydramine, dicyclomine, and oestriol due to very low prevalence). The number of participants in each drug-defined domain varied, ranging between 115 (psychostimulants) and 193,196 (hypertension medications), as did the number of index subjects (between 390 and 358,570 for the corresponding domains). Thirteen of the 20 domains yielded >100,000 index subjects, and all but one produced >25,000. Twenty-five of the 40 PIMs were associated with >1,000 'exposed' index subjects (i.e. those considered exposed to the drug of interest at the time of hospital admission), although the number of exposed index subjects was also wide-ranging - from 28 (hydroxyzine) to 34,122 (digoxin).

Most adjusted ORs derived from the case-time-control design were above one, suggesting that exposure to individual PIMs was generally associated with a higher risk of unplanned hospitalisation. However, our results were not all statistically significant, in some instances possibly due to insufficient power. Adjusted ORs tended to be similar to or lower than the corresponding unadjusted ORs, but not always.

Statistical significance was achieved for sixteen PIMs (Figure 6-3). Of these, fourteen were associated with an increase in unplanned hospitalisations, with adjusted ORs ranging between 1.07 (1.03-1.11) for digoxin (a cardiac glycoside) and 2.37 (1.25-4.50) for meperidine/pethidine (an opioid analgesic more frequently prescribed to WA inpatients than to those in a community setting). Other PIMs associated with an elevated hospitalisation risk included indomethacin and naproxen (non-steroidal antiinflammatory drugs); promethazine (systemic antihistamine); thioridazine (antipsychotic); oxazepam and diazepam (anxiolytics); temazepam (hypnotic sedative); amiodarone (cardiac rhythm regulator); ferrous sulphate (iron supplement); bisacodyl (laxative); oxybutynin (urinary antispasmodic); and nitrofurantoin (urinary tract antibacterial). Nifedipine, a calcium channel blocker (OR 0.89; 0.83-0.95), and conjugated oestrogens (OR 0.89; 0.80-0.98) appeared to have a protective effect against unplanned hospitalisations.

Figure 6-4 presents estimates of the number and proportion of unplanned hospitalisations attributed to the drug of interest in exposed index subjects, for PIMs associated with a significantly higher risk of hospitalisation. The

proportion of unplanned hospitalisations attributed to these PIMs (in the exposed) ranged from 6.3% (2.4-10.1%) for digoxin to 57.8% (19.9-77.8%) for meperidine/pethidine, although most proportions were between 13% and 33%. The estimated number of unplanned hospitalisations attributed to each of these 14 PIMs in our study population (July 1994 to December 2005) ranged between 97 (meperidine/pethidine) and 5,144 (temazepam). The most commonly prescribed PIMs tended to yield higher counts of unplanned hospitalisations, despite not necessarily having the highest proportions of hospitalisations attributed to drug exposure. Temazepam, oxazepam, diazepam, digoxin, amiodarone, and ferrous sulphate were all associated with >100 unplanned hospitalisations per year, naproxen closely following at 99 per year. These counts arose in a population averaging approximately 170,000 residents aged ≥65 years annually.

## **6.4 DISCUSSION**

### **6.4.1 PRINCIPAL FINDINGS**

Using linked health data, this study applied a case-time-control design to a large population of elderly Western Australians to examine associations between PIMs from the general Beers' list and unplanned hospitalisations. In our study, overall PIM exposure was associated with an elevated risk of unplanned hospitalisation (adjusted OR 1.18; 1.15-1.21), this risk increasing with the number of different PIMs and PIM quantity taken. Fifteen percent of unplanned hospitalisations in exposed index subjects (1,980 per year) were attributed to PIM exposure.

Sixteen PIMs demonstrated a statistically significant effect on unplanned hospitalisations, which appeared protective for two drugs - nifedipine and conjugated oestrogens. Of the 14 others, meperidine (pethidine) was associated with the highest risk of unplanned hospitalisation (adjusted OR 2.37; 1.25-4.50), whilst exposure to nitrofurantoin, promethazine, indomethacin, thioridazine, temazepam, diazepam, oxazepam, amiodarone, naproxen, ferrous sulphate, oxybutynin, bisacodyl, and digoxin appeared to increase the likelihood of unplanned hospitalisation by 7-50%, depending on the drug. Furthermore, 6-58% of unplanned hospitalisations in exposed index subjects were considered attributable to exposure to each of these 14 PIMs. PIMs attributed the greatest

hospitalisation counts included temazepam, oxazepam, diazepam, digoxin, amiodarone, ferrous sulphate, and naproxen.

We were unable to ascertain from our research why certain PIMs were associated with a greater risk of unplanned hospitalisation than other drugs. Our methods were more likely to detect a significant risk for more common high-risk drugs, for medications with serious adverse outcomes, and for those associated with acute rather than long-term effects. Many of the PIMs we have highlighted have strong sedative properties and other symptoms related to the central nervous system, which could potentially have led to confusion, disorientation, and ultimately falls and fractures. Alternatively, the cause of related cognitive problems may have been difficult to detect, and patients may have been hospitalised for further investigation. Other PIMs of interest were associated with heart and renal complications, which are often quite serious and also have multiple causal pathways. Further research in this area, beyond the scope of our study, seems justified.

#### **6.4.2 COMPARISON WITH OTHER STUDIES**

A number of recent investigations based on the 2003 Beers list have provided some evidence in support of adverse health outcomes related to PIM exposure,<sup>90,106,109-118</sup> despite inconclusive results from earlier reviews.<sup>36,107,108</sup> If we specifically focus on the likelihood of hospitalisation, three American studies,<sup>110,116,117</sup> each involving several thousands of elderly people, reported significantly higher rates of hospitalisations in patients taking Beers medications. Fick et al.<sup>110</sup> also demonstrated that PIM users were much more likely to have problems directly related to their medication, whereas Albert et al.<sup>116</sup> showed an association between hospitalisation risk and both the number of PIMs prescribed and recency of PIM use. Conversely, Budnitz et al. estimated that only 6.6% of elderly Americans hospitalised due to ADEs following an emergency department (ED) visit were due to Beers medications.<sup>31</sup> However, cases included in the Budnitz study were those explicitly attributed to drug use by the treating clinician and two-thirds related to unintentional drug overdose. Given the ambiguous nature of some medication side-effects, some of which are associated with multiple causes, it is possible that the Budnitz study was too restrictive, concentrating on ADEs with very obvious links to drug exposure, such as unintentional drug overdoses. This would include bleeding in

relation to warfarin and oral antiplatelet agents, as well as hypoglycaemia in relation to insulins and oral hypoglycaemic agents, which were likely more readily recognised by physicians.

Two Taiwanese studies, one involving 574 ambulatory care patients<sup>106</sup> and the other ~1.5 million ED presentations,<sup>112</sup> both concluded that exposure to Beers medications was linked to an increased risk of hospitalisation, the first reporting an adjusted OR of 1.62 (1.04-2.53) for PIM users and the other demonstrating a significantly higher mean count of hospitalisations over a one-year period in patients prescribed PIMs during ED visits. Similarly, a one-year Japanese study<sup>118</sup> revealed a 68% higher rate of hospitalisation and a 33% increase in medical costs in patients prescribed Beers medications. Furthermore, Ruggiero et al.<sup>90</sup> found higher odds of hospitalisation in Italian nursing home residents using PIMs from the Beers list, particularly in those taking  $\geq 2$  PIMs (OR 1.73; 1.14-2.60).

Passarelli et al.<sup>217</sup> initially reported that exposure to Beers' 2003 PIMs was a strong predictor of ADEs (OR 2.32; 1.17-4.59) in Brazilian inpatients aged  $\geq 60$  years, although only 11.3% of these ADEs were the likely cause of hospitalisation. A subsequent study in the same setting failed to extend this association to ADE-caused hospitalisations, however.<sup>218</sup> Similarly, in an Irish study of 597 acute hospitalisations, Gallagher et al.<sup>111</sup> first reported that nearly half the patients exposed to Beers medications were admitted due to an ADE related to their PIM exposure. Yet, this seemingly strong link between Beers PIMs and ADE hospitalisations could not be replicated in later investigations in the same environment.<sup>219,220</sup>

With one exception, our elderly cohort was much larger than that of other studies. This not only increased the overall power of our study, but also allowed us to investigate the apparent effects of individual PIMs, the impact of multiple PIMs, and dose-response effects, which most other investigations could not achieve reliably. Moreover, some of the other studies did not attempt to ascertain the PIM exposure status of patients at the time of admission as we have, and most were not restricted to unplanned hospitalisations. However, Fick et al.,<sup>110</sup> Budnitz et al.,<sup>31</sup> as well as the Irish<sup>111,219,220</sup> and Brazilian<sup>217,218</sup> research, sought to identify explicitly the hospital-related events that likely resulted from adverse drug effects, which we were unable to achieve due to

study limitations. This design variation, as already mentioned, may not necessarily have been a weakness in our study, given that explicit selection of cases known to be ADE-related may be too restrictive. In any event, although our case-time-control design was different to the approaches used elsewhere, our ORs were similar to comparable results from other studies.

### **6.4.3 STRENGTHS AND LIMITATIONS**

A strength of our study is its large sample sizes. This generated narrow confidence intervals for the overall PIM study and for a number of the sub-studies within drug-defined domains. Admittedly, for some of the more specialised medications, especially those less commonly prescribed, confidence limits were still fairly wide.

Additionally, unlike the more conventional method of examining ICD external cause codes on inpatient records to identify potential ADEs, our approach took patients' drug exposure status upon admission into account and was able to examine individual medications (not being constrained by broad ICD categories).

Furthermore, our study applied three levels of defence against confounding: a crossover configuration to control for fixed confounders (known and unknown); matched reference subjects selected from a group taking medications with similar indications to the PIMs of interest to control for unmeasured and unknown time-variant confounders; and regression modelling to adjust for measured patient-specific time-variant confounders (e.g. health and medication profile over time). Although these measures may not have fully controlled for the potential time-trend bias associated with the basic case-time-control design (e.g. reverse causation bias),<sup>26,27,153</sup> our preliminary work in this field, which applied sensitivity analysis, stratification and negative controls in our regression models, has demonstrated superior internal validity compared with the standard case-control and case-crossover designs, and the basic case-time-control design without adjustment for measurable time-variant confounders.<sup>209</sup> Analogous to the case-case-time-control design,<sup>214,215</sup> we restricted the sampling frame for reference subjects to the same drug-defined domain as each index subject to confer an important advantage by more complete adjustment for time-trend bias.

Difficulties in the ascertainment of drug exposure at the specific times of interest were also of concern, as no information was available on the daily dose specifically prescribed for each dispensed drug, nor on patient compliance. Much attention was devoted to the derivation of exposure status from average recommended daily doses, but this could not have been completely accurate for every subject. Assuming similar levels of exposure misclassification at both 'case time' and 'control time' for each subject (i.e. non-differential measurement error), our estimated ORs may possibly have been attenuated slightly (i.e. pushed towards null) as a result,<sup>208</sup> perhaps counter-balancing some of the OR inflation resulting from unadjusted reverse causation bias.

Furthermore, our pharmaceutical data had some coverage limitations. It excluded drugs prescribed in public hospitals, over-the-counter medications, and prescriptions for which a pharmaceutical claim could not be made. However, unlike other situations described in the literature,<sup>221</sup> the problem of a 'sick-stopper' effect from unmeasured exposure during inpatient care was reduced in this study by the use of unplanned hospitalisation (not death) as the outcome and avoidance of exposure ascertainment windows that overlapped inpatient stays. Moreover, in our population of elderly people, most of whom would have had very low co-payment requirements, these coverage issues unlikely impacted on study results to any great extent, as most non-hospital scripts for medications of interest would have been recorded in this age group.

#### **6.4.4 THE 2012 BEERS CRITERIA UPDATE**

In April 2012, the American Geriatrics Society published an updated version of the Beers Criteria.<sup>16</sup> Although resource constraints have prevented us from repeating our analysis with these more recent definitions, we believe that most of our results would still be applicable with the current Beers list. Of the PIMs included in our study, only five have been removed from the latest Beers update. Two (propoxyphene and ethacrynic acid) are no longer or seldom prescribed<sup>213</sup> (in America and Australia). They are examples of some of the PIMs for which the lack of statistical significance in our results may possibly reflect a low prevalence of exposure rather than a low risk of unplanned hospitalisation. Due to their low prevalence, it is also unlikely that exclusion of these drugs from the list of Beers medications would affect our overall results (i.e. for all PIMs) to any great extent.

Two other drugs (ferrous sulphate and fluoxetine) were omitted because related concerns are not restricted to older patients.<sup>213</sup> Since our study only included people aged  $\geq 65$  years, we are unable to compare estimated risks for these PIMs between older and younger adults. Our results do suggest an elevated risk of unplanned hospitalisation in older people taking ferrous sulphate, although this is less clear for fluoxetine. These Beers exclusions are worth highlighting, especially in relation to the Budnitz findings.<sup>31</sup> The Beers Criteria list medications for which elderly patients are at greater risk of ADEs than other adults, a fact that is often forgotten. We suspect that the subsets of antithrombotics and diabetes medications identified by Budnitz as high-risk drugs in the elderly in relation to emergency hospitalisation may have been omitted from the 2003 Beers list not because they were considered low-risk in older people, but because they were judged equally problematic in both young and older adults. Would clinicians more readily endorse a PIM list for the elderly if it incorporated all medications associated with a high risk of potential harm in older people, including those that are also problematic in younger adults? This point may warrant further debate.

Of the five PIMs on our list that were omitted from the 2012 Beers Criteria, bisacodyl was the only one excluded due to insufficient evidence.<sup>213</sup> This is interesting, since we have estimated a 15% (95% CI 4-26%) increase in unplanned hospitalisation in elderly patients taking this medication. Should other studies report similar results, bisacodyl may perhaps find its way back onto the Beers list.

The revised Beers Criteria also include a number of new medications, most of which are drugs that were introduced to the American market in the last decade. As many belong to the same drug classes as PIMs from the 2003 Beers Criteria, they may be associated with similar risks as related PIMs from the previous version, but not necessarily. One may argue that, being newer they are likely safer. However, given the more rigorous approach to the selection of Beers medications in this latest round, we suspect that some new drugs may also be associated with quite high risks or potential harm in older people. It is beyond the scope of this paper to examine them all individually. Obviously, future studies in this area should include these more recent PIMs in their research protocols, as well as disease-specific PIMs, when feasible. Of



particular interest is the estimated effect of sliding-scale insulin treatment, which now appears on the current Beers list.

#### **6.4.5 CONCLUSIONS**

Medications listed in the Beers Criteria have long been the subject of ongoing debate. Do we prevent harmful effects by avoiding them (where possible) in elderly patients? Our study adds support to the mounting evidence that PIMs from the 2003 Beers Criteria are associated with adverse outcomes, especially in relation to general PIMs (i.e. drugs to be avoided in all elderly patients) and their association with unplanned hospitalisations. Moreover, our study has identified 14 individual PIMs linked to a significantly high risk of unplanned hospitalisation, exposure to which may possibly account for up to one third or even one half of all unplanned hospitalisations in exposed elderly patients. Thus, restraint when considering prescribing Beers medications in the elderly seems justified, paying particular attention to PIMs associated with a high risk of hospitalisation and to the concurrent use of multiple PIMs. In situations where these drugs cannot be avoided, older patients should be monitored closely.

For countries developing their own criteria for medications deemed potentially inappropriate in the elderly, our results highlight particular drugs to consider in the development of these criteria.

#### **ACKNOWLEDGMENTS**

We thank the National Health and Medical Research Council for research funding; the Western Australian Department of Health (DoH) and Australian Department of Health and Ageing for supplying project data; and the Data Linkage Branch (DoH) for undertaking the record linkage.

**Conflict of interest:** The authors have no conflicts of interest to declare.

**Table 6-1 Potentially inappropriate medications (PIMs) in Western Australians aged ≥65 years (1993-2005):<sup>a</sup> associations between exposure to any PIM and unplanned hospitalisations**

<b>Statistics</b>	<b>Results</b>
Individual participants <sup>b</sup> (number of people in study cohort)	245,436
Number/proportion of participants contributing as index subjects	120,332 (49.0%)
Number of index subjects (i.e. unplanned hospitalisation cases)	383,150
Number/proportion of male index subjects	174,453 (45.5%)
Index subjects' mean age at hospital admission (years)	78.4
Number of exposed index subjects (Exp Idx) & proportion	149,289 (39.0%)
Unadjusted odds ratio (Unadj OR) <sup>c</sup>	1.31 (1.28-1.33)
Unadjusted odds ratio p-value	<0.0001
Adjusted odds ratio (OR) <sup>c</sup>	1.18 (1.15-1.21)
Adjusted odds ratio p-value	<0.0001
Attributable fraction: AF = (OR-1) / OR (%) <sup>c</sup>	15.3% (13.3-17.1%)
Estimate of index hospitalisations attributed to PIM (AF x Exp Idx) <sup>c</sup>	22,773 (19,922-25,500)
Number/proportion of exposed index subjects with drug ecode <sup>d</sup>	9,172 (6.1%)

<sup>a</sup> Although the study period covered 1993-2005 in this population, index cases related to unplanned hospital admissions between July 1994 and December 2005 only, in patients aged ≥67 years upon admission; these additional constraints were required to ensure sufficient lead-up time for the control observation period.

<sup>b</sup> Individual participants were those who took medications used to treat similar conditions to those indicated for any of the PIMs included in the study (i.e. medications from the same broad drug classes and corresponding drug-defined domains); these people were considered to be part of the study's population at risk.

<sup>c</sup> 95% confidence interval shown in parentheses.

<sup>d</sup> Exposed index subjects with drug ecode refers to hospitalisations among index subjects who were exposed to a general PIM from the Beers list at the time of admission and for which any ICD external cause code (ecode) related to accidental poisoning or adverse drug effect was recorded on the corresponding inpatient discharge summary. Acceptable codes included those in the ranges E850-E858 and E930-E949 (ICD-9-CM)<sup>158</sup> or X40-X44 and Y40-Y59 (ICD-10-AM).<sup>159</sup>

**Table 6-2 Potentially inappropriate medications (PIMs) in Western Australians aged ≥65 years (1993-2005):<sup>a</sup> associations between exposure to individual PIMs and unplanned hospitalisations**

Domain drug class	PIM	Participants <sup>b</sup>	Index subjects <sup>c</sup>	Index exposure <sup>c</sup>	Unadjusted OR <sup>d</sup>	Adjusted OR <sup>d</sup>	PIM attribution <sup>e</sup>
Antirheumatics	Indomethacin	174,585	307,276	3,675 (1.2%)	1.36 (1.25-1.48)	1.38 (1.25-1.52)	1,008 (27.4%)
	Naproxen			6,741 (2.2%)	1.21 (1.14-1.29)	1.20 (1.12-1.29)	1,138 (16.9%)
	Piroxicam			5,487 (1.8%)	0.97 (0.90-1.03)	1.01 (0.94-1.09)	76 (1.4%)
Analgesics	Dextropropoxyphene	193,196	358,570	211 (0.1%)	1.16 (0.77-1.75)	1.24 (0.78-1.98)	41 (19.6%)
	Meperidine/pethidine			168 (<0.1%)	2.59 (1.46-4.59)	2.37 (1.25-4.50)	97 (57.8%)
Anti-Parkinson drugs	Orphenadrine	10,017	27,545	33 (0.1%)	1.43 (0.60-3.40)	1.14 (0.44-2.96)	4 (12.4%)
Antihistamines (systemic)	Hydroxyzine	25,064	68,355	28 (<0.1%)	1.10 (0.35-3.44)	1.05 (0.25-4.45)	1 (4.3%)
	Cyproheptadine			1,492 (2.2%)	1.08 (0.96-1.23)	1.08 (0.95-1.24)	112 (7.5%)
	Promethazine			886 (1.3%)	1.49 (1.25-1.77)	1.50 (1.24-1.81)	294 (33.2%)
Antipsychotics	Thioridazine	79,914	188,508	1,058 (0.6%)	1.30 (1.09-1.54)	1.35 (1.11-1.63)	273 (25.8%)
Anxiolytics, hypnotics/sedatives	Oxazepam	60,497	146,960	14,988 (10.2%)	1.29 (1.22-1.36)	1.22 (1.15-1.30)	2,743 (18.3%)
	Alprazolam			1,229 (0.8%)	1.23 (1.01-1.49)	1.16 (0.94-1.43)	171 (13.9%)
	Diazepam			10,963 (7.5%)	1.34 (1.27-1.42)	1.26 (1.18-1.34)	2,241 (20.4%)
	Temazepam			24,125 (16.4%)	1.35 (1.29-1.41)	1.27 (1.21-1.34)	5,144 (21.3%)
Antidepressants	Amitriptyline	90,128	215,207	8,922 (4.1%)	1.11 (1.04-1.18)	1.07 (0.99-1.14)	545 (6.1%)
	Doxepin			4,958 (2.3%)	1.03 (0.94-1.12)	1.01 (0.92-1.12)	64 (1.3%)
	Fluoxetine			2,870 (1.3%)	1.08 (0.96-1.22)	1.07 (0.93-1.22)	180 (6.3%)
Psychostimulants	Dexamphetamine	195	390	56 (14.4%)	1.62 (0.74-3.52)	1.27 (0.49-3.28)	12 (20.9%)
Cardiac rhythm regulators	Disopyramide	39,596	128,241	168 (0.1%)	1.00 (0.63-1.59)	1.24 (0.77-1.99)	32 (19.2%)
	Digoxin			34,122 (26.6%)	1.12 (1.08-1.17)	1.07 (1.03-1.11)	2,143 (6.3%)
	Amiodarone			11,632 (9.1%)	1.28 (1.19-1.37)	1.21 (1.12-1.30)	2,003 (17.2%)
Hypertension drugs	Methyldopa	180,539	335,259	2,038 (0.6%)	1.08 (0.94-1.24)	1.13 (0.97-1.32)	239 (11.7%)
	Nifedipine			11,699 (3.5%)	0.83 (0.78-0.88)	0.89 (0.83-0.95)	-1,431 (-12.2%)
	Clonidine			261 (0.1%)	1.27 (0.91-1.78)	1.06 (0.74-1.53)	15 (5.9%)
High ceiling diuretics	Ethacrynic acid	74,222	227,139	227 (0.1%)	1.79 (1.16-2.75)	1.53 (0.94-2.51)	79 (34.8%)
Antithrombotics	Diovidamol	90,124	212,187	3,548 (1.7%)	1.10 (0.98-1.23)	1.01 (0.89-1.15)	35 (1.0%)
	Ticlopidine			109 (0.1%)	1.49 (0.75-2.97)	1.50 (0.69-3.25)	36 (33.3%)
Diabetes drugs	Chlorpropamide	37,032	83,666	68 (0.1%)	0.62 (0.33-1.15)	0.76 (0.39-1.45)	-22 (-32.3%)
Iron preparations	Ferrous sulphate	35,918	117,120	11,259 (9.6%)	1.21 (1.15-1.28)	1.19 (1.12-1.25)	1,758 (15.6%)
Peptic ulcer/reflux drugs	Cimetidine	132,452	284,092	2,989 (1.1%)	1.02 (0.93-1.13)	1.09 (0.98-1.22)	252 (8.4%)
Laxatives	Bisacodyl	53,653	164,718	4,505 (2.7%)	1.32 (1.22-1.43)	1.15 (1.04-1.26)	574 (12.7%)
Bowel disorder drugs/belladonna & derivatives	Belladonna alkaloids	5,791	18,195	506 (2.8%)	1.21 (0.98-1.49)	1.22 (0.98-1.53)	92 (18.2%)
	Propantheline			91 (0.5%)	1.17 (0.73-1.88)	1.38 (0.81-2.35)	25 (27.6%)
Urinary antispasmodics	Oxybutynin	9,798	28,127	3,497 (12.4%)	1.22 (1.11-1.35)	1.16 (1.04-1.30)	493 (14.1%)
Urinary tract antibacterials	Nitrofurantoin	173,341	331,509	1,980 (0.6%)	1.52 (1.34-1.73)	1.50 (1.30-1.73)	658 (33.2%)
Oestrogen-only medication	Ethinylloestradiol	33,242	53,332	69 (0.1%)	1.35 (0.78-2.33)	1.50 (0.85-2.64)	23 (33.3%)
	Oestradiol			1,889 (3.5%)	0.91 (0.80-1.04)	0.94 (0.81-1.08)	-131 (-7.0%)
	Oestrone			2,954 (5.5%)	1.01 (0.91-1.13)	1.07 (0.96-1.20)	196 (6.6%)
	Oestrogens-conjugated			2,429 (4.6%)	0.85 (0.78-0.94)	0.89 (0.80-0.98)	-313 (-12.9%)
	Fosfestrol sodium			147 (0.3%)	1.76 (1.01-3.07)	1.41 (0.74-2.70)	43 (29.0%)

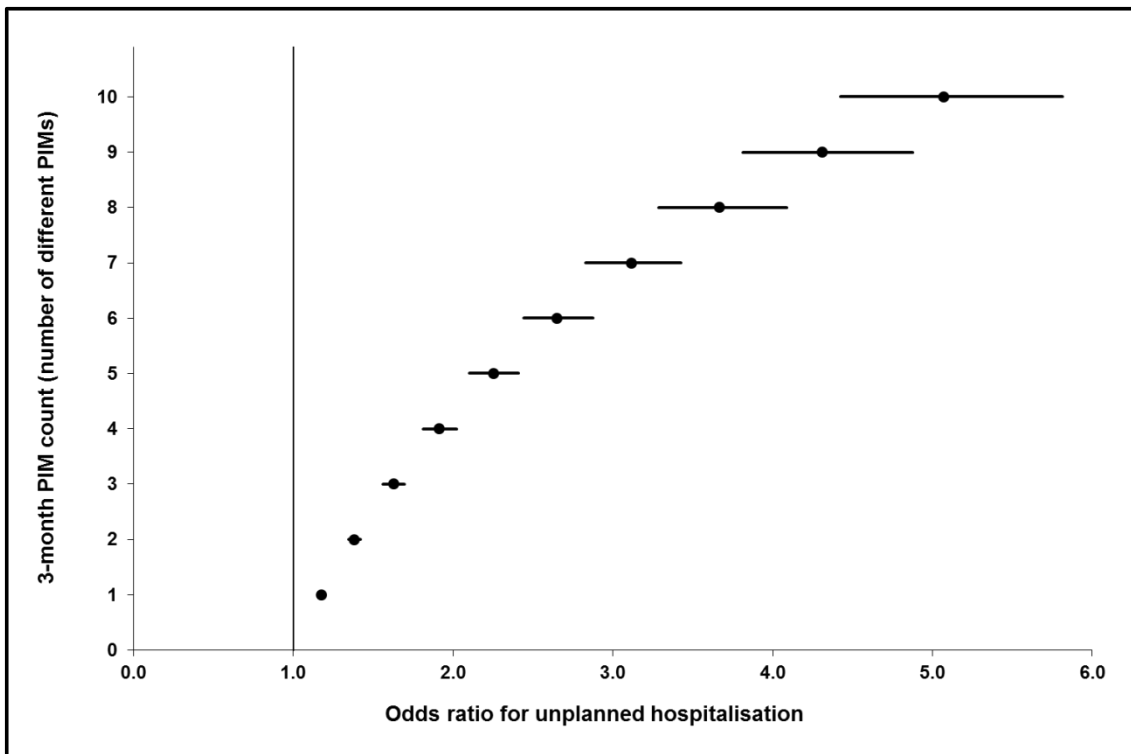
<sup>a</sup> Although the study period covered 1993-2005 in this population, index cases related to unplanned hospital admissions between July 1994 and December 2005 only, in patients aged ≥67 years upon admission; these additional constraints were required to ensure sufficient lead-up time for the control observation period.

<sup>b</sup> In each sub-study, participants were those who took medications from the domain drug class (i.e. drugs used to treat similar conditions to those indicated for PIMs of interest).

<sup>c</sup> 'Index subjects' refers to unplanned hospitalisation cases, each participant potentially contributing multiple times as an index subject; 'index exposure' gives count/proportion of index subjects exposed to PIM at time of admission.

<sup>d</sup> Odds ratios (OR), both unadjusted and adjusted for potential confounding factors, are presented with 95% confidence intervals.

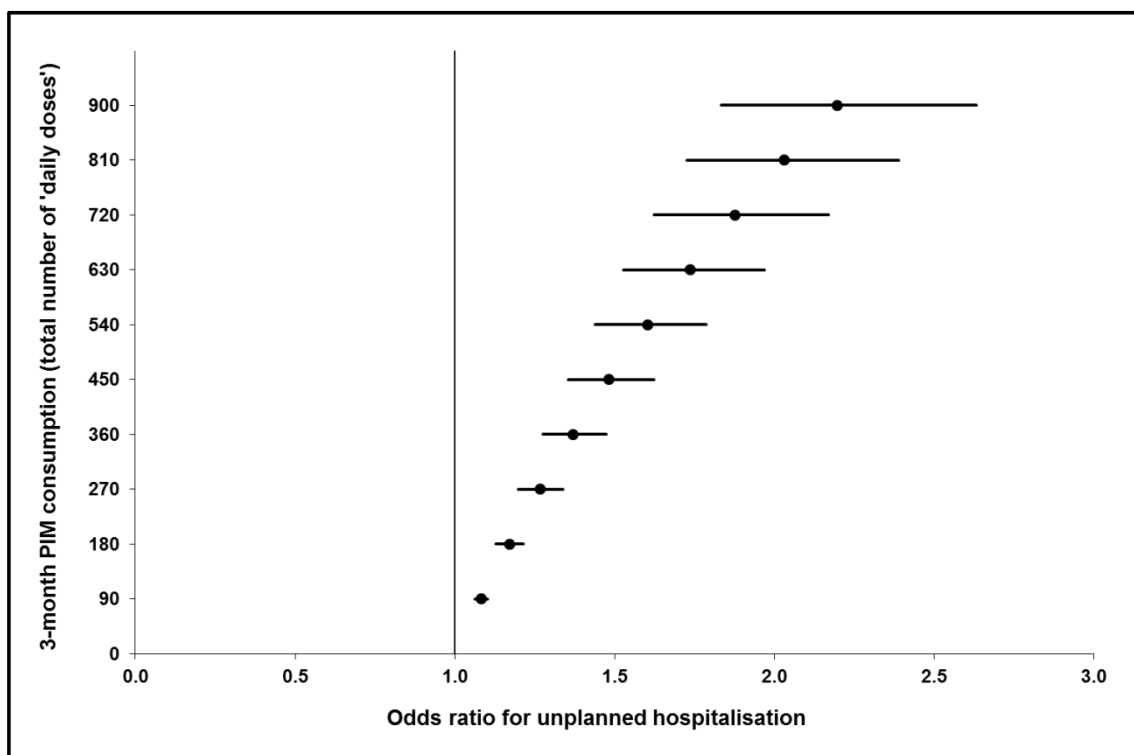
<sup>e</sup> 'PIM attribution' provides an estimate of the count/proportion of hospitalisations attributed to PIM in exposed index subjects; proportion = attributable fraction (AF) = (OR-1)/OR and count = AF x no. exposed index subjects.



**Figure 6-1 Potentially inappropriate medications (PIMs) in Western Australians aged  $\geq 65$  years (1993-2005):<sup>a</sup> associations between PIM exposure and unplanned hospitalisations based on number of different PIMs taken over three months<sup>b</sup> (adjusted odds ratios and 95% confidence intervals)**

<sup>a</sup> Although the study period covered 1993-2005 in this population, index cases related to unplanned hospital admissions between July 1994 and December 2005 only, in patients aged  $\geq 67$  years upon admission; these additional constraints were required to ensure sufficient lead-up time for the control observation period.

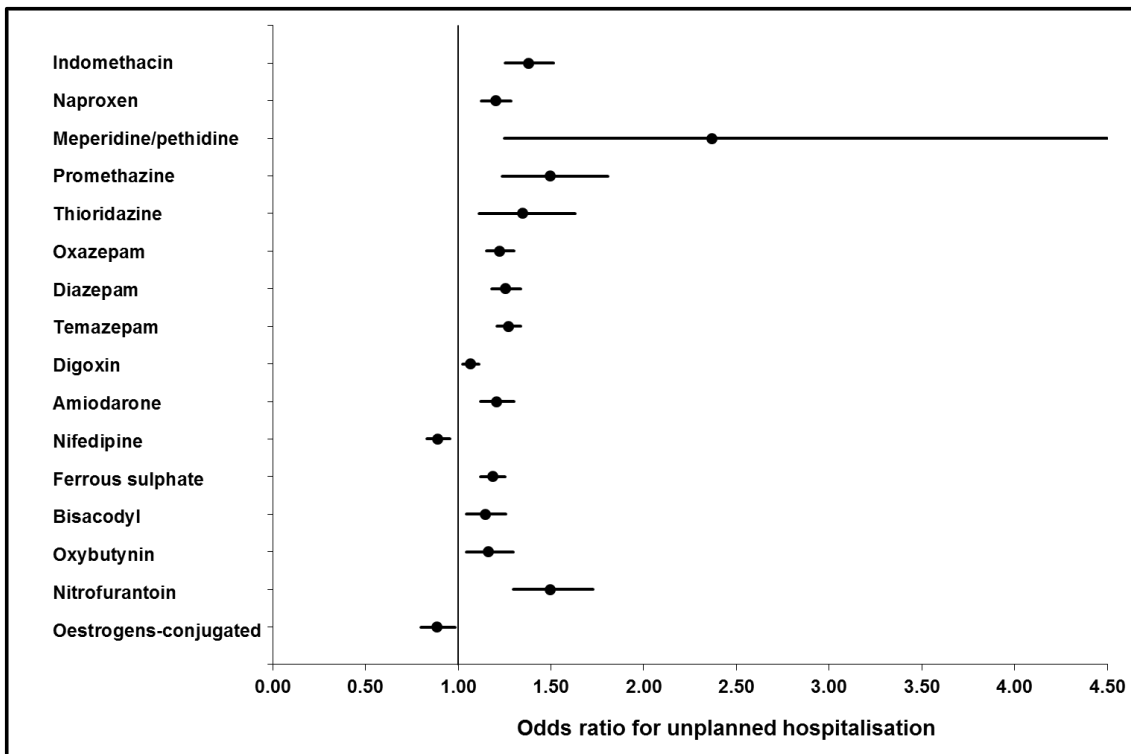
<sup>b</sup> Number of different PIMs taken was determined based on drug consumption during the three-month period preceding the case and control times (including the case/control dates).



**Figure 6-2 Potentially inappropriate medications (PIMs) in Western Australians aged  $\geq 65$  years (1993-2005):<sup>a</sup> associations between PIM exposure and unplanned hospitalisations based on total number of PIM 'daily doses' taken over three months<sup>b</sup> (adjusted odds ratios and 95% confidence intervals)**

<sup>a</sup> Although the study period covered 1993-2005 in this population, index cases related to unplanned hospital admissions between July 1994 and December 2005 only, in patients aged  $\geq 67$  years upon admission; these additional constraints were required to ensure sufficient lead-up time for the control observation period.

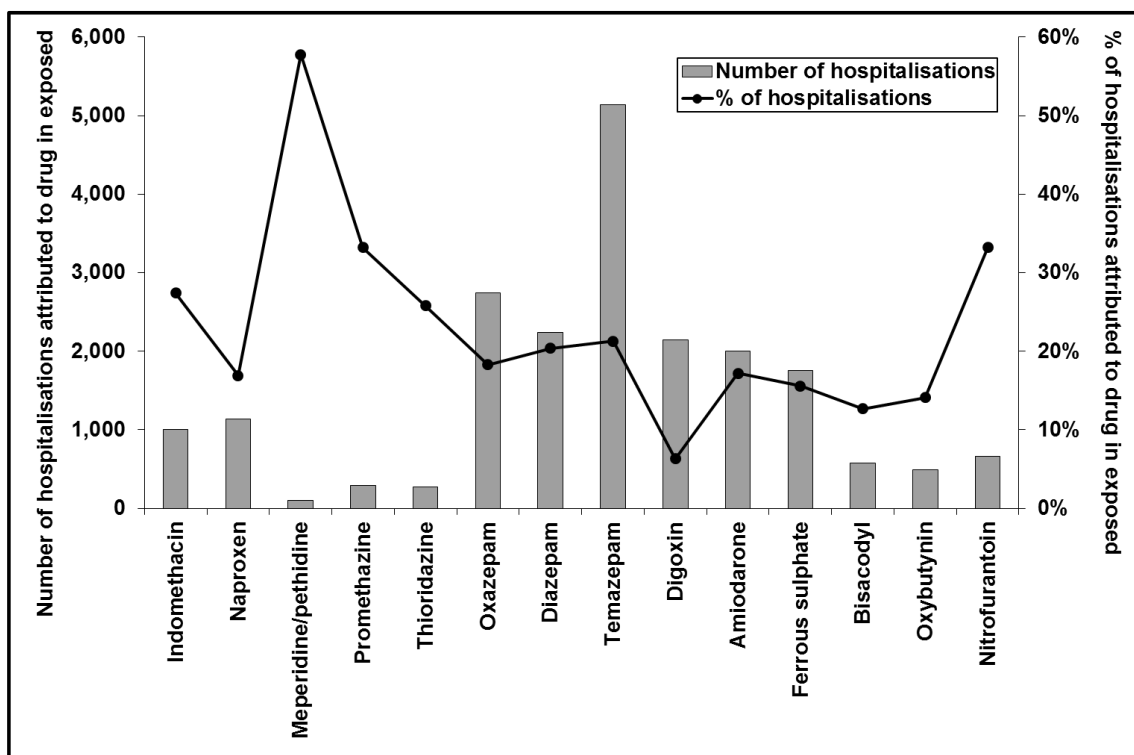
<sup>b</sup> Total number of PIM 'daily doses' taken was determined based on drug consumption during the three-month period preceding the case and control times (including the case/control dates) Each 'daily dose' represented exposure to one medication for one day, where the quantity taken was the average dose recommended per day, based on drug form, route and strength.



**Figure 6-3 Potentially inappropriate medications (PIMs) in Western Australians aged  $\geq 65$  years (1993-2005):<sup>a</sup> associations between exposure to specific PIMs<sup>b</sup> and unplanned hospitalisations (adjusted odds ratios and 95% confidence intervals)**

<sup>a</sup> Although the study period covered 1993-2005 in this population, index cases related to unplanned hospital admissions between July 1994 and December 2005 only, in patients aged  $\geq 67$  years upon admission; these additional constraints were required to ensure sufficient lead-up time for the control observation period.

<sup>b</sup> PIM exposure was determined based on exposure status at case and control times.



**Figure 6-4 Potentially inappropriate medications (PIMs) in Western Australians aged  $\geq 65$  years (1993-2005):<sup>a</sup> estimates of number<sup>c</sup> and proportion<sup>b</sup> of unplanned hospitalisations attributable to PIM exposure for specified PIMs**

<sup>a</sup> Although the study period covered 1993-2005 in this population, index cases related to unplanned hospital admissions between July 1994 and December 2005 only, in patients aged  $\geq 67$  years upon admission; these additional constraints were required to ensure sufficient lead-up time for the control observation period.

<sup>b</sup> The proportion of hospitalisations considered to be attributable to the specified PIM was based on the attributable fraction (AF) derived from the primary adjusted odds ratio (OR) for the corresponding regression analysis, where  $AF = (OR - 1) / OR$ .

<sup>c</sup> The number of hospitalisations considered to be attributable to the specified PIM was calculated as the product of the attributable fraction (AF) multiplied by the number of exposed index subjects (i.e. patients exposed to the PIM at the time of hospital admission).





# CHAPTER 7 POTENTIALLY INAPPROPRIATE MEDICATIONS AND UNPLANNED HOSPITALISATIONS - FOCUS ON GENERAL PRACTITIONER CARE

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The research component presented in chapter 6 generated overall results for all elderly Western Australians included in the study cohort who were potential candidates for receiving PIMs. However, it remained unclear whether the apparent risk of unplanned hospitalisation associated with PIM exposure applied equally to various sub-groups within this population. One could perhaps have compared study results between men and women, or in different age groups within the study population. Instead, attention was shifted towards factors that could not have been determined without the inclusion of records from the Australian Government in the study's linked data sets.

One such factor was the level of ongoing GP care, which was derived using Medicare claims data. By examining the pattern of patients' GP visits, it was possible to create a statistical indicator to represent ongoing care, essentially based on the periodicity of GP visits. Patients could then be allocated to separate groups according to their apparent level of ongoing care, and the analysis repeated for each group independently.

This chapter revolves around this research component, which compared the estimated risk of unplanned hospitalisation associated with PIM exposure in patients with different levels of ongoing GP care. The contents of this chapter were included in the following manuscript:

- Price SD, Holman CDJ, Sanfilippo FM, Emery JD. Does ongoing GP care in elderly patients help reduce the risk of unplanned hospitalisation related to Beers potentially inappropriate medications? Under review; submitted to *Geriatrics and Gerontology International* on 06/04/2014.

Supplementary statistics related to the study component presented in this chapter are provided in Appendix I.4.



## **Does ongoing GP care in elderly patients help reduce the risk of unplanned hospitalisation related to Beers potentially inappropriate medications?**

### **ABSTRACT**

**Objectives:** To compare estimates of unplanned hospitalisations associated with exposure to Beers potentially inappropriate medications (PIMs) in elderly people receiving different levels of ongoing general practitioner (GP) care.

**Design:** Enhanced case-time-control design applied to pharmaceutical claims and other linked health data (1993-2005).

**Setting:** Western Australian population.

**Participants:** 245,436 individuals aged  $\geq 65$  years with  $\geq 1$  claim for a medication from a PIM-related drug class.

**Main outcome measures:** Odds ratios for unplanned hospitalisation, from which attributable fractions, numbers, proportions and rates of admissions related to PIM exposure were derived.

**Results:** Overall, 383,150 unplanned hospitalisations ('index subjects') were identified. PIM exposure was associated with a similar relative risk of unplanned hospitalisation in elderly people receiving the lowest and highest levels of ongoing GP care, but with a decreasing risk in the three highest tiers; adjusted ORs (95% CIs; attributable fractions) were 1.15 (1.09-1.21; 12.9%), 1.36 (1.27-1.46; 26.6%), 1.20 (1.15-1.26; 16.9%) and 1.13 (1.09-1.17; 11.4%), for groups from the lowest to highest levels. However, those with higher GP coverage had higher rates of PIM-related hospitalisation. Similar patterns were demonstrated for commonly used high-risk PIMs (temazepam, diazepam, oxazepam, naproxen and digoxin).

**Conclusions:** Increased requirement for ongoing GP contact in less healthy elderly people appears to help minimise their risk of unplanned hospitalisation due to PIM-related harm. GPs should continue to avoid Beers medications in older patients where possible, given their greater predisposition to medication exposure (including PIMs) and adverse drug events. Nonetheless, close monitoring of elderly patients who need to use PIMs may be beneficial.

**Keywords:** Pharmacoepidemiology, drugs in the elderly, prescribing, medication - safe use, research - general practice, hospital utilisation

## **7.1 INTRODUCTION**

The susceptibility of older people to adverse drug events has led to the development of lists of 'potentially inappropriate medications' (PIMs) to be avoided in the elderly, such as the Beers Criteria.<sup>15</sup> Numerous studies have examined the prevalence of drugs from the Beers list in elderly populations, while others have concentrated on the association between Beers medications and adverse health outcomes.

However, to our knowledge, no one has compared the risk of PIM-related adverse outcomes in older patients receiving varying levels of ongoing general practitioner (GP) care. Older patients who see their GP very regularly may often do so because of declining health, which is associated with increased medication use (including PIMs) and susceptibility to hospitalisation. Conversely, extensive GP follow-up might also protect these patients from serious harm due to PIM exposure, through close monitoring for adverse drug effects.<sup>4</sup>

In this large linked-data study (1993-2005), we compared estimates of unplanned hospitalisations associated with exposure to Beers medications in Western Australian (WA) residents aged  $\geq 65$  years receiving different levels of ongoing GP care. We present our results for all PIMs from the general Beers list (combined) and for individual high-risk PIMs most commonly used in this population.

## **7.2 METHODS**

### **7.2.1 SELECTION CRITERIA AND DATA PREPARATION**

This study linked Australian Pharmaceutical Benefits Scheme (PBS),<sup>22</sup> Medicare<sup>23</sup> and residential aged care<sup>25</sup> data with inpatient, death and electoral roll records from the WA Data Linkage System<sup>138</sup> through probabilistic linkage. The study protocol was approved by The University of WA's Human Research Ethics Committee.

The study methodology has been described elsewhere.<sup>209,222</sup> To summarise, the cohort consisted of people who were  $\geq 65$  years old by the end of 2004, continuously lived in WA during 1993-2005 (until death) and had  $\geq 1$

pharmaceutical claim during that time. About 80-85% of WA elderly residents were captured annually.

Details for all PBS drug items were assembled into a large reference database, which included 2007 Anatomical Therapeutic Chemical (ATC) codes,<sup>163</sup> average daily doses ascertained from three sources,<sup>165,167,204</sup> and period of drug effect (defined as five times the drug's elimination half-life).<sup>170,171</sup> This information was merged to the PBS master file for 1993-2005.

Each item from the 2003 Beers list<sup>15</sup> was then defined according to the 2007 ATC classification,<sup>163</sup> and the ATC code list for 'general' PIMs (i.e. excluding disease-specific criteria, but including PIMs with dosage and duration constraints) applied to the PBS data set. Forty-three individual PIMs were identified through this process and grouped into 20 broad drug classes (i.e. drug domains), each class consisting of medications used to treat similar conditions to those treated by related PIMs.

### **7.2.2 CASE-TIME-CONTROL DESIGN**

Associations between PIM exposure and unplanned hospitalisations were expressed as odds ratios (ORs) obtained from a case-time-control design.<sup>26,27</sup> Hence, identified index subjects acted both as cases and as their own historical controls, while background time trends in exposure were adjusted using matched reference subjects drawn from the same drug-defined patient domain as the index subjects.

Index subjects were patients within the drug domain who had experienced an unplanned (i.e. emergency) hospital admission between 1 July 1994 and 31 December 2005 whilst aged  $\geq 67$  years, thus ensuring sufficient lead-up time for the control observation period. Individuals could be included multiple times as index subjects, but patients with  $>50$  index admissions ( $\leq 0.1\%$ ) were excluded. Each index subject was matched by gender, overall 'GP coverage' category and year of birth to a randomly selected reference subject from the drug-defined domain. To determine the level of GP coverage, each GP visit identified in the Medicare data set was allocated a 'coverage' period of 61 days (overlapping periods merged together), from which overall and annual coverage proportions were calculated. Derived quartiles helped define GP coverage categories, which provided a general indicator of ongoing GP monitoring for each patient.

For each index and reference subject, 'case-time' and 'control-time' records were created, where the case time was the index subject's admission date and the control time usually 365 days prior. If the preferred times were within a hospital stay, the admission date of the overlapping hospitalisation was used instead. These records included nursing home status at the specified time; hospital days, overall Charlson comorbidity index<sup>160</sup> and GP coverage percentage, all for the previous year; and a drug consumption profile for the preceding 90 days (plus the case or control date), which included the number of broad medication categories involved, the overall number of daily doses consumed (for any drug) and a daily dose count for each broad drug category. Additionally, PBS claims were checked to ascertain the PIM exposure status, which was set to 'exposed' if the period bound by the supply date and exposure effect end date for a relevant prescription overlapped with the case or control time. The end date was calculated by adding the number of drug consumption days associated with the script to the supply date (-1) plus the period of drug effect (up to 7 days) and a 7-day latency period.

For each PIM sub-study, conditional logistic regression models with robust analysis of variance (COVS option) were applied using the SAS 9.2 PHREG procedure. The OR of primary interest was derived from the coefficient of the cross-product between exposure and the binary index/reference indicator,<sup>26</sup> adjusted models controlling for all health and drug consumption indicators mentioned earlier. This analysis was performed separately for each GP coverage group, and repeated for all PIMs combined and for individual PIMs.

### **7.2.3 ESTIMATION OF PIM-RELATED UNPLANNED HOSPITALISATIONS**

Using the OR derived from the interaction term in the adjusted models described above, we calculated the attributable fraction (AF) of unplanned hospitalisations associated with PIMs of interest within the exposed, where  $AF=(OR-1)/OR$ . An estimate of the number of unplanned hospitalisations attributed to PIMs was then derived as  $AF \times$  number of exposed index subjects.<sup>216</sup>

To further compare the unplanned hospitalisation outcomes in different GP coverage groups, crude rates were estimated. This was achieved by first generating the study cohort's person-year follow-up time for each GP coverage group, including those with a predominant age  $\geq 67$  years for each calendar year

and restricting the time period to July 1994-December 2005, as per the index admissions. Rates were then calculated (per 100,000 person-years) using counts of unplanned hospitalisations attributed to PIMs in exposed patients; those not attributed to PIMs in the exposed; and those occurring in unexposed patients.

### **7.3 RESULTS**

From an initial cohort of 251,305 participants, 245,436 (97.7%) had either taken a PIM from the 'general' Beers list during 1993-2005 or a drug used to treat conditions similar to the indications for prescribing these PIMs. They comprised the patient domain for this study. Of these, 187,616 (76.4%) had actually been prescribed a PIM.

Overall, 383,150 unplanned admissions ('index subjects') were included, which involved 120,332 patients. Although the number of participants in each GP coverage group loosely reflected a quartile distribution, those in the highest level of GP care were clearly over-represented in terms of number of unplanned admissions, reflecting their likely poorer health. The proportion of male index subjects decreased considerably with increasing GP coverage (from 62.4% to 35.8%), although the mean age was around the overall average of 78 years in all groups. The proportion of subjects exposed to a PIM at the time of admission was similar for the lowest and third tier of GP coverage (~34%), but increased from 28.3% to 48.6% in the three highest tiers (Table 7-1).

Exposure to a PIM was associated with a significant increase in unplanned hospitalisations in all groups. Furthermore, a decreasing OR trend was apparent in the three highest tiers of GP coverage, both before and after adjustment for patients' health profile and medication intake over time. For the lowest GP coverage tier, the adjusted OR was similar to that of the highest tier (Table 7-1/Figure 7-1).

Corresponding estimates of the proportion of unplanned hospitalisations attributed to PIMs in exposed index subjects followed a similar pattern to the one described for ORs. However, despite their lower relative risk, those in the upper tier of GP coverage were associated with the highest estimates of unplanned hospitalisations attributable to PIM exposure.

For the individual high-risk PIMs most commonly used in our population (e.g. temazepam, diazepam, oxazepam, naproxen and digoxin), our results (Table 7-2) mirrored those presented for overall PIM exposure.

In terms of unplanned hospitalisation rates (Figure 7-2), the lowest tier of GP coverage had the lowest number and proportion of unplanned hospitalisations attributed to PIMs annually. For the other three groups, the annual count of PIM-related admissions rose, but the proportion fell with increasing levels of GP coverage.

## **7.4 DISCUSSION**

This study applied a case-time-control design to linked health data from a large WA elderly population to compare the association between Beers medications and unplanned hospitalisations in elderly people with different levels of ongoing GP care. No other study has specifically concentrated on differences between groups with varying patterns of GP contact in relation to PIMs and adverse health outcomes. A strength of our study is its large sample sizes, which produced narrow confidence intervals even for individual GP coverage groups. Furthermore, our study applied three levels of defence against confounding: a crossover configuration to control for fixed confounders; matched reference subjects to control for unmeasured time-variant confounders; and regression modelling to adjust for measured patient-specific time-variant confounders (e.g. general health and drug consumption indicators).

### **7.4.1 MAJOR FINDINGS**

PIM exposure was associated with an increased risk of unplanned hospitalisations at all levels of GP coverage. Our adjusted ORs, which estimated a 13-36% increase in unplanned hospitalisations in elderly people exposed to Beers' PIMs (depending upon the GP coverage group), were similar to or slightly lower than those obtained in other comparable studies in a community setting (OR range 1.27-1.78).<sup>106,116-118</sup> From these ORs, we deduced that 11.4-26.6% of unplanned hospitalisations were attributed to PIMs in exposed subjects.

The relative risk of unplanned admission associated with PIM exposure decreased in elderly people with increasingly higher levels of GP coverage, suggesting that better ongoing GP monitoring may have a protective effect



against PIM-related hospitalisations. However, due to the rising levels of PIM use and unplanned hospitalisation in older patients receiving increasing levels of ongoing GP care (likely due to declining health), the absolute burden of hospitalisations attributed to PIMs increased with each higher tier of GP coverage.

This pattern did not apply to elderly people with the lowest level of ongoing GP care though. People in this group had a higher than expected level of PIM use and unplanned hospitalisation, but a low relative risk of hospitalisation associated with PIM exposure. We suspect this GP coverage group may have consisted of a heterogeneous elderly population, one possibly involving two distinct sub-groups. One sub-group likely included fairly healthy elderly, with low exposure to medication overall, few hospital admissions, and a low need for frequent GP contact. Because of their good physiological condition, they were probably less prone to potential harm from PIMs. Consequently, they would get minimal benefit from the protective effect of frequent GP visits against PIM-related hospitalisations, even though physicians might be less cautious in prescribing PIMs to them.

The other sub-group would have been less healthy, with high levels of medication use and unplanned hospitalisations, which would explain the inflated rate of unplanned hospitalisation for the group as a whole. Despite benefitting from ongoing GP monitoring, this second sub-group may have experienced fewer GP visits due to various health care access issues. Elderly people from this sub-group were likely at high risk of PIM-related hospitalisation (for those taking PIMs), this fact being masked in our group-level results by the healthy sub-group's much lower relative risk. Alternatively, some older people from this sub-group may have paid regular visits to a specialist physician rather than a GP (thus benefitting from ongoing medical practitioner monitoring despite their allocation to a low-level GP coverage category), which may also partially account for the low relative risk of PIM-related hospitalisation in the lowest GP coverage tier.

These explanations are in line with our other results, which support a decline in the relative risk of unplanned hospitalisation with increasing GP coverage in relation to PIM exposure. Unfortunately, data and resource limitations have prevented us from exploring these theories any further.

Our study also suggests that GP coverage patterns related to unplanned hospitalisations and overall PIM exposure likely apply to individual PIMs as well. This was apparent for several commonly used high-risk PIMs, including various benzodiazepines, naproxen and digoxin. Admittedly, OR confidence intervals between adjacent GP coverage groups overlapped to a greater degree for individual PIMs. Thus, additional research is required to confirm these results.

#### **7.4.2 LIMITATIONS**

Despite the rigorous measures applied in this study to control for confounding effects, we are mindful of the potential for time-trend bias, which has been associated with the case-time-control design in some circumstances.<sup>26,27,153</sup> Although sensitivity and other comparative analyses applied in our earlier work suggest that our approach is fairly robust,<sup>209</sup> some residual confounding is likely reflected in our results, given the limitations of our administrative data.

Difficulties in the ascertainment of drug exposure at the specific times of interest were also of concern, as derivation of exposure status from average recommended daily doses could not have been completely accurate for every subject. Assuming non-differential measurement error at both case and control time for each subject, our estimated ORs may possibly have been attenuated slightly (i.e. pushed towards null) as a result,<sup>208</sup> perhaps counter-balancing some of the potential OR inflation stemming from unadjusted time-trend bias.

Furthermore, our PBS data sets did have coverage limitations, excluding drugs prescribed in public hospitals, over-the-counter medications, and prescriptions for which a claim could not be made.<sup>223</sup> However, given the very low co-payment thresholds in most elderly people, these coverage issues unlikely had much impact on study results.

We also acknowledge that our grouping of elderly people according to level of ongoing GP care were not perfect. As already mentioned, it appears people with the lowest level of GP coverage may have been a hybrid group. Furthermore, we used patients' overall average GP coverage percentages for grouping and matching purposes. Although we did control further in the analysis for GP coverage in the year immediately preceding the case and control times, our results may have been affected slightly by potential misclassification in the allocation of subjects to the appropriate GP coverage group.

### **7.4.3 CONCLUSIONS**

Our study provides further evidence in support of an elevated risk of serious harm resulting from exposure to Beers medications in older people, suggesting that this risk is evident in most elderly, with some variations depending upon their level of ongoing GP care. Older people may choose to visit their GP more regularly because of their declining health but, thankfully, persistent continuity of care in elderly patients who need it most appears to help minimise their risk of greater medication-related harm.

Physicians should continue to avoid Beers medications in the elderly where possible, especially in less healthy older patients, due to the latter's greater predisposition to medication exposure (including PIMs) and adverse drug events. However, in situations where PIM use is judged to be clinically appropriate, close monitoring in older patients should prove beneficial.

### **ACKNOWLEDGMENTS**

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We also thank the Western Australian Department of Health (DoH) and Australian Department of Health and Ageing for supplying the project data, and the Data Linkage Branch (DoH) for undertaking the record linkage.

**Competing interests:** No relevant disclosures.

**Table 7-1 Potentially inappropriate medications (PIMs) in Western Australians aged ≥65 years (1993-2005):<sup>a</sup> association between exposure to any PIM and unplanned hospitalisations for groups with varying levels of general practitioner coverage**

Statistics	Average annual general practitioner coverage <sup>d</sup> (1993-2005)				
	0-6 months	>6-8 months	>8-10 months	>10 months	Overall
Domain participants <sup>b</sup> (number of people in PIM study cohort)	67,553	50,122	59,645	68,116	245,436
Number/proportion of participants contributing as index subjects	30,140 (44.6%)	20,051 (40.0%)	29,576 (49.6%)	40,565 (59.6%)	120,332 (49.0%)
Number of index subjects (i.e. unplanned admission cases)	92,397	52,324	87,070	151,359	383,150
Number/proportion of male index subjects	57,662 (62.4%)	25,189 (48.1%)	37,454 (43.0%)	54,148 (35.8%)	174,453 (45.5%)
Index subjects' mean age at admission (years)	78.7	77.6	77.9	78.6	78.4
Number of index subjects exposed to PIMs (Exp Idx) & proportion	31,019 (33.6%)	14,789 (28.3%)	29,939 (34.4%)	73,542 (48.6%)	149,289 (39.0%)
Unadjusted odds ratio (Unadj OR) <sup>c</sup>	1.30 (1.24-1.36)	1.59 (1.50-1.69)	1.35 (1.29-1.41)	1.21 (1.18-1.25)	1.31 (1.28-1.33)
Unadjusted odds ratio p-value	<0.001	<0.001	<0.001	<0.001	<0.001
Adjusted odds ratio (OR) <sup>c</sup>	1.15 (1.09-1.21)	1.36 (1.27-1.46)	1.20 (1.15-1.26)	1.13 (1.09-1.17)	1.18 (1.15-1.21)
Adjusted odds ratio p-value	<0.001	<0.001	<0.001	<0.001	<0.001
Attributable fraction: AF = (OR-1) / OR (%) <sup>c</sup>	12.9% (8.3-17.2%)	26.6% (21.4-31.5%)	16.9% (13.0-20.8%)	11.4% (8.6-14.2%)	15.3% (13.3-17.1%)
Estimate of index admissions attributed to PIM (AF x Exp Idx) <sup>c</sup>	3,998 (2,587-5,320)	3,938 (3,172-4,653)	5,072 (3,883-6,215)	8,406 (6,317-10,414)	22,773 (19,922-25,500)

<sup>a</sup> Although the study period covered 1993-2005 in this population, index cases related to unplanned hospital admissions between July 1994 and December 2005 only, in patients aged ≥67 years upon admission; these additional constraints were required to ensure sufficient lead-up time for the control observation period.

<sup>b</sup> Domain participants were those who took medications used to treat similar conditions to those indicated for any of the PIMs included in the study (i.e. medications from the same broad drug classes); these people were considered to be part of the study's population at risk.

<sup>c</sup> 95% confidence interval shown in parentheses.

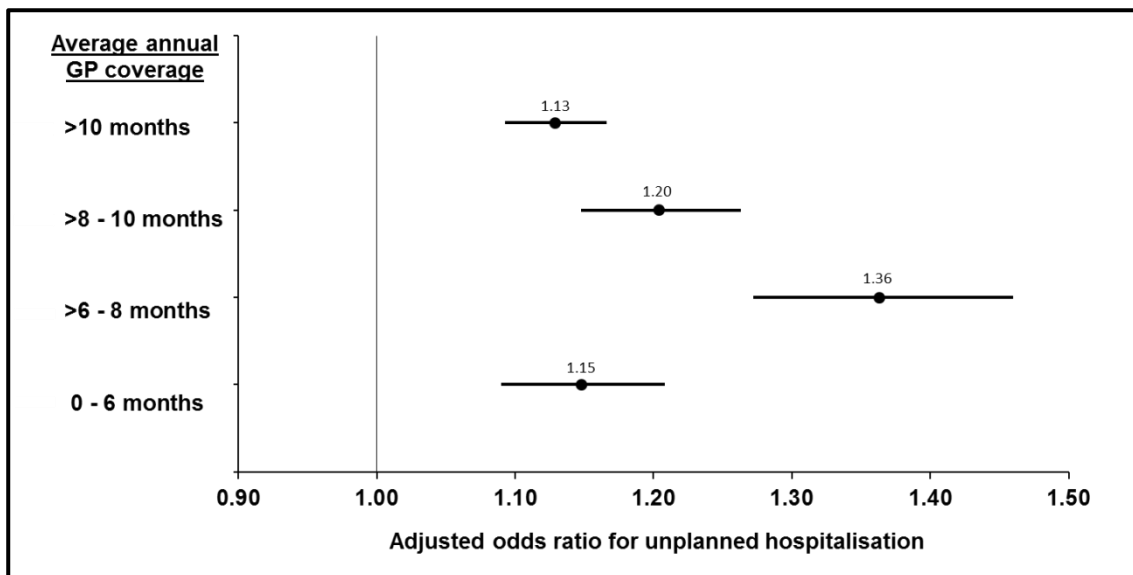
<sup>d</sup> Average annual general practitioner (GP) coverage was obtained from patients' proportion of GP coverage over 1993-2005, where each GP visit was allocated a 61-day coverage period (adjacent and overlapping periods being merged together). GP coverage categories were then derived from approximate quartiles, providing a general indicator for the level of ongoing GP monitoring.

**Table 7-2 Potentially inappropriate medications (PIMs) in Western Australians aged  $\geq 65$  years (1993-2005):<sup>a</sup> association between exposure to individual PIMs and unplanned hospitalisations (adjusted odds ratios and 95% confidence intervals) for groups with varying levels of general practitioner coverage**

PIM	Average annual general practitioner coverage <sup>b</sup> (1993-2005)				
	0-6 months	>6-8 months	>8-10 months	>10 months	Overall
Temazepam	1.27 (1.13-1.42)	1.44 (1.18-1.77)	1.39 (1.23-1.58)	1.23 (1.15-1.31)	1.27 (1.21-1.34)
Diazepam	1.23 (1.07-1.42)	1.67 (1.32-2.10)	1.51 (1.30-1.75)	1.15 (1.06-1.25)	1.26 (1.18-1.34)
Oxazepam	1.24 (1.08-1.43)	1.30 (1.02-1.65)	1.30 (1.12-1.51)	1.18 (1.09-1.28)	1.22 (1.15-1.30)
Naproxen	1.15 (0.99-1.33)	1.37 (1.11-1.68)	1.29 (1.11-1.48)	1.15 (1.04-1.27)	1.20 (1.12-1.29)
Digoxin	1.10 (1.00-1.21)	1.14 (0.99-1.30)	1.13 (1.03-1.25)	1.02 (0.97-1.08)	1.07 (1.03-1.11)

<sup>a</sup> Although the study period covered 1993-2005 in this population, index cases related to unplanned hospital admissions between July 1994 and December 2005 only, in patients aged  $\geq 67$  years upon admission; these additional constraints were required to ensure sufficient lead-up time for the control observation period.

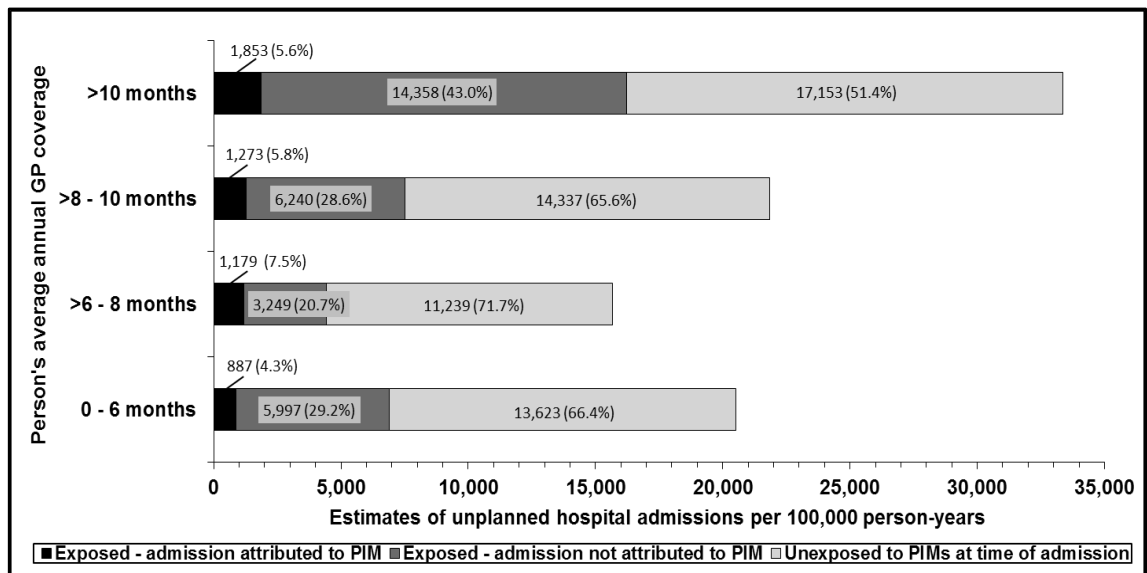
<sup>b</sup> Average annual general practitioner (GP) coverage was obtained from patients' proportion of GP coverage over 1993-2005, where each GP visit was allocated a 61-day coverage period (adjacent and overlapping periods being merged together). GP coverage categories were then derived from approximate quartiles, providing a general indicator for the level of ongoing GP monitoring.



**Figure 7-1 Potentially inappropriate medications (PIMs) in Western Australians aged  $\geq 65$  years (1993-2005):<sup>a</sup> association between PIM exposure and unplanned hospitalisations (adjusted odds ratios and 95% confidence intervals) for groups with varying levels of general practitioner coverage<sup>b</sup>**

<sup>a</sup> Although the study period covered 1993–2005 in this population, index cases related to unplanned hospital admissions between July 1994 and December 2005 only, in patients aged  $\geq 67$  years upon admission; these additional constraints were required to ensure sufficient lead-up time for the control observation period.

<sup>b</sup> Average annual general practitioner (GP) coverage was obtained from patients' proportion of GP coverage over 1993-2005, where each GP visit was allocated a 61-day coverage period (adjacent and overlapping periods being merged together). GP coverage categories were then derived from approximate quartiles, providing a general indicator for the level of ongoing GP monitoring.



**Figure 7-2 Potentially inappropriate medications (PIMs) in Western Australians aged  $\geq 67$  years (July 1994-December 2005):<sup>a</sup> estimates of unplanned hospital admissions per 100,000 person-years for groups with varying levels of general practitioner coverage,<sup>b</sup> broken down by PIM exposure status**

<sup>a</sup> Although the study period covered 1993-2005 in a population aged  $\geq 65$  years, index cases related to unplanned hospital admissions between July 1994 and December 2005 in patients aged  $\geq 67$  years upon admission, to ensure sufficient lead-up time for the control observation period. Consequently, rates were calculated for this time period and age group.

<sup>b</sup> Average annual general practitioner (GP) coverage was obtained from patients' proportion of GP coverage over 1993-2005, where each GP visit was allocated a 61-day coverage period (adjacent and overlapping periods being merged together). GP coverage categories were then derived from approximate quartiles, providing a general indicator for the level of ongoing GP monitoring.





## CHAPTER 8 POTENTIALLY INAPPROPRIATE MEDICATIONS AND UNPLANNED HOSPITALISATIONS - FOCUS ON HIGH-LEVEL AGED CARE

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In parallel with the analysis outlined in chapter 7, the research component presented in this chapter focused on differences in the apparent risk of unplanned hospitalisation associated with PIM exposure between residents of high-level aged care facilities and all other elderly Western Australians. Patients' aged care status was derived from the study's residential aged care records, which were obtained from data sets maintained by the Australian Government, as per the GP care analysis.

Ideally, the research team would have liked to isolate low-level aged care residents as well in these comparisons. Unfortunately, some limitations of the aged care data prevented the correct ascertainment of low-care status in the earlier years of the study. The introduction of additional community care programs during the study period for patients with low-care requirements also created some difficulties. Consequently, only patients receiving high-level residential aged care services were isolated from the rest. Furthermore, due to the low counts of elderly people in high-level aged care facilities in our study cohort, statistical analyses for individual PIMs were not undertaken as part of this research component.

The contents of this chapter were included in the following manuscript:

- Price SD, Holman CDJ, Sanfilippo FM, Emery JD. Are high-care nursing home residents at greater risk of unplanned hospital admission than other elderly patients when exposed to Beers potentially inappropriate medications? Accepted for publication by *Geriatrics and Gerontology International* on 21/10/2013; released online for early view on 03/12/2013. doi: 10.1111/ggi.12200.

Supplementary statistics related to the study component presented in this chapter are provided in Appendix I.5.



## **Are high-care nursing home residents at greater risk of unplanned hospital admission than other elderly patients when exposed to Beers potentially inappropriate medications?**

### **ABSTRACT**

**Aim:** To compare the risk of unplanned hospitalisation in high-care nursing home residents taking Beers potentially inappropriate medications (PIMs) against that of other elderly.

**Methods:** Using an enhanced case-time-control design and conditional logistic regression applied to the pharmaceutical claims and other linked data of 245,436 Western Australians aged  $\geq 65$  years (1993-2005), the study derived odds ratios for unplanned hospitalisation in each group, from which attributable fractions, numbers, proportions and rates of PIM-related admissions were derived.

**Results:** Overall, 383,150 unplanned hospitalisations were identified. PIM exposure was associated with a similar proportional increase in unplanned hospitalisations in high-care nursing home residents as in other older people; adjusted OR 1.21 (95% CI 1.10-1.34; attributable fraction 17.5%) vs. 1.19 (1.16-1.21; 15.7%). However, high-care nursing home residents had much higher estimated rates of hospitalisations attributed to Beers medications than other elderly (3,951 vs. 1,394 per 100,000 person-years). The relative risk of unplanned hospitalisation rose similarly in both groups with increasing numbers of different PIMs taken (OR 5.1 for 10 vs. 0 PIMs), but was affected more markedly by three-month PIM consumption in nursing home residents (OR 4.85 (2.40-9.83) for 900 vs. 0 PIM daily doses) than in other seniors (2.10 (1.73-2.55)).

**Conclusions:** High-care nursing home residents do not appear to have a greater relative risk of unplanned hospitalisation when given PIMs, but do incur a higher absolute burden than other elderly. Physicians should exert caution with Beers medications in all older patients, restricting the number of different PIMs and PIM quantity prescribed whenever possible.

**Keywords:** Aged, hospitalisation, inappropriate prescribing, nursing homes, pharmacoepidemiology

## **8.1 INTRODUCTION**

Older people are generally more susceptible to adverse drug events due to physiological deterioration, polypharmacy and other age-related factors.<sup>4-6</sup> This has led to the development of lists of ‘potentially inappropriate medications’ (PIMs) to be avoided in the elderly, such as the Beers Criteria.<sup>15</sup>

Numerous studies have examined the prevalence of PIMs in elderly populations, while others have concentrated on the association between PIMs and adverse health outcomes. However, little is known on whether nursing home residents are at greater risk of PIM-related adverse events than other elderly people. Due to poor health, nursing home residents may have a greater predisposition to medication exposure (including PIMs) and to serious outcomes such as unplanned hospitalisations. However, close monitoring by aged care staff may help protect nursing home residents from serious PIM-related harm.

Our large population-based study (1993-2005) examined the association between exposure to Beers medications<sup>15</sup> and unplanned hospitalisations in Western Australian (WA) residents aged  $\geq 65$  years. It compared estimates applicable to high-care nursing home residents with those of other WA elderly based on exposure to general PIMs upon hospitalisation (dichotomous measure), number of different PIMs taken, and overall PIM quantity consumed over three months.

## **8.2 METHODS**

### **8.2.1 DATA LINKAGE AND COHORT SELECTION**

This study linked Australian Pharmaceutical Benefits Scheme (PBS),<sup>21,22</sup> Medicare<sup>23,24</sup> and residential aged care<sup>25</sup> data with inpatient, death and electoral roll records from the WA Data Linkage System<sup>138</sup> through probabilistic linkage. The study protocol was approved by The University of Western Australia’s Human Research Ethics Committee.

The cohort was restricted to people aged  $\geq 65$  years by the end of 2004, who continuously resided in WA during 1993-2005 (until death) and had  $\geq 1$  pharmaceutical claim during that time, thus ensuring that study participants had ascertainable drug exposures. Eight percent were subsequently excluded due to problem data (e.g. records post-death, no gender on any record). The resulting cohort captured 80-85% of WA elderly residents.

### **8.2.2 DRUG REFERENCE DATABASE**

Details of all PBS items from available schedules (August 1991-June 2007)<sup>200</sup> were assembled into a reference database, retaining the last published entry for each item. Anatomical Therapeutic Chemical (ATC) codes were reconciled with the 2007 World Health Organization (WHO) ATC drug classification.<sup>201</sup> Since the prescribed dose was not recorded on PBS claims, average prescribed daily doses from the Australian Bettering the Evaluation and Care of Health (BEACH)<sup>165</sup> general practice data, MIMS Australia<sup>167</sup> registered drug information, and 2008 WHO ATC Defined Daily Doses (DDDs)<sup>146</sup> were compared to derive average daily doses for each item, based on drug form, route and strength. Furthermore, each drug's elimination half-life was obtained (predominantly from MIMS),<sup>167</sup> from which the period of drug effect, defined as five times the drug's half-life,<sup>170,171</sup> was estimated.

### **8.2.3 DRUG GROUPS AND DOMAINS**

Each item from the 2003 Beers list<sup>15</sup> was defined according to the 2007 ATC classification.<sup>201</sup> Following integration of patient and drug reference variables with the PBS master data file for 1993-2005, the ATC code list for 'general' PIMs (i.e. excluding disease-specific criteria) was applied to determine which of these PIMs were supplied to WA residents aged  $\geq 65$  years during the study period. This process identified 43 individual PIMs, which were grouped into 20 broad drug classes (i.e. drug domains), each class consisting of medications used to treat similar conditions to those treated by related PIMs.

### **8.2.4 CASE-TIME-CONTROL DESIGN**

The relationship between PIM exposure and unplanned hospitalisations was expressed as an odds ratio (OR) obtained from an enhanced case-time-control design.<sup>26,27</sup> This involved index subjects acting both as cases and as their own historical controls, while background time trends in predisposition to exposure were adjusted using similarly constructed case and control observation windows in a reference group drawn from the same general domain of patients as the index subjects. The patient domain in this instance consisted of everyone in the study cohort who had ever been prescribed a drug from any of the 20 broad medication classes associated with PIMs during 1993-2005.

Index subjects were patients within the drug domain who had experienced an unplanned (i.e. emergency) hospital admission between 1 July 1994 and 31

December 2005 whilst aged  $\geq 67$  years, thus ensuring sufficient lead-up time for the control observation period. Many individuals were included in the analysis as multiple index subjects, although a few ( $\leq 0.1\%$ ) with  $>50$  index admissions were excluded. Two records were created for each index subject, one representing the 'case time' (i.e. the admission date) and the other the 'control time' (usually 365 days prior but, if the patient was in hospital at this preferred control time, the admission date of that earlier hospitalisation was used instead).

Each index subject was matched by gender, aged care status and year of birth to a randomly selected reference subject from the study's domain. The aged care status was a dichotomous variable that identified whether the person was receiving high-level residential aged care in a nursing home at 30 June of the index admission year. If the person was alive at index admission but dead by mid-year, the aged care status from the previous calendar year was used instead. Subjects born prior to 1900 were allocated a birth year of 1900 for matching purposes only. 'Case time' and 'control time' records were created for each reference subject as per the corresponding index subjects, matching the case and control dates as closely as possible.

Once created, the case and control time records for index and reference subjects were populated with variables required to control for potential confounding, including nursing home status at the specific time stated on the record (i.e. case or control time); hospital days, overall Charlson comorbidity index<sup>160</sup> and 'general practitioner (GP) coverage' percentage, all for the previous year; and a drug consumption profile for the preceding 90 days (plus the case or control date), which included the number of broad medication categories involved, the overall number of daily doses consumed (for any drug) and a count of daily doses for each broad drug category. To determine the GP coverage percentage, each GP visit identified in the Medicare data set was allocated a 'coverage' period of 61 days (overlapping periods merged together), from which coverage proportions were calculated for the period of interest. This measure provided a general indicator of patients' ongoing GP monitoring.

Additionally, PBS records were checked to ascertain exposure status at each case and control date. If a prescription was found for a PIM and the time period bound by its supply date and exposure effect end date overlapped with the case

or control time, the PIM exposure status was set to 'exposed'. The end date was calculated by adding the prescription's number of drug consumption days (i.e. script's drug quantity / average daily dose) to the supply date (-1) plus the period of drug effect (up to seven days) and a seven-day latency period. Thus, the exposure status indicated the potential for a hospital admission at the case or control time to have resulted from the effects of PIM exposure.

Once the case and control details were finalised, conditional logistic regression models with robust analysis of variance were applied using the SAS 9.2 PHREG procedure, with the COVS option and stratification based on a unique identifier for each subject. The OR of primary interest was derived from the coefficient of the cross-product between exposure and the binary index/reference indicator.<sup>26</sup> The adjusted model controlled for all health and drug consumption indicators mentioned earlier.

This analysis was performed separately for each aged care group (i.e. high-level nursing home residents versus other elderly). The initial models used a dichotomous variable as the PIM exposure measure, but subsequent analyses substituted this variable with the number of different PIMs and the number of PIM daily doses taken in the three-month period prior to the case or control time to enable the examination of associations related to PIM polypharmacy and dose-response, respectively.

#### **8.2.5 PIM-RELATED UNPLANNED HOSPITALISATIONS**

Using the OR derived from the interaction between PIM exposure and the index/reference indicator, the attributable fraction (AF) of unplanned hospitalisations associated with PIMs within the exposed was calculated, where  $AF = (OR - 1) / OR$ . An estimate of the number of unplanned hospital admissions attributed to PIMs was then derived as  $AF \times \text{count of exposed index subjects}$ .<sup>173,174,216</sup>

To further compare the unplanned hospitalisation profile in the two groups (high-level aged care versus other elderly), crude rates were computed. This was achieved by first generating the study cohort's person-year follow-up time for each group (based on high-level aged care status at 30 June of each calendar year), including those with a predominant age  $\geq 67$  years for each year, and restricting the time period to July 1994-December 2005, as per the index admissions. Rates were then calculated (per 100,000 person-years) using

counts of unplanned admissions attributed to PIMs in exposed patients; those not attributed to PIMs in the exposed; and those occurring in unexposed patients.

### **8.3 RESULTS**

In our population of 251,305 elderly people, 245,436 (97.7%) had either taken a PIM from the 'general' Beers list during 1993-2005 or a drug used to treat conditions similar to the indications for prescribing these PIMs. Of these, 187,616 (76.4%) had actually been prescribed a PIM, and 120,332 (49.0%) had hospital admissions that met the criteria for inclusion as 'index subjects'.

Table 8-1 summarises overall study results for both high-care nursing home residents and other elderly. Overall, 383,150 unplanned admissions ('index subjects') were included, 20,525 (5.4%) of which involved high-care nursing home residents. The proportion of male index subjects was much lower, the mean age higher, and the proportion exposed to a PIM at the time of admission higher in the high-level aged care group than in other WA elderly. For a detailed comparison between the two groups regarding exposure to specific PIMs upon admission, please refer to Table 8-2.

Exposure to a PIM was associated with a significant increase in unplanned hospitalisations in both groups. Unadjusted results suggested a lower relative risk of PIM-related unplanned hospitalisation in the high-care group. However, after adjusting for patients' health profile and medication intake over time, this difference was no longer evident (adjusted OR 1.21 (1.10-1.34) versus 1.19; (1.16-1.21)). Corresponding estimates of the proportion of unplanned hospitalisations attributed to PIMs in exposed index subjects were also similar in both groups (Table 8-1).

The relative risk of unplanned hospitalisation also rose in a similar manner in both groups with increasing counts of different PIMs taken over three months, ORs for both suggesting a risk in those taking 10 different PIMs 5.1 times that of PIM-unexposed counterparts (Figure 8-1). However, high-care nursing home residents seemed affected to a greater extent by increasing PIM quantities than other elderly. For instance, high-level aged care residents taking 900 PIM daily doses over three months had a relative risk of unplanned hospitalisation 4.85



(2.40-9.83) times that of high-care residents unexposed to PIMs, whereas the corresponding OR in other elderly was 2.10 (1.73-2.55) (Figure 8-2).

Finally, nursing home residents receiving high-level care not only had higher overall rates of unplanned hospitalisations and of unplanned hospitalisations while exposed to PIMs than other WA elderly, they also had considerably higher rates of unplanned hospital admissions attributed to PIM exposure (3,951 versus 1,394 per 100,000 person-years) (Figure 8-3).

## **8.4 DISCUSSION**

This study examined the association between PIM exposure and unplanned hospitalisations in a large WA population aged  $\geq 65$  years, comparing high-care nursing home residents with all other elderly people. Data linkage facilitated the establishment of a fairly comprehensive health profile for each individual, permitted extensive cross-validation of demographic details, and allowed the ascertainment of patients' drug exposure status upon admission.

### **8.4.1 MAJOR FINDINGS**

After adjusting for confounding factors (including health and medication profiles), the association between exposure to general Beers medications and unplanned hospitalisations was similar in both the high-care nursing home residents and other WA elderly. Our adjusted ORs for both groups suggested a likely increase in unplanned admissions around 20% in subjects exposed to PIMs. These results were similar to or slightly lower than those obtained in other comparable studies involving older people in nursing home (OR 1.27)<sup>117</sup> and community settings (OR range 1.62-1.78).<sup>106,116,118</sup> From our ORs, we deduced that 17.5% (8.9-25.2%) of unplanned hospitalisations in high-care nursing home residents were attributed to PIMs in exposed subjects, and 15.7% (13.7-17.6%) in other elderly.

Our results also suggested that the likelihood of unplanned hospitalisation increases with the number of different PIMs and overall PIM quantity taken, in both groups of elderly. This is not surprising, given that polypharmacy and high medication intake are linked to an increased risk of adverse drug events.<sup>4-6</sup> In both groups, the risk of unplanned hospitalisation increased five-fold when taking 10 different PIMs compared to none. However, the impact of PIM quantity on unplanned hospitalisations in nursing home residents seemed to be

greater than in other elderly. For example, high-level aged care residents taking the equivalent of ten average daily doses of PIMs every day over three months (~900 daily doses) appeared to have nearly five times the risk of unplanned hospitalisation of PIM-unexposed nursing home residents, whereas a similar comparison in other elderly yielded only a two-fold risk increase. One may speculate that perhaps nursing home residents were particularly sensitive to higher doses of PIMs due to their increased levels of physiological deterioration, which increased their susceptibility to adverse drug effects when taking high doses. More in-depth investigations beyond the scope of our study would be required to gain a better understanding of this apparent difference.

Despite similar overall relative risks of PIM-related unplanned hospitalisations in both groups of elderly, high-care nursing home residents had substantially higher rates of unplanned hospitalisations attributed to PIMs than other older people. This is likely due to their poorer health and thus, greater requirement for medications (including PIMs) and susceptibility to hospitalisation. Our nursing home subjects' much higher rates of unplanned admissions, overall and while exposed to PIMs, support this premise.

Given the much smaller size of the high care group, the expectation that exposure to most individual PIMs would be low, and limitations in resources, we concentrated on associations that were related to overall PIM exposure in this study. However, the PIM exposure statistics from Table 8-2 suggest that further comparative analysis may be warranted for some individual PIMs in future, especially temazepam (sedative), digoxin (cardiac glycoside), and oxazepam (anxiolytic). These PIMs were highly prevalent in our index population, especially in subjects who were high-care nursing home residents.

#### **8.4.2 LIMITATIONS**

Despite an extensive clean-up and cross-validation process, made possible through data linkage, our research was subject to some data quality and availability issues, as per other studies involving administrative health data. In particular, our PBS data had some coverage limitations. It excluded drugs prescribed in public hospitals, over-the-counter medications, and prescriptions for which a pharmaceutical claim could not be made.<sup>223</sup> However, in our elderly population, most of whom would have had very low co-payment requirements, these coverage issues unlikely impacted on study results to any great extent, as

most non-hospital scripts for medications of interest would have been recorded in this age group.

Furthermore, difficulties in the ascertainment of drug exposure at the specific times of interest were of concern, as no information was available on the daily dose specifically prescribed for each dispensed drug. Much attention was devoted to the derivation of exposure status from average recommended daily doses, but this could not have been completely accurate for every subject. Assuming similar levels of exposure misclassification at both case and control times for each subject (i.e. non-differential measurement error), our estimated ORs may possibly have been attenuated slightly (i.e. pushed towards null) as a result.<sup>208</sup>

This OR attenuation may, however, have been counter-balanced to some extent by an opposite effect stemming from residual time trend bias related to the case-time-control design.<sup>26,27,153</sup> To address this problem, we adjusted for each subject's health status and overall drug consumption over time using a number of relevant variables, in addition to the inclusion of matched reference subjects. Our prior work suggests that this approach improves internal validity.<sup>209</sup> Nonetheless, data limitations may have prevented us from fully adjusting for time-dependent confounders.

We also acknowledge that the aged care status criteria used to match index and reference subjects were imperfect. Since this variable changed over time, we used people's status at 30 June of the index admission year for matching purposes. Although we did control further in the analysis for aged care status at the specific case and control times, our results may have been affected slightly by associated misclassification.

#### **8.4.3 CONCLUSIONS**

Our study not only provides further evidence in support of an increased risk of serious harm resulting from exposure to Beers medications in older people, but also refutes the hypothesis that high-level aged care residents have a higher relative risk of unplanned hospitalisation in relation to PIM exposure than other elderly people. However, high-care nursing home residents appear to have a substantially higher rate of unplanned hospitalisations attributed to PIMs than other elderly, likely due to their frailty and predisposition to both medication exposure and hospitalisation. Given an apparent 20% increase in unplanned

hospitalisations among PIM elderly users residing in nursing homes and elsewhere, physicians should continue to exert caution when prescribing Beers medications in all patients aged  $\geq 65$  years, restricting the number of different PIMs and PIM quantity prescribed whenever possible.

### **ACKNOWLEDGMENTS**

We thank the Australian National Health and Medical Research Council for funding the research; the Western Australian Department of Health (DoH) and Australian Department of Health and Ageing for supplying the project data; and the Data Linkage Branch (DoH) for undertaking the record linkage.

**Disclosure statement:** No potential conflicts of interest were disclosed.

**Table 8-1 Potentially inappropriate medications (PIMs) in Western Australians aged  $\geq 65$  years (1993-2005):<sup>a</sup> association between exposure to any PIM and unplanned hospitalisations in high-level aged care residents versus other elderly**

Statistics	High-level aged care status <sup>b</sup>	
	High care	Other
Number of index subjects (i.e. unplanned admission cases)	20,525	362,625
Number/proportion of male index subjects	6,893 (33.6%)	167,560 (46.2%)
Index subjects' mean age at admission (years) <sup>d</sup>	83.5 (83.4-83.6)	78.1 (78.0-78.1)
Number of exposed index subjects (Exp Idx) & proportion <sup>c</sup>	10,336 (52.9%)	138,953 (38.3%)
Unadjusted odds ratio (Unadj OR) <sup>d</sup>	1.19 (1.11-1.28)	1.33 (1.30-1.35)
Unadjusted odds ratio p-value	<0.001	<0.001
Adjusted odds ratio (OR) <sup>d</sup>	1.21 (1.10-1.34)	1.19 (1.16-1.21)
Adjusted odds ratio p-value	<0.001	<0.001
Attributable fraction: AF = (OR-1) / OR (%) <sup>d</sup>	17.5% (8.9-25.2%)	15.7% (13.7-17.6%)
Estimate of index admissions attributed to PIM (AF x Exp Idx) <sup>d</sup>	1,808 (923-2,605)	21,792 (19,063-24,494)

<sup>a</sup> Although the study period covered 1993-2005 in this population, index cases related to unplanned hospital admissions between July 1994 and December 2005 only, in patients aged  $\geq 67$  years upon admission; these additional constraints were required to ensure sufficient lead-up time for the control observation period.

<sup>b</sup> High care subjects were those who were receiving high-level aged care services in a nursing home at 30 June of the index admission year; other subjects included all other elderly (i.e. those receiving low-level hostel or community aged care services and those living in a private home without any aged care support at that time).

<sup>c</sup> Exposed index subjects were those who were taking  $\geq 1$  PIM immediately prior to hospital admission.

<sup>d</sup> 95% confidence interval shown in parentheses.

**Table 8-2 Potentially inappropriate medications (PIMs) in Western Australians aged  $\geq 65$  years (1993-2005):<sup>a</sup> number and proportion of index subjects exposed to individual PIMs<sup>b</sup> immediately prior to hospital admission by high-level residential aged care status**

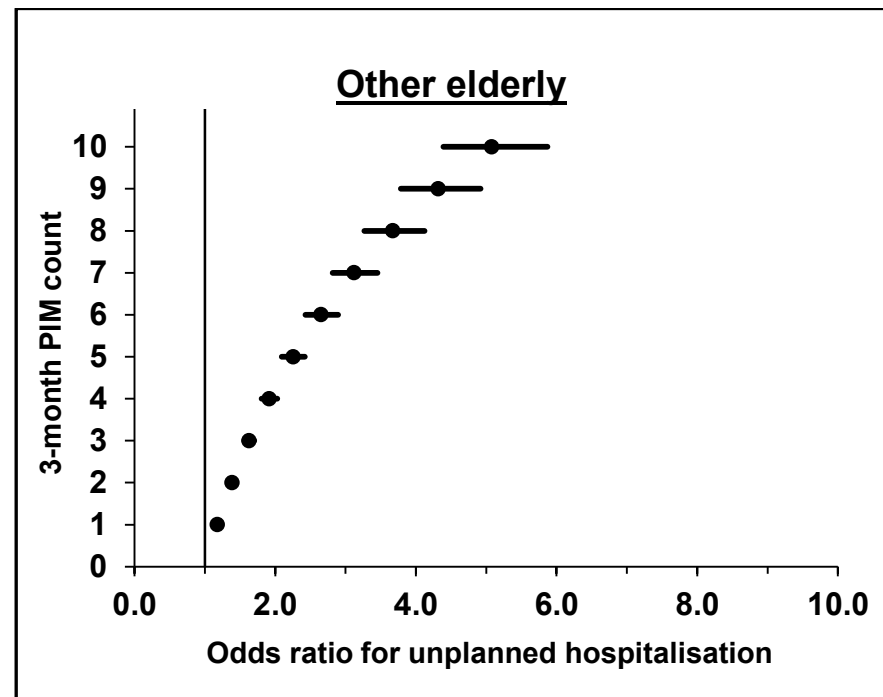
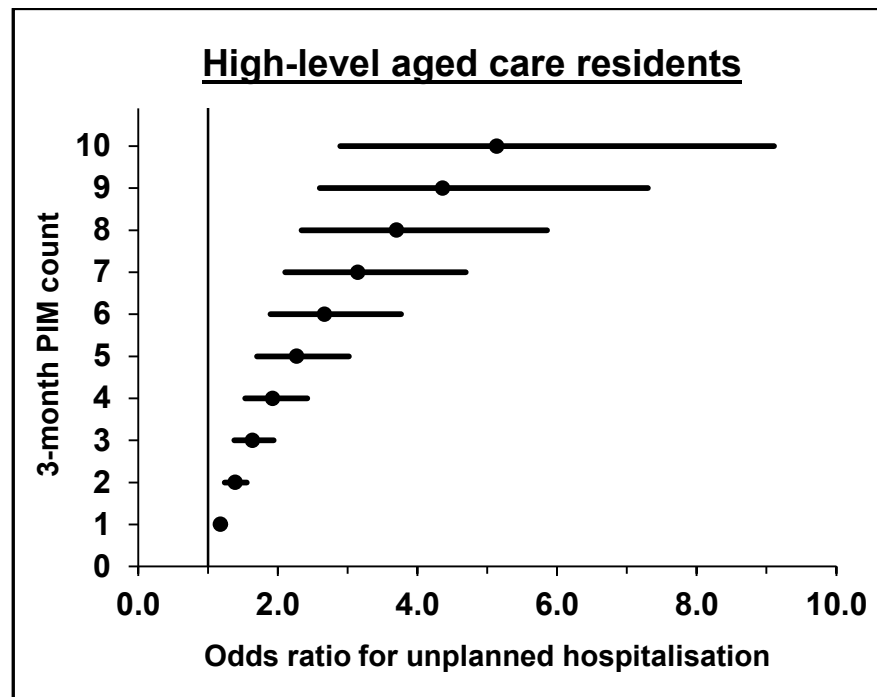
Medication class	PIM	High-level aged care status <sup>c</sup>	
		High care (n=20,525)	Other (n=362,625)
Antirheumatics	Indomethacin	88 (0.4%)	3,587 (1.0%)
	Naproxen	240 (1.2%)	6,501 (1.8%)
	Piroxicam	182 (0.9%)	5,305 (1.5%)
Analgesics	Dextropropoxyphene	8 (<0.1%)	203 (0.1%)
	Meperidine/pethidine	17 (0.1%)	151 (<0.1%)
Antihistamines (systemic)	Cyproheptadine	110 (0.5%)	1,382 (0.4%)
	Promethazine	45 (0.2%)	841 (0.2%)
Antipsychotics	Thioridazine	235 (1.1%)	823 (0.2%)
Anxiolytics, hypnotics/sedatives	Oxazepam	1,391 (6.8%)	13,597 (3.7%)
	Alprazolam	53 (0.3%)	1,176 (0.3%)
	Diazepam	787 (3.8%)	10,176 (2.8%)
	Temazepam	4,767 (23.2%)	40,268 (11.1%)
Antidepressants	Amitriptyline	501 (2.4%)	8,421 (2.3%)
	Doxepin	214 (1.0%)	4,744 (1.3%)
	Fluoxetine	304 (1.5%)	2,566 (0.7%)
Cardiac rhythm regulators	Digoxin	2,009 (9.8%)	32,113 (8.9%)
	Amiodarone	439 (2.1%)	11,193 (3.1%)
Hypertension drugs	Methyldopa	42 (0.2%)	1,996 (0.6%)
	Nifedipine	329 (1.6%)	11,370 (3.1%)
	Clonidine	13 (0.1%)	248 (0.1%)
High ceiling diuretics	Ethacrynic acid	9 (<0.1%)	218 (0.1%)
Antithrombotics	Dipyridamole	325 (1.6%)	3,223 (0.9%)
Iron preparations	Ferrous sulphate	995 (4.8%)	10,264 (2.8%)
Peptic ulcer/GORD <sup>d</sup> drugs	Cimetidine	118 (0.6%)	2,871 (0.8%)
Laxatives	Bisacodyl	688 (3.4%)	3,817 (1.1%)
Bowel disorder drugs/ belladonna & derivatives	Belladonna alkaloids	32 (0.2%)	474 (0.1%)
	Propantheline	112 (0.5%)	975 (0.3%)
Urinary antispasmodics	Oxybutynin	350 (1.7%)	3,147 (0.9%)
Urinary tract antibacterials	Nitrofurantoin	237 (1.2%)	1,743 (0.5%)
Oestrogens <sup>b</sup>	Oestrogens-all	169 (0.8%)	7,302 (2.0%)

<sup>a</sup> Although the study period covered 1993-2005 in this population, index cases related to unplanned hospital admissions between July 1994 and December 2005 only, in patients aged  $\geq 67$  years upon admission; these additional constraints were required to ensure sufficient lead-up time for the control observation period.

<sup>b</sup> Forty-three PIMs were included in the study. However, the six oestrogens (ethinyloestradiol, oestradiol, oestriol, oestrone, conjugated oestrogens and fosfestriol sodium) are combined into one entry in this table and the following PIMs are omitted: orphenadrine, diphenhydramine, hydroxyzine, dexamphetamine, disopyramide, ticlopidine, chlorpropamide, and dicyclomine. This was required due to low cell counts, in order to protect patient confidentiality.

<sup>c</sup> High care subjects were those who were receiving high-level aged care services in a nursing home at 30 June of the index admission year; other subjects included all other elderly (i.e. those receiving low-level hostel or community aged care services and those living in a private home without any aged care support at that time).

<sup>d</sup> GORD refers to gastro-oesophageal reflux disease.

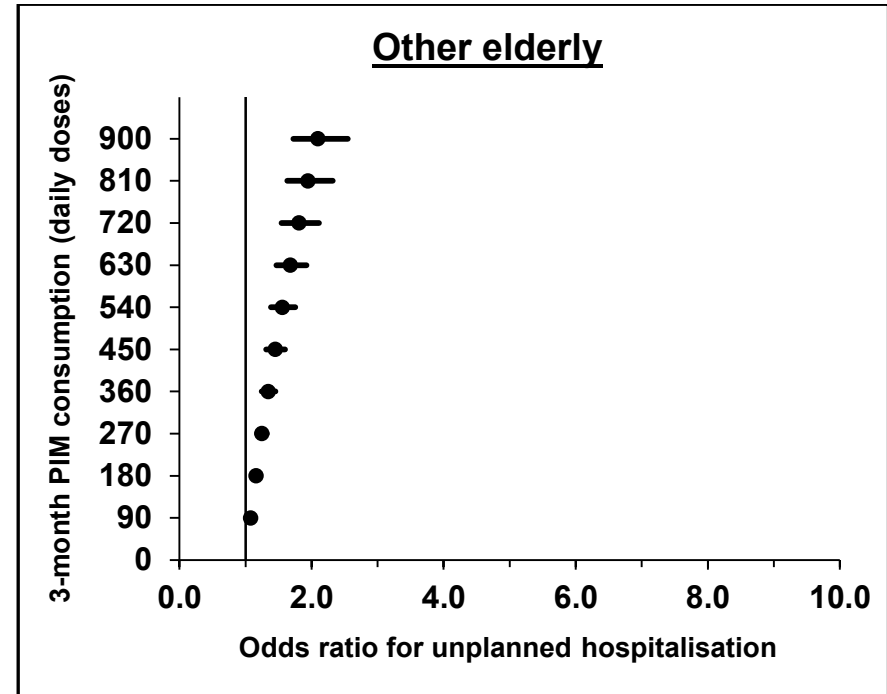
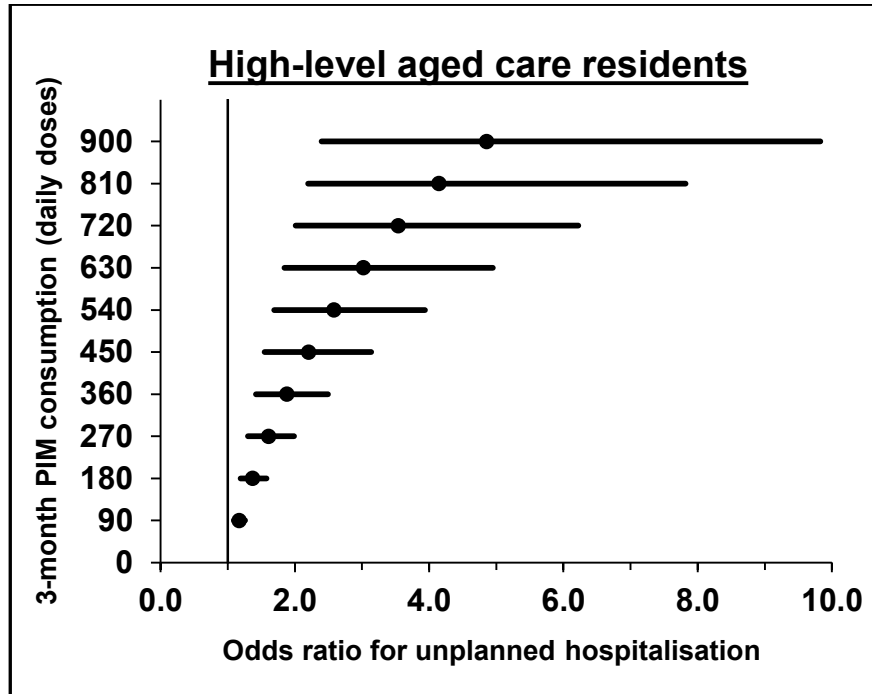


**Figure 8-1 Potentially inappropriate medications (PIMS) in Western Australians aged  $\geq 65$  years (1993-2005):<sup>a</sup> association between number of different PIMS taken<sup>b</sup> and unplanned hospitalisations (adjusted odds ratios and 95% confidence intervals) in high-level aged care residents versus other elderly<sup>c</sup>**

<sup>a</sup> Although the study period covered 1993-2005 in this population, index cases related to unplanned hospital admissions between July 1994 and December 2005 only, in patients aged  $\geq 67$  years upon admission; these additional constraints were required to ensure sufficient lead-up time for the control observation period.

<sup>b</sup> Number of different PIMs taken was determined based on drug consumption during the three-month period preceding the case and control times (including the case/control dates).

<sup>c</sup> High care subjects were those who were receiving high-level aged care services in a nursing home at 30 June of the index admission year; other subjects included all other elderly (i.e. those receiving low-level hostel or community aged care services and those living in a private home without any aged care support at that time).



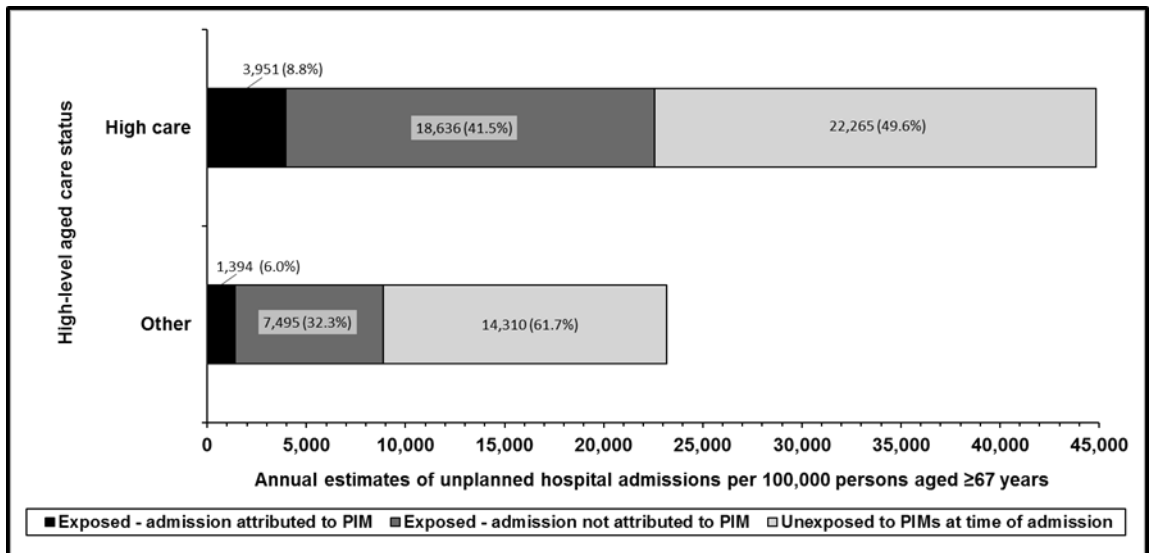
**Figure 8-2 Potentially inappropriate medications (PIMS) in Western Australians aged  $\geq 65$  years (1993-2005):<sup>a</sup> association between three-month PIM consumption<sup>b</sup> and unplanned hospitalisations (adjusted odds ratios and 95% confidence intervals) in high-level aged care residents versus other elderly<sup>c</sup>**

<sup>a</sup> Although the study period covered 1993-2005 in this population, index cases related to unplanned hospital admissions between July 1994 and December 2005 only, in patients aged  $\geq 67$  years upon admission; these additional constraints were required to ensure sufficient lead-up time for the control observation period.

<sup>b</sup> PIM consumption was determined based on total count of daily doses taken during the three-month period preceding the case and control times (including the case/control dates) Each daily dose represented exposure to one medication for one day, where the quantity taken was the average dose recommended per day, based on drug form, route and strength.

<sup>c</sup> High-level aged care residents were those who were receiving high-care services in a nursing home at 30 June of the index admission year; other elderly included all other subjects (i.e. those receiving low-level hostel or community aged care services and those living in a private home without any aged care support at that time).





**Figure 8-3 Potentially inappropriate medications (PIMs) in Western Australians aged  $\geq 67$  years (July 1994-December 2005):<sup>a</sup> estimates of unplanned hospital admissions per 100,000 person-years in high-level aged care residents versus other elderly,<sup>b</sup> broken down by PIM exposure status**

<sup>a</sup> Although the study period covered 1993-2005 in a population aged  $\geq 65$  years, index cases related to unplanned hospital admissions between July 1994 and December 2005 in patients aged  $\geq 67$  years upon admission, to ensure sufficient lead-up time for the control observation period. Consequently, rates were calculated for this time period and age group.

<sup>b</sup> High care subjects were those who were receiving high-level aged care services in a nursing home at 30 June of each calendar year; other subjects included all other elderly (i.e. those receiving low-level hostel or community aged care services and those living in a private home without any aged care support at that time).



# CHAPTER 9 POTENTIALLY INAPPROPRIATE MEDICATIONS AND UNPLANNED HOSPITALISATIONS - FOCUS ON POLYPHARMACY WITH HIGH-RISK DRUGS

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General statistics based on broad drug classes, such as those presented in chapter 4, are sometimes used to assess the potential risk of an adverse outcome in patients being prescribed medications within these drug classes. This may be necessary when more specific information about individual medications is not readily available, but is it appropriate? This likely depends on the drug itself, on the concurrent intake of other medications, and on various patient and health care characteristics.

The research component presented in this chapter explored some aspects of this particular issue. It compared risk estimates of unplanned hospitalisation associated with drug exposure in elderly Western Australians taking medications from broad classes of known high-risk drugs, which are usually prescribed for appropriate reasons, with and without the concurrent intake of specific PIMs from the Beers Criteria. For a few high-risk drug groups, it also compared hospitalisation risk estimates related to specific PIMs with those associated with the broad drug class to which they belong.

To a certain extent, these comparisons provided the means for assessing the value of being able to estimate the risk of adverse outcomes at the individual drug level (as opposed to the broader drug class level), which would not have been possible in this study without the linked pharmaceutical claims data.

The contents of this chapter were included in the following manuscript:

- Price SD, Holman CDJ, Sanfilippo FM, Emery JD. Impact of specific Beers Criteria medications on associations between drug exposure and unplanned hospitalisation in elderly patients taking high-risk drugs: a case-time-control study in Western Australia. *Drugs and Aging* 2014; 31(4):311-325. doi: 10.1007/s40266-014-0164-6.

Supplementary statistics related to the material presented in this chapter are provided in Appendix I.6.



# **Impact of specific Beers Criteria medications on associations between drug exposure and unplanned hospitalisation in elderly patients taking high-risk drugs: a case-time-control study in Western Australia**

## **ABSTRACT**

**Background:** Certain broad medication classes have previously been associated with high rates of hospitalisation due to related adverse events in elderly Western Australians, based on clinical coding recorded on inpatient summaries. Similarly, some medications from the Beers Criteria, considered potentially inappropriate in older people, have been linked with an increased risk of unplanned hospitalisation in this population.

**Objective:** To determine whether risk estimates of drug-related hospitalisations are altered in elderly patients taking 'high-risk drugs' (HRDs) when specific Beers potentially inappropriate medications (PIMs) are taken into consideration.

**Methods:** Using the pharmaceutical claims of 251,305 Western Australians aged  $\geq 65$  years (1993-2005) linked with other health data, we applied a case-time-control design to estimate odds ratios (ORs) for unplanned hospitalisations associated with anticoagulants, antirheumatics, opioids, corticosteroids and four major cardiovascular drug groups, from which attributable fractions (AFs), number and proportion of drug-related admissions were derived. The analysis was repeated taking exposure to eight specific PIMs into account, and results compared.

**Results:** 1,899,699 index hospitalisations were involved. Twelve to 57% of index subjects were exposed to each HRD at the time of admission, although the proportions taking both a HRD and one of the selected PIMs were much lower (generally  $\leq 2\%$ , but as high as 8% for combinations involving temazepam and for most PIMs combined with hypertension drugs). PIMs included (indomethacin, naproxen, temazepam, oxazepam, diazepam, digoxin, amiodarone, and ferrous sulphate) all tended to increase ORs, AFs and drug-related hospitalisation estimates in HRD combinations, although this was less evident for opioids and corticosteroids. Indomethacin had the greatest overall impact on HRD ORs/AFs. Indomethacin (OR 1.40; 95% CI 1.27-1.54) and naproxen (OR 1.22; 1.14-1.31) were associated with higher risks of unplanned

hospitalisation than other antirheumatics (overall OR 1.09; 1.06-1.12). Similarly, among cardiac rhythm regulators, amiodarone (OR 1.22; 1.13-1.32) was riskier than digoxin (OR 1.08; 1.04-1.13). For comparisons of drug-related hospitalisation estimates, temazepam yielded the greatest absolute increases, especially with hypertension drugs.

**Conclusions:** Indomethacin and temazepam should be prescribed cautiously in elderly patients, especially in drug combinations. Furthermore, it appears other antirheumatics should be favoured over indomethacin/naproxen and, in situations where both drugs may be appropriate, digoxin over amiodarone. Our methodology may help assess the safety of new medications in drug combinations in preliminary pharmacovigilance investigations.

**Keywords:** Inappropriate prescribing, adverse drug events, unplanned hospitalisation, pharmaceutical claims, case-time-control design, Australian elderly

## 9.1 INTRODUCTION

Adverse drug events (ADEs) are common in ageing patients.<sup>1,2</sup> Older people are major consumers of medication, and are more susceptible to ADEs due to physiological deterioration (e.g. renal and liver function decline; cognitive, sensory and motor function impairment); increasing number of comorbidities; polypharmacy; and other age-related factors. These factors can lead to pharmacokinetic and pharmacodynamic complications; propensity for drug-drug and drug-disease interactions; and difficulties adhering to physicians' instructions about medication intake, all of which are associated with drug-related problems.<sup>4-8,17,29</sup> In America, ADEs account for nearly 100,000 emergency hospitalisations annually in people aged  $\geq 65$  years.<sup>31</sup> In Australia, 15-22% of unplanned hospital admissions are drug-related in this age group.<sup>32</sup>

Furthermore, medications considered potentially inappropriate in the elderly are frequently prescribed in older people. A number of lists of such medications have been developed in the last few decades,<sup>9-12</sup> the Beers Criteria<sup>13-16</sup> being the most commonly referenced. Prevalence estimates of Beers medications vary in different elderly populations, but most are around 10-40%.<sup>36,64</sup>

A widespread approach for reporting ADE-related hospitalisations at the population level involves the use of clinical coding from inpatient records.<sup>19,194</sup>

This approach is not only subject to under-reporting, but is also restricted to broad medication categories due to constraints of the coding scheme.<sup>18-20,34,194</sup> Nonetheless, using this approach, Western Australian (WA) studies have identified anticoagulants, antirheumatics, opioids, corticosteroids, cytotoxics and cardiovascular agents as broad drug classes associated with high rates of ADE-related hospitalisations.<sup>18,20,34</sup>

Our own investigations, which linked WA pharmaceutical claims with inpatient and other records, estimated that 7-45% of unplanned hospital admissions in older patients exposed to medications from each of these drug classes (cytotoxics excluded) were likely attributable to their drug exposure (although two cardiovascular sub-groups appeared protective).<sup>209</sup> Our research also examined Beers' medications using similar methods, identifying 14 potentially inappropriate medications (PIMs) that seemed to increase the risk of unplanned hospitalisation significantly in the elderly.<sup>222</sup> Results from these two separate studies led us to the following question: "To what extent are risk estimates of unplanned hospital admissions altered in elderly patients taking medications from broad classes of high-risk drugs (HRDs) when exposure to specific Beers medications is taken into consideration?" Detection of an increased risk of serious adverse events (i.e. unplanned hospitalisations) when a PIM of interest was taken in combination with medications from certain broad HRD classes (versus the estimated HRD risk overall), would prompt physicians not to rely on estimated safety figures for these drug classes as a whole when assessing the HRD risk in patients who are also taking the PIM in question. Conversely, assessment of the risk associated with the combined effect of specific PIMs with medications from HRD groups would also provide a better estimate of the likelihood of serious harm in subgroups of patients taking various HRDs, when a specific PIM was being considered as an additional prescription drug. The increased potential for interactions when therapeutic drugs are taken in combination, over and above the independent effect of each medication, suggested to us that an increase in risk was likely,<sup>1</sup> but to what extent?

This paper presents the results of our analyses in relation to this question. Using a case-time-control design,<sup>26,27</sup> we assessed the impact of exposure to specific PIMs in elderly Western Australians taking HRDs in terms of unplanned hospitalisation. For some PIMs, we also compared associations between

specific PIMs and unplanned hospitalisation against those of the broad drug classes to which they belong. Given the potential for confounding by indication in observational studies of this nature, we sought to enhance our study design to the greatest extent possible in an attempt to overcome related issues.

## **9.2 METHODS**

### **9.2.1 DATA LINKAGE AND PARTICIPANT SELECTION**

This study linked Australian Pharmaceutical Benefits Scheme (PBS),<sup>21,22</sup> Medicare<sup>23,24</sup> and residential aged care<sup>25</sup> data with inpatient, death and electoral roll records from the WA Data Linkage System<sup>138,142</sup> through probabilistic linkage. This linkage involved full names and addresses, phonetic compression and other identifiers. A previous evaluation of linked chains for WA core data sets has estimated that <0.3% contained incorrect links.<sup>138</sup> For the Australian (i.e. national) data sources, the linkage was performed on key fields from a patient register (rather than individual records), for which a unique person identifier was available. Once linkage between the WA Data Linkage System and the patient register was completed (based on key patient details), data custodians were able to retrieve all health records belonging to each patient, using their person identifier. The study protocol was approved by The University of WA's Human Research Ethics Committee. Participants were not required to provide informed consent as identification details were not released to the researchers.

Participants included people aged  $\geq 65$  years by the end of 2004, who continuously lived in WA during 1993-2005 (until death) and had at least one pharmaceutical claim during that time, thus ensuring that those included had ascertainable drug exposures. Due to problem data (e.g. records post-death, no gender on any record), 8% were subsequently excluded. Comparisons against official statistics of the WA estimated residential population aged  $\geq 65$  years<sup>161</sup> suggest that our ultimate cohort captured 80-85% of WA elderly residents annually.

### **9.2.2 ESTABLISHMENT OF DRUG REFERENCE DATABASE**

Details of all PBS items from available schedules (August 1991-June 2007)<sup>200</sup> were assembled into a reference database, reconciling Anatomical Therapeutic Chemical (ATC) codes with the 2007 World Health Organization (WHO) ATC classification.<sup>163,201</sup> Average daily doses were determined for each item by



comparing prescription statistics from BEACH (Australian Bettering the Evaluation and Care of Health),<sup>165,202,203</sup> MIMS Australia,<sup>166,167,169</sup> and the 2008 WHO ATC Defined Daily Doses (DDDs),<sup>146,204</sup> taking drug form, route and strength into account. Precedence was given to the most appropriate information applicable to older Australians. Additionally, each drug's elimination half-life was obtained (predominantly from MIMS),<sup>166,167,169</sup> from which the period of drug effect, defined as five times the drug's half-life,<sup>170,171</sup> was estimated. Finalised entries were merged to the PBS master file.

### **9.2.3 DEFINITION OF HRD GROUPS AND DOMAINS**

Previously identified HRDs included anticoagulants, antirheumatics (mostly non-steroidal antiinflammatory drugs (NSAIDs)), corticosteroids, opioids, cytotoxics and cardiovascular agents.<sup>18,20,34</sup> Cytotoxics were excluded from this study because they were predominantly administered in public hospitals for which prescriptions were not recorded in the PBS data. Cardiovascular agents were expanded to include cardiac rhythm regulators, beta-blockers, hypertension drugs and serum lipid-reducing agents. Code definitions for each of these medication groups were established using the 2007 ATC classification.<sup>163,201</sup> ATC definitions for corresponding 'drug domains' were also agreed, where each drug domain consisted of medications used to treat similar conditions to those treated by the related HRD. Patients taking medications from each drug domain (i.e. 'patient domain') were considered to be potential candidates for being prescribed a HRD of interest. They formed the cohort of participants associated with each HRD sub-study. ATC definitions for each HRD group and corresponding drug domain are provided in a previous publication.<sup>209</sup>

### **9.2.4 CASE-TIME-CONTROL DESIGN**

Associations between HRDs and unplanned hospital admissions were expressed as odds ratios (ORs) derived from a case-time-control design.<sup>26,27</sup> Thus, index subjects acted both as cases and as their own historical controls, while background time trends in exposure due to ageing, disease progression and treatment patterns were adjusted using similarly constructed case and control observation windows in a reference group selected from the same patient domain as the index subjects. As already mentioned, in this study the patient domain included everyone in the overall cohort who had been

prescribed a therapeutic drug used to treat similar conditions to the indications for the HRD group of interest during 1993-2005.

Index subjects were individuals within the patient domain who had experienced an unplanned (i.e. emergency) hospital admission between 1 July 1994 and 31 December 2005 whilst aged  $\geq 67$  years. These additional age and time constraints ensured sufficient lead-up time for the control observation period. Many patients were included in the analysis as multiple index subjects, although a few ( $\leq 0.1\%$ ) who had  $>50$  index admissions were excluded given concerns about representativeness. Two records were created for each index subject, one for the 'case time' (i.e. the admission date) and the other for the 'control time' (usually 365 days prior). When index subjects were in hospital at this preferred control time (2-3% of instances), the admission date of that earlier hospitalisation was used as control time instead.

Each index subject was matched by gender, general practitioner (GP) coverage category for the entire study period, and year of birth to a randomly selected reference subject from the sub-study's patient domain. To determine the GP coverage category, each GP visit identified in the Medicare data set was allocated a 'coverage' period of 61 days, overlapping periods for each person being merged together. The GP coverage category was then derived from the proportion of days with GP coverage over the study period, categories loosely based on quartiles applicable to the study cohort. Persons born before 1900 were allocated a year of birth of 1900 for matching purposes only. Case and control time records were created for each reference subject as per the index subjects, ensuring case and control dates were matched with those of corresponding index subjects as closely as possible.

Once created, the case and control time records for index and reference subjects were populated with the time-dependent variables required to adjust for potential confounding in the regression models, including nursing home status at the case or control time; hospital days, overall Charlson comorbidity index<sup>160</sup> and GP coverage percentage, all for the previous year; and a drug consumption profile for the preceding 90 days (plus the case or control date), which included the number of broad medication categories involved, the overall count of daily doses taken (for any drug) and a daily dose count for each broad drug category.

Additionally, PBS records were processed to determine whether the subject was exposed to any medication from the sub-study's HRD drug group at each case and control date. If a prescription was found for a relevant drug and if the time period bound by its supply date and exposure effect end date overlapped with the case or control date, the exposure status was set to 'exposed'. The exposure effect end date was calculated by adding the number of drug consumption days associated with the script (i.e. total quantity / average daily dose) to the supply date (-1) plus the period of drug effect (up to seven days) and a seven-day latency period. Thus, the exposure status did not strictly identify whether the subject was taking a relevant HRD at the case or control time. Instead, it was used to reflect whether the effects of HRD exposure could potentially have caused a hospital admission at the case or control time.

For each HRD sub-study, conditional logistic regression models were applied using the SAS 9.2 PHREG procedure, with stratification based on a unique identifier for each subject.<sup>154</sup> The COVS option was specified to ensure the generation of robust sandwich covariance estimates,<sup>172</sup> thus accounting for the potential within-cluster correlation associated with multiple hospitalisations per person. The OR of primary interest was derived from the coefficient of the cross-product between exposure and the binary index/reference indicator, which represented the association between exposure and unplanned hospitalisation in the index subjects, over and above apparent time-trend effects that applied to both index and reference subjects.<sup>26</sup> The adjusted model controlled for all health and drug consumption indicators mentioned earlier (refer to last footnote in Table 9-2), except for the three-month count of daily doses for the drug group of interest.

#### **9.2.5 ESTIMATION OF UNPLANNED HOSPITALISATIONS ATTRIBUTED TO DRUG GROUP**

Using the OR derived as above, the attributable fraction (AF) of unplanned hospitalisations associated with each HRD group (within the exposed) was calculated, where  $AF = (OR - 1) / OR$ . The estimate of unplanned hospitalisations attributed to each HRD group was then derived as  $AF \times$  number of exposed index subjects.<sup>173-175,216</sup>

#### **9.2.6 DERIVATION OF PIM-REFINED ESTIMATES**

Using a process analogous to that described for HRDs, our previous research produced ATC definitions for all medications from the 2003 Beers Criteria<sup>15</sup> and

corresponding drug domains, and applied a case-time-control design to all 'general' PIMs from the Beers list (i.e. drugs to avoid in all elderly independent of diagnosis) that were available in WA over the study period. Of the 43 individual PIMs examined, 14 demonstrated significant associations with unplanned hospitalisations in adjusted models.<sup>222</sup> All were initially included in this study. However, as some PIMs (meperidine/pethidine, thioridazine, bisacodyl, oxybutynin, nitrofurantoin and promethazine) did not affect HRD ORs significantly (predominantly due to low prevalence), the list was subsequently restricted to eight, as follows: indomethacin, naproxen, temazepam, oxazepam, diazepam, digoxin, amiodarone and ferrous sulphate. Please refer to the footnotes of Tables 9-1 and 9-2 for ATC definitions of these medications. Exposure to these PIMs was ascertained for all index and reference subjects at the case and control times, as per exposure to HRDs. This was repeated for each HRD sub-study. It should be noted that indomethacin and naproxen, as well as being specific PIMs in the analyses, were also members of the antirheumatic HRD group. Similarly, digoxin and amiodarone were treated as both specific PIMs and as members of the cardiac rhythm regulator HRD group.

Once this exposure information had been obtained, the following covariates were added to the existing HRD conditional logistic regression models: the binary exposure variable for a given PIM (e.g. PIM1exp); the interaction term between this PIM exposure variable and the HRD group's exposure status (e.g. PIM1exp\*HRDexp); and the interaction term between PIM exposure and the cross-product between HRD exposure and the binary index/reference indicator (e.g. PIM1exp\*HRDexp\*index). The ORs of interest were those that applied to index subjects only in relation to their exposure to both the HRD and the PIM of interest. They were calculated as follows:

$$OR = e^{a + b}$$

where a = model coefficient for HRDexp\*index and b = model coefficient for PIM1exp\*HRDexp\*index. The 'b' term represented the added effect associated with the use of PIM1 in index subjects taking medication from the HRD group.

As per the overall analysis for HRDs, the ORs involving PIM terms were adjusted for potential confounding using all available covariates. Furthermore, these adjusted ORs were used to derive corresponding AFs and estimates of

hospital admissions attributed to drug exposure when both the specified PIM and a medication from the HRD group were taken.

Finally, estimates of hospitalisations attributed to drug exposure were refined according to PIM exposure by splitting the index subjects exposed to medications from each HRD group based on their additional exposure to specific PIMs and applying the most appropriate AF to each subset. Where refinements involved two PIMs, the AFs originated from regression models in which PIM exposure was represented as a class variable. Differences were then calculated between the PIM-refined estimates and those obtained by multiplying corresponding 'PIM-negative' AFs by the total number of index subjects exposed to each HRD, where 'PIM-negative' referred to patients who were exposed to a given HRD but not to PIMs involved in the refinement process.

### **9.3 RESULTS**

An overview of participants and index subjects for each HRD sub-study is presented in Table 9-1. The overall study cohort consisted of 251,305 individuals. However, participants in each HRD patient domain (i.e. sub-study cohort) numbered between 39,596 (cardiac rhythm regulators) and 193,196 (opioids). These people received 569,369-4,825,066 prescriptions during the study period. Overall, 1,899,699 unplanned admissions ('index subjects') were included, each sub-study yielding 128,241-358,570 admissions, which were associated with 29,919-108,513 patients. Around 45-46% of the index subjects were male and the mean age was 78-79 years.

The proportion of index subjects exposed to a medication from each HRD group at the time of admission ranged between 12-13% (anticoagulants and opioids) and 57% (hypertension drugs). Proportions of index subjects exposed to a HRD as well as a PIM were much lower (generally  $\leq 2\%$ ). However, these proportions were higher for exposure to a HRD with temazepam and for most PIMs combined with hypertension drugs (up to 8.1% for both). For the sub-study on cardiac rhythm regulators, the proportions specifically taking digoxin and amiodarone (both of which are cardiac rhythm regulators) at the time of admission were 26.6% and 9.1% respectively.

Adjusted ORs for unplanned hospital admissions, corresponding AFs, and estimates of hospital admissions attributed to HRDs overall and in combination with selected PIMs are presented in Table 9-2. When no consideration was given to individual PIMs, adjusted ORs for hypertension and serum lipid-reducing agents were below one, suggesting that these drugs may have had an overall protective effect against unplanned hospitalisations. Adjusted ORs for the other HRD groups (without consideration for concurrent PIM exposure) ranged between 1.08 (95% CI 1.05-1.11) for beta-blockers and 1.81 (1.75-1.88) for opioids, and corresponding AFs ranged between 7.4% and 44.9%.

We compared HRD ORs involving PIM combinations with both the ORs for the HRD groups as a whole and with ORs for those not taking the specified PIMs (i.e. PIM-negative ORs). However, as PIM-negative ORs were almost identical to overall ORs for most PIMs, only the overall ORs are shown in Table 9-2. For temazepam, PIM-negative ORs were slightly lower than overall ORs though (e.g. 1.11 vs. 1.13 for anticoagulants), except for the opioid sub-study (1.83 vs. 1.81).

Most PIM/HRD combinations produced higher ORs for unplanned hospitalisation than corresponding overall and PIM-negative ORs. This was particularly evident for indomethacin, which appeared to increase the hospitalisation risk significantly for all HRD groups except corticosteroids. Naproxen and temazepam also raised a number of ORs, although naproxen had a greater effect on results for anticoagulants, corticosteroids and opioids, whereas temazepam produced higher ORs consistently for broad cardiovascular drug groups. Similarly, oxazepam seemed to augment ORs related to cardiovascular drug groups, despite not demonstrating much effect on results for other HRDs. Diazepam, digoxin, amiodarone and ferrous sulphate also affected results for some HRDs, although none of these PIMs had much effect on opioid and corticosteroid ORs.

In terms of the HRD groups, ORs for the hypertension medications were the most affected by drug combinations with PIMs. Other cardiovascular drug groups, antirheumatics and anticoagulants were affected by several PIMs as well. Conversely, with only a few exceptions, ORs for opioids and corticosteroids seldom seemed to be affected when exposure to PIMs was taken into consideration.

Figure 9-1 compares the unplanned hospitalisation ORs associated with specific antirheumatic and cardiac rhythm regulator PIMs against the overall ORs obtained for the broad HRD group to which they belong. For antirheumatics, both indomethacin and naproxen (which accounted for 5.9% and 10.8% of the antirheumatic exposure, respectively), were associated with a significantly higher risk of unplanned hospitalisation than the group of antirheumatic drugs as a whole. Furthermore, ORs suggested that indomethacin was possibly linked to a higher hospitalisation risk than naproxen (although the difference in the strength of these associations was not statistically significant). For cardiac rhythm regulators, the OR for amiodarone was higher than that for digoxin. Neither was significantly different from the OR for the entire HRD group, which was expected since 98.3% of the exposure to cardiac rhythm regulators involved digoxin (72.3%), amiodarone (22.1%) or both (3.9%).

Figures 9-2 and 9-3 compare the overall AF for those exposed to a medication from each HRD group with that of elderly people exposed to both the main drug group and a specified PIM. These figures concentrate on non-cardiovascular and cardiovascular HRDs, respectively. For the sake of simplicity, PIM-negative AFs for each PIM are not shown; most would be slightly lower than the overall AF. Most AFs were greater when drug exposure involved a combination of a medication from a main drug group with a specific PIM. Indomethacin exposure in combination with most HRDs generally produced the greatest AF increases (as opposed to other PIM exposure), except for corticosteroids and hypertension drugs; naproxen and diazepam had the greatest influence for the latter, respectively. AFs for opioids and corticosteroids were the least affected when these drugs were combined with individual PIMs, whereas the AF for hypertension drugs was most affected.

Figure 9-4 shows differences between PIM-refined and PIM-negative estimates of hospitalisations considered attributable to drug exposure for each HRD group. PIM-refined estimates were those obtained by applying specific AFs to subsets of index subjects exposed to HRDs depending upon their concurrent PIM exposure status, whereas PIM-negative ones were those that would be expected if all index subjects exposed to a HRD were unexposed to the PIMs under consideration. Index subjects taking hypertension drugs were most

affected by additional exposure to specific PIMs in terms of increases in estimated hospital admissions attributed to drug exposure, although those taking serum lipid-reducing agents, beta-blockers and antirheumatics were also noticeably affected. For most broad drug groups, the PIM associated with the greatest absolute difference in attributable hospital admissions was temazepam. This was particularly apparent for index subjects taking hypertension drugs, for which a difference of 7,145 admissions was estimated over the study period when temazepam exposure was taken into account.

## **9.4 DISCUSSION**

This study investigated whether intake of specific PIMs from the Beers Criteria affected risk estimates of unplanned hospitalisation in elderly Western Australians exposed to medications from broad classes of 'high-risk drugs'. The linkage of pharmaceutical claims data with inpatient and other records not only allowed us to bring together exposure and outcome information for each person and to use different techniques to estimate excess hospitalisations associated with medication exposure, but also permitted the isolation of individual medications in this process (which was not possible from clinical coding). Furthermore, our large cohort and the extended study duration gave us the power to evaluate individual drugs on their own as well as in combination with other medications.

### **9.4.1 MAJOR FINDINGS**

Our results suggest that most of the Beers medications we investigated tended to increase the risk estimates associated with drug exposure and unplanned hospitalisation for at least some, if not most of the broad drug groups included in the study. This was not only evident when comparing ORs, but was also reflected in corresponding AFs and derived estimates of unplanned hospitalisations considered attributable to medication exposure. This is not surprising, given that Beers medications have been identified as drugs to be avoided in the elderly due to their potential harm.<sup>15</sup> Furthermore, concurrent use of multiple medications can lead to drug interactions, which may increase the risk of adverse drug reactions.<sup>1</sup>

One could argue that the proportion of unplanned hospitalisations associated with exposure to these drug combinations is fairly low, each combination generally affecting <2% of our index subjects. However, in our elderly



population, which consisted of ~170,000 older WA residents annually, >32,000 unplanned hospitalisations were attributed to these drug combinations between July 1994 and December 2005, an average of 2,785 per year. For those patients potentially affected, this undoubtedly represents a very important issue.

With respect to individual PIMs, indomethacin had the greatest impact on relative effect measures for most HRD groups and their association with unplanned hospitalisation, although naproxen and diazepam were also strong modifiers. In absolute terms, temazepam, which was the most commonly prescribed PIM in combination with HRDs, appeared to be the most influential. Thus, clinicians should be particularly cautious when contemplating the use of these PIMs in patients who are already taking medications from a relevant HRD group (or vice versa).

For HRD classes, it is difficult to single out which group of patients warrant the most precaution when contemplating therapy combinations involving the PIMs discussed in this paper. Although elderly patients taking hypertension drugs were most affected by an apparent increase in risk of unplanned hospitalisation when taking the majority of these PIMs, hypertension drugs demonstrated an overall protective effect against unplanned hospitalisation when these PIMs were not taken into consideration. Conversely, older people taking opioids and corticosteroids seemed least affected by the additional intake of any given PIM. However, this may relate to the fact that medications from these broad drug groups were already associated with a very high risk of unplanned hospitalisation (81% and 48% increases compared with the unexposed), which may not have been altered substantially by the introduction of an additional medication.

Our comparisons of ORs for individual PIMs against those of the broad drug class to which they belong should also be highlighted. Although the apparent increase in risk of unplanned hospitalisation in those taking antirheumatics was a modest 9% overall when compared with the unexposed, the corresponding figures for indomethacin and naproxen were much higher (40% and 22%, respectively). Fortunately, the prescribing of these two drugs has been declining in the Western Australian population and most likely elsewhere, as newer and safer drugs are being introduced onto the market. In any event, these differences illustrate the need to exert caution when examining risk-

related results for broad drug classes, as these results may not be applicable uniformly to individual medications within these drug classes. For cardiac rhythm regulators, comparisons against overall results for the entire drug class are less relevant, since 98% of the exposed were taking a PIM of interest. Nonetheless, our ORs do suggest a higher increased risk of unplanned hospitalisation for amiodarone (22%) than digoxin (8%). These two drugs are generally prescribed for somewhat different indications (in Australia at least) – amiodarone (Class III antiarrhythmic) used in various cases of tachyarrhythmia, digoxin (cardiac glycoside) in the treatment of congestive heart failure.<sup>166,167</sup> However, in situations where both drugs may be appropriate (e.g. maintenance therapy for atrial fibrillation), digoxin should be favoured over amiodarone for safety.

#### **9.4.2 PERUSAL OF THE LITERATURE AND REVIEW OF ADE MECHANISMS**

Identifying other study results that are directly comparable with ours has proved difficult. Most publications on the potential adverse effects of drug combinations have focused on the prevalence of potential drug-drug interactions, as defined in various compendia.<sup>224-228</sup> In these publications, digoxin, amiodarone, and NSAIDs (e.g. indomethacin, naproxen) are prominent on lists of major drug-drug interactions.<sup>224-237</sup> Studies reporting more specifically on multi-drug adverse events<sup>224,225,235-239</sup> have indicated that counts of actual ADEs resulting from exposure to drug combinations were considerably lower than corresponding counts of potential drug-drug interactions; associated lists of the most common drug combinations seldom provided statistics that represented a relative risk or rate of occurrence with respect to drug exposure; the medications most frequently implicated in ADEs generally reflected drug consumption patterns in the study population; and several studies were not specific to the elderly. Thus, this information is mostly peripheral to our research.

However, the literature does explain the likely mechanisms responsible for potential ADEs, in support of our findings regarding PIMs and high-risk drug combinations. For instance, the interaction between NSAIDs and anticoagulants such as warfarin is well established. Most NSAIDs, including indomethacin and naproxen, inhibit platelet aggregation and cause gastrointestinal toxicity that may lead to inflammation and ulceration, thus

predisposing patients to gastrointestinal and other bleeding.<sup>240-244</sup> Therefore, it is not surprising that older patients taking anticoagulants in our study, who were also exposed to indomethacin or naproxen, were at a much increased risk of unplanned hospitalisation compared with anticoagulant users who were not. Similarly, NSAIDs inhibit COX-2 and prostaglandin synthesis, which leads to decreased sodium excretion, subsequent expansion of intravascular volume and fluid retention.<sup>242,245</sup> Consequently, NSAIDs may interfere with antihypertension therapy and have been linked with the aggravation of heart failure, other cardiovascular events and renal impairment, all of which may affect patients who are taking a range of cardiovascular drugs.<sup>242-244</sup> The Beers Criteria also warn against the use of indomethacin due to its adverse effects related to the central nervous system.<sup>15</sup> This may possibly explain the increased risk of unplanned hospitalisation associated with indomethacin in patients taking opioids, and the higher risk associated with indomethacin overall compared with naproxen.

Comparing digoxin and amiodarone is also interesting when considering the ADE mechanisms involved. In the early 1970s, toxicity was of major concern in people taking digoxin, one study reporting that 25% of patients taking this PIM were diagnosed with definite toxicity.<sup>246</sup> Symptoms of toxicity include acute fatigue, anorexia, nausea, visual disturbances, confusion, drowsiness and others.<sup>246,247</sup> Subsequently, recommended dosage levels were lowered, and by the mid-1990s, the prevalence of digoxin toxicity had been reduced to ~4% in patients being treated with this medication.<sup>246</sup> Nonetheless, patients with renal failure remain at higher risk, as well as those taking diuretics and calcium channel blockers.<sup>246,247</sup> Digoxin toxicity is not the only potential adverse effect associated with this PIM, however. Combinations of digoxin with calcium channel blockers (hypertension drugs) can lead to complete heart block in some situations, whereas digoxin with beta-blockers may induce bradycardia.<sup>245,247</sup>

In contrast, amiodarone has not been linked with a high prevalence of toxicity. However, it may lead to a heart block in combination with a calcium channel blocker, as per digoxin.<sup>247</sup> Additionally, amiodarone may interact with other drugs through the inhibition of cytochrome P450 enzymes, increasing patients' sensitivity to most NSAIDs, warfarin, beta-blockers, calcium channel blockers, statins and a number of benzodiazepines (e.g. diazepam). This may possibly

lead to overdose and associated symptoms.<sup>248</sup> This latter mechanism may account for the higher impact of amiodarone than digoxin on the risk of unplanned hospitalisation in several groups of study participants taking high-risk drugs.

Diazepam, temazepam and oxazepam are benzodiazepines, a class of drugs with strong sedative and other central nervous system properties that may lead to cognitive impairment, confusion, falls, fractures and other related adverse outcomes.<sup>249-252</sup> They are associated with a high level of ADEs even in monotherapy.<sup>252</sup> Although clinically significant interactions have been identified between benzodiazepines and other medications, most drug classes involved have not been included in this study, with one exception: opioid analgesics.<sup>252</sup> Surprisingly, our results have not demonstrated an elevated risk of unplanned hospitalisation in patients taking opioids when used in combination with any of the three benzodiazepine PIMs included in our analysis.

For completeness, we also mention ferrous sulphate, which is known to cause constipation when taken in high doses.<sup>15,238</sup> Publications reporting major drug interactions in the elderly do not generally mention this substance. However, one would expect other drugs also associated with constipation (e.g. opioids, calcium channel blockers)<sup>238</sup> to exacerbate the problem if taken in combination with iron supplements. Our findings for hypertension drugs appear to support this premise, but our opioid results do not. The strong impact of ferrous sulphate on the risk of unplanned hospitalisation for anticoagulant and beta-blocker groups is also difficult to interpret in our results. The residual effects of protopathic bias are possible with this medication, whereby the underlying reason for prescribing iron supplements (e.g. anaemia, which may be associated with other, potentially undiagnosed conditions) may be the source of the apparent interaction.<sup>152</sup> Further investigations would be required to ascertain whether this is the case, but this would require additional data.

### **9.4.3 STUDY LIMITATIONS**

Like most research involving administrative health data, this study was subjected to data quality and availability issues. Although the WA Data Linkage System is a well-established data linkage facility,<sup>138,142</sup> a slightly greater proportion of invalid links than usual were likely created in this instance, given the lesser quality of the linkage fields extracted from Australian (i.e. national)

sources. Additional staff members were appointed to identify and resolve improbable links, but some would likely have been missed. Nonetheless, given the large size of the data sets, it is unlikely that the few glitches would have impacted on the results to any great extent.

Similarly, the researchers also conducted an extensive clean-up and cross-validation process upon receipt of the data, addressing most problems, but they could not have eliminated them entirely. In particular, ascertainment of drug exposure at specific times was difficult, as no information was available on the daily dose specifically prescribed for each dispensed drug, nor on patient adherence. Much attention was devoted to the derivation of exposure status from average recommended daily doses, but this could not have been completely accurate for every subject.

Furthermore, our PBS data set had some coverage limitations. It excluded medications prescribed within public hospitals, over-the-counter drugs, and prescriptions for which a PBS claim could not be made.<sup>223</sup> However, since our elderly participants likely had a concession card and very low co-payment requirements, most non-hospital scripts for medications of interest would have been recorded in this age group. Consequently, these coverage issues were not expected to affect our results to any great extent.

Our own exclusions also eliminated elderly people with no PBS record during 1993-2005 and those who appeared not to have lived in WA for the entire study period (until death). Since the excluded individuals were probably younger, healthier and wealthier than the study population average, we expect our overall results may have slightly overestimated the impact of drug exposure on unplanned hospitalisation compared with corresponding figures applicable to all older people living in WA or possibly elsewhere.

Additionally, we acknowledge that the case-time-control design is dependent upon inherent assumptions and conditions, especially in relation to time trend bias.<sup>26,27,153</sup> Our preliminary work has demonstrated that our enhanced approach appears to control reasonably well against related confounding, improving internal validity compared with the case-control and case-crossover designs, and the basic case-time-control design without adjustment for measurable time-variant confounders.<sup>209</sup> Nonetheless, it is unlikely that our models were able to fully adjust for potential protopathic (reverse causation)

bias, a form of systematic error that arises when early manifestations of the outcome prior to its formal ascertainment drive up exposure.<sup>152</sup>

Given the ongoing development of new therapeutic drugs since the start of our project, a repeat of our study using more recent data and updated drug definitions would certainly be beneficial. Still, all of the selected PIMs continue to be available in Australia<sup>253</sup> and all but one were included in the latest revision of the Beers Criteria.<sup>16</sup> Ferrous sulphate was excluded as a PIM, not due to lack of evidence of the drug's potential harm in older people, but because the associated problems are not restricted to the elderly.<sup>213</sup>

#### **9.4.4 CONCLUSIONS**

This study used robust methods involving pharmaceutical claims, linked data and a case-time-control design to examine individual drugs in combination or in comparison with broad classes of HRDs and their associations with unplanned hospitalisation in the elderly. Based on our results, indomethacin and temazepam appear particularly problematic in terms of hospitalisation risk when used with HRDs. Clinicians should be particularly cautious in prescribing these medications to their elderly patients, especially in drug combinations. Furthermore, from a safety perspective, our results suggest that other antirheumatics should be favoured over indomethacin and naproxen and, in situations where both drugs may be appropriate, digoxin over amiodarone.

Our methodology has broader applications, however. Additional research seems warranted to compare a wide range of individual drugs within each HRD group, to determine which ones appear to be potential drivers of adverse outcomes. This need not be limited to the drug groups identified in this study. For instance, a number of PIMs from the Beers Criteria belong to other drug classes. One could investigate various anxiolytics or sedatives, for example, to determine which ones appear safest or most dangerous. Of course, our methods would be quite useful in investigations of the potential harm associated with combinations of individual medications, especially those suspected of elevating the risk of ADEs. In particular, we propose our approach as an additional tool for assessing the potential harm of new medications and their combined effects with other drugs in preliminary pharmacovigilance investigations.

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The authors have no conflicts of interest to declare.

**Table 9-1 High-risk medications and unplanned hospitalisations in Western Australian elderly (1993-2005) - profile of study population and medication exposure status<sup>a</sup> of index subjects at the time of admission**

Statistics	Anti-coagulants	Anti-rheumatics	Opioids	Cortico-steroids	Cardiac rhythm regulators	Beta-blockers	Hypertension drugs	Serum lipid-reducing agents
Domain participants (people in sub-study cohort) <sup>b</sup>	90,124	174,585	193,196	84,960	39,596	89,017	180,539	100,787
Domain prescription count (all drugs)	1,697,870	3,317,418	4,825,066	569,369	614,754	2,717,155	12,236,135	4,517,199
Number (%) participants contributing as index subjects	57,609 (63.9%)	92,903 (53.2%)	108,513 (56.2%)	53,369 (62.8%)	29,919 (75.6%)	55,179 (62.0%)	99,635 (55.2%)	50,295 (49.9%)
Index subjects (i.e. unplanned admission cases)	212,187	307,276	358,570	197,385	128,241	195,311	335,259	165,470
Male index subjects (%)	99,926 (47.1%)	138,319(45.0%)	160,977 (44.9%)	90,258 (45.7%)	58,402 (45.5%)	88,532 (45.3%)	151,908 (45.3%)	82,445 (49.8%)
Index subjects' mean age at admission (years)	78.1	78.3	78.5	78.0	79.5	78.2	78.5	76.4
Index subjects exposed to main drug group (all)	26,088 (12.3%)	61,595 (20.0%)	45,772 (12.8%)	30,740 (15.6%)	44,730 (34.9%)	60,755 (31.1%)	192,674 (57.5%)	69,286 (41.9%)
Index subjects exposed to main drugs+indomethacin	216 (0.1%)	3,675 (1.2%)	1,117 (0.3%)	393 (0.2%)	498 (0.4%)	737 (0.4%)	2,166 (0.6%)	662 (0.4%)
Index subjects exposed to main drugs+naproxen	259 (0.1%)	6,741 (2.2%)	1,862 (0.5%)	819 (0.4%)	714 (0.6%)	1,232 (0.6%)	3,800 (1.1%)	1,174 (0.7%)
Index subjects exposed to main drugs+temazepam	3,994 (1.9%)	9,465 (3.1%)	10,477 (2.9%)	5,445 (2.8%)	7,553 (5.9%)	8,102 (4.1%)	27,098 (8.1%)	8,779 (5.3%)
Index subjects exposed to main drugs+oxazepam	1,018 (0.5%)	3,172 (1.0%)	3,261 (0.9%)	1,679 (0.9%)	2,142 (1.7%)	2,694 (1.4%)	8,834 (2.6%)	2,647 (1.6%)
Index subjects exposed to main drugs+diazepam	743 (0.4%)	2,692 (0.9%)	3,048 (0.9%)	1,349 (0.7%)	1,450 (1.1%)	2,105 (1.1%)	6,381 (1.9%)	2,176 (1.3%)
Index subjects exposed to main drugs+digoxin	8,312 (3.9%)	5,096 (1.7%)	4,006 (1.1%)	3,074 (1.6%)	34,122 (26.6%)	5,825 (3.0%)	23,836 (7.1%)	5,485 (3.3%)
Index subjects exposed to main drugs+amiodarone	2,997 (1.4%)	1,618 (0.5%)	1,532 (0.4%)	1,128 (0.6%)	11,632 (9.1%)	2,458 (1.3%)	8,614 (2.6%)	3,695 (2.2%)
Index subjects exposed to main drugs+ferrous sulphate	1,056 (0.5%)	2,104 (0.7%)	1,837 (0.5%)	1,086 (0.6%)	2,138 (1.7%)	1,827 (0.9%)	7,258 (2.2%)	1,926 (1.2%)

<sup>a</sup> Table entries for the medication exposure status provide the count and proportion (in parentheses) of index subjects considered exposed to the specified drugs at the time of admission. For the World Health Organization Anatomical Therapeutic Chemical (ATC)<sup>163,201</sup> code specifications for the high-risk drug groups, please refer to Price et al. (2013).<sup>209</sup> ATC definitions for the specified Beers potentially inappropriate medications are as follows: indomethacin (M01AB01); naproxen (M01AE02); temazepam (N05CD07); oxazepam (N05BA04); diazepam (N05BA01); digoxin (C01AA05); amiodarone (C01BD01); and ferrous sulphate (B03AA07, B03AD03).

<sup>b</sup> Domain participants for each sub-study were selected from an overall cohort of 251,305 individuals.



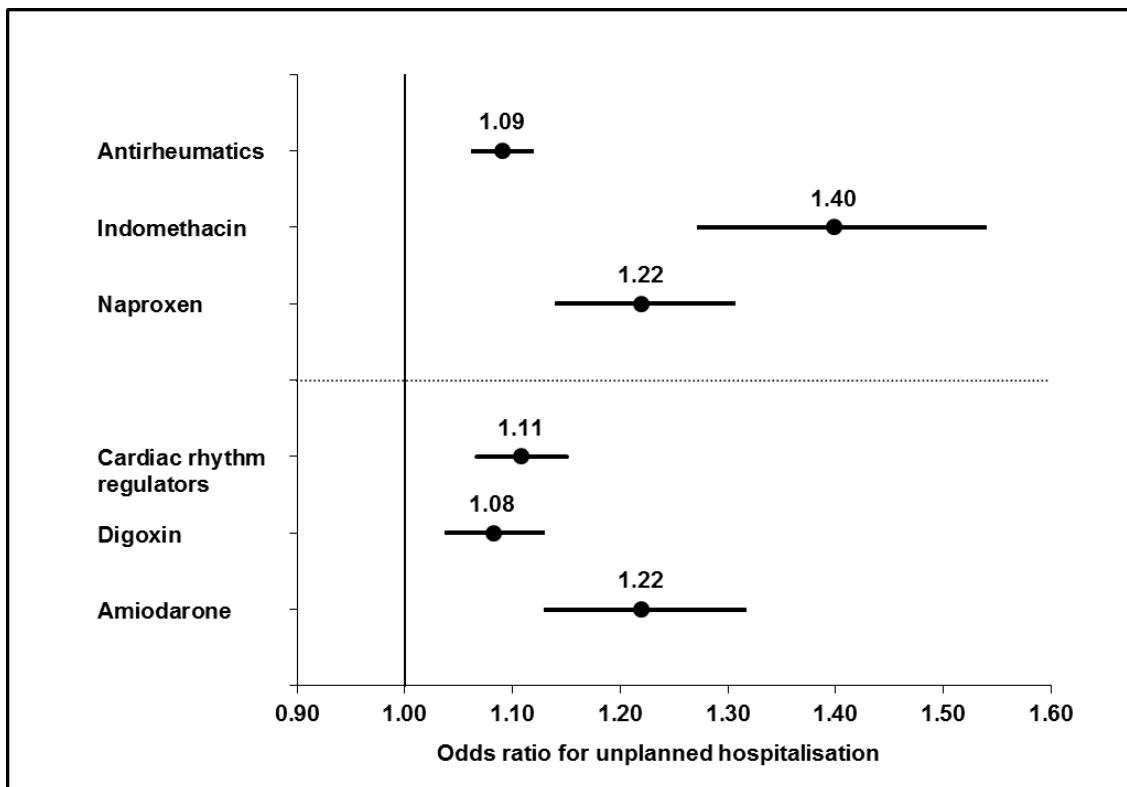
**Table 9-2 High-risk medications and unplanned hospitalisations in Western Australian elderly (1993-2005) - adjusted odds ratios and estimates of hospital admissions attributed to drug exposure<sup>a</sup> for combinations of high-risk drugs (HRDs) with specific potentially inappropriate medications (PIMs) from the Beers Criteria<sup>b</sup>**

Beers Criteria medication	Statistics	Anti-coagulants	Anti-rheumatics	Opioids	Cortico-steroids	Cardiac rhythm regulators	Beta-blockers	Hypertension drugs	Serum lipid-reducing agents
None (i.e. PIM intake not considered)	Adjusted odds ratio (OR) <sup>c</sup>	1.13	1.09	1.81	1.48	1.11	1.08	0.92	0.85
	95% confidence interval	(1.07-1.19)	(1.06-1.12)	(1.75-1.88)	(1.42-1.54)	(1.07-1.15)	(1.05-1.11)	(0.90-0.94)	(0.82-0.88)
	Attributed admissions (%)	2,960 (11.3%)	5,138 (8.3%)	20,539 (44.9%)	9,913 (32.2%)	4,360 (9.7%)	4,500 (7.4%)	-17,669 (-9.2%)	-12,323 (-17.8%)
Indomethacin (Antirheumatic)	Adjusted odds ratio (OR) <sup>c</sup>	2.36	1.40	2.97	1.54	1.72	1.47	1.13	1.26
	95% confidence interval	(1.43-3.90)	(1.27-1.54)	(2.40-3.67)	(1.12-2.11)	(1.31-2.25)	(1.21-1.80)	(1.00-1.28)	(1.01-1.56)
	Attributed admissions (%)	124 (57.6%)	1,048 (28.5%)	741 (66.3%)	137 (34.9%)	208 (41.9%)	236 (32.0%)	254 (11.7%)	135 (20.4%)
Naproxen (Antirheumatic)	Adjusted odds ratio (OR) <sup>c</sup>	1.87	1.22	2.13	2.11	1.11	1.32	1.05	0.96
	95% confidence interval	(1.26-2.79)	(1.14-1.31)	(1.81-2.51)	(1.69-2.64)	(0.90-1.35)	(1.14-1.53)	(0.96-1.14)	(0.82-1.11)
	Attributed admissions (%)	121 (46.6%)	1,216 (18.0%)	989 (53.1%)	431 (52.7%)	68 (9.6%)	299 (24.3%)	174 (4.6%)	-55 (-4.7%)
Temazepam (Hypnotic/sedative)	Adjusted odds ratio (OR) <sup>c</sup>	1.30	1.22	1.79	1.57	1.27	1.30	1.17	1.05
	95% confidence interval	(1.14-1.48)	(1.14-1.30)	(1.65-1.95)	(1.41-1.75)	(1.16-1.38)	(1.20-1.40)	(1.11-1.23)	(0.97-1.13)
	Attributed admissions (%)	915 (22.9%)	1,694 (17.9%)	4,630 (44.2%)	1,979 (36.3%)	1,592 (21.1%)	1,850 (22.8%)	3,898 (14.4%)	394 (4.5%)
Oxazepam (Anxiolytic)	Adjusted odds ratio (OR) <sup>c</sup>	1.15	1.16	1.77	1.58	1.34	1.24	1.03	1.05
	95% confidence interval	(0.90-1.47)	(1.05-1.29)	(1.54-2.03)	(1.33-1.88)	(1.16-1.55)	(1.10-1.40)	(0.95-1.11)	(0.92-1.20)
	Attributed admissions (%)	132 (13.0%)	440 (13.9%)	1,417 (43.4%)	617 (36.7%)	546 (25.5%)	523 (19.4%)	249 (2.8%)	126 (4.8%)
Diazepam (Anxiolytic)	Adjusted odds ratio (OR) <sup>c</sup>	1.37	1.38	1.78	1.60	1.22	1.18	1.25	1.01
	95% confidence interval	(1.05-1.78)	(1.23-1.54)	(1.55-2.04)	(1.32-1.93)	(1.03-1.44)	(1.03-1.34)	(1.15-1.37)	(0.88-1.15)
	Attributed admissions (%)	199 (26.8%)	737 (27.4%)	1,337 (43.9%)	505 (37.5%)	261 (18.0%)	317 (15.0%)	1,292 (20.3%)	15 (0.7%)
Digoxin (Cardiac rhythm regulator)	Adjusted odds ratio (OR) <sup>c</sup>	1.09	1.20	1.79	1.49	1.08	1.23	0.98	0.96
	95% confidence interval	(1.00-1.18)	(1.09-1.31)	(1.55-2.06)	(1.29-1.72)	(1.04-1.13)	(1.12-1.34)	(0.92-1.03)	(0.86-1.07)
	Attributed admissions (%)	672 (8.1%)	835 (16.4%)	1,767 (44.1%)	1,015 (33.0%)	2,586 (7.6%)	1,078 (18.5%)	-611 (-2.6%)	-240 (-4.4%)
Amiodarone (Cardiac rhythm regulator)	Adjusted odds ratio (OR) <sup>c</sup>	1.41	1.32	1.85	1.67	1.22	1.42	1.10	1.10
	95% confidence interval	(1.23-1.61)	(1.10-1.58)	(1.45-2.36)	(1.27-2.19)	(1.13-1.32)	(1.20-1.67)	(1.00-1.22)	(0.95-1.27)
	Attributed admissions (%)	865 (28.9%)	390 (24.1%)	703 (45.9%)	451 (40.0%)	2,098 (18.0%)	725 (29.5%)	790 (9.2%)	330 (8.9%)
Ferrous sulphate (Iron preparation)	Adjusted odds ratio (OR) <sup>c</sup>	1.54	1.24	1.62	1.50	1.16	1.46	1.08	0.98
	95% confidence interval	(1.22-1.95)	(1.09-1.42)	(1.35-1.94)	(1.21-1.85)	(1.00-1.34)	(1.26-1.69)	(0.99-1.17)	(0.85-1.15)
	Attributed admissions (%)	372 (35.2%)	407 (19.4%)	702 (38.2%)	362 (33.3%)	289 (13.5%)	574 (31.4%)	531 (7.3%)	-31 (-1.6%)

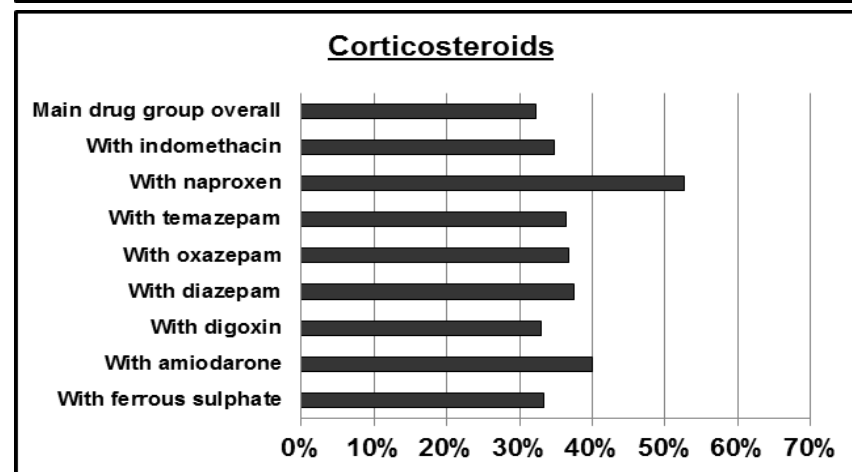
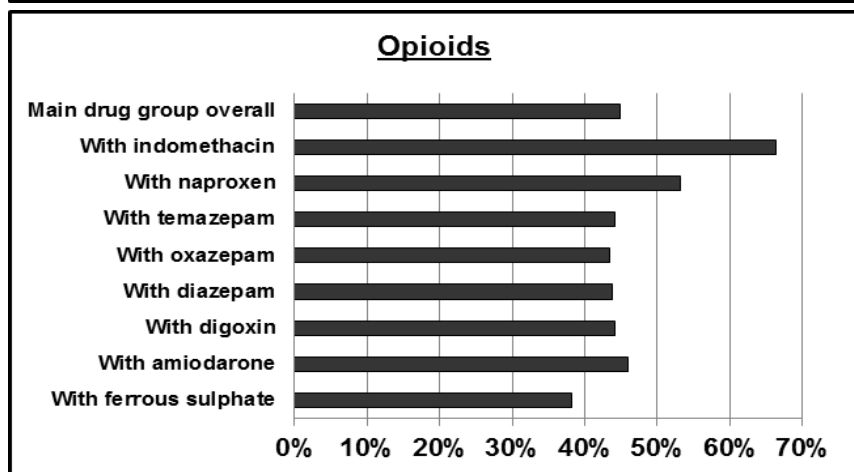
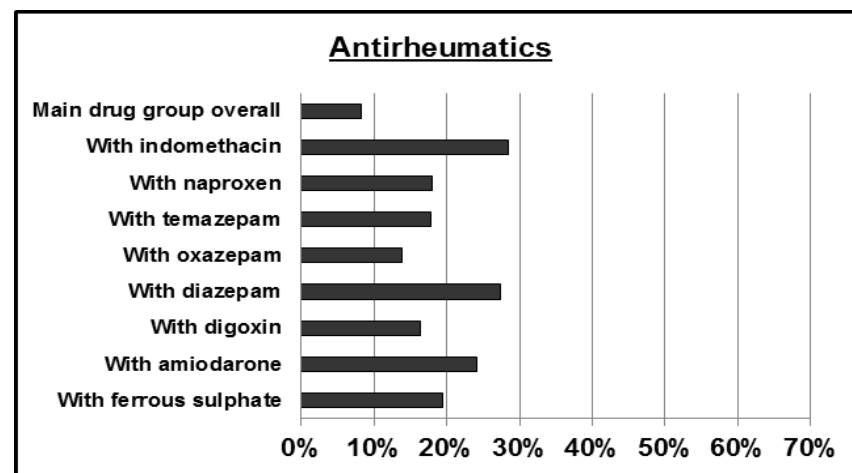
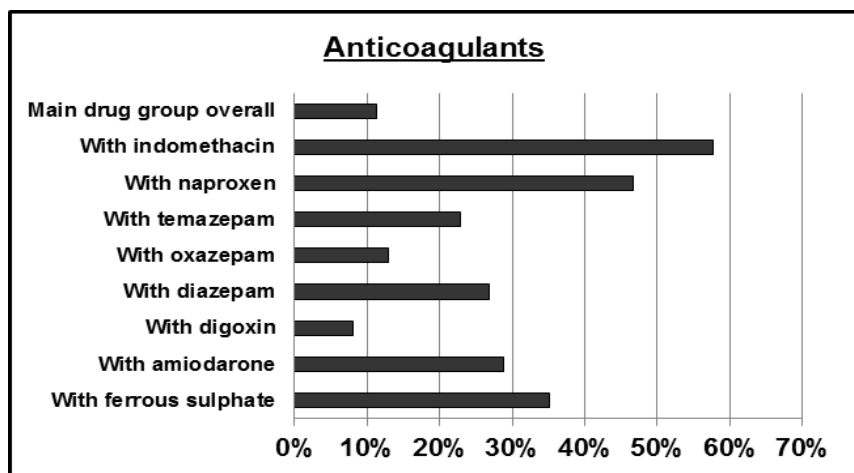
<sup>a</sup> Estimates of hospital admissions attributed to drug exposure in exposed index subjects (and corresponding proportions in parentheses) are shown in the table for each medication combination in rows labelled "Attributed admissions (%)"; proportion = attributable fraction (AF) = (OR-1)/OR and count = AF x number of index subjects exposed to PIM/HRD combination (as specified) at the time of hospital admission.

<sup>b</sup> For the World Health Organization Anatomical Therapeutic Chemical (ATC)<sup>163,201</sup> code specifications for the high-risk drug groups, please refer to Price et al. (2013).<sup>209</sup> ATC definitions for the specified Beers potentially inappropriate medications are as follows: indomethacin (M01AB01); naproxen (M01AE02); temazepam (N05CD07); oxazepam (N05BA04); diazepam (N05BA01); digoxin (C01AA05); amiodarone (C01BD01); and ferrous sulphate (B03AA07, B03AD03).

<sup>c</sup> Conditional logistic regression models were adjusted for the following time-dependent variables: nursing home status at the case or control time; hospital days, overall Charlson comorbidity index<sup>160</sup> and GP coverage percentage, all for the previous year; and a drug consumption profile for the preceding 90 days (plus the case or control date), which included the number of broad medication categories involved, the overall number of daily doses consumed (for any drug) and a count of daily doses for each broad drug category (except the high-risk drug group of interest).

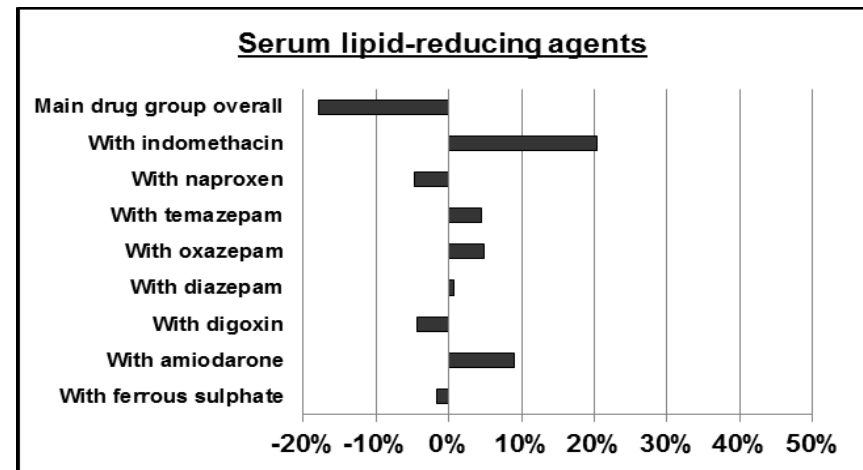
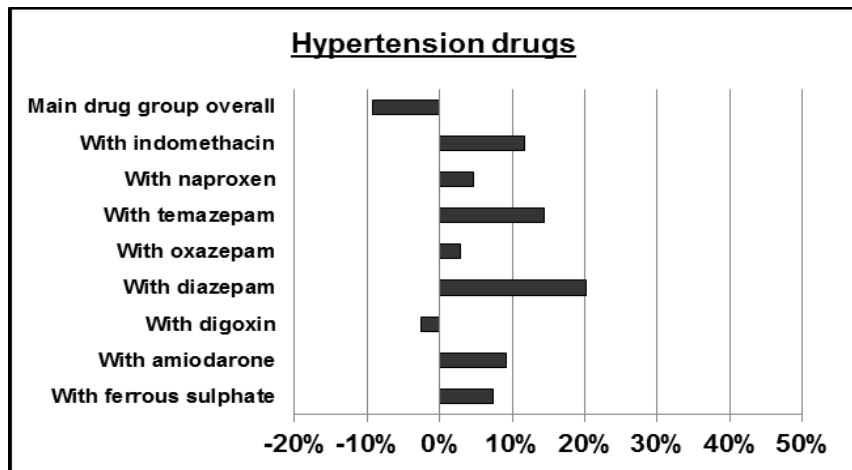
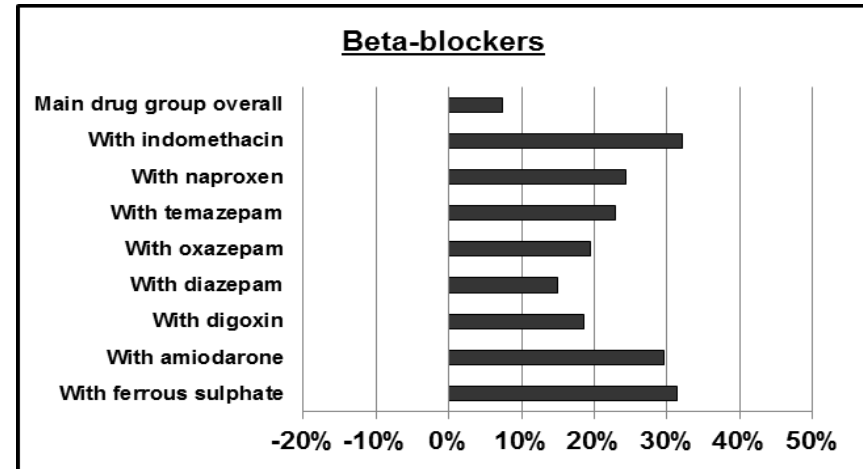
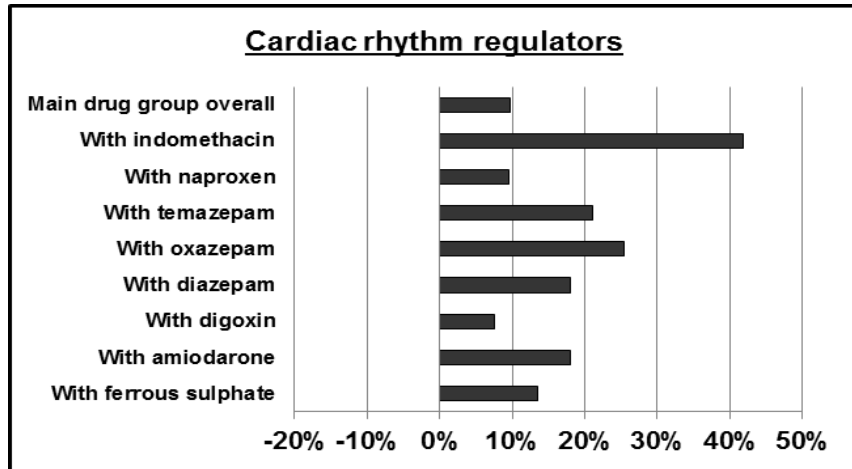


**Figure 9-1 High-risk medications and unplanned hospitalisations in Western Australian elderly (1993-2005) - adjusted odds ratios and 95% confidence intervals for antirheumatics and cardiac rhythm regulators and for specific medications from the Beers Criteria included in these broad classes of high-risk drugs**



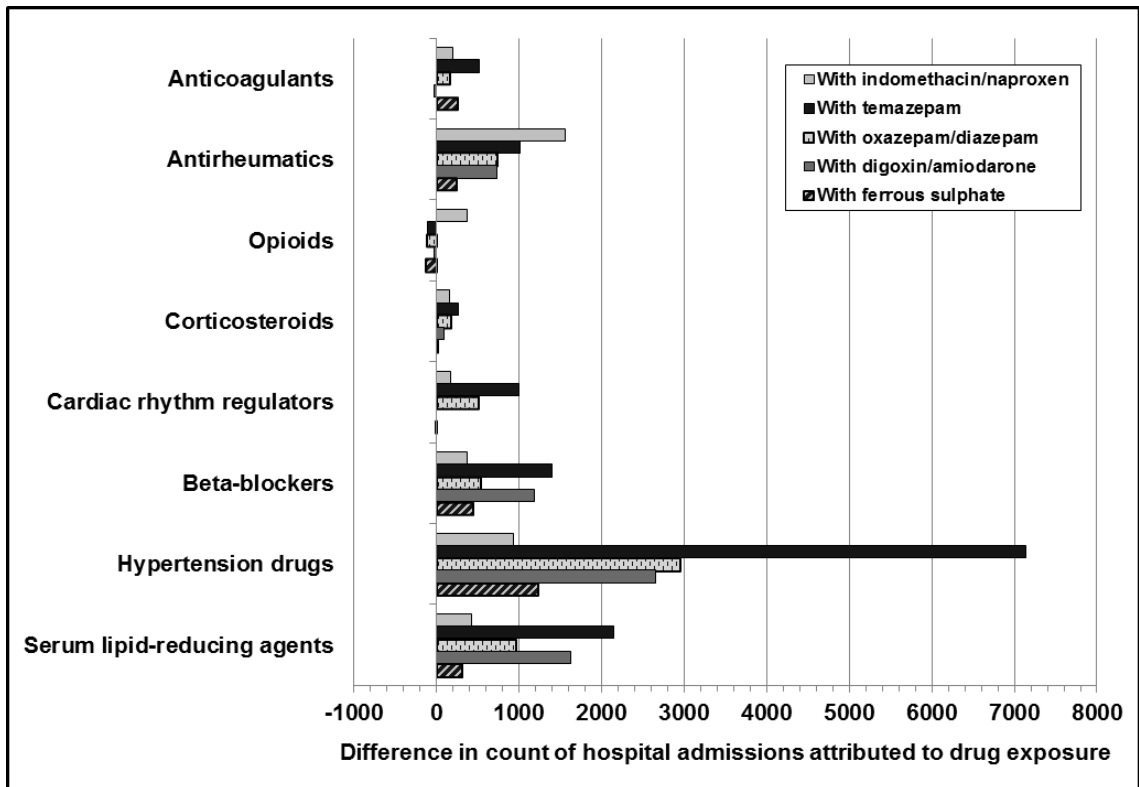
**Figure 9-2 High-risk medications and unplanned hospitalisations in Western Australian elderly (1993-2005) - estimated proportions of hospital admissions attributed to drug exposure<sup>a</sup> for combinations of non-cardiovascular high-risk drugs (HRDs) with specific potentially inappropriate medications (PIMs) from the Beers Criteria**

<sup>a</sup> Percentages shown in the diagrams represent estimated proportions of hospital admissions attributed to drug exposure in index subjects exposed to the main HRD group, overall or in combination with a given PIM (as specified); they are the attributable fractions (AFs) associated with the specified drug combination, where  $AF=(OR-1)/OR$  and  $OR=$ adjusted odds ratio.



**Figure 9-3 High-risk medications and unplanned hospitalisations in Western Australian elderly (1993-2005) - estimated proportions of hospital admissions attributed to drug exposure<sup>a</sup> for combinations of cardiovascular high-risk drugs (HRDs) with specific potentially inappropriate medications (PIMs) from the Beers Criteria**

<sup>a</sup> Percentages shown in the diagrams represent estimated proportions of hospital admissions attributed to drug exposure in index subjects exposed to the main HRD group, overall or in combination with a given PIM (as specified); they are the attributable fractions (AFs) associated with the specified drug combination, where  $AF = (OR - 1) / OR$  and  $OR = \text{adjusted odds ratio}$ .



**Figure 9-4 High-risk medications and unplanned hospitalisations in Western Australian elderly (1993-2005) - differences<sup>a</sup> in the estimated counts of hospital admissions attributed to drug exposure with concurrent intake of specific potentially inappropriate medications (PIMs) from the Beers Criteria**

<sup>a</sup> The differences shown were obtained by subtracting the 'PIM-negative' estimates (i.e. counts of unplanned hospitalisations that would be expected if all index subjects exposed to a HRD were unexposed to the specified PIMs) from the 'PIM-refined' estimates (i.e. those obtained by applying more explicit attributable fractions (AFs) to subsets of index subjects exposed to HRDs depending upon their concurrent PIM exposure status). For cardiac rhythm regulators, the difference related to digoxin/amiodarone has been suppressed as 98% of index subjects exposed to cardiac rhythm regulators were taking at least one of these two PIMs.



## CHAPTER 10 GENERAL DISCUSSION

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This major research project applied pharmacoepidemiological methods to linked health data from both Australian and WA Government sources to demonstrate their use in pharmacovigilance and medication prevalence applications. Along the way, it uncovered results with implications for policy and practice, detected a number of limitations and identified new avenues to explore. This final chapter discusses these important findings, concentrating on:

- The use of linked health data in WA pharmacovigilance applications
- Application of the case-time-control design in observational studies to estimate the risk of unplanned hospitalisation associated with drug exposure
- The apparent risk of unplanned hospitalisation related to high-risk drug use in elderly Western Australians
- Exposure to medications from the Beers Criteria in the WA elderly and the associated risk of unplanned hospitalisation.

The chapter concludes with an assessment of the overall significance and implications of the study and its findings, and presents ideas for future directions.

### **10.1 AUSTRALIAN LINKED HEALTH DATA IN PHARMACOVIGILANCE INITIATIVES**

As mentioned at the start of this thesis, this research project was among the first few to receive linked health data that brought together records originating from both Australian and WA Government sources. Although research based on WA linked health data is well established in this Australian state, the use of records maintained by the Commonwealth Government of Australia was another matter. Hence, it is worth taking the time to assess the various processes involved in setting up the linked project data, and to identify how these processes could be improved in the establishment of a more permanent research facility to support pharmacovigilance and other medication safety initiatives in Australia.

#### **10.1.1 DATA EXTRACTION AND LINKAGE PROCESSES**

Data extraction processes for this linked data project were part of the WA State/Commonwealth Cross-Jurisdictional Data Linkage program, which was

implemented in 2002. People more closely involved with the program implementation have likely provided their own feedback on its strengths and limitations. In particular, it is hoped that the program's overall governance, technical aspects of the data extraction and linkage, communication mechanisms and other program attributes have all been evaluated formally. The PhD candidate is not in a position to assess all of these program components. Nonetheless, some aspects of the program did affect data recipients and are worthy of comment here, from a researcher perspective.

Upon implementation of the program, data custodians and WA Data Linkage personnel undoubtedly worked very hard to isolate the required linkage keys, undertake the data linkage, and extract the data for each project. Given the expertise of the WA Data Linkage Branch,<sup>138,142</sup> the linkage process would certainly have been performed with utmost care, thus producing high quality links.

However, based on the data received, it was clear that records from Australian Government sources for the earlier years of the study were not as complete or accurate as more recent ones. This would have had some impact on linkage quality, especially for individuals who did not survive beyond the first few years of the study. The project's research team eliminated a number of related problems by restricting the study period to 1993 and beyond, despite receiving data from 1990 onwards. There were also a few issues with Medicare card recipients sharing their card with other family members, which occasionally resulted in the wrong person being specified on PBS records. Efforts were made to eliminate these patients from the study where possible (e.g. exclusion of individuals with health records post-death), but it would have been impossible to eliminate them all. Given the large size of the study cohort, it seems unlikely that these few glitches would have affected the study results to any great extent. Nonetheless, it is important to acknowledge their existence.

Fortunately, substantial improvements in the quality of health data from Australian Government sources have occurred over time, with the implementation of more extensive validation processes. In particular, the patient identification checks, now required at point-of-sale upon supply of prescription drugs, should eliminate some of the problems previously encountered due to Medicare card-sharing. These various measures will



ensure the generation of even better quality outputs from Australian pharmacoepidemiological research projects in future.

Perhaps the greatest lesson learned in relation to the cross-jurisdictional linkage program is the need for ongoing commitment, support and resourcing from all parties. Although everyone involved seemed quite enthusiastic about the program at the outset, changes in personnel over time and lack of additional resources to support the program's specific requirements proved costly to the researchers. The WA Data Linkage team was very helpful throughout the project. However, after some time, it became obvious that some senior Australian Government officers who oversaw the program no longer supported it. In fact, some of their actions threatened the successful completion of this project (and others). Furthermore, due to staff movements in lower Australian Government ranks, situations arose whereby no one was available with appropriate skills to understand the researchers' data specifications or to extract the required data. Most importantly, once the data were extracted, it was seldom possible to find anyone to respond to data-related queries. Should a more permanent Australian cross-jurisdictional health data facility be established, all of these issues should be taken into consideration, ensuring that adequate funds, personnel and expertise are available, not only for program governance, project negotiations and data extractions, but also for ongoing support of data recipients, especially in relation to metadata and the specific contents of extracted records from each data source.

#### ***10.1.2 ESTABLISHMENT OF A DRUG REFERENCE DATABASE***

Another essential component of this project was the establishment of a drug reference database. In the early stages, given the project's strong focus on exposure to medications (as well as unplanned hospitalisations), much emphasis was placed on exploring the pharmaceutical claims data, which had not previously been available in WA health research. Knowledge of which medications were supplied to each patient, the likely duration of each prescription, and estimation of the specific time period during which drug exposure could potentially cause an ADE were all crucial in the conduct of this study. Yet, the only variables supplied from the PBS database from which this information could be derived were a numeric item code, a supply date, and the

number of scripts involved (i.e. repeat prescriptions). Thus, obtaining the necessary details required some initiative and a considerable amount of effort.

Establishing a PBS reference database to meet these requirements was not without its challenges. Published schedules containing PBS details for the study period were not readily available in electronic format. The electronic files eventually supplied by the data custodians came in different formats, and much of the information required for calculations and drug classification was embedded within large text strings. Additionally, ATC codes for each PBS item had been allocated according to the classification that was current at the time the schedule was released and had to be reconciled with a specific ATC version. Furthermore, since the pharmaceutical claims did not include any details about prescribed dosage, average daily doses that reflected the likely prescribed dose for each item as accurately as possible had to be estimated. Half-life details and an estimated period of effect for each item were also required.

The tasks involved in obtaining all of this information in the appropriate format were performed very diligently, including the restructuring of input files into the right format; the creation of automated string parsing routines; manual checking, comparison and collation of information from multiple sources; and creation of verification programs to assess the proposed values. The work undertaken was undoubtedly adequate for the intended purposes. However, in retrospect, it would likely have been preferable if this work had been allocated to a separate project and resourced more adequately, and if the project outlined in the grant proposal had only been initiated once this infrastructure was well established. In other words, the set-up of medication resources for this project required a great deal more effort than had been anticipated.

Should a more permanent resource be established in future as a PBS reference database, additional work would be required to automate and refine the various processes further for ongoing use, minimising the need for manual checks where possible. For the allocation of average prescribed daily doses, the BEACH<sup>165</sup> data would still be useful. However, the BEACH summary statistics should be extracted for each strength of a given drug, as well as overall and by drug form, for greater accuracy. The WHO DDD<sup>146,204</sup> values may still be useful for some drugs, but experience from this project has shown that these values

are generally best reserved for international drug utilisation comparisons, as quite often they do not reflect Australian prescribing patterns adequately. For some studies, especially those that concentrate on medications used in the treatment of chronic diseases, it would also be worth exploring the possibility of allocating daily dose parameters to each patient individually, based on their own specific prescribing patterns (i.e. periodicity of drug supply). This may not be possible to achieve on a large scale, but would likely be appropriate in more targeted studies focusing on a small number of drugs.

Ultimately, all allocated daily dose values, as well as half-life and period of effect estimates, should be reviewed by an expert consensus panel before being adopted for ongoing use. This was initially intended for this project. However, the review of more than 3,000 entries in this manner proved to be unfeasible, given time and resource constraints. Additionally, the validation routines developed to verify the daily dose allocations could be refined further. Moreover, for ongoing therapeutic drug surveillance, processes would need to be put in place to update the drug reference information on a regular basis. All of these tasks would ideally require dedicated resources in the establishment of a more permanent Australian pharmacovigilance facility. Of course, much of this work, especially in relation to average daily doses, would become unnecessary if the prescriber's dosage instructions were recorded explicitly on the PBS database for each pharmaceutical claim. Hopefully, this proposed alternative will one day become reality.

### ***10.1.3 LINKED HEALTH DATA IN SUPPORT OF AUSTRALIAN PHARMACOVIGILANCE***

This project has certainly shown that linked health data involving Australian pharmaceutical claims and other health records (from both national and state-based sources) can play a useful role in the conduct of observational studies in support of Australian pharmacovigilance. Despite some limitations, the project was able to examine drug use patterns in elderly Western Australians and provide some measures of the effects of medication exposure on unplanned hospitalisation in this population.

However, it is important to recognise that, like most other studies involving large administrative health databases, the analysis could only identify associations between potential predictive factors and drug exposure, and between drug exposure and unplanned hospitalisation. In other words, one should be highly

cautious in drawing any causal inferences using observational studies of this nature. Furthermore, despite making every effort to control for potential confounding, the derived estimates (e.g. ORs, AFs and counts of hospitalisations attributable to drug exposure) were likely affected to some extent by some residual bias. This issue is discussed in more detail in section 10.2. Nonetheless, the estimates derived from this study are certainly a good starting point in the identification of medications associated with potential safety issues in the elderly, and for which further investigations appear warranted.

Another point to consider when using Australian pharmaceutical claims in pharmacoepidemiological studies is the fact that dispensed drug prescriptions are only recorded on the PBS database if the incurred cost is beyond a specified co-payment threshold. This is less of an issue for elderly patients, most of whom receive a concession as senior citizens. Consequently, their co-payment threshold is very low and most of their dispensed drugs are recorded on the PBS database. For younger populations, one may be tempted to conclude that the study of more expensive drugs would be appropriate (i.e. those with an allocated cost above the co-payment threshold applicable to the general population). This would certainly be true for prevalence studies. However, in many studies that examine the relationship between drug exposure and specific outcomes, parameters of overall drug intake are desirable in the analysis to adjust for potential confounding factors. Thus, most often, there is a need to assess coverage issues associated with PBS co-payment thresholds beyond their direct impact on the specific medications being studied.

The pharmaceutical claims used in this study also excluded over-the-counter medications and those dispensed from public hospitals. Some of these coverage issues will continue to exist in future Australian studies, as it is unlikely that records of over-the-counter drug purchases will become available in central data repositories any time soon. However, the PBS data collection is making some progress in the implementation of data capture systems to record the dispensing of medications prescribed from public hospitals. Full capture of hospital prescriptions would certainly improve the overall coverage of drug prescribing in Australian research.

The establishment of an ongoing pharmacoepidemiological research program involving linked Australian health data should build upon the experiences of this

project and of other research involving Australian pharmaceutical claims. These research initiatives all contribute to a better understanding of PBS claims and of how they can be used in combination with other data in medication prevalence, safety and effectiveness applications.

## **10.2 THE CASE-TIME-CONTROL DESIGN**

The case-time-control design<sup>26</sup> was used quite extensively in this research project to estimate the relative risk of unplanned hospitalisation associated with exposure to specific medications. Although the strengths and limitations of this design have already been discussed in the manuscripts presented in this thesis, it is worth expanding on these deliberations here, focusing on the appropriateness of the case-time-control design in our research and on whether the approach used could be enhanced further in future applications to better control for potential bias.

### **10.2.1 APPROPRIATENESS OF THE STUDY DESIGN**

As mentioned previously, the case-time-control design is best suited to applications involving intermittent exposures, transient effects and acute events, as per the case-crossover design.<sup>149,150</sup> Given their unexpected nature, unplanned hospital admissions (the adverse outcomes of interest in this study), can certainly be classified as acute events, especially those that are associated with the harmful effects of medications. Generally speaking, medications are taken intermittently and most have short-term (i.e. transient) effects.

However, it should be acknowledged that at least some of the medications examined in this study, especially those used in the treatment of chronic conditions, are commonly prescribed for long-term use. This would certainly apply to some cardiovascular and psychotropic medications. Given the long-term use of these medications, some related adverse effects might develop as a result of cumulative drug exposure and may be more chronic in nature. For subjects taking these medications, both the exposure status and the harmful effect that could potentially lead to an unplanned hospitalisation would not alter between the 'case time' and 'control time' windows. Consequently, they would not be included in analytical models, as only discordant pairs are taken into consideration in conditional logistic regression analysis. This would reduce the power to detect adverse events related to drug exposure in these circumstances. Nonetheless, the case-time-control design would still detect the

impact of serious adverse outcomes associated with the introduction of these medications into patients' treatment regimens, the effects of which would generally be transient.

### **10.2.2 CONTROL FOR POTENTIAL BIAS**

Epidemiological studies involving large administrative databases, such as this one, are recognised for their increased power to detect associations between exposures and outcomes of interest. Conversely, at times they are also criticised for the lack of information available to control for potential confounding factors in the analysis. Case-crossover and case-time-control designs get around this problem to some extent, through the use of intrinsic 'self-control', which eliminates the need to include static within-subject characteristics (known and unknown) in multivariate regression models. Although the case-crossover design may be unable to control for unknown time-dependent variables, the case-time-control design has good potential to do so by introducing matched reference subjects. However, this can only be effective if the rates of change of the main exposure variable, of unmeasured confounding factors and of the outcome of interest progress as a similar trend in both index and reference subjects.<sup>27</sup>

In this study, the researchers attempted to satisfy this assumption to the greatest extent possible by selecting reference subjects from a pool of patients who were being treated for similar health conditions as the index subjects (i.e. all had taken medications prescribed for similar indications and all were at risk of being prescribed the medications of interest). Furthermore, reference subjects were selected at random and matched to index subjects based on gender, year of birth and an overall indicator of ongoing GP care (or nursing home status in one study component). Recognising that this might not be sufficient to control for all potential confounding effects, the candidate also chose to enhance the case-time-control design initially proposed by Suissa<sup>26</sup> by including as many relevant time-dependent variables as possible in the multivariate regression models (especially those related to health status and medication intake) to further adjust for measurable time-varying factors. The availability of such variables was increased through the use of linked health data. Furthermore, robust sandwich covariance estimates<sup>172</sup> were generated to

account for the potential within-cluster correlation associated with multiple hospitalisations per person.

These additional precautions would certainly have enhanced the base model associated with the case-time-control design. However, in some instances at least, they were likely insufficient to eliminate all potential biases, especially in relation to protopathic bias or confounding by indication.<sup>152</sup> Very accurate measures of disease progression over time would be required to do so, which could not be produced readily due to data limitations. Improved disease severity measures would not only permit closer matching of reference subjects with index subjects, but would also allow additional variables of disease severity to be introduced in the regression models to adjust for related confounding effects. In future, it may be possible to rectify this problem somewhat by including patient survey details or additional health care data from other sources (e.g. GP consultation summaries, information extracted from hospital inpatient notes, etc.) in the data linkage process. Given related confidentiality, ethics and data collection issues, it is unlikely that this could be achieved on a large scale in WA in the near future, at least not at a population level. Nonetheless, these options should be contemplated in smaller, more targeted studies that are similar in nature to this one. Furthermore, greater comparability in the matching of index and reference subjects may be possible in future studies through the inclusion of health measures applicable around the time of the index admission (especially ones related to disease status and severity), as additional or alternative matching criteria.

Despite these suggested improvements, the overall approach used in this study should still be considered to be an appropriate choice for conducting research of this nature, given the broad scope of the study and its intended purpose (i.e. general medication safety surveillance). Of course, the case-time-control design may not be suitable in all situations. A full range of available study design options should always be considered before making a decision on the approach that is most appropriate in each new medication-related application.

### **10.2.3 INCLUSION OF MULTIPLE HOSPITALISATIONS PER PATIENT**

A further variation of the case-time-control design incorporated into the study protocol was the inclusion of some patients multiple times as index cases (i.e. once for every unplanned hospitalisation occurring within the relevant time

period). It is true that, by including patients as index cases more than once in the analysis, there is an increased chance that the 'control time' selected for a given index case will in fact be a 'case time' for that patient as well (i.e. immediately followed by the outcome of interest). This could potentially result in a reduction in the number of discordant pairs in the conditional logistic regression models, if one assumes that the patient has a similar profile (including drug intake) at both case and control times, given that the control time is also a case time. This may dilute the results or, at the very least reduce the ability to detect an apparent effect of exposure.

Conversely, it is also possible that a hospitalisation that precedes a given index case time may be associated with a number of factors that might influence both the likelihood of medication exposure and of a subsequent hospitalisation. This could manifest itself as an increase in the apparent effect of exposure on unplanned hospitalisation when multiple index cases are included per person.

Alternatively, hospitalisations preceding case times might produce underestimates in relation to medication exposure, since prescriptions during a hospital stay were not recorded on the PBS dataset. Thus, some subjects might have been classified as 'unexposed' at case time when they were actually 'exposed'. This could potentially reduce the magnitude of odds ratios in this instance.

By comparison, the inclusion of only the first hospitalisation per patient would certainly reduce the power of the study, since patients averaged around four unplanned hospitalisations (i.e. four index cases) in each sub-study. Furthermore, because index subjects were selected over a period of 11½ years, the analysis would likely be biased towards prescribing patterns in the earlier part of the study period if only the first outcome event were selected per patient. In sub-studies involving drug groups comprised of multiple medications, this would possibly produce higher odds ratios than those reported, given that, over time, newer safer medications would likely have superseded older ones in each drug group.

These various issues were taken into consideration while developing the study design. However, in light of past experience in the use of WA hospitalisation data, it was felt that the proportion of 'control' times that would occur during or immediately prior to another previous hospitalisation would be very low; that



most hospitalisations would be of short duration; and that the scenarios experienced by the index subjects would also apply to the reference subjects, which controlled to some extent for potential time trend effects (including the likelihood of hospitalisation). Furthermore, the inclusion of a large number of variables in the analysis to represent each subject's health and medication profile prior to the case or control time (including the number of hospital days for a one-year period immediately preceding the times of interest) would further adjust for potential bias associated with the factors outlined above. Thus, given the study's long duration, it was felt that the additional power obtained through the inclusion of all unplanned hospitalisations for each patient, as well as the more comprehensive sampling over time associated with this approach, would likely outweigh the confounding issues that might be introduced by the possible unadjusted effects, in a small number of subjects, of factors associated with hospitalisations occurring shortly before certain case times.

To verify this rationale, additional analyses were conducted on two high-risk drug sub-studies presented in chapter 4, for which extensive sensitivity analysis was undertaken (i.e. corticosteroids and opioids). In this instance, only the first unplanned hospitalisation for each person was selected as an index subject. The case and control times for the selected index subjects and their matched reference subjects were then included in the regression models. For corticosteroids, the revised model yielded very similar results to the one involving all unplanned hospitalisations per patient - i.e. adjusted odds ratio 1.51 (95% CI 1.38-1.65) vs. 1.48 (1.42-1.54), although, as expected, the confidence interval was wider, primarily due to the smaller number of subjects. For the opioid sub-study, the revised model produced higher adjusted odds ratios than the analysis involving multiple unplanned hospitalisations per patient - 2.21 (2.04-2.38) vs. 1.81 (1.75-1.88). These results likely reflect improvements in the safety of newer opioid analgesics (which are under-represented in this subset model) over time, but may also be influenced by other factors already discussed. In any event, it seems the results presented in this thesis are more likely to underestimate than overestimate apparent effects of medication exposure on unplanned hospitalisations, at least in relation to this type of potential confounding.

### **10.3 UNPLANNED HOSPITALISATIONS RELATED TO HIGH-RISK DRUGS IN ELDERLY WESTERN AUSTRALIANS**

The first study component in this project examined associations between exposure to medications from broad groups of high-risk drugs with unplanned hospitalisations in elderly Western Australians. It derived estimates of the number and proportion of drug-related unplanned hospitalisations for each drug group (among the exposed), and compared these estimates with corresponding figures obtained from ADE-related ICD external cause codes recorded on inpatient discharge summaries.

#### **10.3.1 FINDINGS RELATED TO SPECIFIC HIGH-RISK DRUG GROUPS**

The study results indicated that older patients taking opioid analgesics and corticosteroids were at particularly high risk of unplanned hospitalisation, whereas exposure to hypertension drugs and serum lipid-reducing agents appeared to have an overall protective effect. As discussed in chapter 4, these findings suggest that clinicians should be particularly vigilant when they contemplate prescribing opioids and corticosteroids to their older patients, considering other alternatives (including non-drug options) where possible, or monitoring these patients very closely otherwise. Of course, it would be useful to know if specific medications within these drug classes are particularly responsible for this apparent high risk. Furthermore, additional research seems warranted to examine the profile and circumstances of patients taking these drugs more extensively, seeking to determine why these patients are more prone to unplanned hospitalisation, and attempting to identify preventive measures that would reduce unplanned hospitalisations associated with these specific drug groups.

For both the drug groups associated with an increased risk of unplanned hospitalisation and those with an apparent protective effect, there is also a need to refine the analytical models or apply alternative approaches, preferably with more extensive patient details, to further examine the possibility of protopathic bias. This type of bias may either increase or decrease the apparent risk of a particular outcome.<sup>152,254</sup> For instance, patients may start taking a certain drug to treat the early manifestations of the acute illness episode that is destined to result in an unplanned hospital admission. Although their apparent elevated risk of hospitalisation might be the result of drug-related adverse effects, it could also be due to this form of reverse causation. Conversely, clinicians may stop

prescribing certain medications to their patients (especially preventive drugs such as hypertension and serum lipid-reducing agents) because they are experiencing early symptoms of an event that will eventually require inpatient care. This scenario would manifest itself as an inverse association between medication intake and unplanned hospitalisation, giving the false impression of a preventive drug effect. Arguably, these examples of protopathic bias are subtly different from the confounding by indication without reverse causation that can arise when there is a more gradual progression in underlying disease severity over time that leads both to a greater propensity for clinicians to prescribe a medication and concurrently a higher risk of unplanned hospitalisation due to new complications of the illness. The case-time-control method arose as a further development of the case-crossover design in an effort to adjust for the latter type of confounding by indication without reverse causation, but is unlikely to be effective in the former situation where the drug exposure is caused in reverse by the early manifestations of the outcome.

The study component presented in chapter 4 applied different analytical models to the data to investigate whether unadjusted disease progression might have been responsible for the elevated risk of unplanned hospitalisation in relation to opioid and corticosteroid exposure. Our results seemed fairly robust, regardless of the control measures used. Nonetheless, the possibility of protopathic bias could not be excluded altogether, given the limitations of the study's administrative data. In other words, these results should be treated with some caution, until they can be replicated elsewhere, preferably in settings where more extensive patient details are available.

### **10.3.2 COMPARISON AGAINST ADEs RECORDED ON INPATIENT RECORDS**

This same study component found that the estimated number of unplanned hospitalisations attributed to medications from each high-risk drug group was substantially higher (up to 31-fold) when derived from the case-time-control design, as opposed to ADE-related ICD external cause codes recorded on inpatient discharge summaries. Although unadjusted confounding factors may possibly be responsible for a certain degree of over-inflation in the estimates derived from the case-time-control design,<sup>152,254</sup> ADE under-reporting on inpatient discharge records is likely the main reason of this discrepancy. This premise is certainly supported by existing literature.<sup>17-20</sup>

Thus, the study findings provide further evidence for the need to improve the accuracy and completeness of clinical coding in relation to ADE-recording on WA inpatient records or, alternatively, to exercise much increased caution in relying on their accuracy. Physicians also need to be made more aware of ADE-related symptoms for specific drugs, since it is suspected that medication exposure is often omitted as a possible root cause of presenting symptoms. Thorough investigations are particularly important when patients are taking medications, to ensure that those who present with ADEs receive adequate treatment.

## **10.4 BEERS MEDICATIONS IN THE WA ELDERLY**

Although this project conducted some exploratory work involving known high-risk drugs in the elderly, the core of the research focused on a general list of drugs to be avoided in all older people, based on the 2003 Beers Criteria. What has this project taught us about these drugs in the WA elderly? This section discusses the major findings.

### **10.4.1 PIM PREVALENCE AND PREDICTING FACTORS**

Forty-three individual PIMs from the general Beers list were prescribed to our elderly WA population during the period 1993-2005, which represented 31 of 49 general PIM categories. As reported in relation to many countries outside North America,<sup>10,36,67,106,118,255</sup> a number of listed medications were unavailable in Australia during that period or became less commonly used over that time. This highlights the need to tailor PIM lists according to local drug availability, and to update them regularly.<sup>12,36,106</sup> The updates should not only be based on current drug availability, but should also reflect changes in the empirical evidence accrued for each medication in relation to drug safety in the elderly.<sup>111</sup>

Despite the unavailability of certain PIMs in Australia, overall PIM exposure was quite high in the WA elderly population over the study period. Three-quarters of the patients included in the study cohort were exposed to PIMs during that time, the cohort consuming 109,415 PIM daily doses/1000 person-years (i.e. an average of 109 PIM daily doses per person per year).

Both the proportion of older people exposed to PIMs and the rate of exposure declined over time. This may have occurred partly because some listed PIMs were removed from the market or because safer drugs became available.

However, prescribers' increased awareness of PIMs and of their higher propensity to cause harm in older people hopefully contributed to this decline. The annual proportion of older Western Australians exposed to PIMs was still around 40% by the end of the study, however, suggesting that there is still much work to be done in raising awareness of the potential harm associated with these drugs in older people.

The high level of exposure to various benzodiazepines from the Beers list was especially alarming in the study population. In particular, the sedative temazepam was dispensed to 35% of the study cohort during 1993-2005. Digoxin, naproxen, piroxicam, nifedipine, amitriptyline were other commonly used PIMs. As a starting point, ADE prevention measures should perhaps concentrate on raising awareness of the potential harm associated with these particular drugs in older Western Australians.

Prevention initiatives should target all older people and those who care for them, but could possibly focus more specifically on sub-groups at greatest risk of PIM exposure. Results from this study suggest that these sub-groups should include older people who take a large number of different drugs, those who consume large quantities of medication, and those who live in high-level aged care facilities. Of course, this study was restricted to available data. Certain prescriber and health service characteristics may also be associated with a high risk of PIM prescribing.<sup>108</sup> However, evidence in relation to these other factors is currently limited, restricting our ability to determine their influence in relation to PIM exposure. Further research in this area is undoubtedly warranted.

#### **10.4.2 PIM ASSOCIATIONS AND ESTIMATED EFFECTS ON UNPLANNED HOSPITALISATIONS**

Of greatest interest in this study was the estimated effect of PIM exposure on the likelihood of unplanned hospitalisation, in terms of both relative and absolute risk. Related estimates were derived for all PIMs combined and for individual PIMs. They were compared for sub-groups receiving different levels of ongoing GP care, and between residents of high-level aged care facilities and other elderly people. Furthermore, the effects of specific PIMs were assessed in patients taking medications from broad high-risk drug groups.

This study estimated a statistically significant 18% increase in the risk of unplanned hospitalisation in elderly Western Australians taking PIMs, after adjustments for general time trends in this population (through the use of

reference subjects) and changes in individual patients' measurable health status indicators and medication intake over time. This risk increased with the number of different PIMs and PIM quantity (i.e. daily doses) taken. Furthermore, in exposed index subjects, nearly 2,000 unplanned hospitalisations per year (15%) were attributed to PIM exposure, in an annual elderly population of ~170,000 people. These figures represent a substantial risk and add to the mounting evidence on the potential harm associated with the use of Beers' medications in the elderly. Thus, it is important to find appropriate mechanisms to restrict the use of these medications in elderly Western Australians as much as possible.

Although some of the PIMs associated with a particularly high relative risk of unplanned hospitalisation may no longer be prescribed very frequently in the WA elderly, at least not in a community setting (e.g. meperidine/pethidine, thioridazine, and promethazine), others (e.g. nitrofurantoin and indomethacin) were still commonly prescribed in this population by the end of the study period. Since these drugs are still on the Australian PBS, prescribers should be encouraged to avoid them in older people whenever possible. However, for the greatest impact in minimising PIM-related ADEs in older Western Australians, prevention efforts should promote the avoidance of PIMs attributed the most unplanned hospitalisations. In our study, this included several benzodiazepines (temazepam, oxazepam and diazepam), some cardiac rhythm regulators (e.g. digoxin and amiodarone), the NSAID naproxen, and ferrous sulphate.

Our results suggest that PIM-related ADE prevention measures should be directed towards all older people, but especially towards those who have the poorest health and are taking many different drugs, as these people are the most vulnerable and have the highest rates of PIM-related ADEs. This includes elderly people residing in high-level aged care facilities and those in greatest need of ongoing GP care. For all elderly, the prescribing of Beers medications should be strongly discouraged. However, in situations where this is virtually unavoidable and clinically justified, our study suggests that close GP monitoring may help reduce the risk of PIM-related ADEs to some extent.

In regard to the project's last study component, it is well established that polypharmacy and drug interactions are associated with an elevated risk of ADEs.<sup>1,9,17,93,256</sup> Thus, it was not surprising to find that specific PIMs linked with

an elevated risk of unplanned hospitalisation increased the risk of drug-related hospitalisation when taken in combination with medications from known high-risk drug groups. In general, the observed effects of exposure to specific PIMs in sub-groups of patients taking different high-risk drugs were concordant with those obtained from the main PIM study that examined the impact of these drugs in all elderly. For example, as per the main study, indomethacin had a particularly high impact on relative measures of effect and temazepam on absolute measures of the burden of drug-related unplanned hospitalisations when taken in combination with known high-risk drugs. These results further emphasise the need to avoid these specific PIMs in the elderly, not only on their own, but particularly in combination with common high-risk drugs. This study component also reiterated that amiodarone appears riskier than digoxin as a cardiac rhythm regulator, and provided support for the inclusion of indomethacin and naproxen on the Beers list, since these drugs (especially indomethacin) were associated with a significantly higher risk of unplanned hospitalisation than suggested by the corresponding OR for all antirheumatic drugs.

## **10.5 RESEARCH SIGNIFICANCE AND IMPLICATIONS**

This study demonstrated the use of Australian cross-jurisdictional linked health data in drug safety research, with a focus on pharmaceutical claims and unplanned hospital admissions. In the process, it established an Australian pharmaceutical reference database, defined major drug groups and Beers medications using an international drug classification, created a set of computer programs, and developed an approach for identifying potentially harmful medications that shows great promise as part of a pharmacovigilance monitoring system.

Through better understanding of which potentially inappropriate medications are being prescribed to older Western Australians, of the patient characteristics and circumstances that lead to risky prescribing, and of which drugs and drug combinations are associated with the greatest risk of unplanned hospitalisation, this study may help better inform drug prescribing policies and guidelines in Australia and elsewhere.

In particular, given the high prevalence of Beers medication intake in elderly Western Australians and the apparent increased risk of unplanned hospitalisation in older people taking these drugs, it may be beneficial to use the

results of this study and the updated Beers Criteria as a starting point to establish an Australia-specific list of medications to be avoided in the elderly. The latter would complement the prescribing appropriateness indicators<sup>61,62</sup> and other tools used in Australia (e.g. Drug Burden Index)<sup>74,257,258</sup> to guide clinicians and measure the quality of prescribing practices in this country.

## **10.6 FUTURE DIRECTIONS**

This study has also identified other avenues to explore in pharmaco-epidemiological research. Refinements of the analytical methods are still possible and could be investigated and validated further. It would also be beneficial to repeat the high-risk drug component in settings with greater access to extended patient information, especially in relation to opioids and corticosteroids, to confirm that research findings did not result from uncontrolled time-dependent confounding and to identify specific medications that are associated with the greatest risk of serious harm. Furthermore, there is a need to delve more deeply into the role of ongoing GP care in the prevention of PIM-related hospitalisations, especially in relation to the characteristics of patients with the least regular contact with their GPs. Similarly, it would be useful to know with greater certainty why high-care nursing home residents seem more susceptible to PIM-related hospitalisations than other elderly people when taking increased quantities of Beers medications.

Finally, it is worth highlighting that the methods adopted in this study could be applied to an unlimited number of therapeutic drugs and drug combinations. The study's broad scope and constraints of the administrative health data may have restricted the researcher's ability to perform the analysis with the same level of control as would be expected from a randomised clinical trial, for instance. However, a greater focus on specific drugs should ensure that subsequent work in this area is more targeted and better adapted to the specific requirements of the medications of interest, guided by the findings of this study and other results presented in the literature. This is where the true value of this research will become apparent. The present study has simply opened the door to more in-depth exploration of the potential harm of certain medications in elderly Australians and possibly other populations.



## 10.7 CONCLUSION

This project is a small, yet significant component in the development of Australian pharmacoepidemiological research in support of medication safety monitoring. The project should not be viewed in isolation, however. Several other Australian initiatives have made a contribution towards medication safety in this country, including spontaneous reporting mechanisms established by the Therapeutic Goods Administration in 1970,<sup>259</sup> the Drug Utilisation Sub-Committee within the Pharmaceutical Benefits Advisory Committee,<sup>260</sup> the Quality Use of Medicines partnership<sup>261</sup> and NPS MedicineWise<sup>262</sup> (more commonly known as the National Prescribing Service<sup>263</sup> until recent years) within the National Medicines Policy<sup>264</sup> framework, the Medication Safety program of the Australian Commission on Safety and Quality in Health Care,<sup>265</sup> and others. It is also important to acknowledge the analysis performed on Australian pharmaceutical claims data by the Quality Use of Medicines and Pharmacy Research Centre<sup>266</sup> in South Australia, and the '45 and Up Study'<sup>267</sup> in New South Wales, for instance. All of these endeavours, including this project, are helping us gain a better understanding of Australian medication-related policy requirements, of PBS records, and of how the latter can be used in combination with other data in medication prevalence, safety and effectiveness applications.

As this project reaches its conclusion, it is hard not to reflect upon its achievements and where they all lead. In doing so, the title of two journal articles from Australian researchers spring to mind. The first, from Kelman et al., states: "Evaluating medicines: let's use *all* the evidence".<sup>268</sup> It seems it is high time for Australia to establish a more permanent and ongoing platform for conducting pharmacoepidemiological research into the safety and effectiveness of medications, one that involves the linkage of administrative data from various sources, including national and state-based agencies. This requires the collaboration of relevant bodies from around the country, including researchers, policy-makers, government agencies, data custodians, and others. The Quality Use of Medicines and Pharmacy Research Centre has recently formed an affiliation with the Asian Pharmacoepidemiology Network (AsPEN),<sup>136</sup> which should be beneficial. However, ultimately, Australia should strive to establish its own network of pharmacoepidemiological research to support pharmacovigilance, with an integrated linked health data system at its core. Continued

efforts towards this goal by all parties involved should see it come to fruition, but there is no room for complacency.

The other journal article title that deserves to be highlighted in these concluding remarks is this one, from Roughead and Lexchin: “Adverse drug events: counting is not enough, action is needed”.<sup>269</sup> Given its overall aim, this project has focused on the exploration of Australian linked health data and the development of mechanisms to obtain relevant statistics for monitoring medication safety. Generating statistics to assess the magnitude of the problem is certainly important, but we must not lose sight of the ultimate purpose of this information. The results derived from this study and others must be used to develop, implement and evaluate appropriate measures for improving the quality of prescribing and for preventing ADEs in elderly people from WA and elsewhere. Evidence of better health outcomes in relation to medication intake in this most vulnerable population group (especially in terms of ADE reduction rates), following the implementation of preventive measures inspired by our study results, would provide true justification for our efforts. It is hoped that at least a small spark of inspiration towards this most important cause is being ignited through the dissemination of these study results.

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# APPENDICES

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## **APPENDIX A. ETHICS APPROVAL CONFIRMATION DOCUMENTS**

This appendix includes copies of the correspondence received from The University of Western Australia's Human Research Ethics Committee to confirm the project's initial ethics approval and subsequent extensions.



THE UNIVERSITY OF  
WESTERN AUSTRALIA

Research Ethics  
Research Services  
M459

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Telephone: (08) 6488 3703  
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[http://www.research.uwa.edu.au/human\\_ethics](http://www.research.uwa.edu.au/human_ethics)

Our Ref. RA/4/1/1212

23 May 2005

Professor C D J Holman  
School of Population Health - M431  
UWA

#### HUMAN RESEARCH ETHICS COMMITTEE

**Project: Improving Medication Safety in Seniors:  
A Cross-Jurisdictional Linkage Project**

Please be advised that ethical approval of the above project has been granted by the Human Research Ethics Committee.

The Committee is bound by NHMRC Guidelines to monitor the progress of all approved projects until completion to ensure that they continue to conform to approved ethical standards.

The committee requires that all Chief Investigators report **immediately** anything that might affect or impact upon ethical approval of the project, including adverse events affecting subjects.

Approval should be sought in writing **in advance** for any amendments to the original application. You are also required as a condition of this approval to inform the Committee if for any reason the research project is discontinued before the expected date of completion.

An annual report form for completion will be sent to you twelve months from this date.

**Please note that approval has been granted for a period of four years. Initial approval is for a period of one year, and, thereafter for future periods of one year at a time subject to the receipt of satisfactory annual reports.** At the end of the four-year period you will be required to complete a new "*Application to Undertake Research Involving Human Subjects*" should you wish to continue with your research. However, in special circumstances, the Chair has the authority to extend the approval period in order to complete a project.

**Please quote Project No RA/4/1/1212 all correspondence associated with this study.**

Yours sincerely

KATE KIRK  
Executive Officer  
(Human Research Ethics Committee)

App. Proj

## Memorandum

Research Ethics  
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M459  
Extension 6488 3703  
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Email [kkirk@admin.uwa.edu.au](mailto:kkirk@admin.uwa.edu.au)  
[http://www.research.uwa.edu.au/human\\_ethics](http://www.research.uwa.edu.au/human_ethics)

---

Our Ref. RA/4/1/1212

13 March 2009

Professor C D J Holman  
School of Population Health - M431  
UWA

### HUMAN RESEARCH ETHICS COMMITTEE

**Project: Improving Medication Safety in Seniors: A Cross-Jurisdictional Linkage Project**

The Human Research Ethics Approval on the above project can be extended for another three years until May 2012. Approval is conditional on the protocols remaining the same as those approved at the time of the original submission and subsequent amendments.

Should you wish to make any changes to the protocols as approved you will need to apply for an amendment. You will also still need to submit your annual reports and a brief report on the project annually in the usual way.



Mr Peter Johnstone  
Manager  
Human Research Ethics Office

APPROVAL OF AMENDMENT BY SECRETARY



THE UNIVERSITY OF  
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*Achieving International Excellence*

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MBDP: M459

Our Ref: RA/4/1/1212

11 April 2012

Professor Cashel Holman  
Population Health (School of)  
MBDP: M431

Dear Professor Holman

**HUMAN RESEARCH ETHICS OFFICE – AMENDMENT REQUEST APPROVED**

*Improving Medication Safety in Seniors: A Cross-Jurisdictional Linkage Project*

**Student(s):**

I confirm receipt of your correspondence requesting an amendment to the protocol for the above project.

Approval has been granted for the amendment as outlined in your correspondence and attachments (if any) subject to any conditions listed below.

Any conditions of ethics approval that have been imposed are listed hereunder:

1. Extension granted to June 2015

If you have any queries, please do not hesitate to contact Kate Kirk on (08) 6488 3703.

Please ensure that you quote the file reference RA/4/1/1212 and the associated project title in all future correspondence.

Yours sincerely

A handwritten signature in black ink, appearing to read 'Peter Johnstone'.

Peter Johnstone  
Manager

## **APPENDIX B. DATA FILE SPECIFICATIONS**

The records used in this project were extracted from six major data sources, as follows:

- Pharmaceutical Benefits Scheme data (files prefixed with PBS)
- Medicare Benefits Scheme data (files prefixed with MBS)
- System for the Payment of Aged Residential Care (SPARC), also known as the Aged and Community Care data (files prefixed with ACC)
- Hospital Morbidity Data System (files prefixed with HMD)
- Death Registry (files prefixed with DTH)
- Electoral Roll data (files prefixed with ELR)

The first three data sources are overseen by Australian Government agencies, whereas the last three are maintained by the Department of Health of Western Australia. Specifications for the extracted data files from each source are presented in the next few pages.

## **B.1 PHARMACEUTICAL BENEFITS SCHEME (PBS) FILE SPECIFICATIONS**

Records received: 81,271,900

Records retained in master file: 62,439,030

Variables included in extracted data files:

<b>Variable description</b>	<b>Variable name</b>	<b>Position</b>	<b>Format</b>
Project's Person Identifier	PID	1-13	Text (Alphanumeric)
Sex	SEX	15	Text (M, F or blank)
Date of Supply	DOS	17-24	Text (YYYYMMDD)
Age at Date of Supply (Years)	AGE	26-28	Text (Numeric values)
PBS Item Number	ITEM	30-34	Text (Numeric values)
Number of Scripts	SCRIPTS	36-39	Numeric

## **B.2 MEDICARE BENEFITS SCHEME (PBS) FILE SPECIFICATIONS**

Records received: 68,703,212

Records retained in master file: 49,117,434

Variables included in extracted data files:

<b>Variable description</b>	<b>Variable name</b>	<b>Position</b>	<b>Format</b>
Project's Person Identifier	PID	1-13	Text (Alphanumeric)
Sex	SEX	15	Text (M, F or blank)
Date of Service	DOS	17-24	Text (YYYYMMDD)
Age at Date of Service (Years)	AGE	26-28	Text (Numeric values)
MBS Item Number	ITEM	30-34	Text (Numeric values)
Number of Services	SERVICES	36-37	Numeric (0, 1, or -1) <sup>a</sup>

<sup>a</sup> SERVICES is an administrative flag field used in the calculation of number of services provided. Most records had a value of 1; 0 was used when a second record was generated for a given service, usually to flag an applicable incentive program; -1 flagged a reversal (i.e. correction for a record that was entered by mistake). All records with a value of 0 or -1 were omitted from the analysis. For records with a value of -1, a corresponding record with value 1 was also excluded to reflect the reversal.

### B.3 AGED AND COMMUNITY CARE (ACC) FILE SPECIFICATIONS

Records received: 450,702 (All appraisal entries were linked to all admission entries in supplied records)

Records retained in master file: 126,378 (Restructured data set - one record per admission and one per appraisal)

Variables included in extracted data file:

Variable description	Variable name	Position	Format
Data Source	SOURCE	1-3	Text (ACC)
Project's Person Identifier	PID	5-17	Text (Alphanumeric)
Linkage Project Record Number	LPNO	19-31	Text (Alphanumeric)
Sex	SEX	33	Text (M, F or blank)
Age at Admission (Years)	AGE	35-37	Text (Numeric values)
Admission Date	ADMDT	39-48	Text (DD/MM/YYYY)
Separation Date	SEPDT	50-59	Text (DD/MM/YYYY)
Care Type Code	CARETYPECD	61	Text (P, B or blank) <sup>a</sup>
Care Type Description (Text)	CARETYPETXT	63-77	Text
Appraisal Date	APPRDT	79-88	Text (DD/MM/YYYY)
Care Level	CARELVL	90-92	Text(Alphanumeric) <sup>b</sup>
Care Program (Text)	CAREPROGTX	94-119	Text <sup>c</sup>
Appraisal Status	APPRSTAT	121-123	Text <sup>d</sup>

<sup>a</sup> Care type values were P=Permanent and B=Benefit Respite; only records with 'P' care types were retained.

<sup>b</sup> Care level values were S1-S4 or 1-5 for high care, and S5-S8 or H1-H13 for low care.

<sup>c</sup> Care programs included 'Residential', 'Extended Aged Care at Home', 'EACH Dementia', and 'Transition Care'; only 'records for 'Residential' care were retained.

<sup>d</sup> Appraisal status is an administrative field used to identify problematic appraisals; following the data release, the data custodians advised that any record with a non-blank value in this field should be deleted, as the information contained in these records was either in the process of being reviewed (i.e. not finalised) or else the record had been superseded.



#### **B.4 HOSPITAL MORBIDITY DATA (HMD) FILE SPECIFICATIONS**

Records received (main data set): 2,271,873

Records retained in master file: 1,761,723

Variables included in extracted data file (main data set):

<b>Variable description</b>	<b>Variable name</b>	<b>Position</b>	<b>Format</b>
Record Type (Data Source)	REC_TYPE	1-3	Text (MOR)
Root Number (Person Identifier)	ROOT	5-17	Text (Alphanumeric)
Linkage Project Record Number	LPNOT	19-31	Text (Alphanumeric)
Sex	SEX	33	Text (1=M, 2=F)
Age at Admission (Years)	AGE	34-36	Text (Numeric values)
Aboriginal Status	ABORIG	37	Text (Values 1-4)
Admission Date	ADM_DATE	38-47	Text (DD/MM/YYYY)
Admission Type	ADM_TYPE	48	Text (Values 1-8)
Separation Date	SEP_DATE	49-58	Text (DD/MM/YYYY)
Separation Type (Mode)	SEP_TYPE	59	Text (Values 1-9)
Length of Stay (Leave Adjusted)	MF_LOS	60-64	Text (Numeric values)
Diagnosis Code 1	DIAGCODE_1	65-70	Text (ICD-9/10 values)
Diagnosis Code 2	DIAGCODE_2	71-76	Text (ICD-9/10 values)
Diagnosis Code 3	DIAGCODE_3	77-82	Text (ICD-9/10 values)
Diagnosis Code 4	DIAGCODE_4	83-88	Text (ICD-9/10 values)
Diagnosis Code 5	DIAGCODE_5	89-94	Text (ICD-9/10 values)
Diagnosis Code 6	DIAGCODE_6	95-100	Text (ICD-9/10 values)
Diagnosis Code 7	DIAGCODE_7	101-106	Text (ICD-9/10 values)
Diagnosis Code 8	DIAGCODE_8	107-112	Text (ICD-9/10 values)
Diagnosis Code 9	DIAGCODE_9	113-118	Text (ICD-9/10 values)
Diagnosis Code 10	DIAGCODE_10	119-124	Text (ICD-9/10 values)
Diagnosis Code 11	DIAGCODE_11	125-130	Text (ICD-9/10 values)
Diagnosis Code 12	DIAGCODE_12	131-136	Text (ICD-9/10 values)
Diagnosis Code 13	DIAGCODE_13	137-142	Text (ICD-9/10 values)
Diagnosis Code 14	DIAGCODE_14	143-148	Text (ICD-9/10 values)
Diagnosis Code 15	DIAGCODE_15	149-154	Text (ICD-9/10 values)
Diagnosis Code 16	DIAGCODE_16	155-160	Text (ICD-9/10 values)
Diagnosis Code 17	DIAGCODE_17	161-166	Text (ICD-9/10 values)
Diagnosis Code 18	DIAGCODE_18	167-172	Text (ICD-9/10 values)
Diagnosis Code 19	DIAGCODE_19	173-178	Text (ICD-9/10 values)

<b>Variable description</b>	<b>Variable name</b>	<b>Position</b>	<b>Format</b>
Diagnosis Code 20	DIAGCODE_20	179-184	Text (ICD-9/10 values)
Diagnosis Code 21	DIAGCODE_21	185-190	Text (ICD-9/10 values)
Procedure Code 1	PROCCODE_1	191-198	Text (ICD-9/10 values)
Procedure Code 2	PROCCODE_2	199-206	Text (ICD-9/10 values)
Procedure Code 3	PROCCODE_3	207-214	Text (ICD-9/10 values)
Procedure Code 4	PROCCODE_4	215-222	Text (ICD-9/10 values)
Procedure Code 5	PROCCODE_5	223-230	Text (ICD-9/10 values)
Procedure Code 6	PROCCODE_6	231-238	Text (ICD-9/10 values)
Procedure Code 7	PROCCODE_7	239-246	Text (ICD-9/10 values)
Procedure Code 8	PROCCODE_8	247-254	Text (ICD-9/10 values)
Procedure Code 9	PROCCODE_9	255-262	Text (ICD-9/10 values)
Procedure Code 10	PROCCODE_10	263-270	Text (ICD-9/10 values)
Procedure Code 11	PROCCODE_11	271-278	Text (ICD-9/10 values)
External Cause Code 1	ECODE_1	279-286	Text (ICD-9/10 values)
External Cause Code 2	ECODE_2	287-294	Text (ICD-9/10 values)
External Cause Code 3	ECODE_3	295-302	Text (ICD-9/10 values)
External Cause Code 4	ECODE_4	303-310	Text (ICD-9/10 values)
Place of Occurrence Code 1	P_OCC_1	311-318	Text (ICD-9/10 values)
Place of Occurrence Code 2	P_OCC_2	319-326	Text (ICD-9/10 values)
Place of Occurrence Code 3	P_OCC_3	327-334	Text (ICD-9/10 values)
Place of Occurrence Code 4	P_OCC_4	335-342	Text (ICD-9/10 values)
Activity Code 1	ACTIVITY_1	343-350	Text (ICD-9/10 values)
Activity Code 2	ACTIVITY_2	351-358	Text (ICD-9/10 values)
Activity Code 3	ACTIVITY_3	359-366	Text (ICD-9/10 values)
Activity Code 4	ACTIVITY_4	367-374	Text (ICD-9/10 values)

Variables included in extracted data files (supplementary data items):

<b>Variable description</b>	<b>Variable name</b>	<b>Position</b>	<b>Format</b>
Linkage Project Record Number	LPNOT	1-13	Text (Alphanumeric)
Patient Type (Client Status)	PAT_TYPE	15	Text (Values 0-7)

<b>Variable description</b>	<b>Variable name</b>	<b>Position</b>	<b>Format</b>
Linkage Project Record Number	LPNOT	1-13	Text (Alphanumeric)
Marital Status	MARITAL	15	Text (Values 1-6)

Variables included in extracted data file (geocode-related data):

<b>Variable description</b>	<b>Variable name</b>	<b>Position</b>	<b>Format</b>
Record Type (Data Source)	REC_TYPE	1-5	Text (MOR)
Root Number (Person Identifier)	ROOT	6-18	Text (Alphanumeric)
Linkage Project Record Number	LPNOT	20-32	Text (Alphanumeric)
SEIFA Disadvantage '96 (CD)	CD_DISAD96	34-41	Numeric (F8.3)
SEIFA Disadvantage '01 (CD)	CD_DISAD01	43-50	Numeric (F8.3)
SEIFA Educ'n/Occup'n '96 (CD)	CD_EDOCC96	52-59	Numeric (F8.3)
SEIFA Educ'n/Occup'n '01 (CD)	CD_EDOCC01	61-68	Numeric (F8.3)
SEIFA Economic Res. '96 (CD)	CD_ECRES96	70-77	Numeric (F8.3)
SEIFA Economic Res. '01 (CD)	CD_ECRES01	79-86	Numeric (F8.3)
SEIFA Urban Advantage '96 (CD)	CD_U_ADV96	88-95	Numeric (F8.3)
SEIFA Rural Advantage '96 (CD)	CD_R_ADV96	97-104	Numeric (F8.3)
SEIFA Advantage '01 (CD)	CD_ADVAN01	106-113	Numeric (F8.3)
SEIFA Disadvantage '96 (SLA)	SLA_DISAD96	115-122	Numeric (F8.3)
SEIFA Disadvantage '01 (SLA)	SLA_DISAD01	124-131	Numeric (F8.3)
SEIFA Educ'n/Occup'n '96 (SLA)	SLA_EDOCC96	133-140	Numeric (F8.3)
SEIFA Educ'n/Occup'n '01 (SLA)	SLA_EDOCC01	142-149	Numeric (F8.3)
SEIFA Economic Res. '96 (SLA)	SLA_ECRES96	151-158	Numeric (F8.3)
SEIFA Economic Res. '01 (SLA)	SLA_ECRES01	160-167	Numeric (F8.3)
SEIFA Advantage '01 (SLA)	SLA_ADVAN01	169-176	Numeric (F8.3)
ARIA Category '96 (CD)	CD_ARIA96	178-202	Text (Category labels)
ARIA Category '01 (CD)	CD_ARIA01	204-228	Text (Category labels)
ARIA Category '96 (SLA)	SLA_ARIA96	230-254	Text (Category labels)
ARIA Category '01 (SLA)	SLA_ARIA01	256-280	Text (Category labels)
Geocode Radius (Precision)	RADIUS	281-320	Text (Numeric values)

SEIFA - Socio-Economic Indexes for Areas<sup>155,156</sup>

ARIA - Accessibility/Remoteness Index of Australia<sup>157</sup>

CD - Collector's District (Australian Census)

SLA - Statistical Local Area (geographical area)

## **B.5 DEATH REGISTRY (DTH) FILE SPECIFICATIONS**

Records received (main data set): 122,319

Records retained in master file: 68,519

Variables included in extracted data file (main data set):

<b>Variable description</b>	<b>Variable name</b>	<b>Position</b>	<b>Format</b>
Record Type (Data Source)	REC_TYPE	1-3	Text (DEA)
Root Number (Person Identifier)	ROOT	5-17	Text (Alphanumeric)
Linkage Project Record Number	LPNOT	19-31	Text (Alphanumeric)
Age (Years)	AGE	33-37	Text (Numeric values)
Age Text (Age Units/Qualifier)	AGETEXT	38-40	Text (Alpha values)
Date of Death 1	DOD1	41-50	Text (DD/MM/YYYY)
Date of Death 2 (If Date Range)	DOD2	51-60	Text (DD/MM/YYYY)
Date of Death Code (Qualifier)	DODCODE	61	Text (Alpha values)
Cause of Death Code	CODCODE	62-65	Text (ICD 9/10 values)

Variables included in extracted data file (geocode-related data):

As per hospital morbidity data (HMD) file specifications on page B7.

## **B.6 ELECTORAL ROLL (ELR) FILE SPECIFICATIONS**

Records received: 324,815

Records retained in master file: Not applicable<sup>a</sup>

Variables included in extracted data file:

<b>Variable description</b>	<b>Variable name</b>	<b>Position</b>	<b>Format</b>
Record Type (Data Source)	REC_TYPE	1-3	Text (ELE)
Root Number (Person Identifier)	ROOT	5-17	Text (Alphanumeric)
Electoral Roll Summary Record ID	ELECT_SUM_ID	19-31	Numeric
Start Date of Electoral Registration	START_DATE	41-50	Text (DD/MM/YYYY)
End Date of Electoral Registration	END_DATE	51-60	Text (DD/MM/YYYY)
Status at Registration Period End	END_TYPE	62-65	Text <sup>b</sup>

<sup>a</sup> File restructured to identify enrolment gap periods instead of enrolment periods and only used to eliminate records from other data sets.

<sup>b</sup> End type categories (i.e. status at end of registration period) included 'Current' (still on the electoral roll at the time of data extraction); 'OutWA' (de-registered due to interstate or overseas migration); and 'OtherDel' (de-registered for other reasons).



## **APPENDIX C. PHARMACEUTICAL PRODUCTS EXCLUDED FROM THE STUDY**

This study concentrated on therapeutic products that are generally systemic in nature and are predominantly used outside hospitals. These products are more likely to cause adverse effects in patients and to be recorded on the Australian Pharmaceutical Benefits Scheme (PBS) database. Thus, all items listed in the international Anatomical Therapeutic Chemical (ATC) classification that referred to the specific medications or drug categories of interest were included in the study's medication definitions, unless they belonged to an ATC drug group from the table shown on the next page.

Further restrictions were imposed on the selection of medications by the Pharmaceutical Benefits Scheme (PBS). Only drugs that appeared on the PBS schedules could be included in the PBS code definitions, as prescriptions for drugs that did not were ineligible for a reimbursement claim and were not recorded on the PBS database.

**Table C-1 ATC drug categories excluded from this study**

<b>ATC prefix<sup>a</sup></b>	<b>Medication group description</b>
A01	Stomatological preparations (e.g. antiinfectives and other agents for local oral/dental treatment)
B05	Blood substitutes and perfusion solutions (e.g. haemodialytics, intravenous (IV) solutions, irrigating solutions)
D (except D01B,D02BB,D05B,D10B)	Dermatological preparations for topical use (e.g. skin ointments, emollients and protectives)
G01, G02B, G02CC	Gynaecological agents for topical use (e.g. vaginal antiinfectives and antiseptics; intrauterine contraceptives)
M02	Topical products for joint and muscular pain (e.g. antiinflammatory preparations)
N01, R02AD	Anaesthetics (general and local)
P03	Ectoparasitides, insecticides and repellents
R01A	Nasal preparations for topical use (e.g. nose drops/sprays)
S01,S02,S03 (except S01EC)	Ophthalmological and otological products (e.g. eye/ear drops; ophthalmological anaesthetic, diagnostic and surgical aids)
V03AN	Medical gases
V04, V08	Diagnostic products (e.g. agents for urine and blood tests; imaging contrast media)
V06	General nutrients (e.g. milk substitutes; protein and amino acid supplements)
V09, V10	Radiopharmaceuticals (both diagnostic and therapeutic)
V03AK, V07, V20	Other non-chemical or non-therapeutic products (e.g. tissue adhesives, incontinence equipment, surgical dressings)

<sup>a</sup> Code definitions are based on the World Health Organization's Anatomical Therapeutic Chemical classification of therapeutic drugs (2007 edition).<sup>163,201</sup>



## APPENDIX D. DRUG FORM CATEGORIES AND ASSOCIATED CONSTRAINTS

The table below lists the codes used in the master PBS reference file to identify the drug form associated with each PBS item, providing a short description for each one. These codes were derived from those used in the Bettering the Evaluation and Care of Health (BEACH) database<sup>165,203</sup> (for matching with BEACH prescribed daily dose statistics) and were included in the Form field of the PBS reference file.

In this study, all PBS items with a drug form code in the range 10-44 (or 99) were included in the analysis, unless they satisfied the exclusion criteria specified in Appendix C. However, note that very few items with drug form codes >41 were included, either because few were listed on the PBS or because they were eliminated by other exclusion criteria.

**Table D-1 Drug form categories used in this study**

<b>Code</b>	<b>Description</b>
10	Oral - Unspecified
11	Oral - Capsule
12	Oral - Tablet
13	Oral - Liquid
14	Oral - Other
21	Systemic - Sublingual
22	Systemic - Rectal
23	Systemic - Transdermal
30	Inhalation - Unspecified
31	Inhalation - Aerosol
32	Inhalation - Powder
33	Inhalation - Solution
41	Parenteral - Injection
42	Parenteral - Implant
43	Parenteral - IV Fluid
44	Parenteral - IV Admixture
45	Parenteral - Dialytic
51	Sense Organ - Eye
52	Sense Organ - Eye & Ear
53	Sense Organ - Ear
54	Sense Organ - Nasal
61	Topical - Dermal/Unspecified
62	Topical - Vaginal
63	Topical - Rectal
64	Topical - Oropharyngeal
71	Treatment Aid - Dressing
74	Treatment Aid - Other
99	Unspecified



## **APPENDIX E. AVERAGE DAILY DOSE ALLOCATION PROCESS**

Since the pharmaceutical claims data for this project did not specify the prescribers' dosage instructions, it was important to find a proxy measure that could be used instead to calculate the period and duration of drug exposure associated with each script. Estimates of the average daily dose prescribed for each PBS item were used for this purpose. Although these estimates would not be as accurate as using the actual prescription details, it was felt that they would be reasonably representative of the doses likely prescribed, if the approach used to derive them was thorough, well informed and as precise as possible.

This appendix provides a general outline of how these average daily doses were allocated. There were, however, numerous exceptions to these rules. Ultimately, the daily dose allocation was based on the application of sound judgment in light of all available information for each PBS item.

Please note that, unlike the World Health Organization's Defined Daily Doses (DDDs), the average daily doses allocated to PBS items in this project were specific to the item's drug strength. For instance, if a given medication applied to two PBS items, one with a drug strength of 50 mg and the other with a drug strength of 100 mg, the first may have been allocated an average daily dose of 100 mg, and the second a daily dose of 200 mg. This divergence from the standard DDD approach was required because the daily dose estimates were predominantly being used to ascertain individual patients' drug exposure at specific points in time, as opposed to the estimation of drug utilisation rates at the population level for international comparisons.

The outline presented here is restricted to the manual allocation process. Following this 'preliminary' allocation, validations were performed (using SAS routines) to compare the expected supply dates derived from daily dose estimates (for subsequent prescriptions) with actual supply dates. Where expected and actual supply dates did not match very closely (on average), further refinements were made to the original estimates. These validations could only be applied to consecutive prescriptions, however.

## **Data Sources**

Allocation of the overall average prescribed daily dose for each PBS item was dependent upon availability of valid information from the following sources:

- Average DDD from the World Health Organization's ATC classification - ATC code and route/subroute level
- BEACH mean and median Prescribed Daily Dose (PDD) for:
  - Australian adults (18+ years) - generic drug level
  - Australian adults (18+ years) - form within generic drug level
  - Australian elderly (65+ years) - generic drug level
  - Australian elderly (65+ years) - form within generic drug level
- MIMS recommended dosage details - form within generic drug level, sometimes based on specific drug strengths (and patient characteristics).

BEACH PDD statistics were considered available if based on at least five cases.

## **Daily Dose Allocation Status**

The status given to the preliminary overall daily dose allocated to each PBS item was one of:

- 1 OK: Multiple sources available and all sources concordant
- 2 OK: One or more sources available - overall daily dose inconclusive but item peripheral
- 3 Review: Multiple sources available - overall daily dose inconclusive and item required
- 4 Review: One source available only - item required
- 5 Review: No sources available - item required
- 9 Not applicable: Insufficient information available - item not required.

## **Daily Dose Allocation Process**

The preliminary daily dose allocation process was essentially based on the following algorithm:

- If no daily dose information is available:
  - Check Internet as additional source for tentative daily dosage.
  - If dosage found on Internet:
    - Record information with MIMS details (on Excel worksheet) and adopt dosage as preliminary daily dose. (Flag entry with "Internet: " prefix.)
    - If item is peripheral to project, set status to 2; otherwise set status to 4.
  - Otherwise (i.e. dosage not found on Internet):
    - If item is required for the project, set status to 5; otherwise set status to 9.
- If one daily dose value is available only:
  - Check if available dosage value makes sense (particularly relevant for BEACH PDD statistics, which were occasionally derived from some erroneous dosage details).
  - If available dosage value is appropriate:
    - Adopt available value as preliminary daily dose.
    - If item is peripheral to project, set status to 2; otherwise set status to 4.
  - Otherwise (i.e. available dosage value is not appropriate):
    - Perform process described above for no daily dose information available.

- If multiple daily dose values are available:
  - If all values are concordant:
    - Adopt concordant value as preliminary daily dose (to nearest half-strength).<sup>a</sup>
    - Set status to 1.
  - If at least two values are concordant:
    - Adopt concordant value as preliminary daily dose (to nearest half-strength).<sup>a</sup>
    - If item is peripheral to project, set status to 2; otherwise set status to 3.
  - Otherwise (i.e. no concordance or inconclusive concordance):
    - If item is peripheral to project, set status to 2; otherwise set status to 3.
    - Allocate the preliminary daily dose based on the following priorities:
      - Source:
        - PDD for 65+ years (if  $n \geq 25$  and not erroneous)
        - PDD for 18+ years (if  $n \geq 25$  and not erroneous)
        - MIMS (if precise enough)
        - DDD
      - PDD Level:
        - If all drug forms belong to the same route of administration:
          - Use aggregated value at the generic drug level
        - Otherwise (i.e. not all drug forms belong to the same route):
          - Use value at the form within generic drug level (if  $n \geq 25$  and not erroneous)
      - PDD Statistics:
        - Use mean as a basis unless erroneous
        - Round to nearest half-strength<sup>a</sup>
      - Complex Cases:
        - If a given drug has multiple drug strengths and/or is associated with multiple indications and available values don't match any particular strength (e.g. 200 mg and 400 mg tablets and mean PDD ~300 mg):
          - Use daily doses that are multiples of strength for separate items
          - Retain average value for all items as a separate field
        - If only one strength but dosage varies by indication or patient characteristics (e.g. 100 mg tablet and mean PDD ~120 mg):
          - Use daily dose value that is multiple of strength
          - Retain mean value as separate field
        - If item refers to compound drug:
          - Specify the component of greatest relevance
          - Record the overall daily dose for that component only<sup>b</sup>

<sup>a</sup> If the PBS item referred to a 100 mg tablet, possible daily dose allocations were 50 mg, 100 mg, 150 mg, 200 mg, etc. (i.e. half-strength increments). If available data for this item suggested an average daily dose of ~120 mg, the item would be allocated a daily dose of 100 mg, whereas if the suggested daily dose was ~130 mg, 150 mg would be allocated. For the majority of PBS items, the daily doses allocated were multiples of the drug strength, however (e.g. equivalent to 1, 2, 3 or more tablets).

<sup>b</sup> Since PDD statistics were usually based on the sum of component strengths (e.g. total weight of a tablet), the allocated daily dose had to be adjusted to reflect the component's strength only.)



## **APPENDIX F. ATC DEFINITIONS FOR HIGH-RISK DRUG GROUPS AND ASSOCIATED DRUG DOMAINS**

The table presented in this appendix provides ATC code definitions for each high-risk drug group included in this study and for its corresponding domain. Drug domains consisted of medications used to treat similar indications to those included in the high-risk drug group.

**Table F-1 ATC definitions for high-risk drug groups and associated drug domains**

<b>High-risk drug group</b>	<b>ATC drug group definition<sup>a</sup></b>		<b>ATC domain definition<sup>a,b</sup></b>	
Anticoagulants	B01AA	Vitamin K antagonists (including warfarin)	B01	Antithrombotic agents
	B01AB	Heparin group		
Antirheumatic/antiinflammatory drugs (excluding corticosteroids and salicylates)	M01	Antiinflammatory and antirheumatic products	M01	Antiinflammatory and antirheumatic products
Opioids and related narcotics (excluding methadone and heroin)	N02A	Opioids (excluding methadone; including therapeutic heroin (i.e. diamorphine), but drug is not available in Australia)	N02	Analgesics
Corticosteroids (systemic)	H02A	Corticosteroids for systemic use, plain	H02A	Corticosteroids for systemic use, plain
	M01BA	Antirheumatics with corticosteroids	M01BA	Antirheumatics with corticosteroids
Hypertension medications (excluding diuretics other than low-ceiling, beta-blocking agents and peripheral vasodilators)	C01D	Vasodilators used in cardiac diseases	C01D	Vasodilators used in cardiac diseases
	C02	Antihypertensives	C02	Antihypertensives
	C03A/B/EA	Low-ceiling diuretics, including thiazides	C03A/B/EA	Low-ceiling diuretics, including thiazides
	C08	Calcium channel blockers	C08	Calcium channel blockers
	C09	Agents acting on the renin-angiotensin system	C09	Agents acting on the renin-angiotensin system
			C07B-E	Beta-blocking agents with antihypertensives
Cardiac rhythm regulators (including cardiac glycosides, excluding beta-blockers)	C01A	Cardiac glycosides	C01A	Cardiac glycosides
	C01B	Antiarrhythmics, Class I & III	C01B	Antiarrhythmics, Class I & III
Beta-blockers	C07	Beta-blocking agents	C07	Beta-blocking agents
Serum lipid-reducing agents	C10	Lipid modifying agents	C10	Lipid modifying agents

<sup>a</sup> Code definitions are based on the World Health Organization's Anatomical Therapeutic Chemical classification of therapeutic drugs (2007 edition).<sup>163,201</sup>

<sup>b</sup> Drugs within each domain definition were those used to treat similar conditions to those included in the definition for the corresponding high-risk drug group; individuals from the study cohort who were prescribed medications from a given domain definition were considered part of the patient domain (sub-study cohort) for the related high-risk drug sub-study (i.e. they were considered to be part of the sub-study's population at risk).



## APPENDIX G. ATC DEFINITIONS FOR BROAD MEDICATION GROUPS USED TO DETERMINE STUDY SUBJECTS' DRUG CONSUMPTION PROFILE

The table presented in this appendix provides ATC code definitions for 22 broad medication groups used to determine the drug consumption profile of index and reference subjects for the three-month period immediately preceding their case and control times (i.e. 90-day period prior plus the case or control date).

**Table G-1 ATC definitions for broad medication groups used to determine study subjects' drug consumption profile**

Broad medication group	ATC <sup>a</sup> definition
Alimentary/gastrointestinal (excluding dental/diabetes drugs)	A02-A09, A11-A16
Diabetes	A10
Antithrombotic	B01
Blood (other)	B02, B03, B06
Cardiovascular	C
Dermatological	D01B, D02BB, D05B, D10B
Genitourinary	G02A, G02CA, G02CB, G02CX, G03, G04
Corticosteroid (systemic)	H02A, H02B
Hormonal (systemic)	H01, H02C, H03- H05
Antiinfection	J
Antineoplastic	L01, L02
Immunomodulator	L03, L04
Antirheumatic/antiinflammatory	M01
Muscle relaxant	M03
Bone/gout	M04, M05
Analgesic	N02
Nervous system	N03-N07
Antiparasitic	P01, P02
Asthma/chronic obstructive pulmonary disease (COPD)	R03
Respiratory (other)	R01B, R02, R05-R07
Glaucoma	S01EC
Other	V01, V03AB, V03AC, V03AE-V03AH, V03AM, V03AX, V03AZ

<sup>a</sup> Definitions are based on the WHO Anatomical Therapeutic Chemical classification (2007).<sup>163,201</sup>



## **APPENDIX H. ATC DEFINITIONS FOR BEERS POTENTIALLY INAPPROPRIATE MEDICATIONS AND ASSOCIATED DRUG DOMAINS**

This appendix provides ATC code definitions for each potentially inappropriate medication (from the Beers Criteria) included in this study. These medications are presented by drug domain, for which definitions are also specified. Drug domains grouped medications used to treat similar indications together.

**Table H-1 ATC definitions for Beers potentially inappropriate medications and associated drug domains**

Drug domain	Domain ATC <sup>a</sup> def'n	PIM name	PIM ATC <sup>a</sup> definition
Antirheumatics	M01	Indomethacin	M01AB01
		Naproxen	M01AE02
		Piroxicam	M01AC01
Analgesics	N02	Dextropropoxyphene	N02AC04
		Meperidine/pethidine	N02AB02
Anti-Parkinson drugs	N04	Orphenadrine	N04AB02
Antihistamines (systemic)	R06, N05BB01	Diphenhydramine	R06AA02
		Hydroxyzine	N05BB01
		Cyproheptadine	R06AX02
		Promethazine	R06AD02
Antipsychotics	N05A	Thioridazine	N05AC02
Anxiolytics, hypnotics/sedatives	N05B/C (excl. N05BB01)	Oxazepam	N05BA04
		Alprazolam	N05BA12
		Temazepam	N05CD07
		Diazepam	N05BA01
Antidepressants	N06A	Amitriptyline	N06AA09
		Doxepin	N06AA12
		Fluoxetine	N06AB03
Psychostimulants	N06B	Dexamphetamine	N06BA02
Cardiac rhythm regulators	C01A/B	Disopyramide	C01BA03
		Digoxin	C01AA05
		Amiodarone	C01BD01
Hypertension drugs	C01D, C02, C03A/B/EA, C07B-E, C08, C09	Methyldopa	C02AB01
		Nifedipine	C08CA05
		Clonidine	C02AC01
High ceiling diuretics	C03C	Ethacrynic acid	C03CC01
Antithrombotics	B01	Dipyridamole	B01AC07, B01AC30
		Ticlopidine	B01AC05
Diabetes drugs	A10	Chlorpropamide	A10BB02
Iron preparations	B03A	Ferrous sulphate	B03AA07, B03AD03
Peptic ulcer/reflux drugs	A02B	Cimetidine	A02BA01
Laxatives	A06	Bisacodyl	A06AB02, A06AB52, A06AG02
Bowel disorder drugs/ Belladonna & derivatives	A03A-E	Belladonna alkaloids	A03BA01, A03BA04, A03BB01
		Dicyclomine	A03AA07
		Propantheline	A03AB05
Urinary antispasmodics	G04BD	Oxybutynin	G04BD04
Urinary tract antibacterials	J01CA/CR/E/M/XE	Nitrofurantoin	J01XE01
Oestrogen-only medications	G03C, L02AA	Ethinylloestradiol	G03CA01
		Oestradiol	G03CA03
		Oestriol	G03CA04
		Oestrone	G03CA07
		Oestrogens-	G03CA57
		Fosfestrol sodium	L02AA04

<sup>a</sup> Definitions are based on the WHO Anatomical Therapeutic Chemical classification (2007).<sup>163,201</sup>

## **APPENDIX I. SUPPLEMENTARY STATISTICS**

The large volume of statistics generated as part of this project (from >800 successful program runs, many of which consisted of multiple passes of defined SAS macros) is somewhat overwhelming. It would be impossible to present all of this information in this document. Nonetheless, some relevant statistics that were omitted from the submitted manuscripts due to journal constraints may be of interest. This supplemental material is presented in the following pages.

## ***1.1 SUPPLEMENTARY STATISTICS FOR HIGH-RISK DRUGS EXPLORATION PAPER***

The table shown on the next page presents the results that would have been obtained for the high-risk drug study (chapter 4) if a case-crossover design had been selected to derive odds ratios, as opposed to a case-time-control design.

**Table I-1 Associations and preliminary attribution estimates in relation to high-risk medications and unplanned hospital admissions in Western Australian elderly, 1993-2005 - summary results using a case-crossover design**

Statistics	Anticoagulants	Anti-rheumatic drugs	Opioids	Corticosteroids	Hypertension drugs	Cardiac rhythm regulators	Beta-blockers	Serum lipid-reducing agents
Domain (number of people in sub-study cohort)	90,124	174,585	193,196	84,960	180,539	39,596	89,017	100,787
Index subjects - number of people involved	57,609	92,903	108,513	53,369	99,635	29,919	55,179	50,295
Index subjects - number of index admissions	212,187	307,276	358,570	197,385	335,259	128,241	195,311	165,470
Index subjects - gender distribution (% males)	47.1%	45.0%	44.9%	45.7%	45.3%	45.5%	45.3%	49.8%
Index subjects - mean age at admission (years)	78.1	78.3	78.5	78.0	78.5	79.5	78.2	76.4
Exposed index subjects (Exp ldx)	26,088	61,595	45,772	30,740	192,674	44,730	60,755	69,286
% exposed index subjects	12.3%	20.0%	12.8%	15.6%	57.5%	34.9%	31.1%	41.9%
Unadjusted odds ratio (Unadj OR)	1.72	1.06	2.57	2.03	1.36	1.53	1.34	1.45
Unadjusted OR 95% confidence interval	1.67-1.77	1.04-1.08	2.52-2.62	1.98-2.08	1.34-1.38	1.49-1.56	1.32-1.37	1.42-1.48
Unadjusted OR p-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Adjusted odds ratio (OR)	1.23	1.05	1.91	1.31	1.13	1.22	1.20	1.18
Adjusted OR 95% confidence interval	1.18-1.27	1.02-1.07	1.86-1.96	1.27-1.35	1.11-1.15	1.18-1.26	1.17-1.23	1.15-1.21
Adjusted OR p-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Attributable fraction: AF = (OR-1) / OR (%)	18.4%	4.3%	47.6%	23.4%	11.5%	18.0%	16.7%	15.3%
AF 95% confidence interval (%)	15.3-21.3%	2.2-6.4%	46.3-49.0%	21.1-25.7%	9.7-13.2%	15.3-20.6%	14.5-18.9%	13.0-17.6%
Estimate of index admissions related to drug (AFxExp ldx) <sup>a</sup>	4,792	2,652	21,808	7,184	22,166	8,036	10,168	10,619
Exposed index subjects with relevant drug ecode <sup>b</sup>	1,514	793	658	524	2,987	1,051	1,175	147
% exposed index subjects with relevant drug ecode	5.8%	1.3%	1.4%	1.7%	1.6%	2.3%	1.9%	0.2%

<sup>a</sup> Estimates were derived from more precise AF figures than those displayed in this table.

<sup>b</sup> Exposed index subjects with relevant drug ecode refers to hospitalisations among index subjects who were exposed to a high-risk drug of interest at the time of admission and for which an ICD external cause code related to accidental poisoning or adverse drug reaction potentially from a medication in this high-risk drug group (i.e. codes listed in Table 4-2 for the drug group) was recorded on the corresponding inpatient summary.

## ***1.2 SUPPLEMENTARY STATISTICS FOR PIM PREVALENCE PAPER***

The manuscript on the prevalence of potentially inappropriate medications from the Beers Criteria (chapter 5) examined overall PIM consumption time trends by gender and for the entire cohort, but did not report comprehensively on time trends by age. The table that follows provides this information. It is interesting to note that, although the oldest patients had higher PIM consumption rates than the younger elderly throughout the study period, the older patients experienced a significantly greater rate of decline in their PIM consumption rate than their younger counterparts.



**Table I-2 Potentially inappropriate medications in Western Australian residents aged ≥65 years (1993-2005) - rate of consumption (daily doses/1000 person-years) by five-year age group and calendar year**

<b>Age group<sup>a,b</sup></b>	<b>1993</b>	<b>1994</b>	<b>1995</b>	<b>1996</b>	<b>1997</b>	<b>1998</b>	<b>1999</b>	<b>2000</b>	<b>2001</b>	<b>2002</b>	<b>2003</b>	<b>2004</b>	<b>2005</b>	<b>1993-2005</b>
65-69 years	84,133	84,142	78,326	86,573	84,885	82,801	88,198	86,745	75,813	80,709	70,646	66,813	65,238	80,928
70-74 years	110,506	109,271	101,196	109,347	105,328	102,604	104,156	101,126	86,459	92,230	83,808	79,563	76,079	98,193
75-79 years	138,503	140,032	128,430	134,719	129,691	125,442	128,617	126,005	107,335	113,949	105,785	101,238	93,387	120,312
80-84 years	166,457	166,594	157,373	160,956	155,945	153,511	155,357	150,334	128,941	138,484	130,929	126,099	115,699	146,093
85-89 years	199,348	197,802	186,101	186,548	178,622	171,390	171,300	169,622	142,637	155,203	152,671	150,911	138,662	168,094
≥90 years	215,808	221,614	211,799	205,832	200,420	197,183	188,524	187,353	158,864	165,402	157,741	159,092	149,350	180,875

<sup>a</sup> Age group assigned based on person's most prominent age during each calendar year.

<sup>b</sup> Estimated 1.8%, 3.0%, 3.1%, 2.9%, 2.9% and 3.4% decreases in daily dose rates per year for 65-69, 70-74, 75-79, 80-84, 85-89 and ≥90 year-olds respectively, based on univariate logistic regression ( $p < 0.0001$  for all age groups - ordinal unadjusted models).

### ***1.3 SUPPLEMENTARY STATISTICS FOR MAIN PAPER ON ESTIMATION OF PIM EFFECTS***

In the main paper regarding the estimation of PIM effects on unplanned hospitalisations (chapter 6), the information related to individual PIMs was condensed into one major table. Consequently, a few interesting statistics were excluded from this publication. This appendix presents the same information in an expanded format, which includes these omitted fields.

**Table I-3 Potentially inappropriate medications (PIMs) in Western Australians aged ≥65 years (1993-2005):<sup>a</sup> estimated effects of exposure to pain management, anti-Parkinson, and antihistamine PIMs on unplanned hospitalisations**

Statistics	Antirheumatics			Analgesics		Anti-Parkinson	Systemic antihistamines		
	Indomethacin	Naproxen	Piroxicam	Dextropropoxyphene	Meperidine/pethidine	Orphenadrine	Hydroxyzine	Cyproheptadine	Promethazine
Domain <sup>b</sup> (no. people in sub-study cohort)		174,585			193,196		10,017		25,064
Index subjects – no. people		92,903			108,513		7,002		17,592
Index subjects – no. index admissions		307,276			358,570		27,545		68,355
Exposed index subjects (Exp Idx)	3,675	6,741	5,487	211	168	33	28	1,492	886
% exposed index subjects	1.2%	2.2%	1.8%	0.1%	<0.1%	0.1%	<0.1%	2.2%	1.3%
Unadjusted odds ratio (Unadj OR)	1.36	1.21	0.97	1.16	2.59	1.43	1.10	1.08	1.49
Unadjusted OR 95% confidence interval	1.25-1.48	1.14-1.29	0.90-1.03	0.77-1.75	1.46-4.59	0.60-3.40	0.35-3.44	0.96-1.23	1.25-1.77
Unadjusted odds ratio p-value	<0.0001	<0.0001	0.2913	0.4742	0.0011	0.4200	0.8763	0.2061	<0.0001
Adjusted odds ratio (OR)	1.38	1.20	1.01	1.24	2.37	1.14	1.05	1.08	1.50
Adjusted OR 95% confidence interval	1.25-1.52	1.12-1.29	0.94-1.09	0.78-1.98	1.25-4.50	0.44-2.96	0.25-4.45	0.95-1.24	1.24-1.81
Adjusted odds ratio p-value	<0.0001	<0.0001	0.6992	0.3594	0.0083	0.7867	0.9527	0.2573	<0.0001
Attributable fraction: AF = (OR-1) / OR (%)	27.4%	16.9%	1.4%	19.6%	57.8%	12.4%	4.3%	7.5%	33.2%
AF 95% confidence interval (%)	20.3-34.0%	11.0-22.2%	-5.9-8.2%	-28.2-9.6%	19.9-77.8%	-127.8-66.3%	-308.2-77.5%	-5.8-19.2%	19.2-44.7%
Index admissions attributed to drug (AF x Exp Idx)	1,008	1,138	76	41	97	4	1	112	294
Exposed index subjects with relevant ecode <sup>c</sup>	64	106	76	<5	<5	<5	0	<5	<5
% exposed index subjects with relevant ecode <sup>c</sup>	1.7%	1.6%	1.4%	n/a	n/a	n/a	0.0%	n/a	n/a

<sup>a</sup> Although the study period covered 1993-2005 in this population, index cases related to unplanned hospital admissions between July 1994 and December 2005 only, in patients aged ≥67 years upon admission; these additional constraints were required to ensure sufficient lead-up time for the control observation period.

<sup>b</sup> In each sub-study, domain participants were those who took medications used to treat similar conditions to those indicated for PIMs of interest (i.e. medications from the same broad drug class); these people were considered to be part of the sub-study's population at risk.

<sup>c</sup> Exposed index subjects with relevant ecode refers to unplanned hospitalisations among index subjects who were exposed to the specified PIM at the time of admission and for which a relevant external cause code (ecode) for accidental drug poisoning or adverse drug reaction from the International Classification of Diseases (ICD-9-CM/ICD-10-AM)<sup>158,159</sup> was recorded on the corresponding inpatient summary.

n/a - Not available; due to low counts, the percentage has been withheld to protect patient confidentiality.

**Table I-4 Potentially inappropriate medications (PIMs) in Western Australians aged ≥65 years (1993-2005):<sup>a</sup> estimated effects of exposure to psychotropic PIMs on unplanned hospitalisations**

Statistics	Anti-psychotics	Anxiolytics & hypnotics/sedatives				Antidepressants			Psycho-stimulants
	Thioridazine	Oxazepam	Alprazolam	Diazepam	Temazepam	Amitriptyline	Doxepin	Fluoxetine	Dexamphetamine
Domain <sup>b</sup> (no. people in sub-study cohort)	79,914			60,497			90,128		195
Index subjects – no. people	51,495			38,942			57,365		110
Index subjects – no. index admissions	188,508			146,960			215,207		390
Exposed index subjects (Exp Idx)	1,058	14,988	1,229	10,963	24,125	8,922	4,958	2,870	56
% exposed index subjects	0.6%	10.2%	0.8%	7.5%	16.4%	4.1%	2.3%	1.3%	14.4%
Unadjusted odds ratio (Unadj OR)	1.30	1.29	1.23	1.34	1.35	1.11	1.03	1.08	1.62
Unadjusted OR 95% confidence interval	1.09-1.54	1.22-1.36	1.01-1.49	1.27-1.42	1.29-1.41	1.04-1.18	0.94-1.12	0.96-1.22	0.74-3.52
Unadjusted odds ratio p-value	0.0028	<0.0001	0.0388	<0.0001	<0.0001	0.0020	0.5871	0.2082	0.2256
Adjusted odds ratio (OR)	1.35	1.22	1.16	1.26	1.27	1.07	1.01	1.07	1.27
Adjusted OR 95% confidence interval	1.11-1.63	1.15-1.30	0.94-1.43	1.18-1.34	1.21-1.34	0.99-1.14	0.92-1.12	0.93-1.22	0.49-3.28
Adjusted odds ratio p-value	0.0021	<0.0001	0.1631	<0.0001	<0.0001	0.0813	0.8011	0.3425	0.6281
Attributable fraction: AF = (OR-1) / OR (%)	25.8%	18.3%	13.9%	20.4%	21.3%	6.1%	1.3%	6.3%	20.9%
AF 95% confidence interval (%)	10.2-38.7%	13.2-23.1%	-6.3-30.3%	15.4-25.2%	17.3-25.2%	-0.8-12.4%	-9.1-10.6%	-7.2-18.0%	-104.5-69.5%
Index admissions attributed to drug (AF x Exp Idx)	273	2,743	171	2,241	5,144	545	64	180	12
Exposed index subjects with relevant ecode <sup>c</sup>	19	61	14	45	53	59	30	19	0
% exposed index subjects with relevant ecode <sup>c</sup>	1.8%	0.4%	1.1%	0.4%	0.2%	0.7%	0.6%	0.7%	0.0%

<sup>a</sup> Although the study period covered 1993-2005 in this population, index cases related to unplanned hospital admissions between July 1994 and December 2005 only, in patients aged ≥67 years upon admission; these additional constraints were required to ensure sufficient lead-up time for the control observation period.

<sup>b</sup> In each sub-study, domain participants were those who took medications used to treat similar conditions to those indicated for PIMs of interest (i.e. medications from the same broad drug class); these people were considered to be part of the sub-study's population at risk.

<sup>c</sup> Exposed index subjects with relevant ecode refers to unplanned hospitalisations among index subjects who were exposed to the specified PIM at the time of admission and for which a relevant external cause code (ecode) for accidental drug poisoning or adverse drug reaction from the International Classification of Diseases (ICD-9-CM/ICD-10-AM)<sup>158,159</sup> was recorded on the corresponding inpatient summary.

**Table I-5 Potentially inappropriate medications (PIMs) in Western Australians aged ≥65 years (1993-2005):<sup>a</sup> estimated effects of exposure to cardiovascular, diuretic, and antithrombotic PIMs on unplanned hospitalisations**

Statistics	Cardiac rhythm regulators			Hypertension medications			High ceiling diuretics	Antithrombotics	
	Disopyramide	Digoxin	Amiodarone	Methyldopa	Nifedipine	Clonidine	Ethacrynic acid	Dipyridamole	Ticlopidine
Domain <sup>b</sup> (no. people in sub-study cohort)		39,596			180,539		74,222		90,124
Index subjects – no. people		29,919			99,635		55,178		57,609
Index subjects – no. index admissions		128,241			335,259		227,139		212,187
Exposed index subjects (Exp Idx)	168	34,122	11,632	2,038	11,699	261	227	3,548	109
% exposed index subjects	0.1%	26.6%	9.1%	0.6%	3.5%	0.1%	0.1%	1.7%	0.1%
Unadjusted odds ratio (Unadj OR)	1.00	1.12	1.28	1.08	0.83	1.27	1.79	1.10	1.49
Unadjusted OR 95% confidence interval	0.63-1.59	1.08-1.17	1.19-1.37	0.94-1.24	0.78-0.88	0.91-1.78	1.16-2.75	0.98-1.23	0.75-2.97
Unadjusted odds ratio p-value	0.9981	<0.0001	<0.0001	0.2802	<0.0001	0.1620	0.0081	0.1234	0.2572
Adjusted odds ratio (OR)	1.24	1.07	1.21	1.13	0.89	1.06	1.53	1.01	1.50
Adjusted OR 95% confidence interval	0.77-1.99	1.03-1.11	1.12-1.30	0.97-1.32	0.83-0.95	0.74-1.53	0.94-2.51	0.89-1.15	0.69-3.25
Adjusted odds ratio p-value	0.3749	0.0018	<0.0001	0.1056	0.0010	0.7410	0.0878	0.8819	0.3039
Attributable fraction: AF = (OR-1) / OR (%)	19.2%	6.3%	17.2%	11.7%	-12.2%	5.9%	34.8%	1.0%	33.3%
AF 95% confidence interval (%)	-29.5-49.6%	2.4-10.1%	10.7-23.2%	-2.7-24.1%	-20.2- -4.8%	-35.3-34.6%	-6.5-60.1%	-12.9-13.1%	-44.5-69.2%
Index admissions attributed to drug (AF x Exp Idx)	32	2,143	2,003	239	-1,431	15	79	35	36
Exposed index subjects with relevant ecode <sup>c</sup>	<5	879	270	36	134	<5	11	35	<5
% exposed index subjects with relevant ecode <sup>c</sup>	n/a	2.6%	2.3%	1.8%	1.1%	n/a	4.8%	1.0%	n/a

<sup>a</sup> Although the study period covered 1993-2005 in this population, index cases related to unplanned hospital admissions between July 1994 and December 2005 only, in patients aged ≥67 years upon admission; these additional constraints were required to ensure sufficient lead-up time for the control observation period.

<sup>b</sup> In each sub-study, domain participants were those who took medications used to treat similar conditions to those indicated for PIMs of interest (i.e. medications from the same broad drug class); these people were considered to be part of the sub-study's population at risk.

<sup>c</sup> Exposed index subjects with relevant ecode refers to unplanned hospitalisations among index subjects who were exposed to the specified PIM at the time of admission and for which a relevant external cause code (ecode) for accidental drug poisoning or adverse drug reaction from the International Classification of Diseases (ICD-9-CM/ICD-10-AM)<sup>158,159</sup> was recorded on the corresponding inpatient summary.

n/a - Not available; due to low counts, the percentage has been withheld to protect patient confidentiality.

**Table I-6 Potentially inappropriate medications (PIMs) in Western Australians aged ≥65 years (1993-2005):<sup>a</sup> estimated effects of exposure to alimentary tract and metabolism PIMs (including supplements) on unplanned hospitalisations**

Statistics	Diabetes drugs	Iron pre- parations	Peptic ulcer/ reflux drugs	Laxatives	Bowel disorder drugs/ belladonna alkaloids	
	Chlor- propamide	Ferrous sulphate	Cimetidine	Bisacodyl	Belladonna alkaloids	Propan- theline
Domain <sup>b</sup> (no. people in sub-study cohort)	37,032	35,918	132,452	53,653	5,791	
Index subjects – no. people	21,670	26,656	77,659	39,795	4,350	
Index subjects – no. index admissions	83,666	117,120	284,092	164,718	18,195	
Exposed index subjects (Exp Idx)	68	11,259	2,989	4,505	506	91
% exposed index subjects	0.1%	9.6%	1.1%	2.7%	2.8%	0.5%
Unadjusted odds ratio (Unadj OR)	0.62	1.21	1.02	1.32	1.21	1.17
Unadjusted OR 95% confidence interval	0.33-1.15	1.15-1.28	0.93-1.13	1.22-1.43	0.98-1.49	0.73-1.88
Unadjusted odds ratio p-value	0.1286	<0.0001	0.6460	<0.0001	0.0793	0.5214
Adjusted odds ratio (OR)	0.76	1.19	1.09	1.15	1.22	1.38
Adjusted OR 95% confidence interval	0.39-1.45	1.12-1.25	0.98-1.22	1.04-1.26	0.98-1.53	0.81-2.35
Adjusted odds ratio p-value	0.4013	<0.0001	0.1116	0.0041	0.0773	0.2315
Attributable fraction: AF = (OR-1) / OR (%)	-32.3%	15.6%	8.4%	12.7%	18.2%	27.6%
AF 95% confidence interval (%)	-153.8-31.1%	10.7-20.3%	-2.0-17.8%	4.2-20.5%	-2.2-34.6%	-23.0-57.4%
Index admissions attributed to drug (AF x Exp Idx)	-22	1,758	252	574	92	25
Exposed index subjects with relevant ecode <sup>c</sup>	<5	21	<5	10	<5	<5
% exposed index subjects with relevant ecode <sup>c</sup>	n/a	0.2%	n/a	0.2%	n/a	n/a

<sup>a</sup> Although the study period covered 1993-2005 in this population, index cases related to unplanned hospital admissions between July 1994 and December 2005 only, in patients aged ≥67 years upon admission; these additional constraints were required to ensure sufficient lead-up time for the control observation period.

<sup>b</sup> In each sub-study, domain participants were those who took medications used to treat similar conditions to those indicated for PIMs of interest (i.e. medications from the same broad drug class); these people were considered to be part of the sub-study's population at risk.

<sup>c</sup> Exposed index subjects with relevant ecode refers to unplanned hospitalisations among index subjects who were exposed to the specified PIM at the time of admission and for which a relevant external cause code (ecode) for accidental drug poisoning or adverse drug reaction from the International Classification of Diseases (ICD-9-CM/ICD-10-AM)<sup>158,159</sup> was recorded on the corresponding inpatient summary.

n/a - Not available; due to low counts, the percentage has been withheld to protect patient confidentiality.

**Table I-7 Potentially inappropriate medications (PIMs) in Western Australians aged ≥65 years (1993-2005):<sup>a</sup> estimated effects of exposure to genitourinary PIMs (including sex hormones and urinary tract antibacterials) on unplanned hospitalisations**

Statistics	Urinary antispasmodics	Urinary tract antibacterials	Oestrogen-only medications				
	Oxybutynin	Nitrofurantoin	Ethinyl-oestradiol	Oestradiol	Oestrone	Oestrogens-conjugated	Fosfestrol sodium
Domain <sup>b</sup> (no. people in sub-study cohort)	9,798	173,341			33,242		
Index subjects – no. people	6,781	97,946			16,219		
Index subjects – no. index admissions	28,127	331,509			53,332		
Exposed index subjects (Exp Idx)	3,497	1,980	69	1,889	2,954	2,429	147
% exposed index subjects	12.4%	0.6%	0.1%	3.5%	5.5%	4.6%	0.3%
Unadjusted odds ratio (Unadj OR)	1.22	1.52	1.35	0.91	1.01	0.85	1.76
Unadjusted OR 95% confidence interval	1.11-1.35	1.34-1.73	0.78-2.33	0.80-1.04	0.91-1.13	0.78-0.94	1.01-3.07
Unadjusted odds ratio p-value	<0.0001	<0.0001	0.2820	0.1721	0.7756	0.0013	0.0454
Adjusted odds ratio (OR)	1.16	1.50	1.50	0.94	1.07	0.89	1.41
Adjusted OR 95% confidence interval	1.04-1.30	1.30-1.73	0.85-2.64	0.81-1.08	0.96-1.20	0.80-0.98	0.74-2.70
Adjusted odds ratio p-value	0.0061	<0.0001	0.1590	0.3434	0.2340	0.0213	0.3020
Attributable fraction: AF = (OR-1) / OR (%)	14.1%	33.2%	33.3%	-7.0%	6.6%	-12.9%	29.0%
AF 95% confidence interval (%)	4.2-22.9%	23.0-42.2%	-17.2-62.1%	-23.2-7.0%	-4.6-16.7%	-25.0- -1.8%	-36.1-63.0%
Index admissions attributed to drug (AF x Exp Idx)	493	658	23	-131	196	-313	43
Exposed index subjects with relevant ecode <sup>c</sup>	18	28	0	<5	<5	0	0
% exposed index subjects with relevant ecode <sup>c</sup>	0.5%	1.4%	0.0%	n/a	n/a	0.0%	0.0%

<sup>a</sup> Although the study period covered 1993-2005 in this population, index cases related to unplanned hospital admissions between July 1994 and December 2005 only, in patients aged ≥67 years upon admission; these additional constraints were required to ensure sufficient lead-up time for the control observation period.

<sup>b</sup> In each sub-study, domain participants were those who took medications used to treat similar conditions to those indicated for PIMs of interest (i.e. medications from the same broad drug class); these people were considered to be part of the sub-study's population at risk.

<sup>c</sup> Exposed index subjects with relevant ecode refers to unplanned hospitalisations among index subjects who were exposed to the specified PIM at the time of admission and for which a relevant external cause code (ecode) for accidental drug poisoning or adverse drug reaction from the International Classification of Diseases (ICD-9-CM/ICD-10-AM)<sup>158,159</sup> was recorded on the corresponding inpatient summary.

n/a - Not available; due to low counts, the percentage has been withheld to protect patient confidentiality.

#### ***1.4 SUPPLEMENTARY STATISTICS FOR PIM GP CARE EFFECT MODIFICATION PAPER***

The manuscript that examined variations in the estimated effects of PIM exposure on unplanned hospitalisations in older people with different levels of ongoing GP care (chapter 7) included a diagram to compare unplanned hospitalisation rates in each 'GP coverage' group, broken down by PIM exposure status (Figure 7-2). However, the calculations related to the data presented in this diagram were not provided in the manuscript. Hence, the table included in this appendix contains supplementary statistics to show how these various rates and percentages were derived.



**Table I-8 Potentially inappropriate medications (PIMs) in Western Australians aged ≥65 years (1993-2005):<sup>a</sup> derivation of estimates of unplanned hospital admissions per 100,000 person-years (in those aged ≥67 years, restricting time period to July 1994 - December 2005)<sup>a</sup> for groups with varying levels of general practitioner coverage, broken down by PIM exposure status - derivation and summary statistics**

Derivation statistics	Average annual general practitioner coverage (1993-2005) <sup>b</sup>				
	0 - 6 months	>6 - 8 months	>8 - 10 months	>10 months	Overall
Domain participants <sup>c</sup> (number of people in study cohort)	67,553	50,122	59,645	68,116	245,436
Proportion of participants in GP group	27.5%	20.4%	24.3%	27.8%	100.0%
Average annual population (Jul 1994-Dec 2005)	39,178	29,041	34,651	39,448	142,318
Person-years of follow-up (Jul 1994-Dec 2005)	450,542	333,972	398,488	453,653	1,636,655
Unplanned hospital admissions (Jul 1994-Dec 2005)	92,397	52,324	87,070	151,359	383,150
Rate of unplanned hospital admissions per 100,000 PY	20,508	15,667	21,850	33,364	23,411
Unplanned admissions while exposed to PIMs (Jul 1994-Dec 2005)	31,019	14,789	29,939	73,542	149,289
Rate of unplanned admissions while exposed to PIMs per 100,000 PY	6,885	4,428	7,513	16,211	9,122
Unplanned admissions attributed to PIMs in exposed (Jul 1994-Dec 2005)	3,998	3,938	5,072	8,406	22,773
Rate of unplanned admissions attributed to PIMs per 100,000 PY	887	1,179	1,273	1,853	1,391
Unplanned admissions not attributed to PIMs in exposed (Jul 1994-Dec 2005)	27,021	10,851	24,867	65,136	126,516
Rate of unplanned admissions in exposed not attributed to PIMs per 100,000 PY	5,997	3,249	6,240	14,358	7,730
Unplanned admissions while unexposed to PIMs (Jul 1994-Dec 2005)	61,378	37,535	57,131	77,817	233,861
Rate of unplanned admissions while unexposed to PIMs per 100,000 PY	13,623	11,239	14,337	17,153	14,289
<b>Summary statistics - estimates of unplanned hospital admissions per 100,000 people aged ≥67 years (per year)</b>	<b>Average annual general practitioner coverage (1993-2005)<sup>b</sup></b>				
	<b>0 - 6 months</b>	<b>&gt;6 - 8 months</b>	<b>&gt;8 - 10 months</b>	<b>&gt;10 months</b>	<b>Overall</b>
Exposed - admission attributed to PIM	887 (4.3%)	1,179 (7.5%)	1,273 (5.8%)	1,853 (5.6%)	1,391 (5.9%)
Exposed - admission not attributed to PIM	5,997 (29.2%)	3,249 (20.7%)	6,240 (28.6%)	14,358 (43.0%)	7,730 (33.0%)
Unexposed to PIMs at time of admission	13,623 (66.4%)	11,239 (71.7%)	14,337 (65.6%)	17,153 (51.4%)	14,289 (61.0%)
All unplanned hospital admissions	20,508 (100.0%)	15,667 (100.0%)	21,850 (100.0%)	33,364 (100.0%)	23,411 (100.0%)

<sup>a</sup> Although the study period covered 1993-2005 in a population aged ≥65 years, index cases related to unplanned hospital admissions between July 1994 and December 2005 in patients aged ≥67 years upon admission, to ensure sufficient lead-up time for the control observation period. Consequently, rates were calculated for this time period and age group.

<sup>b</sup> Average annual general practitioner (GP) coverage was obtained from patients' proportion of GP coverage over 1993-2005, each GP visit being allocated a 61-day coverage period (overlapping periods merged together). GP coverage categories were then derived from approximate quartiles, providing a general indicator for the level of ongoing GP monitoring.

<sup>c</sup> Domain participants were those who took medications used to treat similar conditions to those indicated for any PIM from the general Beers' list (i.e. medications from the same broad drug classes); these people were considered to be part of the study's population at risk.

### ***1.5 SUPPLEMENTARY STATISTICS FOR PIM AGED CARE EFFECT MODIFICATION PAPER***

As per the manuscript on GP care, the paper that compared the estimated effects of PIM exposure on unplanned hospitalisations in high-care nursing home residents against apparent effects in other elderly people (chapter 8) included a diagram to compare unplanned hospitalisation rates between the two groups, broken down by PIM exposure status (Figure 8-3). Similarly, the calculations related to the data presented in this diagram were not provided in the manuscript. Hence, the table included in this appendix contains supplementary statistics to show how these various rates and percentages were derived.

**Table I-9 Potentially inappropriate medications (PIMs) in Western Australians aged  $\geq 65$  years (1993-2005):<sup>a</sup> derivation of estimates of unplanned hospital admissions per 100,000 person-years (in those aged  $\geq 67$  years, restricting time period to July 1994 - December 2005)<sup>a</sup> in high-level aged care residents versus other elderly, broken down by PIM exposure status - derivation and summary statistics**

Derivation statistics	High-level aged care status at midpoint of admission year <sup>b</sup>	
	High care	Other
Average annual population (Jul 1994-Dec 2005)	3,979	135,920
Person-years of follow-up (Jul 1994-Dec 2005)	45,762	1,563,075
Unplanned hospital admissions (Jul 1994-Dec 2005)	20,525	362,625
Rate of unplanned hospital admissions per 100,000 PY	44,852	23,199
Unplanned admissions while exposed to PIMs (Jul 1994-Dec 2005)	10,336	138,953
Rate of unplanned admissions while exposed to PIMs per 100,000 PY	22,586	8,890
Unplanned admissions attributed to PIMs in exposed (Jul 1994-Dec 2005)	1,808	21,792
Rate of unplanned admissions attributed to PIMs per 100,000 PY	3,951	1,394
Unplanned admissions not attributed to PIMs in exposed (Jul 1994-Dec 2005)	8,528	117,161
Rate of unplanned admissions in exposed not attributed to PIMs per 100,000 PY	18,636	7,495
Unplanned admissions while unexposed to PIMs (Jul 1994-Dec 2005)	10,189	223,672
Rate of unplanned admissions while unexposed to PIMs per 100,000 PY	22,265	14,310
<b>Summary statistics - estimates of unplanned hospital admissions per 100,000 people aged <math>\geq 67</math> years (per year)</b>	<b>High-level aged care status at midpoint of admission year<sup>b</sup></b>	
	<b>High care</b>	<b>Other</b>
Exposed - admission attributed to PIM	3,951 (8.8%)	1,394 (6.0%)
Exposed - admission not attributed to PIM	18,636 (41.5%)	7,495 (32.3%)
Unexposed to PIMs at time of admission	22,265 (49.6%)	14,310 (61.7%)
All unplanned hospital admissions	44,852 (100.0%)	23,199 (100.0%)

<sup>a</sup> Although the study period covered 1993-2005 in a population aged  $\geq 65$  years, index cases related to unplanned hospital admissions between July 1994 and December 2005 in patients aged  $\geq 67$  years upon admission, to ensure sufficient lead-up time for the control observation period. Consequently, rates were calculated for this time period and age group.

<sup>b</sup> High care subjects were those who were receiving high-level aged care services in a nursing home at 30 June of each calendar year; other subjects included all other elderly (i.e. those receiving low-level hostel or community aged care services and those living in a private home without any aged care support at that time).

## ***1.6 SUPPLEMENTARY STATISTICS FOR PAPER ON ESTIMATED PIM EFFECTS IN PATIENTS TAKING HIGH-RISK DRUGS***

The manuscript on the apparent effects of PIMs in patients taking high-risk drugs (chapter 9) includes a diagram that shows differences in the estimated counts of hospital admissions attributed to drug exposure when concurrent intake of specific PIMs from the general Beers list are taken into consideration (Figure 9-4). The tables found in this appendix provide statistics that show how these differences were calculated.

**Table I-10 High-risk medications and unplanned hospitalisations in Western Australian elderly (1993-2005): derivation of differences<sup>a</sup> in the estimated counts of unplanned hospital admissions attributed to drug exposure with concurrent intake of indomethacin and/or naproxen**

Statistics	Anti-coagulants	Anti-rheumatics	Opioids	Corticosteroids	Cardiac rhythm regulators	Beta-blockers	Hypertension drugs	Serum lipid-reducing agents
Index subjects exposed to main drug group (all)	26,088	61,595	45,772	30,740	44,730	60,755	192,674	69,286
Index subjects exposed to main drug group (no antirheumatic PIM)	25,620	51,296	42,854	29,542	43,536	58,812	186,780	67,465
Index subjects exposed to main drug group+indomethacin	209	3,558	1,056	379	480	711	2,094	647
Index subjects exposed to main drug group+naproxen	252	6,624	1,801	805	696	1,206	3,728	1,159
Index subjects exposed to main drug group+indomethacin+naproxen	7	117	61	14	18	26	72	15
Adjusted odds ratio (OR) - main drug group (no antirheumatic PIM)	1.12	1.06	1.78	1.46	1.10	1.07	0.91	0.84
Adjusted odds ratio (OR) - main drug group+indomethacin	2.46	1.38	2.86	1.43	1.75	1.43	1.11	1.26
Adjusted odds ratio (OR) - main drug group+naproxen	1.92	1.21	2.07	2.06	1.11	1.30	1.04	0.96
Adjusted odds ratio (OR) - main drug group+indomethacin+naproxen	0.00	2.20	6.34	6.85	1.03	4.31	1.92	1.15
Attributable fraction (AF) - main drug group (no antirheumatic PIM)	10.4%	5.8%	43.9%	31.6%	9.3%	6.7%	-9.8%	-18.5%
Attributable fraction (AF) - main drug group+indomethacin	59.4%	27.6%	65.0%	30.2%	42.9%	30.1%	10.1%	20.8%
Attributable fraction (AF) - main drug group+naproxen	47.9%	17.4%	51.6%	51.4%	9.5%	23.1%	3.6%	-4.7%
Attributable fraction (AF) - main drug group+indomethacin+naproxen	-33233.3%	54.4%	84.2%	85.4%	2.9%	76.8%	47.8%	13.3%
Attributed admissions - main drug group (no antirheumatic PIM)	2,663	2,995	18,819	9,335	4,065	3,950	-18,247	-12,470
Attributed admissions - main drug group+indomethacin	124	983	686	115	206	214	211	134
Attributed admissions - main drug group+naproxen	121	1,150	930	414	66	278	133	-55
Attributed admissions - main drug group+indomethacin+naproxen <sup>b</sup>	4	32	40	7	8	8	7	3
Attributed admissions - main drug group (all-antirheumatic adjusted)	2,912	5,160	20,475	9,871	4,345	4,450	-17,896	-12,387
Attributed admissions - main drug group (all-no antirheumatic PIM AF)	2,712	3,596	20,101	9,714	4,177	4,081	-18,823	-12,806
Attributed admissions - main drug group (all-difference)	201	1,564	374	157	168	369	927	419

<sup>a</sup> The differences were obtained by subtracting the 'PIM-negative' estimates (i.e. counts of unplanned hospitalisations that would be expected if all index subjects exposed to a high-risk drug were unexposed to the specified PIMs) from the 'PIM-refined' estimates (i.e. those obtained by applying more explicit attributable fractions (AFs) to subsets of index subjects exposed to high-risk drugs depending upon their concurrent PIM exposure status).

<sup>b</sup> The attributed admission counts shown in this row were calculated using the AF for the main drug group combined with the antirheumatic PIM with the highest OR (indomethacin for most, naproxen for the sub-study on corticosteroids) rather than the AF for the main group combined with both indomethacin and naproxen. The latter AF was considered too unreliable, given the low subject counts from which it was derived and broad confidence interval.

**Table I-11 High-risk medications and unplanned hospitalisations in Western Australian elderly (1993-2005): derivation of differences<sup>a</sup> in the estimated counts of unplanned hospital admissions attributed to drug exposure with concurrent intake of temazepam**

Statistics	Anti-coagulants	Anti-rheumatics	Opioids	Cortico-steroids	Cardiac rhythm regulators	Beta-blockers	Hyper-tension drugs	Serum lipid-reducing agents
Index subjects exposed to main drug group (all)	26,088	61,595	45,772	30,740	44,730	60,755	192,674	69,286
Index subjects exposed to main drug group (no temazepam)	22,094	52,130	35,295	25,295	37,177	52,653	165,576	60,507
Index subjects exposed to main drug group+temazepam	3,994	9,465	10,477	5,445	7,553	8,102	27,098	8,779
Adjusted odds ratio (OR) - main drug group (no temazepam)	1.11	1.08	1.83	1.46	1.09	1.06	0.89	0.83
Adjusted odds ratio (OR) - main drug group+temazepam	1.30	1.22	1.79	1.57	1.27	1.30	1.17	1.05
Attributable fraction (AF) - main drug group (no temazepam)	10.0%	7.2%	45.2%	31.6%	7.9%	5.6%	-12.0%	-19.9%
Attributable fraction (AF) - main drug group+temazepam	22.9%	17.9%	44.2%	36.3%	21.1%	22.8%	14.4%	4.5%
Attributed admissions - main drug group (no temazepam)	2,207	3,772	15,955	7,993	2,944	2,933	-19,839	-12,043
Attributed admissions - main drug group+temazepam	915	1,694	4,630	1,979	1,592	1,850	3,898	394
Attributed admissions - main drug group (all-temazepam adjusted)	3,122	5,466	20,586	9,972	4,536	4,784	-15,942	-11,649
Attributed admissions - main drug group (all-no temazepam AF)	2,606	4,457	20,691	9,714	3,542	3,385	-23,086	-13,791
Attributed admissions - main drug group (all-difference)	516	1,009	-106	258	994	1,399	7,145	2,141

<sup>a</sup> The differences were obtained by subtracting the 'PIM-negative' estimates (i.e. counts of unplanned hospitalisations that would be expected if all index subjects exposed to a high-risk drug were unexposed to the specified PIM) from the 'PIM-refined' estimates (i.e. those obtained by applying more explicit attributable fractions (AFs) to subsets of index subjects exposed to high-risk drugs depending upon their concurrent PIM exposure status).

**Table I-12 High-risk medications and unplanned hospitalisations in Western Australian elderly (1993-2005): derivation of differences<sup>a</sup> in the estimated counts of unplanned hospital admissions attributed to drug exposure with concurrent intake of oxazepam and/or diazepam**

Statistics	Anti-coagulants	Anti-rheumatics	Opioids	Cortico-steroids	Cardiac rhythm regulators	Beta-blockers	Hyper-tension drugs	Serum lipid-reducing agents
Index subjects exposed to main drug group (all)	26,088	61,595	45,772	30,740	44,730	60,755	192,674	69,286
Index subjects exposed to main drug group (no anxiolytic PIM)	24,358	55,881	39,636	27,768	41,199	56,044	177,807	64,576
Index subjects exposed to main drug group+oxazepam	987	3,022	3,088	1,623	2,081	2,606	8,486	2,534
Index subjects exposed to main drug group+diazepam	712	2,542	2,875	1,293	1,389	2,017	6,033	2,063
Index subjects exposed to main drug group+oxazepam+diazepam	31	150	173	56	61	88	348	113
Adjusted odds ratio (OR) - main drug group (no anxiolytic PIM)	1.12	1.08	1.82	1.47	1.10	1.07	0.90	0.84
Adjusted odds ratio (OR) - main drug group+oxazepam	1.16	1.16	1.75	1.60	1.35	1.25	1.02	1.04
Adjusted odds ratio (OR) - main drug group+diazepam	1.40	1.38	1.77	1.62	1.22	1.18	1.24	0.99
Adjusted odds ratio (OR) - main drug group+oxazepam+diazepam	0.84	1.27	2.06	1.32	1.31	1.20	1.65	1.72
Attributable fraction (AF) - main drug group (no anxiolytic PIM)	10.8%	7.3%	45.1%	31.8%	8.7%	6.6%	-10.6%	-19.0%
Attributable fraction (AF) - main drug group+oxazepam	13.9%	13.5%	43.0%	37.4%	26.1%	19.7%	1.6%	3.6%
Attributable fraction (AF) - main drug group+diazepam	28.5%	27.6%	43.4%	38.3%	18.2%	15.3%	19.5%	-1.1%
Attributable fraction (AF) - main drug group+oxazepam+diazepam	-18.6%	21.4%	51.4%	24.0%	23.8%	16.5%	39.4%	41.7%
Attributed admissions - main drug group (no anxiolytic PIM)	2,629	4,091	17,882	8,827	3,574	3,715	-18,882	-12,300
Attributed admissions - main drug group+oxazepam	137	408	1,327	607	543	515	134	90
Attributed admissions - main drug group+diazepam	203	701	1,249	495	253	309	1,176	-23
Attributed admissions - main drug group+oxazepam+diazepam <sup>b</sup>	9	41	75	21	16	17	68	4
Attributed admissions - main drug group (all-anxiolytic adjusted)	2,978	5,242	20,533	9,950	4,386	4,556	-17,505	-12,229
Attributed admissions - main drug group (all-no anxiolytic PIM AF)	2,816	4,510	20,650	9,771	3,881	4,028	-20,461	-13,197
Attributed admissions - main drug group (all-difference)	162	732	-117	178	506	529	2,956	969

<sup>a</sup> The differences were obtained by subtracting the 'PIM-negative' estimates (i.e. counts of unplanned hospitalisations that would be expected if all index subjects exposed to a high-risk drug were unexposed to the specified PIMs) from the 'PIM-refined' estimates (i.e. those obtained by applying more explicit attributable fractions (AFs) to subsets of index subjects exposed to high-risk drugs depending upon their concurrent PIM exposure status).

<sup>b</sup> The attributed admission counts shown in this row were calculated using the AF for the main drug group combined with the anxiolytic PIM with the highest OR (diazepam for most, oxazepam for the sub-studies on cardiac rhythm regulators, beta-blockers and serum lipid-reducing agents) rather than the AF for the main group combined with both oxazepam and diazepam. The latter AF was considered too unreliable, given the low subject counts from which it was derived and broad confidence interval.

**Table I-13 High-risk medications and unplanned hospitalisations in Western Australian elderly (1993-2005): derivation of differences<sup>a</sup> in the estimated counts of unplanned hospital admissions attributed to drug exposure with concurrent intake of digoxin and/or amiodarone**

Statistics	Anti-coagulants	Anti-rheumatics	Opioids	Corticosteroids	Cardiac rhythm regulators	Beta-blockers	Hypertension drugs	Serum lipid-reducing agents
Index subjects exposed to main drug group (all)	26,088	61,595	45,772	30,740	44,730	60,755	192,674	69,286
Index subjects exposed to main drug group (no CRR PIM)	15,531	55,122	40,450	26,730	742	52,840	161,586	60,599
Index subjects exposed to main drug group+digoxin	7,560	4,855	3,790	2,882	32,356	5,457	22,474	4,992
Index subjects exposed to main drug group+amiodarone	2,245	1,377	1,316	936	9,866	2,090	7,252	3,202
Index subjects exposed to main drug group+digoxin+amiodarone	752	241	216	192	1,766	368	1,362	493
Adjusted odds ratio (OR) - main drug group (no CRR PIM)	1.12	1.08	1.82	1.47	1.26	1.06	0.91	0.84
Adjusted odds ratio (OR) - main drug group+digoxin	1.05	1.20	1.79	1.48	1.07	1.21	0.96	0.94
Adjusted odds ratio (OR) - main drug group+amiodarone	1.35	1.34	1.84	1.64	1.19	1.39	1.06	1.08
Adjusted odds ratio (OR) - main drug group+digoxin+amiodarone	1.62	1.20	2.04	1.91	1.40	1.73	1.43	1.39
Attributable fraction (AF) - main drug group (no CRR PIM)	11.0%	7.6%	45.1%	32.0%	20.3%	5.5%	-10.0%	-19.3%
Attributable fraction (AF) - main drug group+digoxin	4.8%	16.7%	44.1%	32.6%	6.1%	17.2%	-4.1%	-6.4%
Attributable fraction (AF) - main drug group+amiodarone	25.8%	25.6%	45.5%	39.1%	16.0%	27.8%	5.2%	7.0%
Attributable fraction (AF) - main drug group+digoxin+amiodarone	38.1%	16.3%	50.9%	47.8%	28.4%	42.2%	30.2%	28.2%
Attributed admissions - main drug group (no CRR PIM)	1,713	4,177	18,237	8,559	151	2,897	-16,176	-11,715
Attributed admissions - main drug group+digoxin	360	813	1,671	939	1,975	940	-912	-319
Attributed admissions - main drug group+amiodarone	580	352	599	366	1,582	581	378	223
Attributed admissions - main drug group+digoxin+amiodarone <sup>b</sup>	194	62	98	75	283	102	71	34
Attributed admissions - main drug group (all-CRR adjusted)	2,847	5,404	20,606	9,938	3,991	4,520	-16,639	-11,776
Attributed admissions - main drug group (all-no CRR PIM AF)	2,878	4,668	20,636	9,843	9,089	3,331	-19,289	-13,394
Attributed admissions - main drug group (all-difference)	-31	736	-31	96	-5,098	1,189	2,649	1,619

<sup>a</sup> The differences were obtained by subtracting the 'PIM-negative' estimates (i.e. counts of unplanned hospitalisations that would be expected if all index subjects exposed to a high-risk drug were unexposed to the specified PIMs) from the 'PIM-refined' estimates (i.e. those obtained by applying more explicit attributable fractions (AFs) to subsets of index subjects exposed to high-risk drugs depending upon their concurrent PIM exposure status).

<sup>b</sup> The attributed admission counts shown in this row were calculated using the AF for the main drug group combined with the CRR PIM with the highest OR (amiodarone for all) rather than the AF for the main group combined with both digoxin and amiodarone. The latter AF was considered less reliable, given the lower subject counts from which it was derived and broader confidence interval. Although the AF involving both PIMs may have been suitable for some sub-studies, it was decided not to use it for the sake of consistency.

CRR - Cardiac rhythm regulator



**Table I-14 High-risk medications and unplanned hospitalisations in Western Australian elderly (1993-2005): derivation of differences<sup>a</sup> in the estimated counts of unplanned hospital admissions attributed to drug exposure with concurrent intake of ferrous sulphate**

Statistics	Anti-coagulants	Anti-rheumatics	Opioids	Cortico-steroids	Cardiac rhythm regulators	Beta-blockers	Hyper-tension drugs	Serum lipid-reducing agents
Index subjects exposed to main drug group (all)	26,088	61,595	45,772	30,740	44,730	60,755	192,674	69,286
Index subjects exposed to main drug group (no ferrous sulphate)	25,032	59,491	43,935	29,654	42,592	58,928	185,416	67,360
Index subjects exposed to main drug group+ferrous sulphate	1,056	2,104	1,837	1,086	2,138	1,827	7,258	1,926
Adjusted odds ratio (OR) - main drug group (no ferrous sulphate)	1.12	1.09	1.82	1.48	1.17	1.07	0.91	0.85
Adjusted odds ratio (OR) - main drug group+ferrous sulphate	1.54	1.24	1.62	1.50	1.16	1.46	1.08	0.98
Attributable fraction (AF) - main drug group (no ferrous sulphate)	10.5%	8.1%	45.2%	32.3%	14.3%	6.9%	-9.6%	-17.9%
Attributable fraction (AF) - main drug group+ferrous sulphate	35.2%	19.4%	38.2%	33.3%	13.5%	31.4%	7.3%	-1.6%
Attributed admissions - main drug group (no ferrous sulphate)	2,622	4,812	19,848	9,577	6,095	4,060	-17,891	-12,074
Attributed admissions - main drug group+ferrous sulphate	372	407	702	362	289	574	531	-31
Attributed admissions - main drug group (all-ferrous sulphate adjusted)	2,994	5,219	20,549	9,938	6,384	4,634	-17,360	-12,105
Attributed admissions - main drug group (all-no ferrous sulphate AF)	2,733	4,982	20,678	9,928	6,401	4,186	-18,591	-12,419
Attributed admissions - main drug group (all-difference)	261	237	-128	11	-17	448	1,232	314

<sup>a</sup> The differences were obtained by subtracting the 'PIM-negative' estimates (i.e. counts of unplanned hospitalisations that would be expected if all index subjects exposed to a high-risk drug were unexposed to the specified PIM) from the 'PIM-refined' estimates (i.e. those obtained by applying more explicit attributable fractions (AFs) to subsets of index subjects exposed to high-risk drugs depending upon their concurrent PIM exposure status).



## **APPENDIX J. PUBLISHED PAPERS**

The following papers have been published since the start of this project, either online (for early view) or in print:

- High-risk drugs exploration paper (chapter 4)
- PIM prevalence paper (chapter 5)
- Main paper on estimation of PIM effects (chapter 6)
- PIM aged care effect modification paper (chapter 8)
- Paper on PIM effects in patients taking high-risk drugs (chapter 9).

A copy of the first page of each paper's published version is included in this appendix.

Published papers removed from the online version of the thesis due to copyright issues.