ERRATA

Page 17, para 3	"can to be" change to "can be"
Page 22, last para	change "needs" to "need"
Page 29, Line 2.	"a disease" delete "a"
Page 31, para 2	"obtained with." delete "with"
Page 41, Line 18	change to "have been" rather than "been"
Page 54, para 3	"led the adoption" change to "led to the adoption"
Page 89, Table.	"antih!mintics" change to "anthelmintics"
	"diphteria" change to "diphtheria"
Page 90, Table.	"betameasone" change to "betamethasone"
Page 140, para 1	"59.6% (63/127)" change to "49.6% (63/127)"
Page 141, Table 5.6	percentage in column Category A reads "59.6%" it should be "49.6%"
Page 144, Table 5.8	change "nosteriodal" to "nonsteroidal"
Page 145, Table	change "hypoglycemic" to hypoglycaemic"
	change "diphteria" to "diphtheria"
Page 146, Table	change "bupivicaine" to "bupivacaine"
Page 150, Table 5.11	Delete "]"
Page 165, Table 5.16	change "sertaline" to "sertraline"
Page 193, para 2	"concur that" change to "concur with that"
Page 233, para 2	"considered ineffective administered" change to "considered ineffective were administered"

ADDENDUM

Page 68, Line 9   "and/or" change to "and"

Page 51, Line 15: Comment: At the time of data collection, local hospital factors at one of the hospitals meant that differences in the intensity of the monitoring process would arise for oncology patients. This, in addition to the practical limitations already discussed in this thesis, necessitated the exclusion of oncology patients at this site and, for consistency, at the remaining hospital sites.

Page 228, Line 6: Comment: In the literature a number of *structured* algorithms have to date been validated using the unstandardised judgements of experts as the "correct answer" to compare results obtained with. However, given that it was precisely the unreliability of such unstandardised judgements that lead to the development of *structured algorithms*, this method to determine validity has since been discredited.

Page 229, Para 3: Comment: It would have been of interest to compare inter and intra-observer reproducibility between the two algorithms for the same adverse drug reaction. However, as the adverse drug reactions reviewed by the *multidisciplinary panel* and the *pharmacy* panel were mutually exclusive this was not possible.

Page 51, Add at the end of Line 18:
"In addition, the practical constraints operating within each hospital meant that duration of data collection determined for the three hospitals was based upon convenience."

When comparing the eligible patient populations from the hospitals involved in this research, statistically significant differences were found with respect to age and gender in two of the three streams of data collection. Although these differences were reported to be statistically significant they were not classified as clinically significant. For further explanation please refer to Page 120, Para 4 and Page 191 Para 4.

Page 197, Line 3 to read:
"These results confirm previous reports of the limited usefulness of spontaneous monitoring and provide further evidence that this method should not be used in isolation to measure the frequency of ADRs."

Spontaneous monitoring and *retrospective intensive monitoring* were used to determine the frequency of adverse drug reactions arising within the inpatient population. For further explanation as to why these methods were used in preference to *prospective intensive monitoring* please refer to Page 28, Para 1.

Page 206, para 1 Comment: Although the costing system at GH provides data on an individual basis, the system was being upgraded at the time of data collection. Individual costing data was therefore not available for the cases identified over the period of data collection.

The consequences of drug related problems in paediatrics.

Kylie Easton-Carter

BPharm, BPharm.Sci(Hons), Grad Dip Hosp Pharm

A thesis submitted for the degree of Doctor of Philosophy from the Victorian College of Pharmacy, Monash University.

March 2001

Department of Pharmacy Practice
Victorian College of Pharmacy
Monash University
381 Royal Pde
Parkville
Victoria 3052
Australia

Table of Contents

Abstract

Australia's policy on the Quality Use of Medicines (QUM) aims to achieve appropriate medication use and thus improve health outcomes. While the goals of this policy extend to *all* Australians, recent reports have provided fragmented information indicating that QUM may not be optimal in the paediatric population. Research enabling a broader appreciation of the impact of sub-optimal medication use in this population is therefore required.

Within the adult population these data have been obtained by investigating the clinical and economic consequences of drug related problems (DRPs). The corresponding data on DRPs were limited in the paediatric population for DRPs occurring at a range of levels of severity.

In order to address this information deficit this multi-centre study explored three streams of data collection: emergency department attendances associated with DRPs; hospital admissions associated with DRPs; and adverse drug reactions (ADRs) arising within the inpatient population. The economic implications of the emergency department attendances and hospital admissions associated with the DRPs identified were also investigated.

The three Victorian hospitals involved in this study were the Royal Children's Hospital, Geelong Hospital and Box Hill Hospital. All unplanned medical patients attending the emergency departments or admitted to one of these hospitals were considered eligible for inclusion in the first two streams of data collection. The investigator and the attending medical practitioner or clinical pharmacist screened eligible patients. Adverse drug reactions arising within the inpatient populations were identified using *spontaneous* and *retrospective intensive monitoring*. A *multidisciplinary panel* or *pharmacy panel* reviewed information collected and a causality, preventability and clinical significance classification was established. The economic implications of the DRPs identified were determined using a *cost of illness* approach.

Combining data from the three hospitals, the frequency of emergency department attendances associated with DRPs was determined to be 3.3% (95% CI 2.9 – 3.7%). The frequency of hospital admissions associated with DRPs was determined to be 4.3% (95% CI 3.6% - 5.0%). A high proportion of the DRPs identified were deemed preventable. Areas to be targeted with strategies to prevent or reduce the impact of DRPs were identified.

Although the frequency of ADRs arising within the inpatient populations was determined, under-reporting appeared to significantly influence the results reported. As the monitoring methods employed are used commonly in Victorian hospitals this finding has important implications for the monitoring of ADRs within the paediatric population.

The direct and indirect costs were determined to be $715,941.73 for the 407 DRP cases identified, of which $300,413.07 was associated with DRPs considered to be preventable.

As a result of this research, information is now available on the clinical and economic implications of DRPs within the paediatric population. This study has reported the frequency of DRPs identified to be similar to that reported within the adult population, but the areas to be targeted by prevention strategies differ. Given that the need to prevent DRPs is recognised within the adult population it is now time to pay attention to the younger end of the age spectrum and act to reduce the consequences of DRPs in paediatrics.

Statement of originality

The work presented in this thesis is, to the best of my knowledge and belief, original except as acknowledged in the text. This thesis has not been submitted in part or in whole for the award of any other degree or diploma in any university or other institution. Full acknowledgement has been made where the work of others have been cited or used.

Kylie Easton-Carter
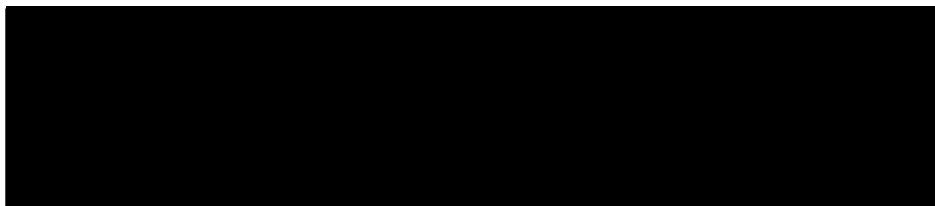
March 2001

Communications arising from this thesis

Published Abstracts:

Easton KL, Brien JE, Parsons B, Starr M. Hospital admissions associated with drug related problems in paediatrics. *Aust J Hosp Pharm* 1996; 26(6) Suppl 1: S15 [0-15]

Conference Proceedings:

Easton-Carter K, Chapman C, Brien J. Drug related problems in paediatrics: an Australian perspective. American College of Clinical Pharmacists Annual Meeting, Los Angeles, November 2000

Easton-Carter K, Chapman C, Brien J. Paediatric emergency department attendances: a multi-centre study. Society of Hospital Pharmacists Biennial Clinical Conference, Gold Coast, October 2000

Easton-Carter K, Chapman C, Brien J. Drug related problems in paediatrics: implications for prevention. New South Wales State Branch Conference of the Society of Hospital Pharmacists of Australia. Wollongong, July 2000.

Easton KL, Lilley B, Brien J. Adverse drug reactions in paediatrics: are we getting the full picture? Clinical Controversies: issues in Therapeutics. The Society of Hospital Pharmacists of Australia. Hobart, December 1998.

Easton KL, Brien J, Lilley B. Paediatric emergency department attendances associated with drug related problems in paediatrics. Australasian Pharmaceutical Science Association Conference. Hobart, December 1998.

Easton KL, Lilley B, Brien J. Paediatric emergency department attendances and hospital admissions associated with adverse drug reactions. Victorian State Branch Conference of the Society of Hospital Pharmacists of Australia. Geelong, October 1998.

Easton KL, Brien JE. Investigating drug related problems. Proceedings of the Australasian Pharmaceutical Science Association. Sydney, November 1997.

Easton KL, Brien JE. Methodologicial issues in research into drug related hospital admissions. Proceedings of the 23rd Federal Conference of the Society of Hospital Pharmacists of Australia. Adelaide, November 1997.

Acknowledgements

The work performed in this thesis would not have been possible if it were not for the helpfulness and support of a number of people.

Of my supervisors, I would especially like to thank Professor Jo-anne Brien, who has been extremely generous with her vast knowledge, ideas and advice. Her encouragement and support, particularly in the final stages of this work has been exceptional and very much appreciated. I thank her for being a calming influence during difficult times and for reminding me that other parts of my life should not be neglected. The experiences and opportunities Jo-anne has provided me with during this work will be valuable long after this thesis has been completed. Thank you Jo-anne.

I would also like to thank Professor Colin Chapman for his vast experience, knowledge and patience in helping me complete the work provided in this thesis. In spite of his busy schedule, he afforded me time and guidance where it was needed, for this and so much more I thank him.

This work would not have been possible without the fantastic support and dedication of the members of the *multidisciplinary* and *pharmacy* panels. The knowledge and experience displayed by Dr Michael Starr, Dr Noel Cranswick, Mr Brian Lilley, Mr Tony Stratford, Ms Alison Menner, Ms Thirza Titchen, Ms Christine Kemp and Ms Suzanne Beulke in undertaking their role on these panels was invaluable.

I am also extremely grateful for the statistical advice of Dr Ian Storey, the assistance with the epidemiology aspects of this work provided by Associate Professor Michael Abramson, and the health economics guidance provided by Dr Terri Jackson. Thank you for so kindly providing me with your time when it was required.

The support provided by members of the Royal Children's Hospital, Geelong Hospital, and Box Hill Hospital pharmacy departments and emergency

departments was instrumental in allowing this work to be undertaken. In particular I would like to thank Mr Brian Lilley and Dr Peter Barnett at the Royal Children's Hospital, Mr Greg Weeks, Dr David Eddey and Dr Michael Ragg at the Geelong Hospital, and Ms Carmela Corallo and Dr Andrew Maclean from Box Hill Hospital.

I am also indebted to Ms Jane Widdleson and Mr Jeremy Hose for their assistance in providing aspects of the costing data required for this project. Thank you also to Ms Belinda Tilley, Ms Roslyn Edsel and Ms Carole Neill from the Medical Records departments of the three hospitals investigated in this study.

Thank you also to the members of the Department of Pharmacy Practice at the Victorian College of Pharmacy for their support. In particular I would like to thank Dr Jennifer Marriott and Dr Kay Stewart for their assistance and encouragement.

Thank you to the Commonwealth Department of Health and Aged Care who provided the funding for this work through a Quality Use of Medicines Evaluation Program (QUMEP) postgraduate scholarship.

I would also like to thank my friends and family for their support. I could not have undertaken this task without the encouragement and love of Mum, Dad, Marrianne, Ian, Shelia, Nanna, Paul, Sarah, Clare and Brett. Thank you Mum for your company in America and thank you to Dad for proof reading this work. I am also grateful to the Carters for their love and support. To my husband Matthew, I thank you for providing me with the love and emotional support that has enabled me to complete this work. These few words of thanks cannot possibly do justice to my feelings of gratitude to you all.

Finally, I would like to express my love and gratitude to my Pop for inspiring me to test my boundaries and for willing me to succeed. This thesis is dedicated to you Pop. As you always said *"Just imagine what I could have done if I had tried"*.

1 The Quality Use of Medicines in paediatrics

The goal of Australia's policy on the Quality Use of Medicines (QUM) is to improve health outcomes for *all* Australians by optimising medicinal drug use.[1,2] The policy proposes medication use be optimised by ensuring that all medicines be used: *judiciously*, with use only when appropriate; *appropriately*, where a medication is chosen taking into account the condition being treated along with the potential benefits and risks of therapy; *safely*, with minimisation of misuse, overuse and underuse; and *efficaciously* by achieving the goals of therapy.[1] Achieving these goals is important because medication use was reported as the most common health-related action undertaken in the 1995 National Health Survey, with 59% of persons having used a medication in the two weeks prior to interview.[3] Furthermore, while it is acknowledged that appropriate medication use can significantly improve health outcomes,[3] reports in the literature have also demonstrated that inappropriate use can cause much unnecessary harm[4-7].

The paediatric population are significant consumers of both prescription and non-prescription medicines,[8] with the 1995 National Health Survey indicating that 50.5% of those between 0 and 14 years of age had used a medication in the two weeks prior to interview[3]. Recent literature reports that QUM may not be optimal within the paediatric population,[8] a point highlighted by studies that indicate that medication is not always used *judiciously, appropriately, safely* or *efficaciously* within this population[9, 10].

With respect to medications not being used *judiciously*, Nyquist et al indicated that 44% of all paediatric patients investigated received antibiotics inappropriately for the common cold.[11] Furthermore, an Australian Health Innovations study, in which parents of paediatric patients were interviewed, highlighted the inappropriate administration of sedating antihistamines to these patients to assist in dealing with behavioural problems as one of the obstacles to achieving QUM.[8]

The ability to use medicines *appropriately* by taking into account the potential benefits and risks of treatment has been reported to be limited in the paediatric population by the extensive *unlicensed* or *off-label* use of medicines.[9, 12, 13] This situation commonly arises due to a lack of clinical trials undertaken within the paediatric population.[14, 15] The lack of clinical trials means that instead of extensive evidence, treatment may be based less on published information and more on assumptions and extrapolations from data available on the adult population.[16] The validity of such an approach is questionable due to the pharmacokinetic and pharmacodynamic differences that exist between the paediatric and adult populations.[16-18] Turner reported such use to be common in the Australian inpatient population with 36% of paediatric patients in a specialist paediatric teaching hospital receiving *unlicensed* or *off-label* medications.[9] The report of the Working Party on the Registration of Drugs for Use in Children and the Australian Association of Paediatric Teaching Centres policy document "Pharmaceuticals for Children" have highlighted this issue as an obstruction to achieving QUM.[19, 20]

The Australian Health Innovations study identified non-adherence and complacency, resulting in the under and overuse of medicines respectively, as two problems which reduce the chance of ensuring medications are used *safely* in the paediatric population.[8] Adherence with drug therapy in paediatrics has been reported to range from 7% to 89%,[21, 22] rates that are similar to the range reported in the adult population.[23] Reasons for non-adherence in the paediatric population are complex,[22-24] with patients, families, health care providers, disease states, and pharmaceutical factors all reported to influence adherence[23].

Complacency regarding the safety of non-prescription drugs has also been reported to hinder medications being used *safely* in the paediatric population by increasing their chance of overuse.[8] This point is illustrated by the fact that one in five mothers surveyed in an Australian study declared that they could safely increase the recommended dose of a non-prescription drug for their child.[8] Heubi et al reported the potential dangers of exceeding the recommended doses of non-prescription drugs in their study investigating

hepatotoxicity associated with the therapeutic use of paracetamol.[25] The authors found that for 14 of the 21 cases of hepatotoxicity identified in patients less than three years of age, the dose of paracetamol administered exceeded the recommended weight-based dosage.[25]

The need for paediatric doses to be calculated on the basis of age and weight is another factor that has been noted to reduce the chance of medications being used *safely* within the paediatric population.[26] This need has been reported to increase the risk of medication errors by health care professionals and parents alike thus adding another potential barrier to QUM within this population.[27-29]

In order to ensure medicines are used *safely* the policy on QUM advocates that medication misuse should be minimised.[1] Reports in the literature indicate that medication misuse in the form of accidental or intentional poisonings are common within the paediatric population.[30-32] This issue has been recognised at a national level with the reduction of poisonings for persons between 0 to 4 years of age identified as a national health priority.[10]

Finally, reports also indicate that medicines are not necessarily used *efficaciously* in the paediatric population, in that the goals of therapy are not always achieved.[33, 34] The management of asthma in paediatrics is one such example because, despite asthma being noted as a disease state that can be well controlled with appropriate drug therapy,[35] Ordonez et al reported that only 25% of children admitted to hospital with asthma had been prescribed appropriate preventative therapy prior to admission[33]. Hence, if the appropriate drugs are not being used it is impossible to achieve the goals of therapy by delivering beneficial changes in actual health outcomes.

A number of obstacles to achieving QUM are therefore evident within the paediatric population. While individual studies provide important information on specific areas where QUM is not optimal, it is possible that they only provide small fragments of a much larger picture. More data are therefore

required to enable the full impact of the sub-optimal use of medicines within the paediatric population to be appreciated.

1.1 Drug related problems and QUM

Within the adult population an appreciation of the impact of sub-optimal medication use has been obtained by investigating drug related problems (DRPs) associated with emergency department attendances and hospital admissions.[5, 6, 36-39] Strand et al defined DRPs as any "undesirable patient experience that involves drug therapy and that actually or potentially interferes with a desired outcome".[40] Eight categories of DRPs were determined on the basis that a patient has a medical condition: that requires drug therapy (a drug indication) but the patient is not receiving a drug for that indication; for which the wrong drug is being taken; for which too little of the correct drug is being taken; for which too much of the correct drug is being taken; resulting from an adverse drug reaction (ADR); resulting from a drug-drug, drug-food, drug-laboratory interaction; that is the result of not receiving the prescribed drug; and that is the result of taking a drug for which there is no valid medical indication.[40] It should be noted that ADRs comprise only one component of DRPs.

The frequency of preventable DRPs associated with emergency department attendances and hospital admissions are recognised as important indicators of QUM in the community.[35, 36, 41] This is demonstrated by the fact that the frequency of hospital admissions associated with ADRs are listed as one of the outcome indicators to measure the progress made towards the stated goals of QUM policy.[35] In addition, emergency department attendances associated with DRPs have been reported to provide a broader appreciation of QUM issues by supplying information on DRPs occurring at a different level of severity.[36] The collection of such data in both the Australian,[4, 42] and international adult populations,[43-45] has enabled the clinical and economic impact of DRPs to be established in these populations[4, 46, 47]. In doing so, attention has been focused upon reducing the frequency and impact of DRPs.[47-49] As an example, the consistency of the drugs involved in drug

related hospital admissions in the Australian adult population has led to target areas being identified and prevention strategies proposed.[42, 50, 51] Therefore, as the investigation of emergency department attendances and hospital admissions associated with DRPs is recognised as providing a broader picture on QUM issues in the adult population, it is important to determine if similar information is available for the paediatric population.

1.1.1 Studies investigating emergency department attendances associated with DRPs in the paediatric population

There are no studies investigating emergency department attendances associated with DRPs specifically, either within the Australian or international paediatric populations.

There are, however, 10 studies that investigate drug related emergency department attendances in the broader population,[36-38, 45, 52-57] three of which investigate ADRs only[52-54]. Five of the 10 indicated that paediatric patients were not specifically excluded from data collection.[36, 38, 45, 55, 56] Despite this, adults formed the majority of patients identified in the five studies.[36, 38, 45, 55, 56] Limited paediatric data can to be extracted from only two of these studies, neither of which were conducted in Australia.[45, 55]

The frequency of emergency department attendances associated with DRPs reported in seven of the 10 studies ranged from 1.7% to 28.1%, with the variation in frequencies attributed to methodological differences.[36-38, 45, 55-57]

Given the lack of paediatric data it is pertinent to consider the appropriateness of extrapolating data from studies conducted in the predominantly adult population to the paediatric population. Whyte and Greenan cautioned against such extrapolations as they reported that ADRs experienced by sick children differed from those of adults,[58] with the differences attributable to the distinctive drug usage patterns of childhood[59, 60]. Such differences are illustrated by the Boston Collaborative Drug

Surveillance Program, which found that the mean number and type of drugs administered to paediatric patients differed to that of adults.[59] Furthermore, Mitchell et al reported that, due to differences in therapies between the paediatric and adult populations, experiences in adult populations should not be directly extrapolated to the paediatric population.[61] On the basis of this information it is inappropriate to extrapolate data collected in studies conducted within the adult population to the paediatric population. Data relating to the frequency and characteristics of emergency department attendances associated with DRPs are therefore required in the paediatric population.

1.1.2 Studies investigating hospital admissions associated with DRPs in the paediatric population

A total of nine paediatric studies investigating drug related hospital admissions were identified within the literature.[7, 58, 60-66] Six of the studies investigate ADRs only, so the results cannot be extrapolated to the broader set of events encompassed by DRPs.[58, 60, 61, 64-66] The remaining three studies investigated the broader concept of DRPs,[7, 62, 63] only one of which was conducted in Australia.[7]

The Australian study was a preliminary one conducted in a specialist paediatric teaching hospital by Easton et al.[7, 67] As the preliminary study was conducted in a specialist hospital it is likely that the results obtained will not provide a representative picture of the type of DRPs occurring in non-specialist paediatric institutions.[68, 69] However, the other two paediatric studies may provide an indication as to the relevance of the preliminary study because they were not conducted in specialist paediatric teaching hospitals.[62, 63] These studies report the frequency of hospital admissions associated with DRPs to range between 7.9% and 17.7%,[62, 63] results which contrast the 3.4% calculated for the preliminary study[7]. Although initially promising, what can be drawn from these comparisons is limited due to the differences in the methodologies employed and the reported influence of geographical location.[58, 67]

In their study of ADRs in the paediatric population, Whyte and Greenan highlighted the influence of geographical location by comparing results obtained in the United Kingdom with those reported in similar studies conducted in the United States of America.[58] Compared with American children, those in the United Kingdom received fewer drugs and experienced fewer ADRs while in hospital.[58] Whyte and Greenan also found the prescribing patterns to be different, with symptomatic treatment being more common in American children than in the United Kingdom.[58] This finding is in agreement with that reported by Conroy et al, who noted that paediatric prescribing patterns differed among the five countries they investigated in their study of medication use in paediatrics.[12] The experiences reported by Whyte and Greenan, and by Conroy et al indicate that data obtained in one geographical location may not be able to be extrapolated to another.[12, 58] It is therefore important for studies to be conducted in the Australian paediatric population.

Further research is required to establish if the frequency and characteristics of hospital admissions associated with DRPs reported in the preliminary study by Easton et al provides a representative reflection of the impact of such events.[7]

1.1.3 Studies investigating ADRs within the paediatric inpatient population

While the importance of studies investigating emergency department attendances and hospital admissions associated with DRPs has been reported,[35, 36, 41] the issue of ADRs arising within the inpatient population has also been highlighted as an important QUM issue.[19, 20] In their recent reports the Working Party on the Registration of Drugs for Use in Children and the Australian Association of Paediatric Teaching Centres have recommended that the surveillance of ADRs within the paediatric inpatient population be increased.[19, 20] The drive behind these recommendations stems from two key issues. The first relates to the reported extensive *unlicensed* or *off-label* use of medications in the paediatric inpatient population,[9, 12, 13] a practice

which has been reported by Turner et al to possibly place paediatric patients at an increased risk of ADRs[70]. The second refers to concerns expressed by members of the Working Party that ADRs may be under-reported in this population.[20]

There are no Australian paediatric studies that investigate the frequency of ADRs arising within the paediatric inpatient population, but at an international level there are 14 studies.[58-60, 66, 70-79] The frequency of ADRs reported in these studies ranges from 1.73% to 16.8%, with differences in the frequencies determined attributed to methodological variances.[71, 75] As indicated earlier, extrapolations from studies conducted in paediatric populations from different geographical locations may be inappropriate, therefore data relating to the frequency of ADRs arising within the Australian paediatric inpatient population are required.

1.1.4 Three key areas of data collection

It was on the background described above, which illustrates that QUM is not being achieved in the paediatric population, that the quest for a better understanding of the problems involved began. This investigation revealed a deficit of data relating to the Australian paediatric population in three key areas: emergency department attendances associated with DRPs; hospital admissions associated with DRPs; and ADRs arising within the inpatient population. It is therefore essential that representative data relating to these areas are collected in the Australian paediatric population so that a broader understanding of QUM issues facing this population is obtained.

Aside from the deficit of information relating to the Australian paediatric population in these three key areas, the quest for understanding revealed a large degree of variance in the frequency of events reported, with this variance attributed to methodological differences. As a standard approach to undertaking such studies was not evident, the issues involved in designing a study to investigate DRPs must be reviewed before the research approach taken to address the identified deficits can be finalised.

2 Issues in designing a study to investigate DRPs in paediatrics

Considerable controversy exists concerning the magnitude of DRPs within the adult population.[68, 80] Much of this stems from the many discrepancies reported in the literature on the extent to which these problems occur.[81] For example, the number of adults experiencing ADRs, while an inpatient of a hospital, has been reported to range between 1.5% and 35%.[81] Such discrepancies can, to a large degree, be explained by five factors: differences in the patient populations studied; design strategies; definitions utilised; the inclusion or exclusion of a causality classification; and the inclusion or exclusion of a clinical significance classification.[42, 80, 81] There is, by contrast, little debate over the importance of determining the preventability and economic implications of data collected.[82, 83] In designing a study to investigate DRPs it is essential that each of the above issues be addressed. This chapter will therefore review the relevant literature in order to facilitate the design of a suitable study to investigate the consequences of DRPs in paediatrics.

In Chapter One, three key areas of data collection were identified, each one of which can be considered a mutually exclusive stream of data collection: *emergency department attendances* associated with DRPs; *hospital admissions* associated with DRPs; and ADRs occurring within the *inpatient population*. Recognition that there are three separate streams of data collection is important as the methods required in data analysis may differ between streams.

2.1 Patient population

Part of the debate surrounding the magnitude of DRPs relates to the validity of extrapolating data collected in a specific patient population to that of the broader population.[84] Extrapolation has been reported to be influenced by

the geographical location in which the study was undertaken, the age of subjects investigated, the type of institution and the specific patient population investigated in that institution.[58, 61, 69, 71, 85] In Chapter One, the impact of geographical location and the age of subjects investigated was outlined, leading to the conclusion that data pertaining to the Australian paediatric population were required. In this chapter the other two issues will be addressed.

The first of these concerns the type of institution in which a study is undertaken. A frequent criticism of studies investigating ADRs or DRPs is that the majority of such studies have been conducted in large academic, tertiary care hospitals.[68, 69] The basis of such criticisms is that these hospitals are more likely to provide specialist services and cater for sicker patients who may be at an increased risk of adverse events.[68, 86] The results obtained may therefore not be applicable to the broader population.[68]

The second issue is that associated with the specific patient population investigated. This issue has been noted to influence results reported,[61, 71, 81, 86, 87] as illustrated in a study conducted by Mitchell et al in which the frequency of ADRs leading to hospital admission was 0.2% in a neonatal ward, 22% in an oncology ward and 2% for patients in general medical units[61]. Hence, the inclusion or exclusion of oncology patients could be expected to have a large impact on frequency of ADRs reported. Mitchell et al concluded that the inclusion of unspecified numbers of patients with cancer limits the interpretation of results obtained, therefore oncology patients should be considered separately.[61] Similar statements were not identified in the literature for other specific patient populations.

2.1.1 Appropriate methods to address the issue of patient population

As outlined in Chapter One, extrapolation of data available in the literature to the Australian paediatric population may not be possible, so new data needs to be collected. If this data collection was limited to a large academic, tertiary

care hospital it may reduce the ability to extrapolate results obtained, data collection should therefore be conducted over a number of separate hospitals. The hospitals included should be selected on the basis of different levels of service provided and the population groups utilising these services. Finally, it is put forward that if oncology patients are to be included in data collection, the results must be reported separately from the rest of the patient population.

2.2 Design strategy

In reviewing 25 studies investigating ADRs, Muelhlberger et al concluded that the variation of reported ADR frequencies was largely attributable to different monitoring methods and epidemiological study designs.[88] Others have confirmed these findings.[41, 89-91] The impact of utilising different monitoring methods is highlighted in a study which compared the number of adverse drug events detected via a computer monitoring strategy, chart review and voluntary reporting.[89] Comparing these systems, 275 adverse drug events were detected using computer monitoring, 398 using chart review and 23 via the voluntary reporting system.[89] With respect to the epidemiological study design, the type of design chosen will determine whether or not hypotheses can be tested.[92] Depending on the objectives of a study, whether or not hypotheses can be tested may be of fundamental importance and hence needs to be catered for in the design strategy. Thus, it is clear that the monitoring methods and epidemiological study designs utilised to investigate the consequences of DRPs must be carefully selected.

2.2.1 Design strategy methods

Methods relating to design strategy can be divided into monitoring methods and epidemiological study designs.

2.2.1.1 Monitoring methods

Monitoring methods are those used to detect the presence of the subject under investigation. Spontaneous, pre-selective and intensive monitoring are

the three monitoring methods used most commonly when investigating DRPs or ADRs.[88]

Spontaneous monitoring is a method utilised frequently in research investigating ADRs,[93] and involves the voluntary notification by health care professionals of a suspected event, such as an ADR, to a centralised monitoring agency[94]. The main advantage of this method is that a relatively large population can be monitored in a manner that generally requires little expenditure in terms of both time and finances.[88, 93] However, because it is voluntary, it is extremely unlikely that all cases will be reported using this method.[93] This point is illustrated in a study which indicated that only 4% of identified adverse drug events were detected using spontaneous monitoring.[89] This high level of apparent under-reporting means that it is often impossible to have more than a vague estimate of the true frequency of an event.[93] Thus, the usefulness of *spontaneous monitoring* is often limited to the generation of possible areas of interest regarding the subject under investigation, which can then be followed with more intensive monitoring.[88, 93]

Pre-selective monitoring involves active surveillance of only those patients perceived to be at a high risk of developing the event under investigation.[88] For example, in studies investigating ADRs, advanced age and multiple drug treatments have been proposed as factors which may increase the risk of ADRs.[88] Using pre-selective monitoring, only patients matching these criteria would be reviewed. Not surprisingly, studies utilising pre-selective monitoring have been reported to yield larger numbers of ADRs than comprehensive monitoring.[88] There are, however, two limitations to this type of monitoring: its success depends on the availability of efficient, sensitive and specific pre-selection criteria, as well as a database that enables effective screening of the patient population under investigation; and focusing on a specific patient population at greater risk of developing the event under investigation may confound results obtained.[88]

Intensive monitoring involves active surveillance of the total population under investigation for the event in question.[88] This method has the advantage of

being able to provide data of better quality because more details are available and follow-up is relatively easy.[93] Furthermore, a 10 fold higher number of ADRs have been reported via this method when compared to that of *spontaneous monitoring*.[90] A further advantage is that both the numerator and denominator are known, hence rates of occurrence can be calculated.[93] Despite these advantages, the labour intensity involved in this type of monitoring often restricts its use to the screening of smaller populations or over limited time periods.[88]

An important point that must be considered is whether data are collected in a retrospective or prospective nature. If data collection is conducted retrospectively, information already collected is reviewed for evidence of the event in question.[93] For example, a patient's medical record may be reviewed for evidence of a DRP. The major limitation of this method of data collection stems from the fact that the information reviewed has often been accumulated for reasons different to the purpose of the study, hence, all information required to determine the presence of the subject under investigation may not be available.[93]

In contrast, prospective studies begin at a specific time to investigate all cases of interest apparent from that time on.[93] Because the objectives of a prospective study are defined from the outset, relevant information can be collected or followed up over the data collection period.[93] The quality of information provided by this type of study, and consequently it's significance, are therefore considered greater than that of retrospective studies.[93, 95] The frequency of events detected is also generally greater with prospective studies than retrospective studies.[91] For example, two Australian studies investigated drug related unplanned admissions,[96, 97] one of which was conducted retrospectively and reported the frequency of drug related readmissions to be 0.4%,[96] while the other was conducted prospectively and indicated the frequency to be 1.9%[97]. Despite these advantages, the use of prospective data collection can be restricted by the fact that the time associated with conducting this type of study is generally greater than that required for a retrospective study.

2.2.1.2 Epidemiological study design

The epidemiological study design is the second issue that needs to be explored when considering the design strategy. Epidemiological study designs can be either descriptive or analytical in nature.[92]

As the name implies, descriptive studies are concerned with describing the general characteristics of the disease or related subject under investigation.[92] The most common descriptive study design utilised in this area of research is that of a *case series design*, which describes the characteristics of a number of patients with the subject under investigation.[92] This type of study design has been said to represent an important interface between clinical medicine and epidemiology by its ability to provide much needed information on a new or little investigated event.[98] A *case series design* can also be used to generate hypotheses about the subject under investigation.[92] However, due to limitations inherent in the design of descriptive studies, analytical study designs are required to test the hypotheses generated.[92]

Two types of analytical study designs are commonly utilised in the type of research reported in this thesis: *cohort studies*; and *case-control studies*.[93]

Cohort studies involve following a group of patients exposed to a specific risk factor for the subject under investigation and comparing their experience with that of an unexposed group.[99] At the time that exposure status is defined, all potential subjects must be free from the subject under investigation.[99] Due to their design, *cohort studies* offer a number of advantages for evaluating the relationship between exposure and disease, but they have the drawback of requiring a large number of patients, making this study design extremely time consuming and expensive to conduct.[99] A further limitation is that they are generally inefficient if the subject under investigation is rare.[98]

In contrast to cohort studies, *case-control studies* are considered optimal for the evaluation of rare diseases.[100] With this approach, patients are selected on the basis of whether they do (cases), or do not (controls), have the subject under investigation.[100] Thus, this method retrospectively reviews exposures

thought to be relevant to the development of the subject under investigation. *Case-control studies* have the advantages of being relatively quick and inexpensive in comparison to a *cohort study,* but unless the study is population based, *case control studies* can not directly compute incidence rates.[100] Furthermore, issues of selection and recall bias can limit the usefulness of data obtained using this study design.[100]

2.2.2 Appropriate methods to address the issue of design strategy

Upon reviewing the literature in this area it is clear that the "perfect" design strategy would involve prospective *intensive monitoring* using an analytical study design. This strategy would allow for the optimal detection of cases and for hypotheses to be tested. However, a number of issues make this strategy less than ideal in the context of the research reported in this thesis.

The first relates to using an analytical study design, an approach that provides the advantage of being able to test hypotheses. The practicalities of data collection restricts its use because a *cohort study* is limited by the resources and the time periods required to conduct such a study, and a *case control study* is limited by the need to obtain a community based control group in this setting. There are case-control studies investigating adverse drug events occurring within the inpatient population reported in the literature.[83, 101] However, criticisms have been directed towards the validity of the methods used in such studies because it is claimed that they "push hard at the boundaries of clinical epidemiology and health services research, and a sceptic might wonder whether the envelopes of these disciplines might not have been nicked in the process".[102] A design strategy involving prospective *intensive monitoring* using a descriptive epidemiological study design in the form of a *case series* approach is therefore more appropriate. This type of study design allows the magnitude of DRPs to be estimated and hypotheses proposed concerning potential risk factors.

While a *case series design* using prospective *intensive monitoring* is appropriate, intensive prospective monitoring is labour intensive, resulting in time constraints which restrict the usefulness of this strategy over all three streams of data collection identified in Chapter One. It is proposed therefore that prospective *intensive monitoring*, using a *case series design*, be utilised to investigate emergency department attendances and hospital admissions associated with DRPs only, and that ADRs occurring within the inpatient population be monitored using *spontaneous monitoring* and *retrospective intensive monitoring*.

2.3 Definitions

In comparing drug related event rates observed in different studies it is imperative that the definitions utilised are taken into consideration.[80] This is because there is a lack of a standardised approach to the definitions used within the literature.[69] Problems arise when there are differences in the scope of the definitions utilised.[80, 103] For example, a study conducted by Nelson et al included overdoses with both legal and illegal drugs under the heading of drug related hospital admissions,[44] whereas a study conducted by Hallas et al did not include overdoses[86]. Given the broader scope of the drug related hospital admissions definitions used by Nelson et al it is not surprising that the reported frequency of such admissions was higher (16.2%) than that reported by Hallas et al (11.4%).[44 86] As a result of the potential impact that definitions used can have upon results obtained, Koch-Weser et al stated that "explicit, unequivocal, operationally useful and clinically meaningful definitions...should always be utilised".[104] In order to allow appropriate interpretation of results obtained it is therefore important that operationally useful and clinically meaningful definitions are utilised in the research presented in this thesis.

2.4 Causality

In determining the frequency of DRPs associated with emergency department attendances, hospital admissions and of ADRs arising within the

inpatient population, there is a risk of the misclassification of cases where the event under consideration may possibly be associated with a disease exacerbations rather than DRPs. An estimate of this risk is conveyed through the use of a causality classification. Causality may be defined as a measure of the probability that the event under consideration could be attributed to the DRP or ADR in question. The importance of a causality classification was highlighted by Koch-Weser et al who suggested that "any statement about an adverse effect of a drug should include an estimate of the degree of certainty of the causal relationship between the drug and the untoward event".[104]

The relationship between drug administration, or, in the case of several DRP categories, the omission of drug therapy, and a clinical event is an exceedingly complex one.[105] This is because many factors concerning the patient, the suspected drug, concurrent drugs, non-drug therapies, and non-drug exposures potentially contribute to the occurrence of the event.[105] Consequently, a number of methods to determine causality have been proposed.[103, 106]

2.4.1 Methods to determine causality

Methods to determine causality fall into five main groups: *global introspection; informal guides; structured algorithms; Bayesian probabilistic*; and *Expert systems*.[107]

Global introspection represents the oldest and most popular strategy, and can be described as an attempt made by an assessor to consider each factor that may affect the causal link between one or more administered drugs and a subsequently observed event.[108] Upon consideration of these factors a decision about the probability of drug causation is established.[108] Despite the popularity of *global introspection*, its limitations are well documented.[108] These include the fact that it does not make explicit the information utilised by the assessor, thus eliminating assessor accountability, and that there is poor reproducibility of the results obtained.[108] As stated by Kramer

"reproducibility refers to the extent to which different observers arrive at the same causality assessment".[108] *Global introspection* relies heavily upon the knowledge base of an assessor and hence it is possible to imagine that the best chance of achieving reproducible assessments is to let experts do the global introspecting.[108] However, several studies have reported that experts frequently disagreed when assessing the causality of ADRs using global introspection.[104, 109-111]

It was primarily in response to the poor reproducibility of *global introspection* that the remaining four methods to measure causality were established.[106] The simplest of these methods is the use of *informal guides* which simply act as a reminder of relevant content and thus act as guides to better *global introspection*.[107] As *informal guides* do not provide a formal method for arriving at a result, the limitations are similar to those experienced with *global introspection*.[105]

Structured algorithms can provide a better alternative. Standardised decision aids such as these use predetermined questions to assess case information.[112] These algorithms form the majority of published methods to measure causality, with more than 20 different *structured algorithms* developed since 1972.[106, 112] They are generally designed in a questionnaire format with different weightings allocated depending on the answer to each question.[113] For example, most algorithms ask if a temporal sequence between drug administration and the onset of the adverse event is compatible with drug causation.[113] Compatibility would score in favour of the drug causing the event whereas incompatibility would score against the drug causing the event, and a lack of information would be neutral.[113]

Venulet proposed that the advantages of using *structured algorithms* were that such methods allowed clear identification of items or information involved, improved communication, achieved greater reproducibility of results and provided a checklist function.[114] A number of studies have indicated that the use of *structured algorithms* increases inter-observer agreement,[106, 111] a

factor which is the basis of the major argument advanced by their adherents in favour of the widespread adoption of this method.[105]

Opponents of *structured algorithms* debate the usefulness of inter-observer agreement when it is used as the sole method to determine the reproducibility of algorithms.[105, 115] Hutchinson and Lane question the advantage of claims of good reproducibility because they argue there is a tendency to ask questions that maximise the chance of agreement between evaluators.[105] In doing so they argue that those entirely unexpected but vital imponderables, which play a role in determining the value of a particular piece of evidence, are eliminated.[105] Criticisms have also been directed towards methods utilised to determine the validity of *structured algorithms*.[113, 115, 116] As stated by Kramer "validity is the extent to which an assessment yields the correct answer".[108] In the literature a number of *structured algorithms* have been validated using the unstandardised judgements of experts as the "correct answer" to compare results obtained with.[110, 111, 115, 117] However, given the limitations of *global introspection* and the fact that it was precisely the unreliability of such unstandardised judgements that lead to the development of *structured algorithms*, this method to determine validity has since been discredited.[105, 106, 115]

Hutchinson and Lane proposed that causality methods be assessed for reproducibility and validity using different criteria.[105] In terms of reproducibility, they proposed that repeatability, explicitness and transparency be assessed for each causality method: repeatability should be assessed via both inter and intra-observer reliability; explicitness by requiring that the method allows the rater to make explicit his or her "states of information", including the uncertainty he or she feels about its elements;[106] and transparency by requiring that the causality method indicates clearly how final conclusions are made and the effect each component has upon the final assessment.[105]

In terms of validity, Hutchinson and Lane propose that instead of attempting to compare methods to external "gold standards", which are unavailable in

the field of causality assessment, attention should instead be focused upon the internal characteristics of the causality method under review.[105] The authors propose that, in order to assess validity, a causality method should be measured for completeness, aetiological balancing and have no *a priori* constraints.[105] In terms of completeness, any factor that can affect an assessor's belief regarding a causality assessment must be able to be incorporated by the method into the "state of information".[105] It is, however, not possible to test if this criterion is satisfied, as to do so would require knowledge in advance of all factors that may potentially be of relevance to an assessor.[105] Instead they suggest that it is possible to detect instances in which methods fail to satisfy this criteria.[105] Validity must also be measured in terms of aetiological balancing, which is the ability of the method to consider information balanced against drug versus non-drug causes.[105, 106] Finally, a method must have no *a priori* constraints, meaning that factors backed by a larger evidence base should have the largest influence on the outcome of a causality assessment.[105, 106]

After reviewing 10 of the most commonly used *structured algorithms*, Hutchinson and Lane concluded that none satisfied all reproducibility or validity criteria.[105] Criticisms were primarily directed towards the lack of flexibility provided by algorithms and their apparent failure to address aetiological balancing.[113] Not surprisingly, *global introspection* and *informal guides* also failed to meet the criteria put forward for reproducibility and validity.[105]

It was upon this background that *Bayesian probabilistic* and *Expert systems* methods to measure causality were developed. The Bayesian approach is based upon Bayes theorem and treats the differential diagnoses of a suspected ADR as a special case of a conditional probability evaluation in which the purpose is to calculate the posterior odds that a particular event was caused by the drug rather than any other cause.[113] The posterior odds are calculated on the basis of epidemiological and clinical trial data, along with an extensive case analysis.[113] As a result of reviewing these sources of information a series of formulae are developed to enable a posterior odds

calculation. The final result is obtained by multiplying out the various terms to obtain a posterior odds ratio in favour or against drug causation.[113, 118] The posterior odds ratio is then frequently converted to a posterior probability that ranges between 0% (a nondrug-induced event) and 100% (a definitely drug induced event).[113] The major advantage of this method is that it meets the demanding criteria put forward by Hutchinson and Lane.[105, 113] Despite this obvious advantage, *Bayesian probabilistic* methods require complex model development for each type of ADR.[113, 118] Development of these complex models necessitates comprehensive epidemiological and clinical trial data along with vast information on the case and adverse reaction.[113] The impracticalities of obtaining this information and the complexity of the calculations preclude the use of such methods for assessing causality in a general clinical setting.[106, 113] Furthermore, Lanctot and Naranjo reported that the probabilities of drug causation using the *Bayesian probabilistic* approach were significantly correlated with those determined by a *structured algorithm*, a method which does not impose the same extensive data restrictions as those encountered when using the *Bayesian probabilistic* approach.[113]

Expert systems can be seen as an extension of the *Bayesian probabilistic* approach. *Expert systems,* such as those described by Hutchinson et al extend the Bayesian approach by incorporating expert knowledge and judgement for the assessment of individual ADRs.[119, 103] However, in extending the *Bayesian probabilistic* approach, the impracticalities are further increased by the requirement for expert information on top of the comprehensive epidemiological and clinical trial data required.[107] The extensive additional information required makes the use of *Expert systems* impractical in a clinical environment.[107]

2.4.2 Appropriate methods to determine causality

The most appropriate method to determine causality would be one meeting all criteria put forward by Hutchinson and Lane.[105] However, the only methods that do so are *Bayesian probabilistic* and *Expert systems,* two

methods that are impractical in the context of this study, primarily because of the extensive amount of information required. The limitations of *global introspection* and *informal guides* also render the use of such methods undesirable.[105, 108] This leaves *structured algorithms* which are acknowledged as not ideal, but nonetheless form the mainstay of causality assessment in this type of research.[106, 113, 114]

Of the published algorithms, the Naranjo algorithm is the only one that has been tested for both inter and intra-observer reproducibility.[105, 111] Favourable inter-observer reproducibility has also been shown when using experts and non-experts in the field of ADRs,[111] and significant correlation between this and a more time consuming algorithm has also been demonstrated[111, 120]. The major appeal of the Naranjo algorithm stems from the results of a study comparing the algorithm with the *Bayesian probabilistic* approach.[113] In that study the probabilities of drug causation using the *Bayesian probabilistic* approach were found to correlate with the average Naranjo algorithm scores.[113] The results suggested that the Naranjo algorithm and the *Bayesian probabilistic* evaluations were concordant, however, the *Bayesian probabilistic* approach better distinguished cases that were highly probable or highly improbable when compared to the algorithm.[113] The only factor impeding the extensive use of the Naranjo algorithm in the research reported here is that it was designed to determine causality classifications for ADRs. As mentioned previously, ADRs reflect only one category of DRPs and hence this method has not been developed for the determination of a causality classification for the diversity of cases classified as DRPs.

Structured algorithms to determine causality classifications for the diversity of cases classified as DRPs are scarce within the literature.[6, 80] Confounding this predicament is the diversity of definitions and settings in which these methods were developed. Furthermore, the reproducibility and validity of the available methods have not been established. In recognising these limitations, the algorithm developed by Dartnell et al overcomes the first predicament in that it was developed using similar definitions and in similar

settings to those proposed in this study.[6]   A further advantage is that the study conducted by Dartnell et al was undertaken within the Australian adult population.[6] Thus, utilising this method may enable relevant comparisons to be drawn between adult and paediatric populations. Importantly, this method encompasses the diversity of cases classified as DRPs and hence is appropriate for assessing the causality of DRPs associated with emergency department attendances and hospital admissions.

When judging causality, the importance of a panel consisting of independent investigators has been highlighted.[104]   The significance of such a panel is increased in the research reported in this thesis because it is proposed that the major limitations of algorithms, that is, the lack of flexibility and aetiological balancing, may be reduced if they are used in combination with such a panel.   The lack of flexibility may be overcome by engaging the principal that the aim of using such methods is not to force the evaluator to accept the verdict of the algorithm. Instead the aim should be to have each case reviewed by at least two independent evaluators with any relevant discrepancy leading to dialogue and, where appropriate, alteration of the algorithm in question.[114] Aetiological balancing may be addressed by an undertaking from panel members to be cognisant of the risk of the misclassification of cases where an event may possibly be associated with a disease exacerbation rather than an ADR or DRP.

Therefore, two *structured algorithms* appear appropriate for assessing causality in this thesis.   The Naranjo algorithm is the most suitable for determining causality for ADRs occurring within the inpatient population,[111] with the algorithm developed by Dartnell et al appropriate for assessing causality for emergency department attendances and hospital admissions associated with DRPs[6]. A panel of several independent evaluators, mindful of the factors outlined above, may aid in the reduction of the acknowledged limitations of *structured algorithms*.

2.5 Preventability

When investigating the consequences of DRPs it is important that the preventability of such events is evaluated.[6] Preventability examines the likelihood that the event in question could have been avoided if appropriate measures had been taken.

Schumock and Thornton suggested that preventability data are essential elements which can be fed back into a system to facilitate improvement.[82] Information on the preventability of DRPs and ADRs has proved to be an important factor in enabling the determination of prevention strategies in the adult population.[80, 121] Despite the logical importance of determining preventability, most studies of adverse occurrences associated with drugs have not evaluated this factor.[121] This point was adequately highlighted in the Australian context by a study conducted by Roughead et al which reported that preventability had been addressed in only four of the 14 Australian studies identified.[42] A similar situation is apparent in the paediatric literature because, apart from a preliminary study conducted by Easton et al, the issue of preventability has not been addressed in previous paediatric studies investigating drug related admissions.[7, 67] In an article discussing ADR surveillance in paediatrics Choonandra et al indicated that the lack of comment on the preventability of data reported in previous paediatric ADR studies weakened what could be drawn from the findings reported.[95] In order to propose prevention strategies within the paediatric population, data indicating the proportion of preventable DRPs are essential.

2.5.1 Methods to determine preventability

Several methods of assessing preventability have been reported and can be broadly categorised into *clinician judgement, ADR classification* and *predetermined criteria.*

Clinician judgement as part of an expert panel review has been used in a number of published studies.[5, 121-124] An advantage of this method is that it offers the ability to assess the preventability of a diverse range of adverse

occurrences associated with drugs.[125] Nonetheless there are three main disadvantages in using this method: the time and effort required by the panel; the lack of transparency in the decision making process; and the lack of reproducibility of this method.[124, 125] The disadvantages associated with the sole use of clinician judgement in the form of expert panel review therefore appear to outweigh the advantages.

The second method is based upon the criteria proposed by Rawlins and Thompson to classify ADRs.[126] They proposed that all ADRs be classified as Type A or Type B reactions, where, Type A, or augmented reactions, are predictable and thought to be due to the extension of the pharmacological action of the drug, and Type B, or bizarre reactions, are idiosyncratic reactions which are not predictable.[126, 127] Based upon these classifications, Type A reactions are preventable if patient monitoring can predict them before they occur, and Type B reactions are portrayed as not preventable due to their unpredictability.[127] There are two disadvantages associated with the use of this method: the classification system does not take into consideration the appropriateness of the therapy associated with the reaction;[127] and this method only enables preventability to be determined for ADRs and not for the diversity of cases classified as DRPs.

The third method is that utilising *predetermined criteria*.[125] Schumock and Thornton developed a series of criteria to determine the preventability of ADRs,[82] which has been used subsequently in a number of studies[128-130]. This method provides the advantage of transparency in the decision making process. The nature of the standard format used in this method may reduce the time required in the decision making process and increase reproducibility. A disadvantage is that the predetermined criteria were developed for determining the preventability of ADRs, hence application to the broader concept of DRPs is difficult in its present form.

2.5.2 Appropriate methods to determine preventability

In the context of this thesis it is proposed that preventability be determined by a panel of several independent evaluators utilising set criteria,[125] such as those developed by Schumock and Thornton[82]. Modification of these criteria is required to allow a preventability classification to be determined for the diversity of cases classified as DRPs.

2.6 Clinical significance

An important factor in allowing appropriate interpretation of studies investigating DRPs and ADRs is an estimate of the effect of the event in question on patient outcomes. This may be gauged through the use of a clinical significance classification.

Determining a clinical significance classification is important for two main reasons. Firstly, its use may enable events that have a greater impact upon patient outcomes to be identified and focused upon in prevention strategies.[130, 131] Secondly, the inclusion or exclusion of events of different levels of clinical significance will influence the frequency of DRPs or ADRs reported.[87, 132] For example, Zilleruelo et al found that the frequency of ADRs reported dropped from 34.2% to 20.6% when ADRs classified as *mild* were excluded.[132] It is therefore essential to include a clinical significance classification to allow appropriate interpretation of results obtained.

2.6.1 Methods to determine clinical significance

The level of medical care required to address the complications associated with a DRP or ADR can in itself be seen as an indicator of clinical significance.[133] It is for this reason that the methods to determine clinical significance will be reported separately for emergency department attendances, hospital admissions and inpatients of a hospital.

Ten studies reporting on investigations into emergency department attendances associated with DRPs or ADRs have been published.[36-38, 45, 52-57]

Of these, five investigated clinical significance,[37, 38, 45, 52, 54] with four of the five studies using similar methods[37, 38, 45, 54]. The methods used encompassed the following principles: *mild* reactions require no treatment in the emergency department; *moderate* reactions require drug therapy for symptom resolution; and *severe* reactions require hospitalisation.[38, 54] The method proposed by Stoukides et al embodies each of these principles and may be considered representative of the methods utilised in the four similar studies.[54]

The similarity of methods utilised to classify the clinical significance of emergency department attendances associated with DRPs contrasts with the methods used for hospital admissions associated with such problems. Of the published studies investigating hospital admissions associated with DRPs, or aspects of DRPs, only a limited number determine clinical significance classifications for data reported.[5, 63, 65, 134] Furthermore, the methods used in these studies were often applied to specific subsections of DRPs, such as ADRs or drug interactions only.[5, 63, 65, 134] As the methods utilised were developed to determine a clinical significance classification for only a subsection of DRPs, the criteria used in these methods are unable to incorporate the broader concept of DRPs. The inappropriateness of the methods previously used to determine clinical significance led to a review of generic severity of illness indicators. The appropriateness of such indicators including the Acute Physiologic and Chronic Health Evaluation (APACHE II),[135] Simplified Acute Physiology Score (SAPS II),[136] Duke Severity of Illness Checklist,[137] and the Pediatric Risk of Mortality Score (PRISM) was explored by the investigator[138]. None were deemed appropriate for one or more of the following reasons: they were applicable in the ICU setting only; were costly; they required extensive information; or they needed expert training to utilise.[139] Although an appropriate generic severity of illness indicator for the research reported in this thesis was not found, the importance of length of stay and the level of medical treatment received as components of clinical significance was evident in the indicators reviewed.[133, 140] In a preliminary study conducted by Easton et al a clinical significance classification based upon the level of medical treatment received and a

patient's length of stay was developed.[7] The method developed could be utilised for the diversity of cases classified as DRPs.

A number of methods to determine the clinical significance of ADRs arising in inpatients of a hospital have been published within the literature.[103] One of the first methods to do so was proposed by Venulet.[141] This method encompassed the following general principles: *mild* reactions require no treatment and do not significantly complicate the primary disease; *moderate* reactions have marked symptoms but involvement of vital organ systems is moderate, treatment is required and hospitalisation may be prolonged; and *severe* reactions are fatal, life-threatening or lower a patient's life expectancy.[141] The majority of subsequent methods to determine clinical significance have incorporated principles similar to those outlined by Venulet.[142-145] The criteria proposed by Colodny and Spillane are one such example.[145] Although based upon the criteria put forward by Venulet,[141] the criteria posed by Colodny and Spillane simplify the determination of a clinical significance classification for ADRs arising within the inpatient population[145].

2.6.2 Appropriate methods to determine clinical significance

It is proposed that a clinical significance classification be determined for emergency department attendances associated with DRPs utilising the criteria proposed by Stoukides et al.[54] A suitable method to determine clinical significance for hospital admissions associated with DRPs may be that proposed by Easton et al.[7] With respect to ADRs arising within the inpatient population the method proposed by Coldney and Spillane appears the most appropriate.[145]

2.7 Economic implications of DRPs in paediatrics

Substantial costs are associated with problems with drug therapy,[4] as highlighted by a study from the United States which indicated that a conservative estimate of the economic burden arising from drug related

morbidity and mortality is US$ 30 billion annually, and that this could exceed US$ 130 billion in a worst case scenario[46].

At an international level, studies investigating drug related emergency department attendances in the adult population have reported the average cost to an institution per case identified to range from US$333.81 to US$1847.51.[37, 54] The corresponding average cost per drug related hospital admission has been reported as US$8888,[56] and the extra costs incurred by an institution as a result of an ADRs in the inpatient population to be US$2262[101].

From an Australian perspective, the economic implications of drug related hospital admissions in the adult population have also been investigated,[4, 6, 96] with one study estimating that 80,000 hospital admissions per year are medication related, resulting in hospital costs in the order of A$350 million[4]. A second study reported the annual costs associated with "definitely avoidable" drug related admissions to a Victorian hospital to be A$194,217, whereas "possibly avoidable" admissions were associated with a cost of A$1,673,245 and "unavoidable" drug related admissions A$1,629,494.[6]

The importance of collecting economic data to enable the implementation of cost-effective quality improvement efforts been stated in the literature.[83] To this end, studies investigating the cost savings involved in implementing prevention strategies have been undertaken within the adult population.[43, 47, 49]

In contrast to the adult population, data relating to the economic implications of DRPs within the paediatric population are limited to a single study.[62] Conducted in Lebanon, the study reported on the cost of ADRs associated with hospital admissions within the paediatric population in Lebanese pounds.[62] There are no data pertaining to the Australian paediatric population. To complicate matters, a dearth of studies comparing Australian and Lebanese health care systems makes extrapolation of available paediatric costing data to the Australian setting very difficult. Furthermore, as

more than just differences in exchange rate are involved it would be misleading to convert the costs reported in the Lebanese study to Australian currency and make comparisons.[146] Despite the availability of Australian adult costing data, extrapolation of such data to the paediatric population is probably inappropriate. This is because a number of studies have indicated that differences in resource intensiveness and length of stay patterns exist between paediatric and adult patients, leading to differences in health care costs between these two populations.[147-150] Data pertaining to the economic implications of DRPs within the Australian paediatric population are therefore required.

2.7.1 Methods to determine the economic implications of DRPs

The methods used to calculate the costs obtained are indicated in only a small proportion of studies investigating the economic implications of DRPs. When mentioned, the method used most commonly comprises multiplying the length of stay for identified cases by average daily hospital costs.[4, 43, 96] A more accurate version of this method, which involves collation of hospital costs attributed to individual cases, was the second most common.[151] However, in considering the economic implications of DRPs, the costs to consider are broader than just hospital costs.[152] Furthermore, standard methods to determine the economic implications of such data are available in the literature. These methods can be divided into two distinctly different approaches. The first entails conducting an *economic evaluation* and the second involves undertaking a *cost description study.*[152]

An *economic evaluation* is concerned with making comparisons in terms of both costs and consequences between alternative courses of action.[152] The four main approaches to conducting an *economic evaluation* are: *cost-minimisation*; *cost-effectiveness*; *cost-utility*; and *cost-benefit* analysis.[153]

Cost-minimisation analysis is undertaken when there is an understanding that the outcomes of the procedures under consideration are similar or the

same.[153] Because of this, attention focuses on the cost side of the equation in order to identify the least costly option.[154] Potential problems with this type of analysis arise when two procedures are assumed to be the same but there is no evidence to support this assumption.[155]

Cost-effectiveness analysis is used to assess the efficiency with which health care procedures use limited resources to produce health outputs.[156] Unlike the situation in *cost-minimisation* analysis, the costs of alternative procedures or programs are compared with outcomes measured in natural units, such as cost per life year saved or cost per case cured.[157] Using this approach a "cost-effectiveness ratio" is produced where the "cost per unit of health effect" is provided for each alternative.[158] The alternative with the lowest cost-effectiveness ratio is the most favourable.[158] The main limitations of this approach are that the measure of outcome must be uni-dimensional and hence other important outcomes may be missed, and that it cannot be used to compare programs with different goals.[158]

Cost-utility analysis is an approach in which the outcomes of alternative procedures or programs are measured in terms of the health related "utility" of the participants.[159] As stated by Drummond "utility refers to the value or worth of a level of health status or improvement in health status".[155] Quality adjusted life years are the most commonly used measure in this form of analysis.[159] Procedures and programs are then compared based upon the marginal cost per quality adjusted life year gained.[159] Thus, *cost-utility* analysis goes a step further than *cost-effectiveness* analysis by not just measuring clinical outcomes, such as the number of lives saved, but also the quality of life of those who experienced these outcomes. The exact method by which quality-adjusted life years are determined is, however, an area that is debated in the literature.[160]

A *cost-benefit* analysis differs from the other methods of economic evaluation in that it seeks to place a dollar value upon both the cost and benefits of a procedure or program.[161] *Cost-benefit* analysis can examine one program in isolation, although the alternative of doing nothing or current practice is

implied, or it allows a number of programs to be compared.[158] In either case the outcome of a *cost-benefit* analysis may be expressed as a benefit to cost ratio or in terms of a net cost or benefit, meaning benefit minus costs.[162] The procedure or program with the greatest benefit and least cost is therefore the most favourable option.[162] A limitation of cost-benefit analysis resides in the difficulty in converting some non-monetary units into dollar amounts.[162] As a result of this difficulty, cost-effectiveness and cost-utility analyses are seen more commonly within the health care setting.[161]

The second standard methodology to determine the economic implications of data involves undertaking a *cost description study*, which aims to provide baseline descriptions of the costs and outcomes of a particular illness.[152] This methodology is not to be confused with an *economic evaluation* as no comparisons are made between alternative courses of action.[152]

The majority of *cost description studies* involve utilising a *cost of illness* approach which attempts to describe the economic costs and the health impact on the community of a particular illness. This methodology incorporates three components: direct; indirect; and intangible costs.[163, 164] Direct costs are those borne mainly by the health care system in treating the illness in question,[164] and include medical care expenditures incurred in the diagnosis, treatment, and rehabilitation of illness.[165] Indirect costs are those incurred through lost production as a result of the morbidity or premature mortality associated with the illness.[164] Examples of indirect costs include time spent by patients visiting health care practitioners and time lost from work by family members when someone in the family is ill.[165] Intangible costs attempt to place a dollar figure upon any reduction in quality of life incurred as a result of the illness being investigated.[164, 165]

An advantage of *cost of illness* studies is that that they are useful in providing the information necessary for an economic evaluation.[166] This methodology can also be of value in outlining the relationship between the incidence or prevalence of a disease and the consequential use of health services. Furthermore, *cost of illness* studies can be used to aid in the prioritising of

diseases for future economic evaluation.[166] Criticisms directed towards this methodology primarily focus upon the danger of inappropriate interpretation of information provided.[164, 167, 168] The danger lies in the assumption that, because a particular disease may have a large economic burden, more resources must be devoted towards its prevention.[164, 168] This assumption may arise as *costs of illness* studies only provide data on the costs associated with an illness, and do not mention the cost and effectiveness of available treatments.[164, 168]

2.7.2 Appropriate methods to determine the economic implications of DRPs

The appropriateness of conducting an *economic evaluation* or a *cost description study* depends upon the research question under investigation.[152] If the economic data are being used to provide comparisons between alternative procedures or programs, then an *economic evaluation* is the most appropriate approach.[152] If the aim is to provide a description of the costs involved with a particular disease state then a *cost description study* is more appropriate.[152] Comparisons involving alternative procedures or programs are beyond the scope of this thesis, however, it may still be possible to consider a *cost-benefit* analysis. In such an analysis the alternative could be doing nothing more than what is current practice in the area under investigation.[158] However, reports in the literature caution against the use of this approach because doing nothing above current practice rarely means that no costs are incurred.[152] Instead, the objective of the research presented in this thesis is to provide a description of the economic implications associated with DRPs, therefore a *cost description study* is appropriate and will be undertaken in the form of a *cost of illness* study.

In undertaking a *cost of illness* study either a prevalence or an incidence approach is utilised.[165] The *prevalence approach* involves estimating the direct and indirect costs attributable to all cases of an illness occurring (prevalent) in a given year.[169] Prevalence-based estimates indicate the current costs of different conditions and as such they have traditionally been

used to serve as a basis for policy decisions.[169, 170] However, this role is now limited with *economic evaluations* being used in preference.[153] In contrast, the *incidence approach* estimates the lifelong direct and indirect costs of the new cases of an illness which have their onset (incidence) in a given year.[169] As the *incidence approach* is more demanding in terms of the data required, such studies are not as common as prevalence studies.[164, 169] However, the *incidence approach* is of greater use as *costs of illness* estimated in this way can provide baseline data against which new interventions may be assessed.[164] That is, such data can potentially be utilised in conducting an economic evaluation.[166] Incidence data will be collected in this thesis, so the *incidence approach* to conducting a cost of illness study is appropriate. In applying the *incidence approach* in this thesis, an assumption is made that no lifelong direct or indirect costs are incurred as a result of illness associated with DRPs.

An issue of debate common to *cost of illness* studies, *cost-benefit* and *cost effectiveness* analyses is whether to include or exclude indirect costs.[164] As indicated by Drummond, this confusion is reflected by the fact that the Australian guidelines for *cost-effectiveness* analyses on pharmaceuticals direct that indirect costs be excluded whereas the Ontario guidelines allow inclusion.[164] In a recent review by Koopmanschap, the majority of *cost of illness* studies investigated included both direct and indirect costs.[166] Furthermore, a recent update of the American College of Clinical Pharmacist's position statement entitled "Prospectus on the economic value of clinical pharmacy services" recommended the inclusion of both direct and indirect costs.[171] In an attempt to address this debate Drummond suggested that direct and indirect costs should be presented separately, along with the aggregate amount.[164]

Central to the issue of including or excluding indirect costs in *cost of illness* studies is the method by which the long term costs associated with morbidity or mortality are estimated.[165, 169] In *cost of illness* studies the *human capital* approach is most commonly utilised.[166] This approach regards a person as producing a stream of output that is valued at market earnings, and the value

of life is the discounted future earnings stream.[170] A number of criticisms have been directed towards the *human capital* approach, ranging from ethical objections to placing a monetary value on life, to concerns about using rates of pay to determine this value.[161] Alternatives to the *human capital* approach are the *willingness to pay* and *friction costs* approaches.[165, 172] These methods are not without their critics and have been used rarely to determine indirect costs at a practice level.[161, 173] In the context of this thesis, the *human capital* approach is the most appropriate method to calculate indirect costs. In considering this method, the need to delve further into the debate regarding the advantages and disadvantages of the way in which long term costs are calculated is circumvented by the assumption made that no lifelong direct or indirect costs are incurred as a result of illness associated with DRPs.

The final area of debate relating to *cost of illness* studies pertains to the calculation of intangible costs. Although recognised as important, intangible costs are generally excluded from *cost of illness* studies due to the methodological difficulties inherent in the measurement of such costs.[165] This exclusion is seen as a limitation of *cost of illness* studies, as it has been argued that intangible costs may be the greatest costs resulting from illnesses.[168] The difficulties of the collection of data pertaining to intangible costs are, however, further amplified in paediatric research as a result of the limited tools available to collect such data within this population.[174, 175] It is for these reasons that the *cost of illness* study undertaken in this thesis will not include intangible costs.

It is proposed, therefore, that a *cost of illness* approach will be utilised to collect data on the economic implications of DRPs within the paediatric population investigated. An *incidence approach* to collecting data will be utilised and calculations relating to indirect costs will be included within the data collected. Information regarding the direct and indirect costs calculated will be presented separately along with the aggregate total. Intangible costs will not be calculated in this cost of illness study.

2.8 The research problem

There is a current deficit in both epidemiological and economic data relating to the consequences of DRPs within the Australian paediatric population. Scant information is available in three key areas: *emergency department attendances* associated with DRPs; *hospital admissions* associated with DRPs; and ADRs occurring within the *inpatient population*. A standardised methodological approach to obtaining such data is not evident in the literature. However, it is apparent that the patient population investigated, design strategy used, definitions employed, and the inclusion or exclusion of causality and clinical significance classifications are essential factors to be considered. Information regarding the preventability and economic implications of data collected are essential to enable the development and economic assessment of future prevention strategies aimed at addressing the consequences of DRPs.

2.8.1 The research question

The primary objectives of this study are to determine the:

1) frequency and characteristics of *emergency department attendances* associated with DRPs at three hospitals.

2) frequency and characteristics of *hospital admissions* associated with DRPs at three hospitals.

3) frequency and characteristics of ADRs arising within the *inpatient population* of three hospitals.

4) direct and indirect costs of emergency department attendances and hospital admissions associated with DRPs using a *cost of illness* approach.

As indicated in this chapter, the methodologies required to address each of the above objectives may differ. It is for this reason that the core

methodological issues pertaining to emergency department attendances and hospital admissions associated with DRPs, along with ADRs arising within the inpatient population will be presented in Chapter Three.

The details of data collection associated with determining the frequency of emergency department attendances associated with DRPs will be outlined in Chapter Four. Chapter Five will investigate hospital admissions associated with DRPs. Adverse drug reactions arising within the inpatient population of three hospitals will be reported and discussed in Chapter Six. The methodology, results and discussion relating to the determination of the direct and indirect costs of emergency department attendances and hospital admissions associated with DRPs will be presented in Chapter Seven. Finally, the broader implications of the results reported in this thesis will be reviewed in Chapter Eight and this thesis investigating the consequences of DRPs in paediatrics will then be concluded.

3 Methods to address the issues in designing a study to investigate DRPs in paediatrics

The quality of research investigating the consequences of DRPs depends heavily upon consideration given to a range of methodological issues. The major issues include consideration of the patient population under investigation, design strategies, definitions used, causality, preventability and clinical significance. A comprehensive methodological approach to investigating the consequences of DRPs has not been reported. This chapter will therefore discuss the methods by which the major methodological issues identified in the literature were addressed in this thesis.

The methodology involved will be presented in the context of determining the frequency and characteristics of three mutually exclusive streams of data collection: emergency department attendances associated with DRPs; hospital admissions associated with DRPs; and ADRs arising within the inpatient population. Appreciation of the concept of the three mutually exclusive streams is important, as it will become evident that causality and clinical significance classifications, along with the method of independent case review, differ among the streams. The methodology relevant to the fourth objective, that is, the determination of the direct and indirect costs of DRPs using a *cost of illness* approach, is of a separate nature and will be addressed in Chapter Seven.

3.1 Patient population

This thesis reports on a multi-centre study involving paediatric patients at the following three hospitals:

1) Royal Children's Hospital (RCH), a 298 bed specialist paediatric teaching hospital which provides primary, secondary and tertiary

care and is the major trauma and referral centre for paediatric patients within South Eastern Australia.

2) Geelong Hospital (GH), a 400 bed general regional base teaching hospital which is the sole provider of public acute hospital services and the major provider of health services to the 200,000 people of the greater Geelong area.

3) Box Hill Hospital (BH), a 340 bed general suburban teaching hospital which provides primary and secondary care to Melbourne's eastern suburbs.

Selection of these hospitals was based upon the following factors: all three hospitals provide paediatric services to the community; and the differences inherent in the level of services provided and population groups utilising these services may allow extrapolation of results obtained to a state, and possibly a national level.

The practical limitations already discussed necessitated the exclusion of oncology patients from all three streams of data collection, and trauma patients from the first two streams. The operational definitions for trauma and oncology patients are provided in Appendix One.

Ethics approval to conduct this study was granted at each of the three hospitals. The Monash University Standing Committee on Ethics in Research on Humans also granted approval. Documentation of approval by each of the above institutions can be found in Appendix Two.

3.2 Design strategy

The design strategy employed to investigate emergency department attendances and hospital admissions associated with DRPs was an observational prospective case series using *intensive monitoring.*

The design strategy employed to investigate ADRs occurring within the inpatient population was an observational retrospective case series using *spontaneous monitoring* and *retrospective intensive monitoring*.

3.3 Definitions

3.3.1 Paediatric patient

As specified by the Australian Drug Evaluation Committee and in the Therapeutic Goods Administration Guidelines, a paediatric patient encompasses patients from birth up to and including 17 years of age.[20]

3.3.2 Adverse drug reaction

The World Health Organisation definition for an ADR was used in the research presented in this thesis. This definition states that "any response to a drug that is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis or treatment of disease, or for the modification of physiological function" is an ADR.[176]

3.3.3 Drug related problem

Strand et al defined a DRP as "any undesirable patient experience that actually or potentially interferes with a desired outcome".[40] Eight categories of DRPs* were determined by Strand et al on the basis that the patient has a medical condition:

1)   that requires drug therapy (a drug indication) but the patient is not receiving a drug for that indication;

2)   for which the wrong drug is being taken;

---

* In the tables presented in the following chapters the DRP categories will be abbreviated to: 1) drug indication; 2) wrong drug; 3) too little; 4) too much; 5) ADR; 6) drug interaction; 7) non-adherence; and 8) poisoning.

3)   for which too little of the correct drug is being taken;

4)   for which too much of the correct drug is being taken;

5)   resulting from an ADR;

6)   resulting from a drug-drug, drug-food, drug-laboratory interaction;

7)   that is the result of not receiving the prescribed drug;

8)   that is the result of taking a drug for which there is no valid medical indication.[40]

3.3.4 Non-adherence

Strand et al put forward the concept of non-adherence under the heading of Category Seven.[40] In the context of this study, non-adherence was defined as any non-trivial deviation from the prescribed medication regimen which can be intentional or unintentional, and includes dosage errors (underuse and overuse), interruption of treatment, failure to take drugs at specified times or taking them at incorrect intervals.[177] A determination of non-adherence was based on the medical history obtained during a patient's emergency department attendance or hospital admission and, where applicable, through consultation with the relevant medical personnel responsible for the patient in question.

Allocation guidelines were developed for DRPs, based upon the practice context outlined by Strand et al for each DRP category.[40] These guidelines are provided in Appendix Three.

3.4 Causality

Causality for this study was defined as the measure of the probability that the event under consideration could be attributed to a DRP or ADR.[67] Causality, for patients attending the emergency department or admitted to

hospital with a DRP, was established via a different method to that used for ADRs occurring within the inpatient population, as described below.

3.4.1 Emergency department attendances and hospital admissions associated with DRPs

It was determined that causality, for emergency department attendances and hospital admissions associated with DRPs, be assessed through the use of a *multidisciplinary panel* and a *structured algorithm*. The *structured algorithm* proposed by Dartnell et al was found to be the most appropriate.[6]

Challenges encountered by the *multidisciplinary panel* in the operational use of the algorithm led the adoption of the modified version which is outlined in Table 3.1. The changes involved altering the wording of two of the six criteria to allow all DRP categories to be encompassed. The requirements as to what constituted a *definite* or *probable* classification were also altered to take into account that information on criteria C was not always available. All changes were undertaken with panel consensus. The alterations to the algorithm were made at a very early stage and hence few cases were affected by the changes made. Cases considered by the panel to be potentially affected by this change were, however, reviewed again.

Utilising the criteria set out in Table 3.1 a causality classification of *definite*, *probable* or *possible* was determined. Cases considered *definite* met criteria A, B, D and, if applicable, C from Table 3.1, *probable* met criteria A, B, E and, if applicable, C, and *possible* met criteria A, B and F.

Table 3.1 Modified version of the algorithm proposed by Dartnell et al[6]

	The adverse condition or clinical presentation:
A	followed a reasonable temporal sequence after the patient was given or failed to receive the suspected drug;
B	followed a recognised response or failure to respond to the suspected drug;
C	improved on withdrawing or resuming therapy with the drug;
D	deteriorated on re-exposure; a toxic or sub-therapeutic plasma level was established; a toxic amount of medication was ingested (suspected or known); there are previous *conclusive* reports on this reaction;
E	could not be reasonably explained by the known characteristics of the patient's clinical state;
F	could be explained by the characteristics of the patient's disease.

In addition, the *multidisciplinary panel* determined that all cases allocated to Category Eight would automatically receive a causality classification of *definite*.

A preliminary study conducted in 1996 by Easton et al indicated a significant proportion of paediatric admissions were associated with asthma medication non-adherence.[7, 67] The criteria set out in Table 3.2 were established in response to this finding and were used to standardise data collection and evaluation in these situations.[7, 67]

Table 3.2 Causality classifications for cases involving non-adherence with asthma medications

	Child admitted with exacerbation of asthma, having clearly used medications in a way other than prescribed, and with no other identifiable trigger factor for the exacerbation.
	Child admitted with exacerbation of asthma, having clearly used medications in a way other than prescribed, but with an identifiable trigger factor for the exacerbation.
	Child admitted with exacerbation of asthma, having possibly used medications in a way other than prescribed, but with an identifiable trigger factor for the exacerbation.

3.4.2 Adverse drug reactions occurring within the inpatient population

The Naranjo algorithm was used to determine a causality classification for ADRs occurring in the inpatient population.[111] Using this algorithm an ADR was assigned to a probability category based upon the total score recorded after considering the questions posed in Table 3.3. A causality classification of *definite* was allocated if the total score was greater than or equal to nine, *probable* if the total score was between five and eight, *possible* if the total score was between one and four, and *doubtful* if the total score was less than zero. It should be noted that ADRs with a causality classification of *doubtful* were excluded.

Table 3.3 The Naranjo algorithm[111]

1. Are there previous *conclusive* reports on this reaction?	+1	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0
7. Was the drug detected in the blood (or other fluids) in a concentration known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0
Score			

Total Score _____

3.5 Preventability

Preventability examines the likelihood that the DRP or ADR could have been avoided if appropriate measures had been taken. Preventability was determined utilising the same methodology for all three streams of data collection. The one exception was cases allocated to DRP Category

Eight. The *multidisciplinary panel* recommended that preventability not be assessed for these cases because the majority involved accidental or intentional medication poisonings. For cases where preventability was determined, a modified version of the criteria put forward by Schumock and Thornton was used (See Table 3.4).[82] The addition of question eight was the only modification made to the original criteria proposed by Schumock and Thornton.[82]

Table 3.4 Preventability criteria adapted from Schumock and Thornton[82]

Answer with yes to one of the following questions if the DRP in question may indeed have been preventable.
1. Was the drug involved in the DRP *not* considered appropriate for the patient's clinical condition?
2. Was the dose, route and frequency of administration *not* appropriate for the patient's age, weight and disease state?
3. Were required therapeutic drug monitoring or other necessary laboratory tests *not* performed?
4. Was there a history of allergy or previous reactions to the drug?
5. Was a drug-drug, drug-food, drug-laboratory interaction involved in the reaction?
6. Was a toxic or sub-therapeutic serum drug level documented?
7. Was poor compliance involved in the reaction?
8. Was the condition present for a significant period of time prior to admission and an opportunity to administer a proposed drug recognised as amenable for the condition existed?

Utilising the criteria outlined in Table 3.4 a preventability classification of *yes, no* or *unable* was made. A preventability classification of *unable* was determined if the complexities of the case in question meant that it could not be correctly classified as either preventable or not preventable.

3.6 Clinical significance

Clinical significance was determined using a different method for each of the three streams of data collection. These are described in the subsequent sections.

3.6.1 Emergency department attendances associated with DRPs

The criteria used by Stoukides et al were used to determine clinical significance for patients attending the emergency department.[54] Using the criteria presented in Table 3.5 a clinical significance classification of *mild*, *moderate* or *severe* was established.[54]

Table 3.5 Clinical significance criteria for emergency department attendances associated with DRPs[54]

Mild	The DRP required no treatment.
Moderate	The DRP required treatment for symptom resolution.
Severe	The DRP required hospitalisation.

3.6.2 Hospital admissions associated with DRPs

A clinical significance classification was determined for cases whose hospital admission was associated with a DRP using the criteria proposed by Easton et al (See Table 3.6).[7]

Table 3.6 Clinical significance criteria for hospital admissions associated with DRPs[7]

	A DRP that results in the patient being admitted to hospital for up to 24 hours.
	A DRP that results in the patient being admitted to hospital for 24 - 48 hours.
	A DRP that results in the patient being admitted to hospital for a period greater than 48 hours and/or requires admission to the intensive care unit.
	A DRP that results in a permanent disability or death.

3.6.3 Adverse drug reactions occurring within the inpatient population

A clinical significance classification was determined for ADRs arising within the inpatient population using the criteria determined by Colodny and Spillane (See Table 3.7).[145]

Table 3.7 Clinical significance criteria for ADRs occurring within the inpatient population[145]

	requires no treatment and has an insignificant patient impact.
	requires treatment but is not life-threatening and not likely to result in permanent disability.
	is potentially life threatening and could result in permanent disability or death.

3.7 Independent panel review

It was originally envisaged that one panel of independent assessors would review all case information collected. The impracticalities of one panel dealing with the large volume of case information obtained soon became

evident and a second panel was therefore formed. In order to allow differentiation between the two panels, the first panel was referred to as the *multidisciplinary panel*. The members and function of this panel will be discussed in Section 3.7.1. The second panel was referred to as the *pharmacy panel*. The members and function of this panel will be discussed in Section 3.7.2.

3.7.1 The multidisciplinary panel

The *multidisciplinary panel* was formed to allow the review of all patients identified within the first two streams of data collection. The panel consisted of seven independent members from a variety of disciplines including paediatric medicine, pharmacy, paediatric clinical pharmacology and nursing. In undertaking their role, the members of the panel were instructed to be cognisant of the risk of case misclassification where an admission was possibly associated with a disease exacerbation rather than a DRP. Therefore, where it was more likely that an event was associated with a disease exacerbation, the *multidisciplinary panel* were instructed to classify as such rather than as a DRP.

The functions of the *multidisciplinary panel* were twofold. Firstly, to establish whether inclusion criteria were met. Secondly, panel members allocated each case that fulfilled inclusion criteria to a DRP category and established a causality and preventability classification. As highlighted in Section 3.6, the methods used to determine clinical significance differed between emergency department attendances and hospital admissions. Panel members often reviewed cases from both streams of data collection concurrently, so to avoid confusion as to which method was required they did not determine clinical significance. The investigator established clinical significance classifications for these cases according to the definitions provided in Section 3.6.1 and Section 3.6.2. This was deemed appropriate as the criteria utilised did not require clinical judgements to be made.

Two members of the *multidisciplinary panel* reviewed each case on an independent basis. At least one of them was required to be a medical practitioner. Any discrepancies in the classifications determined were noted in a computer database. In cases where discrepancies arose, the reviewed case notes were annotated with the classifications and any other comments made by the panel members. These were then returned to the panel members who were asked to discuss the relevant case and reach a consensus. The consensus opinions were recorded as the final DRP category, causality and preventability classifications.

Inter and intra-observer reproducibility was measured in order to provide an estimate of the reproducibility of results obtained. Inter-observer reproducibility was measured using the Kappa statistic, which measures the strength of agreement between panel members taking into account agreement that would occur by chance alone.[178] The Kappa statistic is calculated using the following formula:

$$Kappa = \frac{P(A) - P(E)}{1 - P(E)}$$

where

P(A) = the proportion of times that *n* raters agree

P(E) = the proportion of times that *n raters* would be expected to agree by chance.[178]

When the value of Kappa equals one, there is perfect agreement between the two panel members. When the Kappa value equals zero, agreement is no greater than chance alone. Other values of Kappa and their relative strength of agreement are shown in Table 3.8.

Table 3.8 Values of Kappa and strength of agreement[179]

Kappa	Strength of agreement
< 0.20	Poor
0.21 – 0.40	Fair
0.41 – 0.60	Moderate
0.61 – 0.80	Good
0.81 – 1.00	Very Good

Intra-observer reproducibility was established by asking each panel member to review 30 reports that they had passed judgement on at least four months earlier. The panel member again determined a DRP category, causality and preventability classification. The classifications allocated on each separate occasion were then compared using the Kappa statistic.

3.7.2 The pharmacy panel

The *pharmacy panel* was formed to allow the review of ADRs occurring within the inpatient population. The panel consisted of four independent members who were pharmacists. It was deemed appropriate to use pharmacists only on this panel as the methodology used to determine causality has been assessed using experts and non-experts in the field of ADRs.[111] Like the *multidisciplinary panel*, the members of the *pharmacy panel* aimed to be cognisant of the risk of case misclassification where an adverse event was possibly associated with a patient's disease state rather than an ADR.

The functions of the *pharmacy panel* were twofold: to establish whether inclusion criteria were met; and to allocate each case that fulfilled inclusion criteria a causality, preventability and clinical significance classification.

Two members of the *pharmacy panel* reviewed each case on an independent basis. Any discrepancies in the classifications determined were noted in a computer database. In cases where discrepancies arose the reviewed case notes were annotated with the classifications and any other comments made by the panel members. The annotated notes were then returned to the panel members who were subsequently asked to discuss the relevant case and reach a consensus. The consensus opinions were recorded as the final causality, preventability and clinical significance classifications.

Inter and intra-observer reproducibility was measured using the same methodology as that outlined for the *multidisciplinary panel* in Section 3.7.1. The only variation was that with respect to intra-observer reliability a total of 20 cases were reviewed by panel members.

An overview of the methods used for each of the three streams of data collection is presented in Figure 3.1.

Figure 3.1 Overview of methods used for each stream of data collection
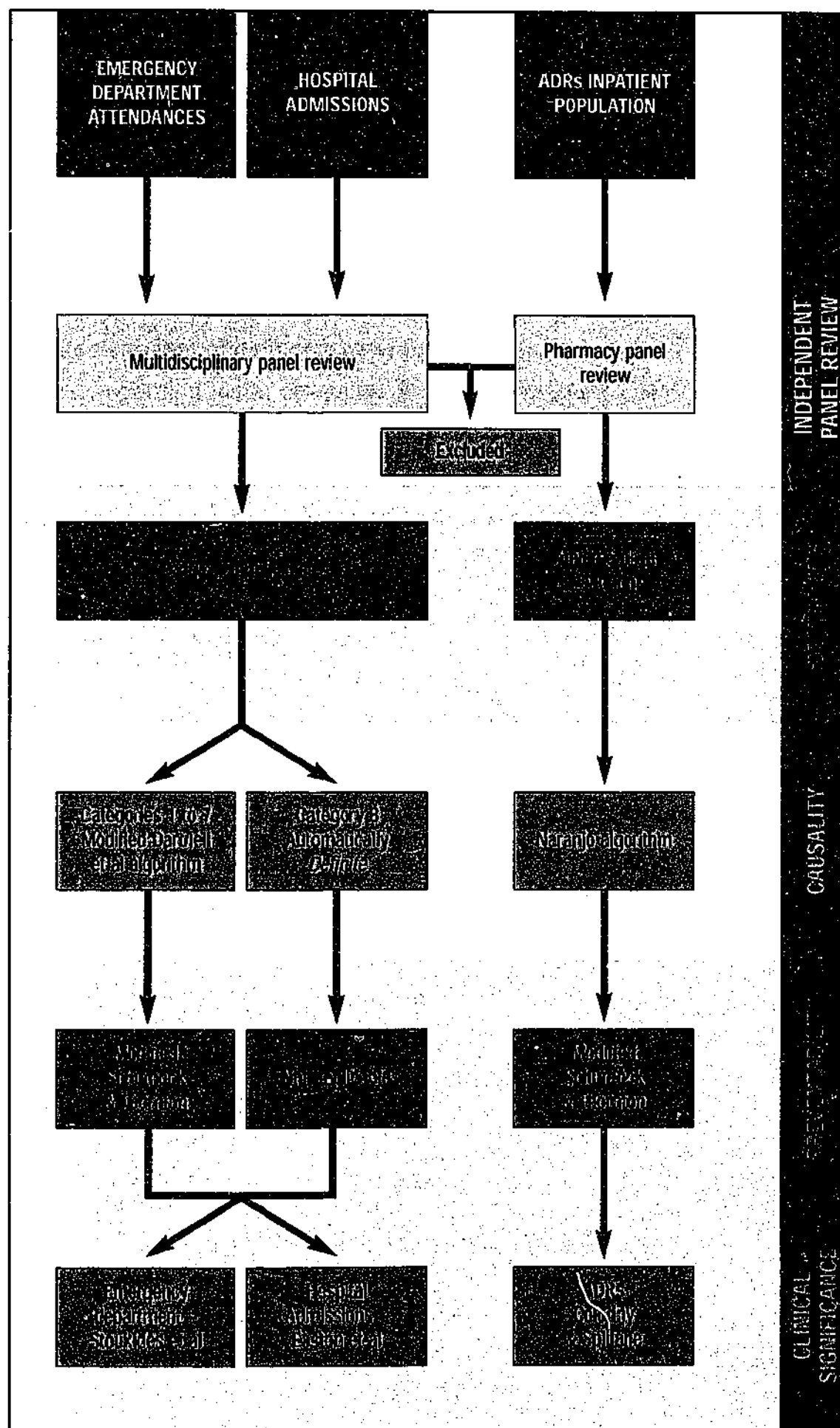
3.8 Conclusions

This chapter has presented the methods by which the major methodological issues highlighted in the literature have been addressed. The methods addressed in this chapter form the core of the methodology used to research the consequences of DRPs in paediatrics in this thesis. As is evident, the exact method by which a number of these core issues are addressed differs among the three streams of data collection. While the core issues relating to all three streams of data collection have been presented in this chapter, the details regarding data collection for *emergency department attendances* associated with DRPs will be outlined in Chapter Four. Similarly, the details relating to *hospital admissions* associated with DRPs will be outlined in Chapter Five, and the details pertaining to the frequency of ADRs arising within the *inpatient population* will be presented in Chapter Six.

4 Emergency department attendances associated with DRPs in paediatrics

Information on the nature and extent of DRPs occurring in the paediatric population are limited, as previously mentioned in Chapter One. This shortfall is evident at both a national and global level. In an effort to address this deficit, data on DRPs within the paediatric population are reported in this thesis by exploring three streams of data collection. In this chapter the first of these three streams is discussed, a stream which investigates the frequency and characteristics of emergency department attendances associated with DRPs at three hospitals.

The structure of this chapter involves the methodological details regarding data collection within the three emergency departments being presented in Section 4.1. In reading this section it should be remembered that the methodologies utilised to determine causality, preventability and clinical significance along with an explanation of the independent panel review process were provided in Chapter Three. The results section provides details on emergency department attendances associated with DRPs for each of the hospitals before combining data to enable further analysis. The brief discussion section presented in this chapter aims to compare the extent of emergency department attendances associated with DRPs reported in this chapter to that reported within the literature. The broader implications of the results presented in this chapter will be discussed in Chapter Eight.

4.1 Methods

4.1.1 Eligibility

All unplanned paediatric medical patients attending the emergency department of the RCH, GH or BH over the periods of data collection were considered for inclusion in this study. Medical patients, in the context of this

stream of data collection, were patients attending the emergency department of the RCH, GH and BH, excluding those attending as trauma or oncology patients.*

4.1.2 Inclusion criteria

An emergency department attendance was considered a study case if an association between the attendance and a DRP was established, but was not considered a study case if such an association was not established.

4.1.3 Data collection

The investigator and/or the attending medical practitioner screened eligible patients presenting to the emergency department. Screening involved the completion of a cover sheet if an attendance was deemed as possibly associated with a DRP. The cover sheet was attached to the standard attendance forms of all paediatric patients attending the emergency department over the period of data collection. The coversheet sought to both remind the attending medical practitioner to consider the patient for inclusion and to guide them towards completing a more detailed checklist. A copy of the coversheet and the checklists are in Appendix Four. The investigator conducted a review of emergency department primary diagnosis codes on each consecutive day of data collection to supplement the screening process. The investigator then conducted a preliminary review of the medical histories of all patients identified. If, at the end of this preliminary review, an eligible patient possibly fulfilled inclusion criteria, admission details were recorded in a specially designed Microsoft Access 97 (Microsoft Corporation, Redmond, WA, USA) database to allow subsequent analysis.

It should be noted that patients admitted to hospital via the emergency department over the periods of data collection reported in this chapter were included and analysed in this stream of data collection only.

---

* The operational definitions for trauma and oncology patients are provided in Appendix One.

4.1.4 Multidisciplinary panel

The *multidisciplinary panel* reviewed information collected for each patient identified and established the likelihood of an association between the emergency department attendance and a DRP. Where such an association was not established, or where a classification of *unsure* was made after discussion between two panel members, the patient was excluded. Where such an association was established a DRP category was allocated. A causality classification was then determined for each case by the *multidisciplinary panel* using the criteria outlined in Section 3.4.1. Using the criteria set out in Section 3.5, a preventability classification was also established. The criteria presented in Section 3.6.1 were then utilised to determine a clinical significance classification.

4.1.5 Data analysis

The data were analysed using the Statistical Package for the Social Sciences (SPSS) for Windows version 10 (SPSS Inc, Chicago, IL, USA). Differences in gender distributions were investigated using a Chi-Square Test. The Mann-Whitney U Test was utilised to establish if significant differences in age existed between cases identified and the eligible population, the two groups of cases identified over different data collection periods at the same hospital, and between cases allocated to the different DRP categories. The Kruskal-Wallis H Test was used to compare age among the eligible patient populations of the three hospitals. A significance level of 0.05 was selected for all tests. The 95% confidence intervals (95% CI) for frequencies reported were determined using confidence intervals for a proportion.[180] Confidence intervals for incidence rates calculated were determined using a Poisson distribution.[181]

4.2 Results

4.2.1 Royal Children's Hospital

An 11-week period of data collection was conducted at the RCH over two separate time periods. The first was from the 23 March 1998 to 1 May 1998 and the second was from the 28 September 1998 to 30 October 1998. The decision to split data collection into two separate periods was made in consultation with emergency department staff, with convenience for emergency department staff the primary reason for the split.

Over the initial 6-week period of data collection 5,619 patients attended the emergency department, and of these, 4,390 met eligibility criteria. Eligible patients were predominantly male (57.2%, 2513/4390) with a mean age of 3.9 years (median 2.0 years, ± SD 4.1).

One hundred and ninety six attendances, possibly associated with DRPs, were identified using the screening process outlined in Section 4.1.3. The *multidisciplinary panel* excluded 59 of the 196 patients with 2 patients subsequently excluded after being classified as *unsure*. The *multidisciplinary panel*, considered 135 cases to have attendances associated with DRPs. Of the 135 cases identified, the proportion of males was significantly less than that of the eligible population (45.2%, p=0.0070). The mean age of cases was 4.3 years (median 2.4 years, ± SD 4.6). The age of cases was not significantly different to that of the eligible population (p=0.265). The DRPs identified were not associated with any deaths, although 17 cases were admitted to hospital, none of whom were admitted to the intensive care unit.

The frequency of emergency department attendances associated with DRPs over this 6-week period of data collection was determined to be 3.1% (95% CI 2.6 - 3.6%).

Over the subsequent 5-week period of data collection, 4,623 patients attended the emergency department, and of these, 3,555 met eligibility

criteria. Eligible patients were predominantly male (57.0%, 2025/3555) with a mean age of 4.1 years (median 2.0 years, ± 4.3).

One hundred and sixty five attendances possibly associated with DRPs were identified, with the *multidisciplinary panel* excluding 56 of them. The *multidisciplinary panel* therefore considered 109 cases to have emergency department attendances associated with DRPs. Of the 109 cases identified, the proportion of males was not significantly different to that of the eligible population (53.2%, p=0.4961). The mean age of cases was 5.9 years (median 3.1 years, ± SD 5.4). The age of cases was significantly higher than that of the eligible population (p<0.001). Drug related problems identified were not associated with any deaths, however, 33 cases were admitted to hospital, with 2 admitted to the intensive care unit.

The frequency of emergency department attendances associated with DRPs over this 5-week period of data collection was determined to be 3.1% (95% CI 2.5 - 3.7%).

Combining the two data collection periods, a total of 10,242 patients attended the emergency department over the 11-week period, of which 7,945 met eligibility criteria. There were no statistically significant differences in terms of gender (p = 0.8185) or age (p = 0.367) for eligible patients attending over the two periods of data collection.

Two hundred and forty four cases were determined by the *multidisciplinary panel* to have emergency department attendances associated with DRP's. Comparing cases identified over the two periods of data collection, no significant differences in the DRP categories represented (p = 0.488), or the gender of cases (p = 0.4569) were detected. The age of cases, was however, significantly higher in those identified during the second period of data collection (p = 0.007). Whilst acknowledging that this is a statistically significant difference it is unlikely that it is of clinical significance and hence the two groups were combined to allow further analysis.

Of the 244 cases identified, the proportion of males was significantly less than that of the eligible population (48.8%, p = 0.0115). The mean age of cases was 5.0 years (median 2.9 years, ± SD 5.0). The age of cases was significantly higher than that of the eligible population (p < 0.001). Drug related problems identified were not associated with any deaths, however 50 cases were admitted to hospital, 2 of which were admitted to the intensive care unit.

The frequency of emergency department attendances associated with DRPs was determined to be 3.1% (95% CI 2.7 - 3.5%). A flow chart of the case identification process is shown in Figure 4.1. The incidence rate was determined to be 1,480 per 100,000 paediatric persons / year (95% CI 1407 – 1558 per 100,000 paediatric persons / year).[*†]

---

[*] The figures used to determine the incidence rate are presented in Appendix Five.
[†] It is essential that the differences between frequency and incidence rate are understood. The differences between the two measures are best illustrated by considering the denominators involved in each of these calculations. To determine the frequency the denominator is the number of eligible emergency department attendances. In contrast, to determine the incidence rate the denominator is the number of persons at risk within the community.

Figure 4.1 Flow chart of the case selection process at RCH

Total number attending emergency
department 23 March – 1 May 1998
5619

Total number attending emergency
department 28 Sept – 30 Oct 1998
4623

Number of ineligible patients:

Number of ineligible patients:

Number of eligible patients:
4390

Number of eligible patients:
3555

Number of patients identified
by screening process:
196

Number of patients identified
by screening process:
165

Number of patients
excluded by panel:

Number of patients
excluded by panel:

Number of emergency department attendances
associated with DRPs at RCH:
244 (3.1%, 95% CI 2.7 – 3.5%)

A summary of the RCH cases allocated to the eight DRP categories is provided in Table 4.1.

Table 4.1 Summary of RCH cases allocated to the DRP categories

DRP category*	Frequency of Cases		Number of cases admitted to hospital
	Number	%	
1 (drug indication)	0	0.0	0
2 (wrong drug)	29	11.9	4
3 (too little)	8	3.3	2
4 (too much)	3	1.2	0
5 (ADR)	106	43.4	6
6 (drug interaction)	0	0.0	0
7 (non-adherence)	24	9.8	12
8 (poisoning)	74	30.3	26[†]
Total	**244**	**100**	**50**

*Definitions for each of the DRP categories are set out in Section 3.3.
[†]Two of these cases were admitted to the intensive care unit

4.2.2 Geelong Hospital

Data collection at GH was conducted over a 4-week period from 5 July 1999 to 30 July 1999.

Over this period 2,588 patients attended the emergency department. Of these, 649 were classified as paediatric patients, with 438 meeting eligibility criteria. Of the eligible patients 48.4% (212/438) were male. The mean age of eligible patients was 5.6 years (median 3.0 years, ± SD 5.7).

Thirty-five attendances possibly associated with DRPs were identified using the screening process outlined in Section 4.1.3. Ten of the 35 patients were

excluded by the *multidisciplinary panel* with a further 3 excluded after being classified as *unsure*. The *multidisciplinary panel* considered 22 cases to have emergency department attendances associated with DRPs. Of the 22 cases identified, the proportion of males was not significantly different to that of the eligible population (31.8%, p = 0.1932). The mean age of cases was 8.3 years (median 1.0, ± SD 7.0). The age of cases was significantly higher than that of the eligible population (p = 0.030). Drug related problems identified were not associated with any deaths, however, 9 patients were admitted to hospital, 1 to the intensive care unit.

The frequency of emergency department attendances associated with DRPs was determined to be 5.0% (95% CI 3.0 – 7.0%). A flow chart of the case identification process is provided in Figure 4.2. The incidence rate was determined to be 1,262 per 100,000 paediatric persons / year (95% CI 1195 – 1334 per 100,000 paediatric persons / year).[*]

---

[*] The figures used to determine the incidence rate are presented in Appendix Five.

Figure 4.2 Flow chart of the case selection process at GH and BH

GEELONG HOSPITAL

BOX HILL HOSPITAL
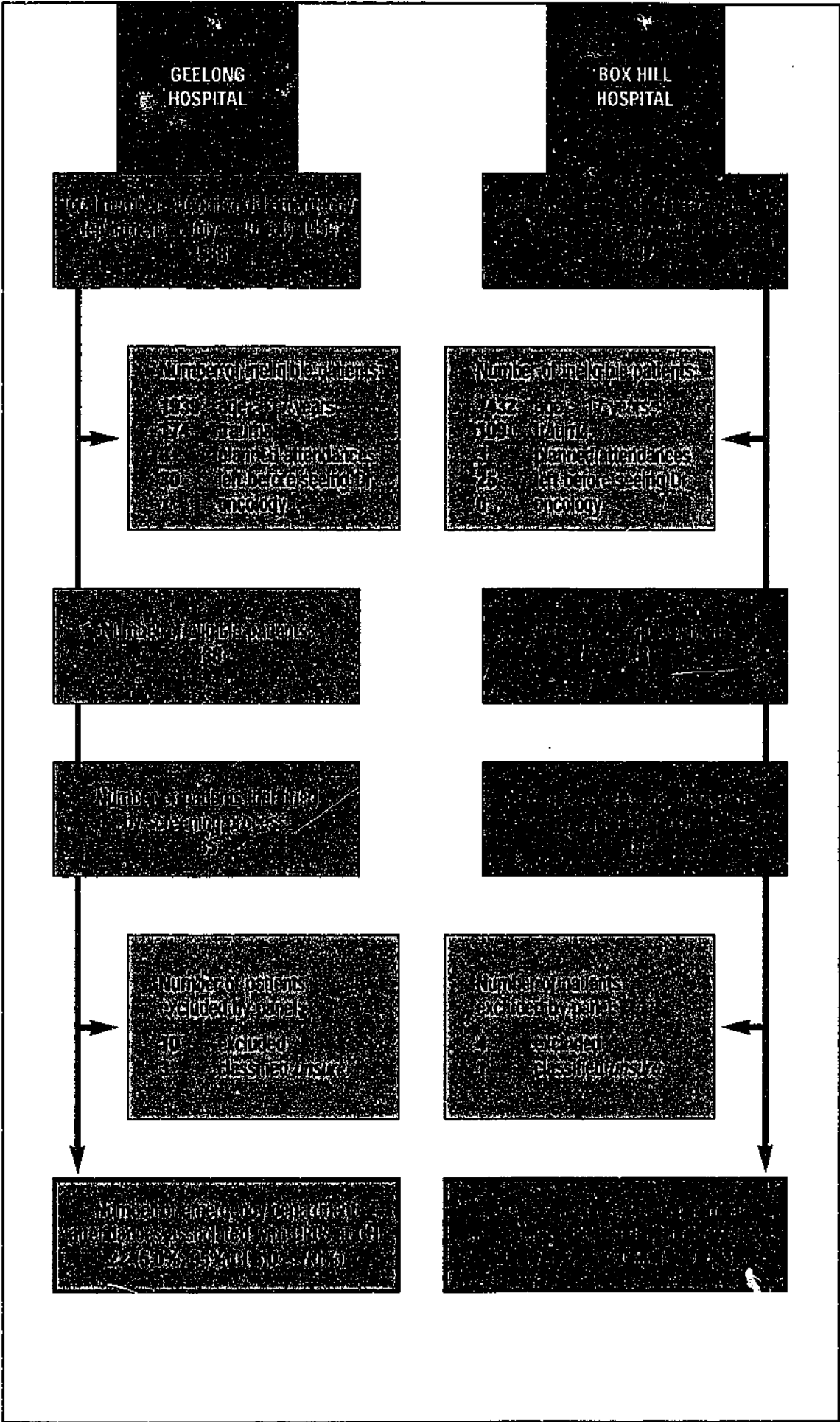
A summary of the GH cases allocated to the eight DRP categories is provided in Table 4.2.

Table 4.2 Summary of GH cases allocated to the DRP categories

DRP category*	Frequency of Cases		Number of cases admitted to hospital
	Number	%	
1 (drug indication)	0	0.0	0
2 (wrong drug)	1	4.5	0
3 (too little)	1	4.5	0
4 (too much)	0	0.0	0
5 (ADR)	4	18.2	2
6 (drug interaction)	0	0.0	0
7 (non-adherence)	1	4.5	1
8 (poisoning)	15	68.2	6[†]
Total	22	100.0	9

*Definitions for each of the DRP categories are provided in Section 3.3.
[†]One of these cases was admitted to the intensive care unit.

4.2.3 Box Hill Hospital

Data collection at BH was conducted over a 3-week period from 15 November 1999 to 3 December 1999.

Over this period, 1,787 patients attended the emergency department, and of these 355 were classified as paediatric patients, with 218 meeting eligibility criteria. Eligible patients were predominantly male (63.3%, 138/218) with a mean age of 5.2 years (median 3.0 years, ± SD 5.0). Nineteen attendances possibly associated with DRPs were identified. The *multidisciplinary panel* excluded 4 of these patients and 1 was subsequently excluded after being classified as *unsure*. The *multidisciplinary panel* determined that 14 cases

had emergency department attendances associated with DRPs. Of the 14 cases identified, the proportion of males was not significantly different to that of the eligible population (57.1%, p = 0.8594). The mean age of cases was 4.6 years (median 2.6 years, ± SD 5.0). The age of cases was not significantly different to that of the eligible population (p = 0.946). Drug related problems identified were not associated with any deaths, however, 3 cases were admitted to hospital, none to the intensive care unit.

The frequency of emergency department attendances associated with DRPs was determined to be 6.4% (95% CI 3.1 – 9.7%). A flow chart of the case identification process is provided in Figure 4.2. The incidence rate was determined to be 1,665 per 100,000 paediatric persons / year (95% CI 1586 – 1746 per 100,000 paediatric persons / year).[*]

A summary of the BH cases allocated to the eight DRP categories is provided in Table 4.3.

Table 4.3 Summary of BH cases allocated to the DRP categories

DRP category[†]	Frequency of Cases		Number of cases admitted to hospital
	Number	%	
1 (drug indication)	1	7.1	1
2 (wrong drug)	0	0.0	0
3 (too little)	1	7.1	0
4 (too much)	0	0.0	0
5 (ADR)	8	57.1	0
6 (drug interaction)	0	0.0	0
7 (non-adherence)	0	0.0	0
8 (poisoning)	4	28.6	2
Total	14	100	3

[†]Definitions for each of the DRP categories are provided in Section 3.3.

---

[*] The figures used to determine the incidence rate are presented in Appendix Five.

4.2.4 Combined data for RCH, GH and BH

Combining the three hospital sites, a total of 11,246 paediatric patients attended the emergency departments over 18-weeks of data collection, and of these 8,601 met eligibility criteria. Eligible patients from the three hospitals were significantly different with respect to both gender ($p = 0.0002$) and age ($p < 0.001$). In terms of gender, a significantly lower proportion of males attended GH when compared to either RCH ($p = 0.0004$) or BH ($p = 0.0004$), whilst the proportion of males attending both RCH and BH were comparable ($p = 0.0798$). With respect to age, patients attending the RCH were significantly younger than those attending either GH ($p < 0.001$) or BH ($p = 0.001$). No significant differences in age were identified between GH and BH ($p=0.889$). While it is acknowledged that eligible patients from RCH, GH and BH were significantly different with respect to gender and age, it was unlikely that these differences are clinically significant and hence data from the three hospitals were combined.

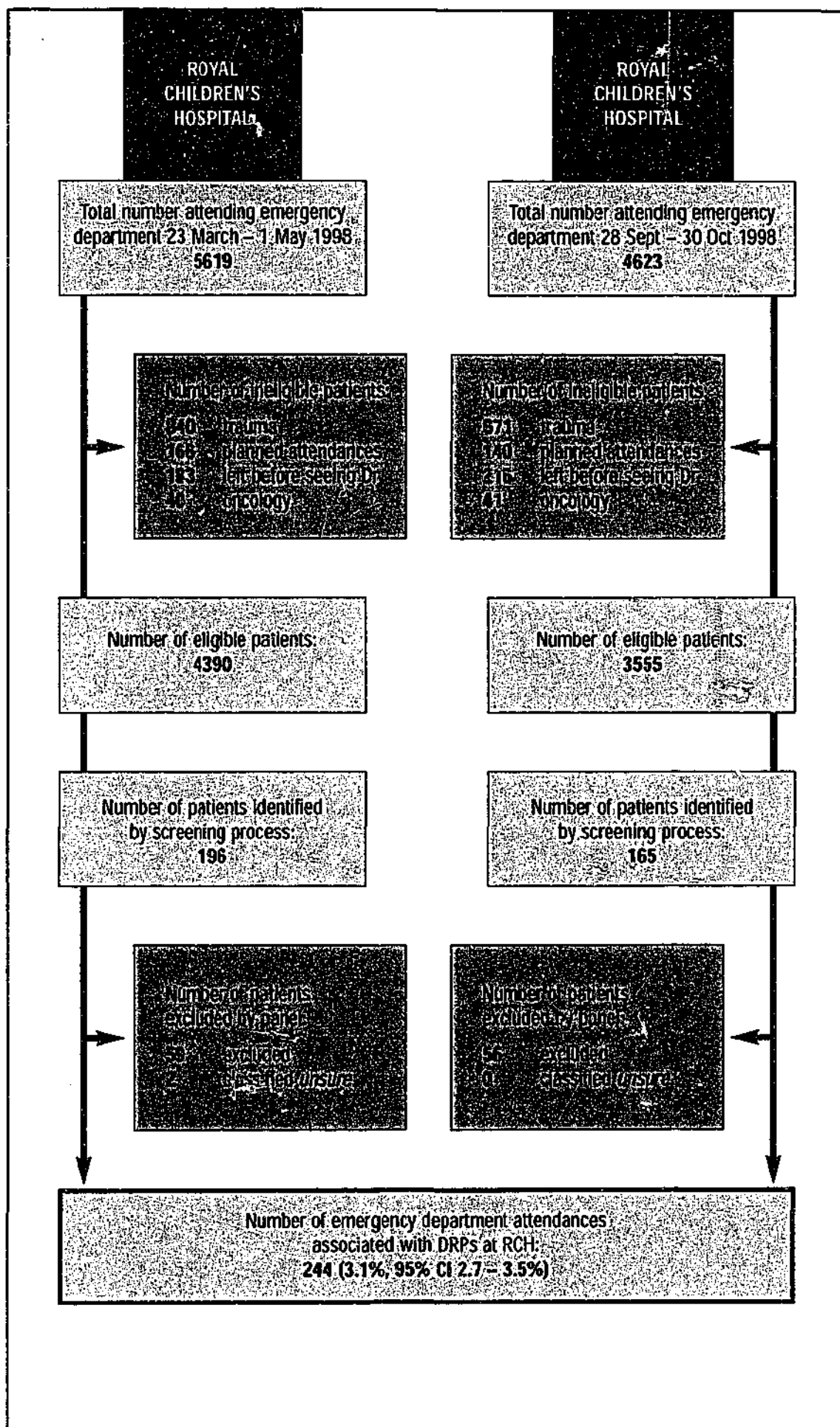Two hundred and eighty cases were assessed by the *multidisciplinary panel* to have emergency department attendances associated with DRPs. Of the 280 cases, the proportion of males was significantly less than that of the eligible population (47.9%, $p = 0.0035$). The mean age of cases was 5.3 years (median 2.9 years, $\pm$ SD 5.2). The age of cases was significantly higher than that of the eligible population ($p < 0.001$). Drug related problems were not associated with any deaths, however 62 cases were admitted to hospital, including 3 to the intensive care units.

The frequency of emergency department attendances associated DRPs was determined to be 3.3% (95% CI $2.9 - 3.7\%$). An incidence rate was not calculated for the combined hospitals because the accuracy of a combined figure would be questionable.*

A summary of the total number of cases allocated to the eight DRP categories is provided in Table 4.4.

---

* See Appendix Five for further details.

Table 4.4 Summary of the total number of cases allocated to the DRP categories

DRP category	Frequency of Cases		Age of cases (years)			Number of cases admitted to hospital
	no.[†]	%	mean	med.[†]	± SD	
1 (drug indication)	1	0.4	Not applicable			1
2 (wrong drug)	30	10.7	3.9	2.9	3.5	4
3 (too little)	10	3.6	7.5	5.9	4.4	2
4 (too much)	3	1.1	1.9	1.1	2.2	0
5 (ADR)	118	42.1	3.6	2.2	3.8	8
6 (drug interaction)	0	0.0	Not applicable			0
7 (non-adherence)	25	8.9	6.9	4.8	5.2	13
8 (poisoning)	93	33.2	7.3	3.0	6.5	34[‡]
Total	280	100.0	5.3	2.9	5.2	62

Definitions for each of the DRP categories are provided in Section 3.3.
[†]Abbreviations: no. = number; med. = median.
[‡]Three of these cases were admitted to the intensive care units.

The age of cases allocated to Category Two was found to be significantly lower than that of cases allocated to either Category Three (p = 0.031) or Category Seven (p = 0.012). The age of cases allocated to Category Five was significantly lower than cases in Category Three (p = 0.005), Category Seven (p < 0.001) and Category Eight (p < 0.001). No other statistically significant differences with respect to age were found.

4.2.4.1 Extrapolation of emergency department data

In order to extrapolate the data presented in this chapter to a state level, information on the number of paediatric emergency department attendances in Victoria over a one-year period was sought. To this end a total of 202,033 paediatric patients were reported to have attended public hospital emergency departments in the 11-months between 1 August 1998 to 30 June 1999

(Personal communication, Wellesley D, Melbourne: Department of Human Services, September 2000). Data for July 1998 were not available, so the average number of patients attending the emergency departments per month was determined for the 11-month period and utilised for the July value. It was therefore estimated that a total of 220,399 paediatric patients attended public hospital emergency departments over the 12-month period.

In light of the eligibility criteria outlined in Section 4.1.1, a large proportion of the patients attending the emergency departments over this time period would not be considered eligible for inclusion if this study was conducted on a state wide basis. An estimate of the number of patients who would be considered eligible was made utilising the combined data from the three hospitals provided in Section 4.2.4. The estimate was based upon the fact that 11,246 paediatric patients attended the three emergency departments, of which 8,601 were considered eligible. Utilising the same proportions it was estimated that of the 202,033 paediatric patients attending public hospital emergency departments, 154,516 would be considered eligible utilising study criteria.

In Section 4.2.4, 3.3% of emergency department attendances over the three hospital sites were determined to be associated with DRPs, so by extrapolating these results, 3.3% of the 154,516 emergency department attendances were potentially associated with DRPs, or 5,037 paediatric patients.

As demographic data regarding emergency department attendances, such as the age of people treated, is not provided to the Commonwealth it was not possible to extrapolate the results obtained to a national level (Personal communication, Pringle E, Canberra: Hospital Financing Section, Department of Health and Aged Care, August 2000).

In an attempt to gauge the validity of the extrapolation to Victoria, medication poisoning* data for children 0 to 4 years of age was extracted from the Victorian Emergency Minimum Dataset from July 1998 to June 1999.[182] This database represents approximately 80% of state-wide emergency department presentations. Over the one-year period, 432 patients between 0 to 4 years were coded as having emergency department attendances associated with medication poisonings (Personal communication, Ashby K, Melbourne: Victorian Injury Surveillance System, August 2000). In Section 4.2.4, 19.2% (54/280) of cases were between 0 and 4 years of age and met the definition for medication poisoning. Therefore, of the 5,037 paediatric emergency department attendances associated with DRPs, 967 (0.192 x 5,037) would be coded as medication poisonings. Using these figures, only 44.7% (432/967) of medication poisonings in this age group were coded in the Victorian Emergency Minimum Dataset.

4.2.4.2 Causality classification

With respect to the 280 cases identified across the three hospital sites, a causality classification of *definite* was determined for 37.9% (106/280) of cases, *probable* for 30.4% (85/280), and *possible* for 31.8% (89/280). The causality classifications allocated to cases within the DRP categories are depicted in Table 4.5.

---

*The Victorian Emergency Minimum Dataset defines medication poisonings as any poisoning that involves drugs, excluding alcohol or illicit drugs. Medication poisonings can therefore be considered one of the types of DRPs allocated to Category Eight.

Table 4.5 Causality classification for cases within the DRP categories

DRP category	Causality Classification		
	Definite	Probable	Possible
1 (drug indication)	0	1	0
2 (wrong drug)	1	10	19
3 (too little)	1	3	6
4 (too much)	0	1	2
5 (ADR)	8	63	47
6 (drug interaction)	0	0	0
7 (non-adherence)	3	7	15
8 (poisoning)	93	0	0
Total	106 (37.9%)	85 (30.4%)	89 (31.8%)

Definitions for each of the DRP categories are provided in Section 3.3.

4.2.4.3 Preventability classification

A preventability classification was established for each case, excluding those allocated to Category Eight. A preventability classification was therefore established for 187 of the 280 cases identified, of which 51.3% (96/187) were deemed preventable, 36.9% (69/187) not preventable, and for 11.8% (22/187) preventability was unable to be determined (See Table 4.6).

Table 4.6 Preventability classifications for cases within DRP categories

DRP category*		Preventability Classifications		
		Yes	No	Unable
1	(drug indication)	1	0	0
2	(wrong drug)	27	0	3
3	(too little)	6	0	4
4	(too much)	3	0	0
5	(ADR)	36	69	13
6	(drug interaction)	0	0	0
7	(non-adherence)	23	0	2
8	(poisoning)	Not applicable		
Total		96 (51.3%)	69 (36.9%)	22 (11.8%)

Definitions for each of the DRP categories are provided in Section 3.3.

4.2.4.4   Clinical significance classifications

A clinical significance classification was established for each of the 280 cases (Table 4.7), with a classification of *mild* determined for 35.7% (100/280), *moderate* for 42.1% (118/280), and *severe* for 22.2% (62/280).

Table 4.7 Clinical significance classifications allocated to cases by DRP category

DRP category	Clinical Significance Classification		
	Mild	**Moderate**	**Severe**
1 (drug indication)	0	0	1
2 (wrong drug)	12	14	4
3 (too little)	0	8	2
4 (too much)	2	1	0
5 (ADR)	57	53	8
6 (drug interaction)	0	0	0
7 (non-adherence)	2	10	13
8 (poisoning)	27	32	34
Total	**100 (35.7%)**	**118 (42.1%)**	**62 (22.2%)**

Definitions for each of the DRP categories are provided in Section 3.3.

4.2.4.5 Multidisciplinary panel agreement

Inter-observer reproducibility for *multidisciplinary panel* members was measured using the Kappa statistic (See Section 3.7.1), which indicates the strength of agreement between panel members, taking into account agreement that would occur by chance alone.

The strength of agreement between panel members when allocating a DRP category was found to be *good*, with a Kappa value of 0.622. It should be noted that for the purpose of data analysis the categories of *no* and *unsure* were combined and 1 case was excluded to enable a Kappa calculation to be calculated. These steps were undertaken on the advice of a statistician for this one calculation only.

The strength of agreement between panel members when allocating a causality classification was found to be *moderate*, with a Kappa value of 0.449.

The strength of agreement between panel members when allocating a preventability classification was found to be *moderate*, with a Kappa value of 0.425.

For 7 cases, the DRP category initially allocated by the *multidisciplinary panel* was altered so that the DRP category of these cases matched the category of analogous cases. This was undertaken after panel consensus.

The intra-observer reproducibility results recorded for *multidisciplinary panel* members are presented in Appendix Six.

4.2.4.6 Drug classes involved in DRPs: an overview

A mean of 1.7 drugs (median 1.0, ± SD 1.0) per case were recorded to have been taken in the week prior to admission. This count included regular and non-regular* drugs, along with documented over-the-counter products and alternative medications. It should be noted that drug products containing multiple ingredients are considered as one entity in this count. The mean number of drugs per case for each DRP category is shown in Table 4.8.

---

* Non-regular drugs included drugs taken on a when required basis along with drugs taken for which there was no valid medical indication.

Table 4.8 Mean total number of drugs for each DRP category

DRP category*		mean	median	± SD
1	(drug indication)	Not applicable		
2	(wrong drug)	1.8	2.0	0.8
3	(too little)	1.9	2.0	0.7
4	(too much)	1.0	1.0	0.0
5	(ADR)	1.8	1.0	1.0
6	(drug interaction)	Not applicable		
7	(non-adherence)	2.0	2.0	0.9
8	(poisoning)	1.4	1.0	1.2

*Definitions for each of the DRP categories are provided in Section 3.3.

Of the 467 drugs recorded, 344 were specifically implicated in the 280 cases identified. An analysis according to the Therapeutic Classification of the 344 drugs is shown in Table 4.9. The individual drugs recorded within each classification are also listed in this table.

Table 4.9 Drugs associated with DRPs by Therapeutic Classification

Therapeutic Classification*	Drugs within classifications
Alimentary System	
- Hyperacidity, reflux and ulcers	ranitidine (1)[t]
- Antispasmodics	hyoscyamine / atropine / hyoscine (1)
- Laxatives	lactulose (1)
Cardiovascular System	
- Antihypertensive agents	clonidine (3), verapamil (1), enalapril (1)
- Beta-adrenergic blocking agents	propranolol (1)
- Antiangina agents	diltiazem (1)
- Cardiac inotropic agents	digoxin (1)
- Antimigraine preparations	pizotifen (1)
Central Nervous System	
- Sedatives, hypnotics	temazepam (4), flunitrazepam (1)
- Antianxiety agents	diazepam (3)
- Antipsychotic agents	clozapine (1), thioridazine (1)
- Antidepressants	paroxetine (1), moclobemide (2), imipramine (1), fluoxetine (1), sertraline (1), venlafaxine (1)
- Movement disorders	levodopa / carbidopa (1)
- Other central nervous system agents	dexamphetamine (2), methylphenidate (2)
- Anticonvulsants	sodium valproate (1), lamotrigine (1), clonazepam (1), ethosuximide (1), vigabatrin (1), carbamazepine (3)
- Antiemetics, Antinauseants	metoclopramide (2)
Analgesia	
- Simple analgesics and antipyretics	paracetamol (29), aspirin (2)
- Combination simple analgesics	paracetamol / codeine / doxylamine (1), paracetamol / codeine (5), paracetamol / promethazine / codeine (3)
Musculoskeletal System	
- Nonsteriodal anti-inflammatory agents	naproxen (3), diclofenac (1), ketoprofen (1), phenylbutazone (1)

Drugs associated with DRPs by Therapeutic Classification (continued)

Musculoskeletal System continued	
- Rubefacients and topical analgesics	camphor / menthol / eucalyptus oil / methyl salicylate (1)
Endocrine and Metabolic Disorders	
- Adrenal steroid hormones	prednisolone (4)
- Insulin preparations	insulin-neutral (2), insulin-biphasic (2), insulin-isophane(2), insulin lispro (1)
- Hypoglycemic agents	gliclazide (1)
Infections and infestations	
- Penicillins	flucloxacillin (3), penicillin V (6), amoxycillin/clavulanic acid (9), amoxycillin (33)
- Cephalosporins	cefaclor (27), cephalexin (2)
- Macrolides	erythromycin (7), roxithromycin (2)
- Other antibiotics and anti-infectives	co-trimoxazole (5), nitrofurantoin (1)
- Antihelmintics	pyrantel (1)
Neoplastic Disorders	
- Antimetabolites	cyclophosphamide (1)
Immunology	
- Vaccines	haemophilus B conjugate (Hib) vaccine (17), diphteria / tetanus / pertussis (Triple Antigen) vaccine (25), measles / mumps / rubella (MMR) vaccine (6), diptheria / tetanus / acellular pertussis / hepatitis B (1)
- Immunomodifiers	Interferon alfa (1)
Respiratory System	
- expectorants, antitussives, mucolytics, decongestants	dextromethorphan / pseudoephedrine / guaiphenesin (1), chlorpheniramine / phenylephrine (8), brompheniramine / phenylephrine / dextromethorphan (1), paracetamol / pseudoephedrine / codeine (1), brompheniramine / phenylephrine (1), pseudoephedrine (1)
- Bronchospasm relaxants	terbutaline (6), salbutamol (1)
- Bronchodilator aerosols and inhalations	salbutamol (6), salmeterol (2)
- Preventative aerosols and inhalations	beclomethasone (3), budesonide (3), sodium cromoglycate (3), fluticasone (1)

Drugs associated with DRPs by Therapeutic Classification (continued)

Allergic Disorders	
- Antihistamines	trimeprazine (1), hydroxyzine (1), loratadine (1), cyproheptadine (1)
Ear, Nose and Oropharynx	
- Topical nasopharyngeal medication	oxymetazoline (1)
- Topical oropharyngeal medication	triamcinolone (1), nystatin (1)
Skin	
- Topical corticosteroids	hydrocortisone (2), betamethasone (2), mometasone (1)
- Topical antifungals	clotrimazole (1)
- Other dermatological products	minoxidil (1)
Surgical Preparations	
- Anaesthetics – local and general	lignocaine / benzalkonium chloride / allantoin (1), lignocaine / phenoxyisopropanol, cetrimide / chlorhexidine (1)
Contraceptive agents	
- Combined oral contraceptive agents	ethinyloestradiol / levonorgesterol (1)
Nutrition	
- oral and parenteral electrolytes	sodium chloride / potassium chloride / sodium acid citrate / glucose (1)
Vitamins and Minerals and other Nutritional supplements	ferrous gluconate (1), ferrous sulphate (3)
Unlisted items	sennosides (1), choline salicylate / cetalkonium chloride (1), chlorbutol / ortho-dichlorobenzene / parachlorobenzene / arachis oil (1), phenolphthalein (1), senega / ammonia (1), poloxamer drops (1), phenobarbitone / atropine (1), calamine / lignocaine / camphor / glycerol (1), menthol / eucalyptus oil / camphor (1), eucalyptus oil (4), doxylamine (1), timoptol (1), liquid paraffin (1), salicylic acid / lactic acid / podophyllin (1)
Alcohol, illicit or unidentified substances	alcohol (3), heroin (3), marijuana (3), amphetamine (3). Unidentified substances: white mixture (1), antibiotics (1), eczema medication (1), herbal tablets (1), multivitamin capsules (1)
Total	**344**

*Classification in this table is according to the indexing used by the MIMS Annual 2000, and as such, the same drug may appear under more than one Therapeutic Classification if different dose forms of the drug are used in different ways.[183]
†The number of cases in which the drug was involved is indicated in parenthesis.

It can be seen from Table 4.9 that the 12 most frequently occurring drugs listed were: amoxycillin; paracetamol; cefaclor; Triple Antigen vaccine; Hib vaccine; amoxycillin / clavulanic acid; erythromycin; chlorpheniramine / phenylepherine; terbutaline; salbutamol; MMR vaccine; and penicillin V.

4.2.4.7 Drug classes involved in DRPs: DRP categories and scenarios

Common disease states and scenarios can be described for many of the cases allocated to the eight DRP categories. These will be presented in this section with the aim of elucidating the nature of the cases allocated to these categories.   The case descriptions for the scenarios put forward are summaries of the documentation contained in the medical histories of the cases presented. It should be noted that more extensive documentation was utilised by *multidisciplinary panel* members to classify cases.

4.2.4.7.1 Category One

Category One, where drug therapy was required but the case was not receiving a drug for that indication, was represented by 1 case (Table 4.10).

Table 4.10 Drugs implicated in Category One

Therapeutic Classification*	Drugs within this classification
Respiratory System - Preventative aerosols and inhalations	fluticasone (1)[†]

*Classification is according to the indexing used by MIMS Annual 2000.[183]
[†]The number of cases in which the drug was involved is indicated in parenthesis.

The *multidisciplinary panel* assigned a causality classification of *probable,* a preventability classification of *yes,* and a clinical significance classification of *severe* for this case. The following is a brief description of the case:

> *A 4 year old male with a past medical history of asthma,
> diagnosed at 2 years of age, presented to the emergency
> department with an acute exacerbation of asthma.   The*

exacerbation commenced on the night prior to attendance with the patient being unwell with a cough and wheeze. On examination he was noted to be afebrile with a red inflamed throat and a papular rash. He also had intercostal recession and decreased air entry without wheeze. The exacerbation occurred on a background of chronic persistent symptoms including "weekly attacks", frequent nocturnal cough and exertional wheeze. These symptoms were being treated with salbutamol and occasional courses of prednisolone. He was admitted to hospital and commenced on sodium cromoglycate, which was subsequently changed to fluticasone upon discharge.

4.2.4.7.2   Category Two

Category Two, where the wrong drug was being taken, was represented by 30 cases (Table 4.11).

Table 4.11 Drugs implicated in Category Two

Therapeutic Classification*	Drugs within this classification
Alimentary System - Antispasmodics	hyoscyamine / atropine / hyoscine (1)†
Endocrine and Metabolic Disorders - Adrenal steroid hormones	prednisolone (1)
Infections and Infestations - Penicillins	penicillin V (1), amoxycillin (7)
- Cephalosporins	cefaclor (5)
- Macrolides	erythromycin (2), roxithromycin (1)
Respiratory System - Bronchospasm relaxants	terbutaline (5), salbutamol (1)
- Bronchodilator aerosols and inhalations	salbutamol (2)
- Preventative aerosols and inhalations	budesonide (1)
Ear, Nose and Oropharynx - Topical oropharyngeal medication	triamcinolone (1), nystatin (1)
Skin - Topical corticosteroids	hydrocortisone (1), betametasone (1)
- Topical antifungals	clotrimazole (1)
Unlisted items	phenobarbitone / atropine (1), liquid paraffin (1)

*Classification is according to the indexing used by MIMS Annual 2000 and as such the same drug may appear under more than one Therapeutic Classification if different dose forms of the same drug are used in different ways.[183]

†The number of cases in which the drug was involved is indicated in parenthesis.

A diverse range of drugs and disease states were implicated in the cases allocated to this category, but despite this diversity four scenarios were evident:

The first scenario is represented by 15 of the 30 cases and involved antibiotics being given for viral infections. The drugs involved were amoxycillin, penicillin V, cefaclor, erythromycin and roxithromycin. In conjunction with antibiotics given for viral infections, terbutaline and / or budesonide were also noted as the wrong drugs in 3 of the 15 cases. The *multidisciplinary panel* determined a causality classification of *definite* for 1 case, *probable* for 5 cases and *possible* for the remaining 9 cases. A preventability classification of *yes* was determined for all cases with the exception of 2, which were classified as *unable*. A clinical significance classification of *mild* was allocated to 9 cases, *moderate* for 6 cases and *severe* for 1 case. The following brief case description captures the nature of this Category Two scenario:

> *A 4 year old male with no significant past medical history presented to the emergency department with an erythematous maculopapular rash. The patient had a 7-day history of a mild upper respiratory tract infection (URTI) with the rash described appearing 2 days prior to attendance. The patient was seen by his local general medical practitioner on the day prior to attendance and was prescribed erythromycin for a "viral infection". As 5 doses of the erythromycin had been given without a change in his condition he was brought into the emergency department for a second opinion. A primary diagnosis of viral exantheme was determined, the erythromycin was ceased, and the patient was discharged.*

The second scenario involved the use of medications not listed as first line therapy for the disease states in question.* [184, 185] Hyoscyamine / atropine / hyoscine, prednisolone, amoxycillin, cefaclor, terbutaline, salbutamol, hydrocortisone and phenobarbitone / atropine were the drugs recorded for the 8 cases which fit this scenario. The *multidisciplinary panel* determined a causality classification of *probable* for 3 cases and *possible* for the remaining

---

* First line therapy for the disease states in question was determined according to the Therapeutic Guidelines: Antibiotic and the Therapeutic Guidelines: Gastrointestinal.

5 cases. All cases were classified as preventable. A clinical significance classification of *severe* was allocated to 1 case, *moderate* for 4 cases and *mild* for 3 cases. This scenario is best represented by the following brief case description in which the drug implicated was prednisolone:

> *A 2 year old female with a past medical history of asthma, diagnosed 1-year prior, presented to the emergency department. The patient had no history of interval asthma symptoms and had been admitted to hospital on a single occasion 1-year prior as a result of her asthma. Upper respiratory tract infections were the only known trigger factor for her asthma. The patient was not on any preventative medications and used salbutamol when required. Two days prior to presenting to the emergency department she developed the symptoms of an URTI for which she was prescribed cefaclor. However, she continued to cough at night and was prescribed prednisolone tablets on the day she attended the emergency department. She was unable to take the prednisolone tablets and hence presented to the emergency department. On examination she was noted to be well with no respiratory distress and no wheeze. An assessment of very mild asthma was made and the prednisolone was ceased. The patient was discharged with a principal diagnosis of an URTI, and was prescribed salbutamol.*

The third scenario involves the dose form supplied being inappropriate for the patient's age. There were 2 cases, with salbutamol the drug involved in each. The *multidisciplinary panel* determined a causality classification of *probable* for case one and *possible* for the second. In both cases the emergency department attendance was deemed preventable. Clinical significance classifications of *severe* and *moderate* were allocated respectively. This scenario is best represented by the following brief description:

A 2 year old female with a past history of asthma, diagnosed 2 months prior, presented to the emergency department. She had not previously attended an emergency department or been admitted to hospital as a result of her asthma. However, she had experienced 4 exacerbations of asthma in the 2 months prior to attendance. Symptoms of an URTI and wheezing developed on the day prior to attendance, for which she was prescribed salbutamol every 3 to 4 hours to be administered via a Volumatic®. Relief was not obtained because she was unable to use the medication properly and she presented to the emergency department on the following day. On examination a diagnosis of a mild to moderate exacerbation of asthma was made and the patient was admitted to hospital. She settled quickly after treatment with salbutamol and ipratropium, was commenced upon a reducing dose of prednisolone and beclomethasone and discharged.

The final scenario refers to ineffective treatment utilised for the cases in question. Five cases were allocated to this scenario. The drugs implicated included: triamcinalone; nystatin; betametasone; clotrimazole; and liquid paraffin. The *multidisciplinary panel* determined a causality classification of *probable* for 1 case and *possible* for the final 4 cases. A preventability classification of *yes* was allocated to 4 cases, with 1 case classified as *unable*. Four cases received a clinical significance classification of *moderate* with the final classified as *severe*. The following case description was considered preventable, with a causality classification of *possible*, and a clinical significance classification of *moderate*:

A 9 year old male with no significant medical history presented to the emergency department with herpetic mouth ulcers. The patient developed the mouth ulcers 3 days prior to his emergency department attendance. He was prescribed triamcinalone ointment, metronidazole suspension and benzydamine / ethanol solution. The mouth ulcers were not improving, so he was brought

into the emergency department. On examination herpetic vesicles were seen around the mouth and on the tongue. A diagnosis of oral herpes simplex was made, the triamcinolone ointment was ceased, and the patient was discharged.

4.2.4.7.3   Category Three

Ten cases were allocated to Category Three, where too little of the correct drug was being taken (Table 4.12).

Table 4.12 Drugs implicated in Category Three

Therapeutic Classification*	Drugs within this classification
Central Nervous System - Anticonvulsants	sodium valproate (1)[†], lamotrigine (1)
Analgesia - Simple analgesics and antipyretics	paracetamol (2)
Endocrine and Metabolic Diseases - Adrenal steroid hormones	prednisolone (2)
- Insulin preparations	insulin-neutral (1), insulin-isophane(1)
Infections and Infestations - Penicillins	penicillin V (1), amoxycillin (1)
Respiratory System - Bronchodilator aerosols and inhalations	salbutamol (1)

*Classification is according to the indexing used by MIMS Annual 2000.[183]
†The number of cases in which the drug was involved is indicated in parenthesis.

A diverse range of drugs and disease states were implicated in these cases, with two scenarios evident for them:

The first, where the dose of the drug concerned was sub-therapeutic for the disease-state in question, involved 8 of the 10 cases. The drugs implicated in this scenario were paracetamol, prednisolone, salbutamol, insulin-neutral, penicillin V or amoxycillin. One case was allocated a causality classification of *definite*, 2 *probable* and the remaining 5 were allocated a *possible* classification by the panel. A preventability classification of *yes* was determined for all except 3 cases, which were classified as *unable*. A clinical significance classification of *severe* was allocated to 1 case with the remaining cases classified as *moderate*. This scenario is best represented by the following brief description:

> *A 14 year old female with a past history of diabetes, which was diagnosed in 1992, presented to the emergency department. Her diabetes was normally treated with insulin-neutral and insulin-isophane. She had recently had a hospital admission with diabetic ketoacidosis. Prior to attendance she had a 4-day history of raised blood sugar levels and a 3-day history of ketones in her urine. This occurred on a background of an URTI. In response to the high blood sugar levels recorded, she increased the doses of her insulin-neutral and insulin-isophane and commenced checking for ketones. She attended the emergency department 4-days later, mildly dehydrated and with symptoms of diabetic ketoacidosis. Her symptoms of diabetic ketoacidosis resolved upon treatment, however at her normal insulin doses her blood sugar levels continued to be high, and hence her insulin doses were increased. Once stabilised upon the increased doses she was discharged.*

The second scenario involves a sub-therapeutic dose being administered as a result of a planned reduction in the dose of the drug in question. Lamotrigine and sodium valproate were the drugs involved. The *multidisciplinary panel* determined a causality classification of *probable* for 1 case and *possible* for the other. Preventability classifications of *yes* and *unable* along with a clinical significance classifications of *severe* and

moderate were determined respectively. The following brief description is of the second case outlined above:

An 11 year old male with a past history of epilepsy attended the emergency department as a result of a general tonic clonic seizure. He had been stable for 18-months prior to the attendance on a 500mg twice a day dose of sodium valproate. Six days prior to attending the emergency department the dose of sodium valproate had been reduced to 400mg twice a day. On the evening of the emergency department attendance he experienced a general tonic clonic seizure while sleeping, which resolved spontaneously after approximately 1 minute. Upon review he was found to be afebrile with no history of recent illness. The seizure was deemed most likely due to the recent decrease in medication. The sodium valproate dose was increased to 500mg twice a day and he was discharged.

4.2.4.7.4   Category Four

Category Four, where too much of the correct drug had been taken, was represented by 3 cases (Table 4.13).

Table 4.13 Drugs implicated in Category Four

Therapeutic Classification*	Drugs within this classification
Analgesia - Combination simple analgesics	paracetamol / codeine / promethazine (1)[†]
Nutrition - Oral and parenteral electrolytes	sodium chloride / potassium chloride / sodium acid citrate / glucose (1)
Unlisted items	poloxamer drops (1)

*Classification is according to the indexing used by MIMS Annual 2000.[163]
[†]The number of cases in which the drug was involved is indicated in parenthesis.

There were no disease states or scenarios in common for cases allocated to Category Four. An example of the type of case allocated to Category Four is outlined in the case description below. The *multidisciplinary panel* found the following case to be preventable with a causality classification of *possible* and a clinical significance classification of *mild*:

> *A 4 year old male with no significant past medical history presented to the emergency department as his parents had difficulty in waking him that morning. He had presented to the emergency department on the previous evening with ongoing ear pain and fever. He was administered 20mLs of paracetamol / codeine / promethazine mixture. The maximum single dose for this mixture based upon the patients body weight was 11mLs.[183] His parents are sure that he was actually given 30mL as they describe the medicine cup, which holds 40mL, being almost full. His parents were unable to wake him in the morning for 1.5 hours, and when he was aroused he was described as being drowsy and wobbly, hence he was brought into the emergency department. On examination he appeared well despite ongoing ear pain and fever. An assessment of otitis media and a possible drug error was made. An incident form was completed. The patient was commenced on amoxycilin and discharged.*

4.2.4.7.5   Category Five

Category Five, where an ADR had occurred, was represented by 118 cases (Table 4.14).

Table 4.14 Drugs implicated in Category Five

Therapeutic Classification*	Drugs within this classification
Central Nervous System	
- Anticonvulsants	vigabatrin (1)[†], ethosuximide (1)
- Antiemetics, Antinauseants	metoclopramide (2)
Infections and infestations	
- Penicillins	penicillin V (4), amoxycillin/clavulanic acid (9), amoxycillin (32), flucloxacillin (1)
- Cephalosporins	cefaclor (27), cephalexin (2)
- Macrolides	erythromycin (7), roxithromycin (2)
- Other antibiotics and anti-infectives	co-trimoxazole (5)
- Antihelmintics	pyrantel (1)
Immunology	
- Vaccines	Hib vaccine (17), Triple Antigen (25), MMR vaccine (6), diptheria / tetanus / pertussis / hepatitis B (1)
- Immunomodifiers	interferon alfa (1)
Respiratory System	
- expectorants, antitussives, mucolytics, decongestants	dextromethorphan / pseudoephedrine / guaiphenesin (1), chlorpheniramine / phenylephrine(1)
Allergic Disorders	
- Antihistamines	trimeprazine (1), hydroxyzine (1), loratadine (1)
Ear, Nose and Oropharynx	
- Topical nasopharyngeal medication	oxymetazoline (1)
Surgical	
- Anaesthetics – local and general	lignocaine / benzalkonium chloride / allantoin (1)
Vitamins and Minerals and other Nutritional supplements	ferrous gluconate (1)
Unlisted Items	sennosides (1), salicylic acid / lactic acid / podophyllin (1)

*Classification is according to the indexing used by MIMS Annual 2000.[183]
†The number of cases in which the drug was involved is indicated in parenthesis.

A diverse range of drugs and disease states were implicated in the cases allocated to Category Five. In spite of this diversity, 34 of the 36 cases considered preventable were found to involve antibiotics. Furthermore, a number of scenarios common to the 118 cases allocated to Category Five were evident, and could be grouped under three headings: hypersensitivity reactions; gastrointestinal reactions; and immunisation reactions.

There are a further three scenarios under the heading of hypersensitivity reactions. The first involves the development of angioedema, and was represented by 6 of the 118 cases. The drugs involved were: amoxycillin / clavulanic acid; amoxycillin; ethosuximide; trimeprazine; and hydroxyzine. The *multidisciplinary panel* determined a causality classification of *definite* for 2 cases, *probable* for 1 case and *possible* for 3 cases. Four of the 6 cases were classified as not preventable with the remaining 2 cases classified as preventable. A clinical significance classification of *severe* was allocated to 1 case, *moderate* to 3 cases and *mild* for 2 cases. This scenario is best represented by the following case description, which refers to a case that was classified as preventable with a causality classification of *definite* and a clinical significance classification of *moderate*:

> *A 10 year old female with a past history of penicillin allergy presented to the emergency department with facial oedema and a feeling of tightness around the throat. In the 4 days prior to attendance she had been on an amoxycillin challenge with an increasing dose of amoxycillin being administered under supervision. She tolerated the first 4 days of the challenge, however, when the dose was increased to 250mg she developed angioedema of the face and lips 4 hours after the dose was administered. On examination the patient had facial swelling with no evidence of rash and a clear chest with no wheeze. Hydrocortisone and promethazine were administered resulting in symptom resolution. She was observed for 8 hours and discharged.*

The second scenario involved the development of a dermatological reaction in the form of a rash. This scenario was represented by 44 cases, with the drugs involved being: amoxycillin; penicillin V; flucloxacillin; dextromethorphan / pseudoephedrine / guaiphenesin; cefaclor; chlorpheniramine / phenylephrine; amoxycillin / clavulanic acid; co-trimoxazole; cefaclor; loratadine; erythromycin; oxymetazoline; and lignocaine / benzalkonium chloride / allantoin. The causality classifications for cases allocated to this scenario were split evenly between the classifications of *probable* and *possible*. Twenty-one of the 44 cases were classified as preventable, 17 not preventable and in 6 cases preventability was unable to be determined. A clinical significance classification of *severe* was allocated to 4 cases, *moderate* to 21 cases and *mild* to 19 cases. The following brief description refers to a case allocated a causality classification of *probable* a preventability classification of *no* and a clinical significance classification of *severe*.

A 2 year old male with no significant past medical history presented to the emergency department with a 24 hour history of a rash that was increasing in size. He was unwell 8 days prior to attendance with a painful ear that was treated with amoxycillin / clavulanic acid. The patient had had this drug twice previously with no adverse sequelae. On the sixth day of treatment a rash the size of a 10-cent piece was noted on the patient's trunk. The rash continued to increase in size and, after review by his local general medical practitioner, the amoxycillin / clavulanic acid was ceased and promethazine was commenced. As the rash continued to worsen he was referred to the emergency department. On examination he was flushed, and febrile with multiple urticarial lesions of a purplish hue. A diagnosis of erythema multiforme was made. He was admitted for observation and the administration of antihistamines, and was discharged home once improved. The principal diagnosis was erythrema multiforme with amoxycillin / clavulanic acid allergy being noted as a second new diagnosis.

The final hypersensitivity scenario involved the development of serum sickness. This scenario encompassed 8 cases in which cefaclor was the drug implicated in 87.5% (7/8) of cases and cephalexin in the remainder. The *multidisciplinary panel* allocated a causality classification of *definite* in 4 cases and *probable* in 4 cases. A preventability classification of *yes* was determined in 3 cases, *no* in 4 cases and *unable* in the remaining case. A clinical significance classification of *moderate* was allocated to 7 cases with a classification of *mild* allocated to the remaining case. A brief description of a case classified as unpreventable with a causality classification of *definite* and a clinical significance classification of *moderate* follows:

> *A 2 year old female, with no significant past medical history, presented to the emergency department. In the 3 weeks prior to presentation she had received 3 course of antibiotics, 1 course of cefaclor for an ear infection, 1 course of an unidentified orange mixture for a foot infection, and finally a second course of cefaclor for an ear infection. Three days prior to attending the emergency department she developed a widespread urticarial rash over the whole body. The cefaclor was continued and the rash slowly disappeared. On the day of presentation she developed an urticarial rash along with red, swollen joints. A diagnosis of serum sickness secondary to cefaclor was made and the cefaclor was ceased. The patient was discharged home on prednisolone and dexchlorpheniramine.*

The only scenario to be included under the heading of gastrointestinal reactions involved the development of vomiting, diarrhoea or abdominal pain. Twenty-one cases were allocated to this scenario with amoxycillin / clavulanic acid, cefaclor, ferrous gluconate, erythromycin, amoxycillin, cephalexin, roxithromycin, penicillin V, co-trimoxazole, pyrantel and sennosides noted as the drugs implicated in the adverse reactions reported. The *multidisciplinary panel* determined a causality classification of *probable* for 10 cases and *possible* for 11 cases. Ten cases were deemed preventable, 10 cases unpreventable, with preventability unable to be

determined for the remaining case. A clinical significance classification of *moderate* was allocated to 4 cases with a classification of *mild* allocated to 17 cases. The following brief description representing this scenario was determined unpreventable and allocated causality and clinical significance classifications of *probable* and *mild* respectively:

> *A 3 year old female with no significant past medical history was diagnosed 6 days prior to attending the emergency department with pneumonia, which was treated with erythromycin. The cough and fever settled, and the patient had been afebrile for 5 of the 6 days prior to attendance. She presented to the emergency department, as her mother was concerned about the diarrhoea and anorexia that had occurred since the commencement of erythromycin and wondered whether the antibiotic should be continued. On examination the patient appeared well with no respiratory distress and a clear chest. A diagnosis of resolving / resolved pneumonia was made with the residual anorexia and mild diarrhoea deemed secondary to erythromycin. The patient's family was advised to continue the erythromycin as the course was due to finish in 2 days and the symptoms were not severe.*

There were three scenario types under the heading of immunisation reactions. The first scenario involved the development of fever and irritability and was represented by 19 cases. The vaccines implicated were Hib vaccine, Triple Antigen vaccine, and diptheria / tetanus / pertussis / hepatitis B vaccine. The *multidisciplinary panel* determined a causality classification of *probable* for 17 cases and *possible* for 2 cases. Eighteen cases were classified as not preventable, with the preventability unable to be determined for the remaining case. A clinical significance classification of *severe* was allocated to 1 case, *moderate* to 10 cases and *mild* to 8 cases. The following description, involving a case determined to be unpreventable with causality and clinical significance classifications of *probable* and *moderate* respectively, outlines this scenario:

> *A 2 month old female full-term baby with no significant past medical history presented to the emergency department with a reaction to an immunisation. She was immunised at 14:00 on the day of presentation with Hib, Triple Antigen and polio vaccines. Since being immunised the baby's mother reported her to be irritable, febrile and her feeding had slightly decreased. On examination the baby looked well and was afebrile. A slight bruise was seen at the immunisation site, but no inflammation was evident. Otherwise the baby was well. A diagnosis of reaction to vaccine was made and the baby was discharged home with paracetamol and promethazine.*

The second immunisation scenario involved the development of an immunisation site reaction. Hib and Triple Antigen were the vaccines implicated in this scenario which involved 6 cases. The *multidisciplinary panel* determined a causality classification of *definite* for 1 case, *probable* for 4 cases and *possible* for 1 case. All cases were classified unpreventable. A clinical significance classification of *severe* was allocated to 1 case, *moderate* to 2 cases and *mild* to the remaining 3 cases. The following case, which was determined to be unpreventable with causality and clinical significance classifications of definite and mild respectively, best represented this scenario:

> *A 5 year old male with a past history of hypoaldosteronism, controlled with fludrocortisone, presented to the emergency department. He had received preschool Triple Antigen vaccination 2 days prior to this attendance. On the day following immunisation his mother noticed swelling and warmth at the site of immunisation, so he was taken to his local general medical practitioner who prescribed flucloxacillin and promethazine. As the reaction was not improving he was brought to the emergency department where a diagnosis of an immunisation site reaction was made. The antibiotics were ceased and the patient was discharged.*

The final scenario involved the development of a rash associated with the administration of MMR vaccine in 6 of the 7 cases allocated to this scenario. Triple Antigen and Hib vaccines were involved in the remaining case. The *multidisciplinary panel* determined a causality classification of *probable* for 2 cases and *possible* for 5 cases. All cases were considered unpreventable. Four of the 5 cases were allocated a clinical significance classification of *moderate* with the remaining cases classified as *mild*. The following brief description of a case with a causality classification of probable and a clinical significance classification of moderate best represents this scenario:

> *A 1 year old female with no significant past medical history presented to the emergency department with an urticarial rash. The patient had her MMR vaccine on the day prior to admission. Later that day a red rash was noted on the back of her neck, which then spread to her trunk and arms. Prednisolone was prescribed by her local general medical practitioner resulting in a slight improvement in the rash. On examination she was afebrile with a general urticarial rash over the face, trunk and arms and slight swelling around her eyes. The patient's ears and throat were normal and her chest was clear with no wheeze. A diagnosis of allergy to vaccine was made and the patient was discharged on promethazine.*

The remaining 7 cases encompass a broad range of clinical scenarios ranging from tachycardia with salbutamol to occulogyric crisis with metoclopramide. Given the diversity of these cases they will not be explored in further detail.

4.2.4.7.6   Category Six

Category Six, where a DRP involved a drug-drug, drug-food or drug-laboratory test interaction, was not represented, as no cases were identified (See Table 4.4).

4.2.4.7.7   Category Seven

The individual drugs implicated in Category Seven, where a case was not receiving the prescribed drug, was represented by 25 cases (Table 4.15).

Table 4.15 Drugs implicated in Category Seven

Therapeutic Classification*	Drugs within classifications
Alimentary system - Laxatives	lactulose (1)[†]
Cardiovascular system - Antihypertensive agents	clonidine (1), enalapril (1)
- Cardiac inotropic agents	digoxin (1)
Central nervous system agents - Other central nervous system agents	dexamphetamine (1)
- Anticonvulsants	carbamazepine (2)
Analgesia - Combination simple analgesics	paracetamol / promethazine / codeine (1)
Endocrine and Metabolic Disorders - Insulin preparations	Insulin-biphasic (2), insulin-isophane (1), insulin-lispro (1)
Infections and Infestations - Penicillins	flucloxacillin (1)
- Other antibiotics and anti-infectives	nitrofurantoin (1)
Respiratory System - Bronchospasm relaxants	terbutaline (1)
- Bronchodilator aerosols and inhalations	salbutamol (1), salmeterol (2)
- Preventative aerosols and inhalations	beclomethasone (3), budesonide (2), sodium cromoglycate (3)
Skin - Topical corticosteroids	hydrocortisone (1), betamethasone (1), mometasone (1)
Alcohol, illicit or unidentified substances	Unidentified – white mixture (1)

*Classification is according to the indexing used by MIMS Annual 2000.[183]
[†]The number of cases in which the drug was involved is indicated in parenthesis.

Emergency department attendances associated with exacerbations of asthma formed the largest proportion of cases allocated to Category Seven. However, as no single disease state accounted for the majority of cases allocated to this category, the scenarios presented below cover a range of different disease states.

The first scenario involves limitations in knowledge leading to inappropriate medication use and was represented by 5 cases. The drugs implicated in these cases were terbutaline, budesonide, salbutamol, salmeterol and an unidentified white mixture. The mean age of cases was 6.6 years (median 5.2, ± SD 3.6). The *multidisciplinary panel* determined that each of the 5 cases had a causality classification of *possible* and each was considered preventable. A clinical significance classification of *moderate* was allocated to 3 cases with the remainder classified as *severe*. The following brief description best describes this scenario:

> *An 11 year male with a past medical history of chronic persistent asthma, diagnosed at 6 months of age, presented to the emergency department. He had been admitted to hospital 6 times as a result of his asthma, 1 admission was to the intensive care unit. One month prior to this attendance he was reduced from 1000mcg to 500mcg of fluticasone under medical supervision. At this time it was intended that the patient would commence salmeterol to act as a steroid sparing agent. The salmeterol was not commenced as the patient did not understand how to use this medication. The patient presented with a moderate exacerbation of asthma after a 2-day history of rhinorrhoea and increasing shortness of breath. He was treated with salbutamol, ipratropium and methylprednisolone which led to symptom resolution. He was discharged on salbutamol, prednisolone and fluticasone.*

The second scenario involved 5 cases, with dexamphetamine, beclomethasone, hydrocortisone, betamethasone, carbamazepine and paracetamol / promethazine / codeine being the drugs implicated. This

scenario involved parental cessation of the drugs in question. The mean age of cases allocated to this scenario was 4.8 years (median 3.7, ± SD 3.2). The *multidisciplinary panel* determined causality classifications of *definite* for 1 case, *probable* for 2 cases and *possible* for 2 cases. All cases were noted to be preventable, with a clinical significance classification of *severe* allocated to 3 cases, *moderate* to 1 case and *mild* to 1 case. The following description is of a case allocated a causality classification of *definite* and a clinical significance classification of *severe*:

> *A 5 year old male with a past history of asthma, diagnosed at 8-months of age, presented to the emergency department. He had been admitted to hospital numerous times in the past as a result of his asthma, but had recently improved with his last hospital admission 2 years prior to the emergency department attendance in question. As a result of this improvement, his beclomethasone dose was reduced from 800mcg daily to 400mcg daily under medical supervision. However, 1 month prior to this attendance his mother ceased the beclomethasone, and he had since had ongoing interval symptoms. He presented to the emergency department with an acute exacerbation of chronic persistent asthma. His symptoms resolved with treatment and he was discharged on 400mcg of beclomethasone daily, salbutamol when required and prednisolone for 3 days.*

The third scenario involved the patients not receiving the drugs involved as a result of losing the device by which the drug was to be delivered or not having a supply of the drug(s). This scenario involved 5 cases and the drugs were sodium cromoglycate, carbamazepine, and flucloxacillin. The mean age of cases allocated to this scenario was 4.4 years (median 4.0, ± SD 3.1). The *multidisciplinary panel* determined all cases to be preventable, with 4 allocated a causality classification of *probable* and 1 a classification of *possible*. A clinical significance classification of *severe* was determined for 2 cases with the remainder classified as *moderate*. The following brief description summarises the type of case included in this scenario:

A 2 year old male with a past medical history of epilepsy presented to the emergency department after experiencing a short general tonic clonic seizure. His epilepsy was normally controlled with carbamazepine, however, he had not received a dose for 3 days as his supply had run out. On examination he was found to be well, alert and active and he was discharged on carbamazepine.

The fourth scenario comprised 6 cases and involved non-adherence with one or more of the following drugs: insulin-isophane; insulin-lispro; insulin-biphasic; beclomethasone; and lactulose. The mean age of cases allocated to this scenario was 12.2 years (median 15.2, ± SD 6.6). The *multidisciplinary panel* determined a causality classification of *possible* for all but 1 of the cases. The remaining case was allocated a causality classification of *probable*. Four cases were determined to be preventable, with each case allocated a clinical significance classification of *severe*. A preventability classification was unable to be established for the final 2 cases, each of which were allocated a clinical significance classification of *moderate*. The following description outlines a case considered preventable with a causality classification of *probable*:

A 17 year old male with a past medical history of poorly controlled diabetes, multiple past hospital admissions for diabetic ketoacidosis, intermittent microalbuminuria and background retinopathy, attended the emergency department after a 2 week history of cough and headaches. During this time he had been eating only 1 meal per day, had reduced his insulin-biphasic dose by half, and had been omitting his morning dose of insulin-biphasic. He presented with diabetic ketoacidosis which, upon admission, was managed with intravenous fluids and an insulin infusion. Subsequently, good control was achieved with reinstitution of his normal insulin-biphasic dose, and he was discharged.

The fifth scenario involved 2 cases with the patients refusing to have the medication in question administered. Nitrofurantoin and mometasone were the drugs involved. The *multidisciplinary panel* determined that the 2 cases were preventable and allocated a causality classification of *possible* to each case. Clinical significance classifications of *severe* and *moderate* were established respectively for the 2 cases, with the patients involved being 9 and 3 years of age respectively. The following scenario describes the case allocated a clinical significance classification of *severe*:

> *A 9 year old female with a past medical history of persistent eczema requiring daily treatment presented to the emergency department. Her eczema had flared in the 2 weeks prior to attendance, as over that time she had refused to use her mometasone cream along with her bath oils and moisturisers, due to stinging. On examination in the emergency department she had extensive red lichenified eczema over her legs. She was subsequently admitted for treatment with wet dressings and antibiotics, along with her normal medications, and was discharged upon resolution of the acute symptoms.*

The final scenario encompasses 2 cases and involved a double dose of the drugs in question being administered. The drugs were digoxin, enalapril or clonidine. Both cases were determined preventable by the *multidisciplinary panel* and were allocated a causality classification of *definite*. A clinical significance classification of *severe* was allocated to the first case with a classification of *mild* determined for the second case. The cases were 3 and 7 years of age respectively. The following brief description refers to the second case outlined above:

> *A 7 year old male with a past medical history of attention deficit hyperactivity disorder presented to the emergency department after being administered a double dose of clonidine. He takes the clonidine, along with methylphenidate, for his attention deficit hyperactivity disorder. He was given his usual dose of clonidine at*

18:00 with a second dose accidently repeated at 20:00. On examination he was drowsy with a pulse rate of 80 and a standing blood pressure of 90/50 mmHg. No other cerebellar disturbances were noted and an electrocardiogram showed no abnormalities. He was observed for 3 hours in the emergency department and later discharged.

4.2.4.7.8   Category Eight

Category Eight, where a case had taken a drug for which no valid medical indication exists, was represented by 93 cases (Table 4.16).

Table 4.16 Drugs implicated in Category Eight

Therapeutic Classification*	Drugs within this classification
Alimentary system	
- Hyperacidity, reflux and ulcers	ranitidine (1)[†]
Cardiovascular System	
- Antihypertensives	clonidine (2), verapamil (1)
- Beta-adrenergic blocking agents	propranolol (1)
- Antiangina agents	diltiazem (1)
- Antimigraine preparations	pizotifen (1)
Central Nervous System	
- Sedative, Hypnotics	temazepam (4), flunitrazepam (1)
- Antianxiety agents	diazepam (3)
- Antipsychotic agents	clozapine (1), thioridazine (1)
- Antidepressents	fluoxetine (1), paroxetine (1), moclobemide (2), imipramine (1), venlafaxine (1), sertraline (1)
- Movement disorders	levodopa /carbidopa (1)
- Other central nervous system agents	dexamphetamine (1), methylphenidate (2)
- Anticonvulsants	carbamazepine (1), clonazepam (1)
- Antiemetics, Antinauseants	metoclopramide (1)
Analgesia	
- Simple analgesics and antipyretics	aspirin (2), paracetamol (28)
- Combination simple analgesics	paracetamol / codeine / promethazine (1), paracetamol / codeine / doxylamine (1), paracetamol / codeine (4)
Musculoskeletal System	
-Nonsteroidal anti-inflammatory agents	ketoprofen (1), diclofenac (1), naproxen (3), phenylbutazone (1)
-Rubefacients, topical analgesics / NSAIDs	camphor / menthol / eucalyptus oil / methyl salicylate (1)
Endocrine and Metabolic Disorders	
- Adrenal steroid hormones	prednisolone (1)

Drugs implicated in Category Eight (continued)

Endocrine and Metabolic Disorders (continued)	
- Insulin preparations	insulin-neutral (1)
- Hypoglycaemic agents	gliclazide (1)
Infections and Infestations	
- Penicillins	amoxycillin (1)
Neoplastic Disorders	
-- Antimetabolites	cyclophosphamide (1)
Respiratory System	
-Expectorants,antitussives, mucolytics, decongestants	Paracetamol / pseudoephedrine / codeine (1), brompheniramine / phenylephrine (3), pseudoephedrine (1), dexchlorpheniramine / pseudoephedrine (2), brompheniramine / phenylephrine / dextromethorphan (1), chlorpheniramine / phenylephrine (3), dexchlorpheniramine / phenylephrine (1)
- Bronchospasm relaxants	salbutamol (1)
Allergic Disorders	
- Antihistamines	cyproheptadine (1)
Skin	
- Other dermatological products	minoxidil (1)
Surgical preparations	
- Anaesthetics – local and general	lignocaine / phenoxyisopropanol / cetrimide / chlorhexidine (1)
Contraceptive agents	
- Combined oral contraceptive agents	ethinyloestradiol / levonorgestrol (1)
Vitamins and Minerals and other Nutritional Supplements	ferrous sulphate (3)
Unlisted	eucalyptus oil (4), doxylamine (1), timolol (1), calamine / lignocaine / camphor / glycerol (1), choline salicylate / cetalkonium chloride, chlorbutol / ortho-dichlorobenzene, para-dichlorodibenzene, arachis oil (1), phenolphthalein (1) senega / ammonia (1), menthol / eucalyptus oil / camphor (1)
Alcohol, illicit or unidentified substances	Alcohol (3), heroin (3), amphetamine (3), marijuana (3). Unidentified (4)

*Classification is according to the indexing used by MIMS Annual 2000.[183]

[†]The number of cases in which the drug was involved is indicated in parenthesis.

A diverse range of drugs were implicated in cases allocated to Category Eight. A number of common scenarios can be determined when the cases allocated to this category are split into two age groups: those less than or equal to 5 years of age; and those greater than 5 years of age. It should be remembered that a causality classification of *definite* was automatically allocated to each case fitting the criteria for Category Eight. As outlined in Section 3.5, the *multidisciplinary panel* recommended that preventability not be assessed for the cases allocated to this category as the majority involved accidental or intentional poisonings.

Fifty-six cases were in the first group, 51.8% (29/56) of which were males. Cases had a mean age of 2.3 years (median 2.2 years, ± SD 1.2). A total of 58 drugs were ingested by the 56 cases identified, of which 32.8 % (19/58) were prescription drugs. The six most common drugs ingested in this age group were paracetamol (13)*, brompheniramine / phenylephrine (3), chlorpheniramine / phenylephrine (3), dexchlorpheniramine / pseudoephedrine (2), eucalyptus (2) and moclobemide (2). There are three scenarios that can be seen for these cases.

The first involved more than one medication being accidentally ingested. The scenario involved 2 cases and the drugs propranolol, ethinyloestradiol / levonorgesterol, chlorphenaramine / phenylephrine and amoxycillin. A clinical significance classification of *moderate* was allocated to one case with a classification of *mild* allocated to the second. The following brief description best describes the scenario in question:

> *A 22 month old female with no significant past medical history presented to the emergency department after an accidental ingestion of her mother's propranolol and ethinyloestradiol / levonorgestrol tablets. The tablets were left on the bench as her mother was just about to take them. She was given activated charcoal in the emergency department and observed for 4 hours.*

---

* The number of cases in which the drug was involved is indicated in parenthesis.

> *She remained clinically well over the observation period and was discharged.*

The second scenario involved 3 cases and concerned the accidental administration of the wrong drug by parents or guardians. Senega / ammonia, eucalyptus oil and menthol / eucalyptus oil / camphor were the drugs implicated in this scenario. One of the 3 cases was allocated a clinical significance classification of *severe* with the remaining cases classified as *mild*. The following description is one of the cases classified as *mild*:

> *A 9 month old male with no significant past medical history presented to the emergency department after an accidental ingestion of senega / ammonia cough mixture. Prior to presentation he had symptoms relating to teething, and a rash. At 03:00 on the morning of presentation his mother accidentally administered 2.5mLs of senega / ammonia cough mixture instead of promethazine. No vomiting had occurred since the ingestion. It was determined that the dose ingested was not toxic and the patient was discharged.*

The final scenario involved 51 cases, and the accidental ingestion of one drug for which there was no valid medical indication. The drugs involved were diverse with the 6 most common drugs listed previously providing the best overview of the drugs implicated. Of interest, the location from which a patient obtained the medications listed above was noted in the medical histories of only 9 cases. In these 9 cases the drugs involved in the accidental ingestions were obtained from the fridge (2 cases), a table (5 cases), the bathroom (1 case) and from a pocket of a suit (1 case). Nineteen cases in this scenario were allocated a clinical significance classification of *mild*, 25 *moderate* and 7 a classification of *severe*. The following description outlines a case with a clinical significance classification of *moderate*.

> *A 1 year old female with no significant past medical history presented to the emergency department after an accidental*

ingestion of metoclopramide tablets. The patient was found at 11:30 with a packet of metoclopramide and it was estimated that she had possibly consumed 3 to 4 of these tablets. On examination she was found to be alert and well with no vomiting or diarrhoea. Activated charcoal was administered and she was subsequently observed for 6 hours. She remained clinically well over the observation period and was discharged.

Thirty-seven cases fell into the older age group, that is, patients greater than 5 years of age. Of the 37 cases 16.2% (6/37) were males. Cases had a mean age of 14.9 years (median 15.6 years, ± SD 2.7). The mean number of drugs taken was 1.7 (median 1.0, ± SD 1.2). The 8 most common drugs involved were: paracetamol (16); paracetamol / codeine (4); ferrous sulphate (3); temazepam (3); alcohol (3); heroin (3); marijuana (3); and amphetamines (3). It should be noted that 34.8% (24/69) of these drugs were prescription medications, 44.9% (31/69) were non-prescription medications with the remainder falling under the category of alcohol, illicit or unidentified substances. Two scenarios were drawn from this age group.

The first scenario involved cases between 6 and 10 years of age and involved 4 cases ingesting or being administered a drug in error. The drugs implicated in this scenario were eucalyptus oil, pseudoephedrine and camphor / menthol / eucalyptus oil / methyl salicylate. Two of these cases were allocated a clinical significance classification of *severe* with the remaining cases allocated a classification of *mild*.

A 6 year old male with no significant past medical history presented to the emergency department after ingesting a pseudoephedrine tablet thinking it was a lolly. The tablet was ingested at 08:00 on the morning of presentation. Other than the patient being more active than normal, no adverse effects were noted. Due to the large dose of pseudoephedrine ingested it was recommended that he be observed for 4 to 6 hours post ingestion.

> *At 4 hours post ingestion he remained clinically well and was discharged.*

The final scenario for this age group involved 33 cases and the intentional ingestion of 1 or more of the following drugs: paroxetine; paracetamol; aspirin; diclofenac; marijuana; paracetamol / codeine; heroin; dexamphetamine; naproxen; amphetamine; temazepam; imipramine; diltiazem; clonidine; amoxycillin; fluoxetine; gliclazide; alcohol; insulin-neutral; ferrous sulphate; cyproheptadine; carbamazepine; doxylamine; venlafaxine; methylphenidate; thioridazine; prednisolone; paracetamol / pseudoephedrine / codeine; and sertraline. Of these cases, 24 were allocated a clinical significance classification of *severe*, 5 *moderate* and 4 *mild*. The following is an example of the type of cases allocated to this scenario:

> *A 17 year old female with a past medical history of depression and 2 drug overdoses presented to the emergency department with a multiple drug overdose. She took the day off school today as she was not feeling well. Her mother came home from work to find her lying down with open packets of paracetamol, amoxycillin and fluoxetine easily visible. On presentation to the emergency department the patient was subdued, however, she smiled at jokes and a medical examination was normal. Activated charcoal was administered and paracetamol levels taken. The paracetamol levels recorded at 4 and 6 hours post ingestion were in the non-toxic range. She was admitted for observation and a psychiatric review and discharged the next day with follow up organised.*

4.3 Discussion

The extent of emergency department attendances associated with DRPs had not previously been studied within the Australian paediatric population. It is apparent from the results reported in this thesis that such DRPs are important contributors to morbidity within this population. This is highlighted by the fact that 3.1% (95% CI 2.7 - 3.5%) of eligible emergency department

attendances were determined to be associated with DRPs at RCH, 5.0% (95% CI 3.0 – 7.0%) at GH and 6.4% (95% CI 3.1 – 9.7%) at BH.

The fact that there were no significant differences in the frequency of emergency department attendances associated with DRPs across the three hospital sites is at odds with reports in the literature.[68, 69] These reports have proposed that the frequency of DRPs may be higher in larger academic tertiary care hospitals compared to hospitals which provide only primary and secondary care.[68, 69]

There were, however, significant differences in the incidence rates reported for the three hospitals. The results reported in this chapter indicated that the rate of emergency department attendances associated with DRPs was significantly higher for paediatric persons within the BH catchment area, followed by the RCH catchment area, and lowest for the GH catchment area. While these results may indicate that the paediatric populations residing within the catchment areas of the three hospitals are significantly different with respect to the risk of emergency department attendances associated with DRPs, caution should be used before accepting this interpretation of these results. The relatively short data collection periods at the hospitals, and the unknown influence of seasonal variations on the occurrence of emergency department attendances associated with DRPs, are the primary reasons for caution. It can be seen in Appendix Five that the incidence rates reported were calculated by extrapolating data obtained to a one-year period. Therefore, the fact that data collection at each site was conducted over less than a continuous one-year period, and at different times of the year, may have influenced the incidence rates reported.

Prior to combining data from the three hospital sites it was evident that there were significant differences between the eligible patient populations in terms of both gender and age. These differences were noted as unlikely to be clinically significant, for the following reasons. Firstly, the frequency of emergency department attendances associated with DRPs over the three hospital sites was not found to be significantly different. Secondly, the

significant differences in both age and gender were not noted consistently at an individual hospital level across the three sites. Thirdly, if the mean ages for patients attending RCH (3.9 and 4.1 years), GH (5.6 years) and BH (5.2 years) are considered, it is very unlikely that there would be any significant pharmacokinetic and pharmacodynamic differences among the three eligible patient populations.[17] Importantly, it can be argued that the differences inherent in the patient populations utilising the three emergency departments may increase the validity of extrapolating findings to the broader paediatric emergency department population when the results are combined.

Combined data from the three hospitals demonstrated 3.3% (95% CI, 2.9 – 3.7%) of paediatric emergency department attendances were associated with DRPs. Comparisons with other studies are difficult because there are no studies that investigate emergency department attendances associated with DRPs specifically within the paediatric population. As indicated in Chapter One, extremely limited paediatric data are able to be extracted from two published studies involving both adults and paediatric patients.[45, 55] Only one of these studies provides data on the frequency of paediatric emergency department attendances associated with DRPs, with the frequency reported to be 1.4%.[45] The retrospective nature of the study, along with the exclusion of DRPs associated with illicit drug use, may have resulted in the lower frequency reported, compared to the present study.[45]

Comparisons with studies conducted within the adult population are also difficult due to differences in definitions, patient populations and study methodologies. Taking these factors into consideration, seven studies investigated the frequency of emergency department attendances associated with DRPs in the adult population.[36-38, 45, 55-57] The frequencies reported by these studies ranges from 1.7% to 28.1%, with five of the seven studies reporting the frequency to range between 1.7% and 4.3%.[36, 38, 45, 55, 56] The 3.3% (95%CI 2.9 – 3.7%) reported in this thesis, therefore falls within the range reported in the adult population.

A more appropriate comparison may be with the only Australian study undertaken in the area, which was conducted by Galbraith.[57] In the Galbraith study it was reported that 7.36% of emergency department attendances in adults were associated with DRPs.[57] The lower frequency of DRPs determined in the research presented in this thesis when compared to that reported by Galbraith may be attributed to differences in study methodology. This opinion is based on the fact that both Galbraith and a separate study conducted by Tafreshi et al conducted patient interviews at the time of attendance.[37, 57] The frequency of emergency department attendances associated with DRPs was found to be higher in these two studies,[37, 57] when compared to those, like the research presented in this thesis, that did not undertake such interviews[36, 38, 45, 55, 56]. It can therefore be hypothesised that patient interviews at the time of attendance may increase the likelihood of detection of DRPs.

The finding that the proportion of males identified as cases in this thesis was significantly less than that of the eligible population highlighted the issue of gender as a possible risk factor. However, the fact that significant differences were not identified in individual BH or GH data casts doubt on this interpretation. Limited discussion regarding gender as a risk factor is available in the emergency department literature, although in the one study that specifically comments on this topic, no gender related differences were identified.[36]

The age of cases identified in the research presented in this thesis was found to be significantly higher than that of the eligible patient population. However, as reported for data relating to gender, this finding was not consistent at the individual hospital level. No comparisons can be drawn with the paediatric emergency department data reported in the literature, because similar information is not available from the two studies that provide limited data on paediatric patients.[45, 55]

The finding that Category Five, where an ADR had occurred, was the most common DRP category encountered concurred with paediatric data extracted

from a study conducted by Schneitman-McIntire et al,[55] and three studies involving adults[36, 37, 55]. However, other adult studies reported non-adherence,[38, 45] or accidental and intentional poisonings to be the most common DRPs[56, 57]. It is of note that data collection for three of the four latter studies was conducted retrospectively.[38, 45, 56] The higher number of ADRs detected in the prospective studies as compared to those conducted retrospectively may indicate that ADRs are difficult to detect retrospectively.

Whilst there was agreement about the most common DRP in paediatrics, the relative frequencies of other DRPs varied. Schneitman-McIntire et al reported the underuse of medication as the second most common problem encountered with no further details provided.[55] This finding contrasts with the research presented in this thesis as Category Eight and Category Two were the second and third most common DRPs identified respectively. Such variations in the type of DRPs identified can be attributed to differences in definitions because Schneitman-McIntire et al did not include the concepts of Category Eight and Category Two in their definition of DRPs.[55] In concordance with the Schneitman-McIntire study,[55] the pattern of DRPs found in this thesis was not evident in the three studies conducted within the adult population that reported ADRs to be the most common problem detected[36, 37, 55]. However, as highlighted by comparisons with the Schneitman-McIntire et al study, variances in the study definitions utilised reduce what can be inferred from comparing these studies.[55]

In determining the validity of the state wide extrapolations it was found that the extrapolations made may overestimate the frequency of emergency department attendances associated with DRPs. This conclusion was reached after comparing the extrapolation made with medication poisoning* data for children 0 to 4 years of age, extracted from the Victorian Emergency Minimum Dataset. The results of a study conducted by Routley et al may be considered relevant at this point.[32] They reported that it is more likely that

---

* It should be recalled that medication poisonings are defined as any poisoning that involves drugs, excluding alcohol or illicit drugs. Medication poisonings can therefore be considered one of the types of DRPs allocated to Category Eight.

the Victorian Emergency Minimum Dataset underestimates the actual number of medication poisonings, because under-reporting is a substantial problem at some of the major hospitals included in the dataset.[32] This point was highlighted by the authors comparing the total number of poisoning[†] related hospital admissions contained in the Victorian Emergency Minimum Dataset with the number recorded in the Victorian Inpatient Minimum Dataset.[32] Only 42.3% of the poisoning admissions recorded in the Victorian Inpatient Minimum Dataset were identified in the Victorian Emergency Minimum Dataset. The level of under-reporting indicated by Routley et al is very similar to the 44.7% estimated in this chapter.[32] It is therefore most likely that the state wide extrapolation made in the research presented in this thesis has not overestimated the scope of the problem.

Choonandra et al indicated that it is important to determine both the extent and preventability of adverse events detected.[95] The finding that 3.3% (95% CI 2.7 – 3.5%) of eligible paediatric emergency department attendances across the three hospital sites were associated with DRPs provides evidence as to the extent of this problem. With respect to preventability, excluding cases allocated to Category Eight, 51.3% of such attendances were determined to be preventable. Although the corresponding paediatric data are not available, studies conducted within the adult population report the preventability of emergency department attendances associated with DRPs to range from 66% to 70.4%.[37, 38] The 51.3% reported in this chapter is therefore lower than that reported in adult studies. A possible factor contributing to this difference is the high use of vaccines within the paediatric population. The Australian Vaccination Schedule stipulates the standard vaccines required for both the paediatric and adult populations, the vast majority of which are administered to paediatric patients.[186] The largely unpreventable nature of the ADRs to these standard paediatric vaccinations that were reported in this thesis may therefore have contributed to the lower proportion of preventable DRPs identified.

[†] This figure includes both medication and non-medication related poisonings.

It has been reported that parents of paediatric patients often utilise paediatric emergency departments in a similar manner to ambulatory care services.[187] The results presented in this thesis may indeed reflect this, because a higher number of DRPs reported in this thesis were allocated a clinical significance classification of *mild* when compared with two studies conducted within the adult population (35.7% versus 18% and 4.2% respectively).[37, 38] It can therefore be hypothesised that adults may be less likely to present to the emergency department as a result of mild DRPs as compared to paediatric patients. If this is the case, the results presented in this study may have the advantage of providing a better reflection of the type of DRPs occurring within the community. An alternative hypothesis, however, is that the reported differences in drug utilisation patterns between paediatric and adult populations were the primary reason for the variance in results reported.[58, 84] The basis of this hypothesis is that the proportion of cases classified as *moderate*, meaning drug therapy was utilised for symptom resolution, in the research presented in this thesis was lower than that reported for the two adult studies (42.1% versus 66% and 56.3% respectively).[37, 38]

With respect to the mean number of drugs taken by cases identified in the research presented in this thesis, comparable paediatric data are not available. Data are however available from the adult population, with one study reporting the mean number of drugs per case to be 1.9 ($\pm$SD 1.6), a figure similar to that reported in this study.[56] Given that a calculation of the mean is sensitive to outlying values, it maybe more appropriate to make comparisons with the median number of medications taken. A study conducted by Schneitman-McIntire et al reported that a median of 3 prescription and non-prescription medications were taken by patients (a figure that increases to 5 if only patients greater than 65 years were considered).[55] Hence, the median number of medications taken by the paediatric cases reported in this chapter was less than the number taken by their adult counterparts experiencing DRPs. Given the lower median number of medications it can be hypothesised that paediatric patients do not need to be on a high number of medications to be at a similar risk of DRPs to their adult counterparts.

Comparisons with paediatric data relating to the types of drugs implicated in DRPs are unable to be made, because such data are unable to be extracted from the limited paediatric data available.[45, 55] Comparisons can be made with studies conducted within the adult population, and in doing so, a divergence in the drugs implicated in DRPs was found between the two populations.[38, 45, 56] For example, albuterol (salbutamol), insulin, warfarin, phenytoin, prednisolone and glyburide (glibenclamide) were listed as the drugs most frequently implicated within the adult population studied by Dennehy et al, quite unlike the drugs reported in this thesis.[38] These findings support the inference made by Mitchell et al that differences in disease states and drug therapy exist between the adult and paediatric population.[61, 69]

The importance of providing qualitative data describing the nature of DRPs has been highlighted in the literature.[188] The scenarios presented in this thesis highlight areas for further discussion. In particular issues such as antibiotics for viral infections, the use of medications not listed as first line therapy or considered ineffective, along with too little or too much of a correct drug prescribed, highlight the difficulties encountered in caring for paediatric patients. The types of ADRs identified, along with issues such as limitations in knowledge and parental cessation of medication, further highlight these difficulties. The broader implications, which arise from the observations that the majority of the DRPs associated with these issues were considered preventable, will be addressed in Chapter Eight.

Although the preventability of cases allocated to Category Eight was not determined, the scenarios and the types of drugs implicated in these scenarios can be used to identify possible factors to prevent such DRPs. This will be done in Chapter Eight.

4.4 Conclusions

The results presented in this chapter make a contribution towards addressing the information deficit on DRPs in the paediatric population. This has been achieved by providing the first data on emergency department attendances

associated with DRPs in the Australian paediatric population. The results presented indicate that the frequency of such events is similar to that reported in the adult population, signifying that paediatric DRPs merit further investigation. In comparison with the adult population, preventability data suggests that it should be possible to reduce the frequency of DRPs in paediatrics. However, the differences in the drugs implicated in DRPs between the two populations indicate that the areas to be targeted for prevention strategies may differ.

5 Hospital admissions associated with DRPs in paediatrics

Studies investigating hospital admissions associated with DRPs have been conducted widely within the adult population. By comparison, there is a paucity of information available for the corresponding paediatric population. Hospital admissions associated with DRPs may represent DRPs of increased clinical significance. Information pertaining to the nature and extent of such DRPs is therefore imperative to determine the consequences of DRPs in this patient group. This second stream of data collection was undertaken to collect this information by investigating the frequency and characteristics of hospital admissions associated with DRPs within the paediatric population of three hospitals.

In this chapter the particulars of data collection in the three hospitals are presented in Section 5.1. It should be noted that the methodologies utilised to determine causality, preventability and clinical significance, along with the independent panel review process were outlined in Chapter Three. The results section details the extent and characteristics of hospital admissions associated with DRPs within the paediatric population investigated. A brief discussion follows which aims to place the results presented in context with comparative studies reported in the literature. A full discussion on the broader implications of the results presented in this chapter is provided in Chapter Eight.

5.1 Methods

5.1.1 Eligibility

All unplanned paediatric medical patients admitted to RCH, GH or BH over the periods of data collection were considered for inclusion in the research presented in this thesis. The term medical patient, in the context of this

stream of data collection, was defined as any patient admitted to a ward at RCH, GH or BH, excluding those admitted as trauma or oncology patients.*

5.1.2 Inclusion criteria

A hospital admission was considered a study case if an association between the hospital admission and a DRP was established, but was not considered a study case if such an association could not be established.

5.1.3 Data collection

The investigator and ward pharmacists screened eligible patients admitted to hospital using a process that involved the completion of a checklist if an admission was deemed to be possibly associated with a DRP. A copy of the checklist is provided in Appendix Seven. The investigator conducted a review of hospital admission preliminary diagnoses on each consecutive day of data collection to supplement the screening process. A preliminary review of the medical histories of patients identified was then conducted by the investigator. If, at the end of this preliminary review, an identified patient possibly fulfilled inclusion criteria, admission details were recorded in a specially designed Microsoft Access 97 (Microsoft Corporation, Redmond, WA, USA) database to allow subsequent analysis.

It should be noted that the emergency departments were not considered wards of the hospitals. Patients attending or admitted to the emergency department only, over the periods of data collection specified in this chapter, were not included in the research reported in this thesis.

5.1.4 Multidisciplinary panel review

The *multidisciplinary panel* reviewed information collected for each patient identified and established the likelihood of an association between the hospital admission and a DRP. Where such an association was not

---

* The operational definitions for trauma and oncology patients are provided in Appendix One.

established, or where a classification of *unsure* was made after discussion between two panel members, the patient was excluded. Where an association was established, cases were allocated to a DRP category. A causality classification was then ascertained for each case by the *multidisciplinary panel* using standardised criteria (See Section 3.4.1). Using the criteria set out in Section 3.5, a preventability classification was established by the panel. The criteria summarised in Section 3.6.2 were utilised to determine a clinical significance classification.

5.1.5 Data analysis

The data were analysed using the Statistical Package for the Social Sciences (SPSS) for Windows version 10 (SPSS Inc, Chicago, IL, USA). Differences in gender distributions were investigated using a Chi-Square Test. The Mann-Whitney U Test was utilised to establish if significant differences in age existed between cases identified and the eligible population. The Kruskal-Wallis H Test was used for making age related comparisons between the eligible patient population of the three hospitals. A significance level of 0.05 was selected for all tests. The 95% confidence intervals (95% CI) for frequencies reported were determined using confidence intervals for a proportion.[180] Confidence intervals for incidence rates calculated were determined using a Poisson distribution.[181]

5.2   Results

5.2.1 Royal Children's Hospital

An 18-week period of data collection was conducted at the RCH from the 11 May 1998 to 13 September 1998. Over this period 11,073 patients were admitted to the hospital, of which 2,745 met eligibility criteria. Eligible patients were predominantly male (58.7%, 1596/2745) with a mean age of 3.9 years (median 2.0 years. ±SD 4.5).

One hundred and fifty seven admissions possibly associated with DRPs were identified using the screening process outlined in Section 5.1.3. Thirty-two of the 157 patients were excluded by the *multidisciplinary panel*, with 6 patients subsequently excluded after being classified as *unsure*. The *multidisciplinary panel* determined that 119 cases had hospital admissions associated with DRPs. Of these, the proportion of males was not significantly different to that of the eligible population ($p = 0.1554$). The mean age of cases was 8.6 years (median 8.7 years, $\pm SD$ 6.2). The age of cases was significantly higher than that of the eligible population ($p < 0.001$). Drug related problems identified were not associated with any deaths, although 7 cases were admitted to the intensive care unit.

The frequency of admissions associated with DRPs was determined to be 4.3% (95% CI 3.5 – 5.1%). A flow chart of the case identification process is shown in Figure 5.1. The incidence rate was determined to be 441 per 100,000 paediatric persons / year (95% CI 402 - 484 per 100,000 paediatric persons / year).[*]

---

[*] The figures used to determine the incidence rate are presented in Appendix Five.

Figure 5.1 Flow chart of the case selection process for RCH, GH and BH
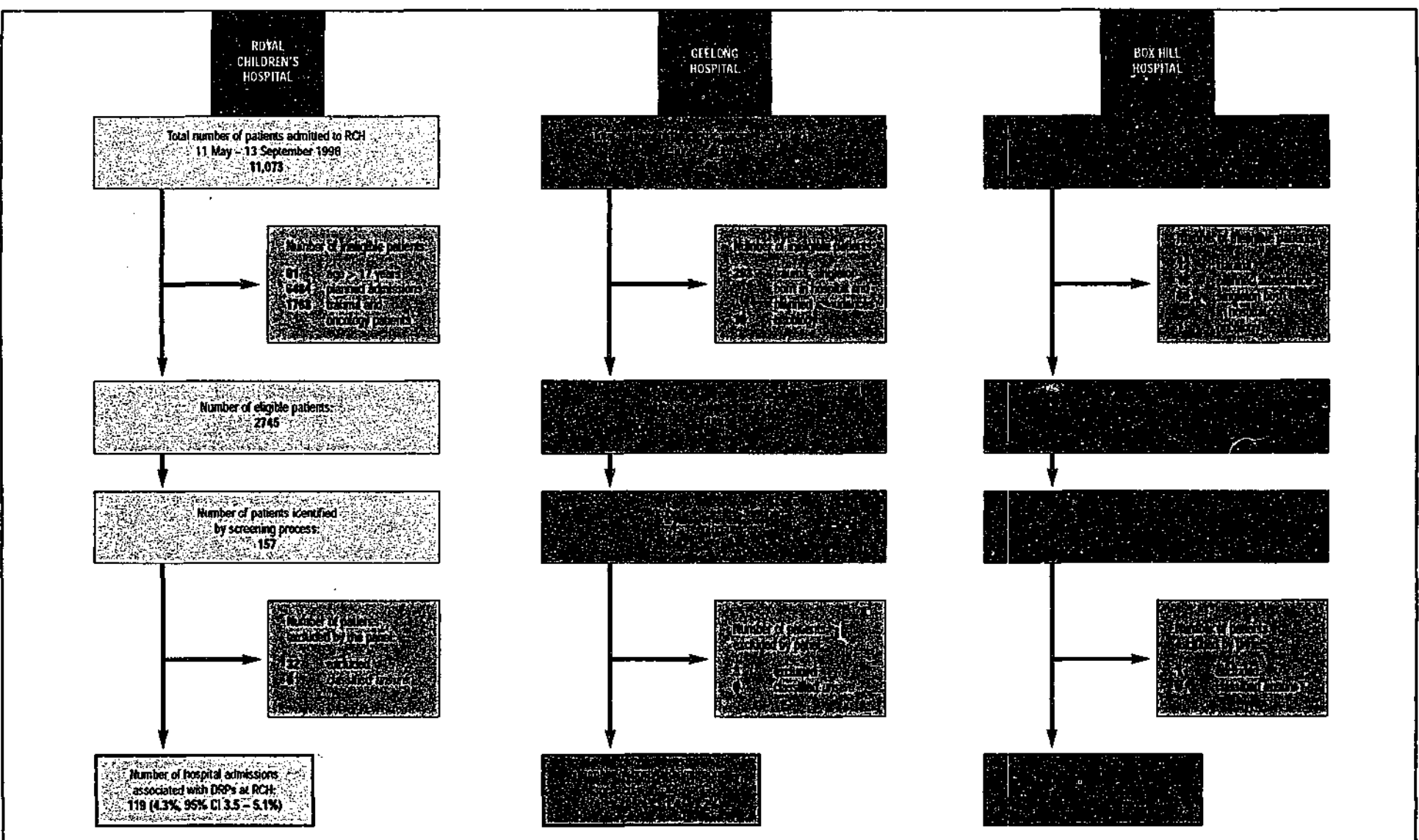
A summary of the RCH cases allocated to the eight DRP categories is provided in Table 5.1

Table 5.1 Summary of RCH cases allocated to the DRP categories

DRP category*		Frequency of Cases		Length of stay (days)		
		Number	%	mean	median	± SD
1	(drug indication)	5	4.2	1.6	2.0	0.6
2	(wrong drug)	2	1.7	3.0	3.0	2.8
3	(too little)	3	2.5	2.7	2.0	2.1
4	(too much)	2	1.7	7.5	8.0	6.4
5	(ADR)	28	23.5	2.3	1.0	2.0
6	(drug interaction)	1	0.8	Not applicable		
7	(non-adherence)	34	28.6	2.3	2.0	1.3
8	(poisoning)	44	37.0	1.5	1.0	1.2
Total		119	100.0	2.1	1.0	1.8

*Definitions for each of the DRP categories are provided in Section 3.3.

5.2.2 Geelong Hospital

Data collection at GH was conducted over a 4-week period from 7 June 1999 to 4 July 1999. Over this period 491 paediatric patients were admitted to GH, of which 188 met eligibility criteria. Males comprised 50.5% (95/188) of the eligible population. The mean age of eligible patients was 4.7 years (median 2.0 years, ±SD 5.3).

Eleven hospital admissions possibly associated with DRPs were identified via the screening process outlined in Section 5.1.3. The *multidisciplinary panel* considered 8 cases to have hospital admissions associated with DRPs. Of the 8 cases identified, 5 were males. Unfortunately, the numbers were too small to allow analysis of gender differences between the eligible population

and cases identified. The mean age of cases was 11.2 years (median 11.8, ±SD 5.7). The age of cases was significantly higher than that of the eligible population ($p = 0.002$). Drug related problems were not associated with any deaths, however 1 case was admitted to the intensive care unit.

The frequency of hospital admissions associated with DRPs over this 4-week period of data collection was determined to be 4.3% (95% CI 1.4 – 7.2%). A flow chart of the case identification process is shown in Figure 5.1. The incidence rate was determined to be 459 per 100,000 paediatric persons / year (95% CI 419 – 503 per 100,000 paediatric persons / year).[*]

A summary of the GH cases allocated to the eight DRP categories are provided in Table 5.2.

Table 5.2 Summary of GH cases allocated to the DRP categories

DRP category*		Frequency of Cases		Length of stay (days)		
		Number	%	mean	median	±SD
1	(drug indication)	0	0.0	Not applicable		
2	(wrong drug)	0	0.0	Not applicable		
3	(too little)	1	12.5	Not applicable		
4	(too much)	0	0.0	Not applicable		
5	(ADR)	1	12.5	Not applicable		
6	(drug interaction)	0	0.0	Not applicable		
7	(non-adherence)	4	50.0	3.0	3.0	2.2
8	(poisoning)	2	25.0	2.0	2.0	0.0
Total		8	100.0	2.3	2.0	1.7

*Definitions for each of the DRP categories are provided in Section 3.3.

---

[*] The figures used to determine the incidence rate are presented in Appendix Five.

5.2.3 Box Hill Hospital

Data collection was conducted at BH over a 1-week period from 8 November 1999 to 14 November 1999. Seventy-nine paediatric patients were admitted to BH over the period of data collection. Of these, 16 met eligibility criteria. Eligible patients were predominantly male (62.5%, 10/16) with a mean age of 5.7 years (median 2 years, ±SD 6.1).

One hospital admission possibly associated with a DRP was identified using the screening process. The *multidisciplinary panel*, using study criteria, excluded this patient and hence no cases were determined to have hospital admissions associated with DRPs over the data collection period at BH. A flow chart of the case identification process is provided in Figure 5.1.

5.2.4 Combined data for RCH, GH and BH

Combining data for the three hospitals, a total of 11,643 patients were admitted over the 23-week period of data collection. Of these, 2,949 met eligibility criteria. Eligible patients from the three hospitals were not significantly different in terms of gender ($p = 0.1149$) or age ($p = 0.079$).

One hundred and twenty seven cases were determined by the *multidisciplinary panel* to have hospital admissions associated with DRPs. Of these, the proportion of males was not significantly different to that of the eligible population (53.5%, $p = 0.4055$). The mean age of cases was 8.8 years (median 9.9 years, ±SD 6.2). The age of cases was significantly higher than that of the eligible population ($p < 0.001$). Drug related problems were not associated with any deaths, however, 8 cases were admitted to intensive care units.

The frequency of hospital admissions associated with DRPs was 4.3% (95% CI 3.6 – 5.0%). An incidence rate was not calculated for the combined

hospital data because the accuracy of the combined figure would be questionable.*

A summary of the total number of cases allocated to the eight DRP categories is provided in Table 5.3.

Table 5.3 Summary of the combined cases allocated to the DRP categories

DRP category[†]	Frequency of Cases		Age of cases (years)			Length of stay (days)		
	no.[‡]	%	mean	med.[‡]	±SD	mean	med.[‡]	±SD
1 (drug indication)	5	3.9	10.7	9.5	5.6	1.6	2.0	0.6
2 (wrong drug)	2	1.6	12.3	12.3	2.5	3.0	3.0	2.8
3 (too little)	4	3.1	6.9	6.4	7.3	2.3	2.0	1.9
4 (too much)	2	1.6	2.4	2.4	3.1	7.5	8.0	6.4
5 (ADR)	29	22.8	6.4	4.0	5.7	2.2	1.0	2.0
6 (drug interaction)	1	0.8	Not applicable			Not applicable		
7 (non-adherence)	38	29.9	11.2	12.7	5.3	2.4	2.0	1.4
8 (poisoning)	46	36.2	8.4	4.1	6.7	1.5	1.0	1.2
Total	127	100.0	8.8	9.8	6.2	2.1	1.0	1.7

[†]Definitions for each of the DRP categories are provided in Section 3.3.
[‡]Abbreviations: no. = number; med. = median.

The age of cases allocated to Category Seven was found to be significantly higher than that of cases allocated to Category Five ($p = 0.001$) or Category Eight ($p = 0.046$). Furthermore, the length of stay of cases allocated to Category Seven was found to be significantly higher than that of cases allocated to Category Eight ($p < 0.001$). No other statistically significant differences with respect to age or length of stay were found between categories containing 10 or more cases.

---

* See Appendix Five for further details.

5.2.4.1   Extrapolation of data

In order to extrapolate the data presented in this chapter to a state level, information on the number of paediatric hospital admissions was obtained. In Victoria, 144,656 paediatric patients were admitted to hospital from 1 July 1998 to 30 June 1999 (Personal communication, Penm R, Canberra: Australian Institute of Health and Welfare, August 2000). In light of the eligibility criteria outlined in Section 5.1.1, a large proportion of the patients admitted to hospital over this time period would not be considered eligible for inclusion if this study was conducted on a state wide basis. Therefore, an estimate of the number of eligible patients was made utilising the combined data from the three hospitals reported in Section 5.2.4. This estimate was based upon the fact that a total of 11,643 patients were admitted to the three hospitals over the period of data collection, of which 2,949 were considered eligible. Utilising the same proportions, it was estimated that of the 144,656 paediatric patients admitted to Victorian hospitals, 36,639 patients would be considered eligible for inclusion utilising study criteria.

In the previous section 4.3% of hospital admissions to the three hospitals were determined to be associated with DRPs. Extrapolating these results, 4.3% of the 36,639 admissions were potentially associated with DRPs. Hence, in Victoria, over the one-year period it was estimated that 1,579 paediatric patients were admitted to hospital with a DRP.

Going then to a national scale, there were 5,735,049 hospital admissions across all age groups for the same time period (Personal communication, Penm R, Canberra: Australian Institute of Health and Welfare, August 2000). Of these, 650,145 involved paediatric patients. It was therefore estimated that, on a national level 7,097 paediatric admissions were associated with DRPs.

In an effort to gauge the validity of the state extrapolation, data relating to medication poisonings* for children 0 to 4 years of age was obtained from the Victorian Inpatients Minimum Dataset for 1 July 1998 to 30 June 1999 (Personal communication, Stanthakis V, Melbourne: Monash University Accident and Research Centre, September 2000). This is a database which collects information from Victorian public and private acute care hospitals. Each record in the database represents an episode of care, and not necessarily one incident because a patient may be transferred between and within hospitals sites for various episodes of care, and will therefore be represented by more than one record. This is estimated to account for 10% of the database. Over this time period 575 paediatric patients in this age group were coded as having hospital admissions associated with medication poisonings. Ninty-nine of these were excluded because they were admitted to emergency departments but not to a ward of a hospital. In Section 5.2.4, 24 of the patients allocated to Category Eight were between 0 and 4 years of age, that is 18.9% (24/127) of the total cases. Hence, of the 1,579 paediatric admissions estimated to be associated with a DRP, 298 would be within this age range and coded as a medication poisoning, a figure that is 51.8% (298/575) of that reported in the Victorian Inpatients Minimum Dataset.

5.2.4.2   Causality classification

A causality classification of *definite* was determined for 42.5% of cases (54/127), *probable* for 24.4% (31/127) and *possible* for 33.1% (42/127). The causality classifications allocated to cases within the eight DRP categories are depicted in Table 5.4.

---

* The Victorian Inpatients Minimum Dataset defines medication poisonings as any poisoning that involves drugs, excluding alcohol or illicit drugs. Medication poisonings can therefore be considered one of the types of DRPs allocated to Category Eight.

Table 5.4 Causality classification for cases within the DRP categories

DRP category*	Causality Classification		
	Definite	Probable	Possible
1 (drug indication)	0	4	1
2 (wrong drug)	0	0	2
3 (too little)	0	1	3
4 (too much)	1	1	0
5 (ADR)	3	14	12
6 (drug interaction)	1	0	0
7 (non-adherence)	3	11	24
8 (poisoning)	46	0	0
Total	54 (42.5%)	31 (24.4%)	42 (33.1%)

*Definitions for each of the DRP categories are provided in Section 3.3.

5.2.4.3 Preventability classification

The preventability of each case, excluding those allocated to Category Eight was established. A preventability classification was therefore determined for 81 of the 127 cases. Of the 81 cases, 46.9% (38/81) were deemed preventable, 30.9% (25/81) not preventable and in 22.2% (18/81) preventability was unable to be determined (Table 5.5).

Table 5.5 Preventability classifications for cases within DRP categories

DRP category*	Preventability Classifications		
	Yes	No	Unable
1 (drug indication)	2	0	3
2 (wrong drug)	2	0	0
3 (too little)	1	2	1
4 (too much)	2	0	0
5 (ADR)	3	23	3
6 (drug interaction)	1	0	0
7 (non-adherence)	27	0	11
8 (poisoning)	Not applicable		
Total	38 (46.9%)	25 (30.9%)	18 (22.2%)

*Definitions for each of the DRP categories are provided in Section 3.3.

5.2.4.4   Clinical significance classifications

A clinical significance classification of *Category A* was established for 59.6% (63/127) of cases, with 21.3% (27/127) allocated to *Category B*, 29.1% (37/127) to *Category C* and no cases allocated to *Category D* (Table 5.6).

Table 5.6 Clinical significance classifications for cases within the DRP categories

DRP category*		Clinical Significance Classification			
		Category A < 24 hours	Category B 24-48 hours	Category C >48 hours &/ICU	Category D disable/death
1	(drug indication)	2	3	0	0
2	(wrong drug)	1	0	1	0
3	(too little)	2	1	1	0
4	(too much)	0	0	2	0
5	(ADR)	17	2	10	0
6	(drug interaction)	1	0	0	0
7	(non-adherence)	11	13	14	0
8	(poisoning)	29	8	9	0
Total		63 (59.6%)	27 (21.3%)	37 (29.1%)	0 (0.0%)

*Definitions for each of the DRP categories are provided in Section 3.3.

5.2.4.5 Multidisciplinary panel agreement

Inter-observer reproducibility for *multidisciplinary panel* members was measured using the Kappa statistic as outlined in Section 3.7.1. The Kappa statistic measures the strength of agreement between panel members, taking into account agreement that would occur by chance alone.

The strength of agreement between panel members when allocating DRP cases was found to be *moderate*, with a Kappa value of 0.545. It should be noted that for the purpose of data analysis the categories *no* and *unsure* were combined. This step was undertaken on the advice of a statistician for this one calculation only.

The strength of agreement between panel members when allocating a causality classification was found to be *fair*, with a Kappa value of 0.369.

The strength of agreement between panel members when allocating a preventability classification was found to be *moderate*, with a Kappa value of 0.488.

In 2 cases the DRP categories initially allocated by the *multidisciplinary panel* were altered so that the categories of these cases matched those of analogous cases. This was undertaken after panel consensus.

The intra-observer reproducibility results recorded for *multidisciplinary panel* members are presented in Appendix Six.

5.2.4.6   Drug classes involved in DRPs: an overview

A mean of 2.0 drugs (median 2.0 drugs, ±SD 1.4) per case were recorded to have been taken in the week prior to admission. This count included regular and non-regular* drugs along with documented over-the-counter and alternative medications. It should be noted that drug products containing multiple ingredients were considered as one entity in this count. The mean number of drugs per case for each category is shown in Table 5.7.

---

* Non-regular drugs included drugs taken on a when required basis along with drugs taken for which there was no valid medical indication.

Table 5.7 Mean total number of drugs per case for each DRP category

DRP category*		Mean	Median	± SD
1	(drug indication)	1.0	1.0	0.0
2	(wrong drug)	1.0	1.0	0.0
3	(too little)	1.5	1.5	0.6
4	(too much)	3.0	3.0	2.8
5	(ADR)	2.2	2.2	2.0
6	(drug interaction)	Not applicable		
7	(non-adherence)	2.2	2.2	1.0
8	(poisoning)	1.8	1.8	1.2

*Definitions for each of the DRP categories are provided in Section 3.3.

Of the 243 drugs recorded, 160 were specifically implicated in the 127 admissions associated with DRPs. An analysis according to the Therapeutic Classification of the drugs specifically implicated in the DRPs detected is indicated in Table 5.8, the individual drugs recorded within each classification are also listed.

Table 5.8 Drugs associated with DRPs by Therapeutic Classification

Therapeutic Classification*	Drugs within classifications
Alimentary System	
- Antidiarrhoeals	sulphasalazine (1)[†]
Cardiovascular System	
- Antihypertensive agents	clonidine (2), verapamil (1), nifedipine (1), enalapril (1)
- Beta-adrenergic blocking agents	propranolol (3), atenolol (1)
- Antiarrhythmic agents	flecanide (1)
- Antimigraine preparations	pizotifen (1)
Central Nervous System	
- Sedatives, hypnotics	nitrazepam (1), oxazepam (3), temazepam (1)
- Antianxiety agents	diazepam (4), alprazolam (1)
- Antipsychotic agents	thioridazine (1), olanzapine (1)
- Antidepressants	dothiepin (3), sertraline (1)
- Other central nervous system agents	dexamphetamine (1)
- anticonvulsants	sodium valproate (5), phenobarbitone (1), phenytoin (2), lamotrigine (2), clonazepam (1)
- Antiemetics, Antinauseants	metoclopramide (1), prochlorperazine (1)
Analgesia	
- narcotic analgesics	dextropropoxyphene (1)
- simple analgesics and antipyretics	paracetamol (6)
- combination simple analgesics	paracetamol / codeine / doxylamine (1), paracetamol / codeine (2)
Musculoskeletal System	
- Nonsteriodal anti-inflammatory agents	naproxen (1), mefenamic acid (1), ibuprofen (1), phenylbutazone (1)
- Muscle relaxants	orphenadrine (1)

Drugs associated with DRPs by Therapeutic Classification (continued)

Endocrine and Metabolic Disorders	
- Adrenal steroid hormones	prednisolone (1)
- Insulin preparations	insulin-neutral (5), insulin-isophane (6), insulin-biphasic (1), insulin-lispro (1)
- Hypoglycemic agents	glibenclamide (1), metformin (1)
Infections and infestations	
- Penicillins	flucloxacillin (7), procaine penicillin (1), penicillin V (1), amoxycillin (1) amoxycillin / clavulanic acid (1)
- Cephalosporins	cefaclor (1)
- Tetracyclines	minocycline (1)
- Macrolides	erythromycin (1)
- Other antibiotics and anti-infectives	teicoplanin (1), co-trimoxazole (2), trimethoprim (1)
- Antimalarials	chloroquine (1)
Immunology	
- Vaccines	haemophilus B conjugate (Hib) vaccine (1), diptheria / tetanus / pertussis (Triple Antigen) vaccine (3), measles / mumps / rubella (MMR) vaccine (1), acellular triple antigen '6 in 1' vaccine (1)
- Immunomodifiers	cyclosporin (1)
Respiratory System	
- expectorants, antitussives, mucolytics, decongestants	dextromethorphan / pseudoephedrine (1)
- Bronchospasm relaxants	aminophylline (1), theophylline (4), terbutaline (1), choline theophyllinate (1)
- Bronchodilator aerosols and inhalations	salbutamol (2), salmeterol (2)
- Preventative aerosols and inhalations	fluticasone (5), beclomethasone (17), sodium cromoglycate (3), budesonide (6)
Allergic Disorders	
- Antihistamines	promethazine (1)

Drugs associated with DRPs by Therapeutic Classification (continued)

Eye - Topical ocular anti-infective preparations	framycetin (1)
Skin - Topical corticosteroids	triamcinolone / neomycin / gramicidin / nystatin (2)
Surgical preparations - Anaesthetics – local and general	bupivicaine (1)
Contraceptive agents - Combined oral contraceptive agents	ethinyloestradiol / levonorgesterol (1)
Nutrition - anorectics and weight reducing agents	phentermine (1)
Vitamins, Minerals and other nutritional supplements	ferrous sulphate (1)
Unlisted items	calcium carbonate (1), echinacea (1), evening primrose oil (1), diphenhydramine (1)
Alcohol, illicit or unidentified substances	heroin (1), unidentified (3)
Total number of drugs specifically implicated in DRPs	**160**

*Classification is according to the indexing used by MIMS Annual 2000 and as such the same drug may appear under more than one Therapeutic Classification if different dose forms of the same drug are used for different indications.[183]
†The number of cases in which the drug was involved is indicated in parenthesis.

The 14 most frequently occurring drugs associated with DRPs were: beclomethasone; flucloxacillin; insulin-isophane; paracetamol; sodium valproate; insulin-neutral; budesonide; fluticasone; diazepam; theophylline; sodium cromoglycate; dothiepin; oxazepam; and Triple Antigen vaccine.

5.2.4.7   Drug classes involved in DRPs: DRP categories and scenarios
Common disease states and scenarios can be described for many of the cases allocated to the eight DRP categories. These will be presented in this section with the aim of elucidating the nature of the cases allocated to these categories.   The case descriptions for the scenarios put forward are

summaries of the documentation contained within the medical histories of cases presented. It should be noted that more extensive documentation was utilised by *multidisciplinary panel* members to classify cases.

5.2.4.7.1   Category One

The individual drugs specified in Category One, where drug therapy is required but the case is not receiving a drug for that indication, are listed according to Therapeutic Classification in Table 5.9.

Table 5.9 Drugs implicated in Category One

Therapeutic Classification*	Drugs within this classification
Respiratory System - Preventative aerosols and inhalations	fluticasone (2)†, beclomethasone (2), sodium cromoglycate (1)

*Classification is according to the indexing used by MIMS Annual 2000.[183]
†The number of cases in which the drug was involved is indicated in parenthesis.

All hospital admissions in this category were as a result of an exacerbation of asthma, with cases falling into two scenarios:

The first involved the required medication noted having been recently ceased under medical supervision, and is represented by 2 of the 5 cases allocated to Category One.   The *multidisciplinary panel* determined a causality classification of *probable* and a preventability classification of *unable* for each of these cases.   A clinical significance classification of *Category A* and *Category B* was listed respectively for each case.   The 2 cases are best represented by the following brief case description:

> *An 8 year old male with a past history of chronic persistent asthma diagnosed at 2 years of age was "weaned off" fluticasone 2-weeks prior to the admission in question by his paediatrician.   He presented to hospital with a 2-week history of increasing frequency of wheeze and marked nocturnal symptoms of asthma.   On*

admission he had marked respiratory distress and wheeze and was treated with frequent salbutamol via nebuliser and intravenous methylprednisolone. The salbutamol was reduced gradually, the intravenous methylprednisolone changed to oral prednisolone, the fluticasone was recommenced and he was discharged from hospital.

The second scenario involved an unrecognised need for preventative treatment and affected the remaining 3 cases allocated to Category One. The *multidisciplinary panel* determined a causality classification of *probable* and a preventability classification of *yes* for 2 of these cases and a causality classification of *possible* and a preventability classification of *unable* for the remaining case. A clinical significance classification of *Category A* was allocated to 1 case and *Category B* for the remaining 2 cases. The 3 cases are broadly represented by the following brief case description:

A 3 year old male with a past history of asthma diagnosed at 6 months of age was admitted to hospital. The patient had not been previously admitted to hospital with asthma but had a history of experiencing nocturnal cough and exercise induced symptoms, and was noted to experience an acute exacerbation of asthma approximately once a month. Treatment prior to admission consisted of salbutamol only. He presented with an acute exacerbation of asthma of moderate severity in conjunction with an URTI. Sodium cromoglycate was commenced and the patient was discharged upon resolution of his acute symptoms.

5.2.4.7.2   Category Two

Category Two, where the wrong drug was being taken, was represented by 2 cases (Table 5.10).

Table 5.10 Drugs implicated in Category Two

Therapeutic Classification*	Drugs within this classification
Respiratory system	
- Bronchodilator aerosols and inhalations	salbutamol (1)[†]
Infections and infestations	
- Penicillins	flucloxacillin (1)

*Classification is according to the indexing used by MIMS Annual 2000.[183]
[†]The number of cases in which the drug was involved is indicated in parenthesis.

There were no disease states or scenarios in common for either of the cases. The *multidisciplinary panel* determined a causality classification of *possible* and a preventability classification of *yes* for each of them. A clinical significance classification of *Category A* and *Category C* were allocated to each case respectively. An example of the type of case allocated to Category Two is given below:

> *A 10 year old female with a past history of persistent methicillin-resistant Staphylococcus aureus (MRSA) axillary abscesses was admitted to hospital. One month prior to the admission in question she was admitted with an MRSA axillary abscess for drainage and treatment with intravenous vancomycin. She was subsequently discharged on flucloxacillin. She presented again 10 days prior to the admission in question with a second MRSA abscess which was drained, and she was again discharged on flucloxacillin. With respect to the admission in question the patient presented with multiple axillary abscesses visible, which resolved upon treatment with intravenous vancomycin and she was discharged on trimethoprim according to MRSA in vitro sensitivities.*

5.2.4.7.3   Category Three

The individual drugs specified in Category Three, where too little of the correct drug was being taken, are listed in Table 5.11. This category was represented by 4 cases.

Table 5.11 Drugs implicated in Category Three

Therapeutic Classification*	Drugs within this classification
Central Nervous System - anticonvulsants	sodium valproate (2)[†], phenobarbitone (1)
Endocrine and Metabolic Disorders - Insulin preparations	insulin-neutral (1), insulin-isophane](1)

*Classification is according to the indexing used by MIMS Annual 2000.[183]
[†]The number of cases in which the drug was involved is indicated in parenthesis.

The hospital admissions in this category were associated with epileptic or diabetic complications. The scenarios for Category Three can therefore be split into the two disease states associated with admissions.

Epileptic complications were the reason for the admission of 3 of the 4 cases in this category. The *multidisciplinary panel* determined a causality classification of *possible* and a preventability classification of *no* for 2 cases. A clinical significance classification of *Category A* was allocated to 2 cases with a classification of *Category C* allocated to the remaining case. The *multidisciplinary panel* determined a causality classification of *probable* and a preventability classification of *yes* for the final case. This case was allocated a clinical significance classification of *Category A*. The characteristics of these cases are different, however, the final case described above provides an example of the cases allocated to this category.

> *A 7 month old (9 Kg) male with a past history of 4 afebrile seizures in the past month was referred for admission. He had been commenced upon sodium valproate 2 days prior to admission at a*

dose of 40mg twice a day. Upon presentation a neurology review suggested the dose of sodium valproate was subtherapeutic and the dose was increased to 20mg/kg/day. The sodium valproate was subsequently changed to carbamazepine during the course of his admission and he was discharged when stabilised.

The fourth case allocated to Category Three was a patient with diabetes. The *multidisciplinary panel* determined a causality classification of *possible*, a preventability classification of *unable,* and a clinical significance classification of *Category 6.* A brief description of this case is provided below:

A 14 year old male with a past history of insulin dependent diabetes mellitus diagnosed at age 12, and a background of behavioural problems and poor diabetic control was admitted to hospital. He presented with persistently high blood sugar levels, lethargy, headaches, leg cramps and mild dehydration. He was admitted for stabilisation, which was achieved by increasing his insulin doses by 10%, and he was discharged on the higher insulin doses.

5.2.4.7.4   Category Four

The individual drugs specified in Category Four, where too much of the correct drug was being taken, are listed in Table 5.12. This category was represented by 2 cases.

Table 5.12 Drugs implicated in Category Four

Therapeutic Classification*	Drugs within this classification
Central Nervous System - Anticonvulsants	phenytoin (1)[†]
Respiratory System - Bronchospasm relaxants	aminophylline (1)

*Classification is according to the indexing used by MIMS Annual 2000.[183]
[†]The number of cases in which the drug was involved is indicated in parenthesis.

There were no disease states in common in this category, however the scenarios involved were similar. The *multidisciplinary panel* determined a causality classification of *probable* and a preventability classification of *yes* for the first case. A causality classification of *definite* and a preventability classification of *yes* were determined for the second case. Both cases were allocated a clinical significance classification of *Category C*. An example of the type of case allocated to Category Four is given below. The case description relates to the second case described above.

> *A 3 month old female with a past history of recurrent bronchiolitis was admitted to hospital and subsequently to the intensive care unit with severe respiratory syncytial virus bronchiolitis and an accidental aminophylline overdose. She was administered the aminophylline intravenously to treat apnoea. A loading dose of 100mg/kg was administered in error instead of 10mg/kg. The aminophylline overdose was treated with activated charcoal via a nasogastric tube and esmolol. Right upper lung lobe collapse and consolidation further complicated her condition. Blood cultures were positive for Haemophilus influenzae so she was treated with penicillin G which was subsequently changed to amoxycillin / clavulanic acid. Her condition improved and she was discharged on amoxycillin / clavulanic acid.*

5.2.4.7.5   Category Five

Category Five, where an ADR had occurred, was represented by 29 cases (Table 5.13).

Table 5.13 Drugs implicated in Category Five

Therapeutic Classification	Drugs within this classification
Alimentary System	
- Antidiarrhoeals	sulphasalazine (1)[†]
Cardiovascular System	
- Beta-adrenergic blocking agents	propranolol (1)
-Antiarrhythmic agents	flecanide (1)
Central Nervous System	
- Anticonvulsants	sodium valproate (1), phenytoin (1), lamotrigine (2), clonazepam (1)
- Antiemetics, Antinauseants	Metoclopramide (1), prochlorperazine(1)
Infections and Infestations	
- Penicillins	flucloxacillin (4), procaine penicillin (1), penicillin V (1), amoxycillin / clavulanic acid (1), amoxycillin (1)
- Cephalosporins	cefaclor (1)
- Tetracyclines	minomycin (1)
- Other antibiotics and anti-infectives	teicoplanin (1), co-trimoxazole (1)
Immunology	
- Vaccines	Hib vaccine (1), Triple Antigen (3) Acellular Triple Antigen '6 in 1' vaccine (1), MMR vaccine (1)
- Immunomodifiers	cyclosporin (1)
Eye	
- Topical ocular anti-infective preparations	framycetin (1)
Skin	
- Toplical corticosteriods	triamcinolone / neomycin / gramicidin / nystatin (2)
Surgical preparations	
- Anaesthetics – local and general	bupivicaine (1)
Contraceptive agents	
- Combined oral contraceptive agents	ethinyloestradiol / levonorgesterol (1)
Unlisted	diphenhydramine (1)

[*]Classification is according to the indexing used by MIMS Annual 2000.[183]
[†]The number of cases in which the drug was involved is indicated in parenthesis.

A diverse range of drugs and disease states were associated with the cases allocated to Category Five. Despite this diversity a number of common scenarios were evident, two of which could be grouped under the heading of hypersensitivity reactions.

The first of the hypersensitivity reaction scenarios was represented by 3 of the 29 cases and involved the development of Stevens Johnson Syndrome, with the drugs implicated being sulphasalazine, phenytoin and procaine penicillin. The *multidisciplinary panel* determined a causality classification of *probable* for 2 of the 3 cases and a preventability classification of *no* and *unable* for the 2 cases respectively. A clinical significance classification of *Category B* was allocated to both of these cases. A causality classification of *definite* and a preventability classification of *no,* along with a clinical significance classification of *Category C* was determined for the third case. This scenario is best represented by the following description of the third case:

> *A 12 year old female with a past history of irritable bowel syndrome diagnosed 2 weeks prior to the admission in question. Five days prior to admission she was commenced upon sulphasalazine. She was not taking any other medications at the time sulphasalazine was commenced, although norfloxacin had been ceased 3 days prior. Three days after the commencement of sulphasalazine she developed an erythematous maculopapular rash over her face, trunk and extremities. The subsequent development of mucositis lead to her presentation and admission to hospital. A diagnosis of Stevens Johnson Syndrome was made after a dermatology review. Treatment with intravenous methylprednisolone and topical preparations led to a gradual improvement and she was discharged 1 week after admission.*

The second hypersensitivity scenario encompassed 6 cases and involved the development of a rash. The drugs involved were flucloxacillin, triamcinolone / neomycin / gramicidin / nystatin, diphenhydramine, penicillin V or co-

trimoxazole. The *multidisciplinary panel* determined a causality classification of *probable* for 2 cases and *possible* for the remaining 4 cases. Four of the 6 cases were classified as not preventable with the remainder classified as unable. Three cases were allocated a clinical significance classification of *Category A* with the remainder allocated a classification of *Category C*. The following brief description best represents this scenario:

> *A 10 month old female with a past history of a urinary tract infection treated 10 days previously with co-trimoxazole was admitted to hospital. When diagnosed with a second urinary tract infection by her general medical practitioner on the day of admission, she was again treated with co-trimoxazole. Two hours after the first dose she developed a generalised maculopapular rash with swollen lips and noisy breathing, and was subsequently admitted to hospital. Her symptoms resolved upon treatment with promethazine and prednisolone. The co-trimoxazole was ceased and the patient was discharged with no further treatment as she was subsequently found to not have a urinary tract infection.*

The next type of scenario involved the development of adverse reactions to immunisations. This scenario included 3 cases and involved Hib, Triple antigen and MMR vaccines. The *multidisciplinary panel* established a causality classification of *possible* and a preventability classification of *no* for 2 of the 3 cases. The final case had a causality classification of *probable* and a preventability classification of *no*. The clinical significance classification allocated to each of the 3 cases was *Category A*. The following brief description of the final case described above is broadly representative of all 3 cases:

> *A 21 month old female with no significant past medical history was administered Triple Antigen vaccine at 11:00 on the day of admission. She was well initially but then began to develop symptoms of a viral illness including fever, cough and a decreased appetite. In the evening she had a generalised tonic clonic seizure*

at approximately 20:00. The seizure resolved upon treatment with intravenous diazepam by the attending medical practitioner. A second febrile generalised tonic clonic seizure was witnessed at another hospital prior to her transfer to the hospital in question. Upon transfer no further seizures and no neurological abnormalities were observed. The next morning she was well, alert and happy with a normal neurological examination. The patient was discharged with a principal diagnosis of 2 atypical febrile convulsions.

The fourth scenario type involved adverse reactions to propranolol and flecanide. In the 2 cases identified, the *multidisciplinary panel* determined a causality classification of *probable*, a preventability classification of *no*, and a clinical significance classification of *Category C* for each one. An example of the type of adverse reaction experienced in this scenario is described in the following case description:

An 11 year old male with a past history of Wolf Parkinson White Syndrome diagnosed at birth and asymptomatic until 9 years of age was commenced upon flecanide therapy for supraventricular tachycardia 4 days prior to the admission in question. He was admitted with dizziness and headaches attributed to the flecanide therapy. The flecanide was subsequently ceased and he was commenced upon sotolol with good resolution of his symptoms and no discernable adverse effects.

The fifth type of scenario involved 3 cases and the following drugs: sodium valproate; lamotrigine; clonazepam; and cyclosporin. This scenario involved elevated levels of the drugs in question leading to the ADRs. It should be noted that the doses prescribed were not considered toxic according to the references cited in Appendix Three. The *multidisciplinary panel* determined a causality classification of *definite* for 1 case with a preventability classification of *no*. A causality classification of *probable* was determined for each of the remaining 2 cases with preventability classifications of *yes* and *no* allocated

to the 2 cases respectively. A clinical significance classification of *Category A* was allocated to all 3 cases. The following brief case description best describes the type of scenario involved in these 3 cases:

> *A 4 year old male with a past history of epilepsy presented to hospital following a 1-month deterioration in seizure control and a prolonged seizure on the day of admission. He had been "weaned off" his carbamazepine 3 months prior to the admission in question with a subsequent increase in his lamotrigine dose. One month prior to admission, sodium valproate was commenced and his lamotrigine dose was further increased. On admission he was found to display symptoms of lamotrigine toxicity, with tremor and focal twitching of the right side. His sodium valproate was ceased and lamotrigine dose decreased resulting in clinical improvement and the patient was subsequently discharged.*

The final type of scenario incorporated 2 cases and involved dystonic reactions to the drugs metoclopramide and prochlorperazine. The *multidisciplinary panel* determined a causality classification of *probable* and a preventability classification of *no* for one case. The second was allocated a causality classification of *definite* and a preventability classification of *yes*. Both cases were allocated a clinical significance classification of *Category A*. The following brief description of the second case best characterises the cases involved in this scenario:

> *A 10 month old female with no significant past medical history was admitted to hospital. She was unwell for 1-week prior to admission with vomiting, diarrhoea, fever and anorexia. She presented with a dystonic reaction secondary to metoclopramide which had been prescribed for vomiting. A differential diagnosis was a febrile convulsion secondary to a viral illness. The reaction resolved upon the administration of benztropine, she recovered quickly and was discharged home. The primary diagnosis was dystonic reaction secondary to metoclopramide.*

The remaining 10 cases encompassed a broad range of clinical scenarios ranging from benign intracranial hypertension secondary to minocycline to allergic conjunctivitis secondary to framycetin. Given the diversity of these cases they will not be explored in further detail.

5.2.4.7.6   Category Six

The individual drug specified in Category Six, where a drug-drug, drug-food or drug-laboratory interaction had occurred is listed in Table 5.14.

Table 5.14 Drug implicated in Category Six

Therapeutic Classification*	Drugs within this classification
Infections and infestations	
- Macrolides	Erythromycin (1)[†]

*Classification is according to the indexing used by MIMS Annual 2000.[183]
[†]The number of cases in which the drug was involved is indicated in parenthesis.

Category Six was represented by one case only. The *multidisciplinary panel* assigned a causality classification of *definite*, a preventability classification of *yes*, and a clinical significance classification of *Category A*. The following is a brief description of the case:

> *A 5 year old male with a past history of steroid resistant nephrotic syndrome, treated with cyclosporin, was admitted to hospital with vomiting and deteriorating renal function. Prior to admission he was prescribed erythromycin for a 2-week history of cough and sore throat. His deteriorating renal function was subsequently found to be associated with cyclosporin toxicity, secondary to an interaction with erythromycin. His cyclosporin doses were withheld for 24 hours and the erythromycin was ceased. His cyclosporin levels returned to normal within 24 hours, and he was recommenced upon cyclosporin before being discharged.*

5.2.4.7.7   Category Seven

Category Seven, where a case was not receiving the prescribed drug, was represented by 38 cases. The individual drugs implicated in the cases allocated to this category are listed in Table 5.15.

Table 5.15 Drugs implicated in Category Seven

Therapeutic Classification	Drugs within this classification
Alimentary System - Antidiarrhoeals	sulphasalazine (1)[†]
Central Nervous System - Anticonvulsants	sodium valproate (1)
Endocrine and Metabolic Disorders - Insulin preparations	insulin-neutral (2), insulin-isophane (3), insulin-lispro (1)
Infections and Infestations - Penicillins	flucloxacillin (2)
- Other antibiotics and anti-infectives	co-trimoxazole (1), trimethoprim (1)
Respiratory System - Preventative aerosols and inhalations	fluticasone (3), beclomethasone (15), sodium cromoglycate (2), budesonide (6), salmeterol (2)

*Classification is according to the indexing used by MIMS Annual 2000.[183]
[†]The number of cases in which the drug was involved is indicated in parenthesis.

Hospital admissions associated with asthma and diabetic complications formed the majority (28/34) of the cases allocated to this category. The scenarios in common to the cases allocated to this category will therefore be split into these two disease states.

Hospital admissions associated with asthma complications can be divided into four scenarios, the first of which involved limitations in knowledge leading

to inappropriate medication use. This scenario was represented by 2 cases with beclomethasone being the drug implicated in each. The *multidisciplinary panel* determined a causality classification of *probable* and a preventability classification of *yes* for the first case. The second was assigned a causality classification of *possible* and a preventability classification of *unable*. Clinical significance classifications of *Category C* and *Category B* were allocated respectively to each of the cases. The following brief description of the second case outlined above broadly describes the cases allocated to this scenario:

> *A 12 year old female with a history of asthma, diagnosed in early childhood, was admitted to hospital. She had been admitted to hospital once previously for asthma. Prior to the admission in question she had a history of significant interval symptoms, waking every second night with nocturnal wheeze, and wheezing upon attempts at exercise. The patient was using salbutamol on at least an every second day basis. She had a beclomethasone inhaler but only utilised it during an acute exacerbation of asthma due to a limited understanding of the use of this medication. She was admitted with an acute exacerbation of asthma which resolved with appropriate treatment. She was educated regarding the regular use of the beclomethasone inhaler, provided with an asthma plan and discharged.*

The second asthma-related scenario involved 5 cases and the parental cessation of the following drugs: beclomethasone; and salmeterol. The mean age of cases was 5.0 years (median 4.1, ± SD 3.3). The *multidisciplinary panel* determined a causality classification of *possible* for 3 of the 5 cases. A preventability classification of *yes* and a clinical significance classification of *Category A* was determined for 2 of the 3 cases with preventability and clinical significance classifications of *unable* and *Category C* assigned respectively to the outstanding case. The fourth and fifth cases were allocated causality classifications of *probable*, preventability classifications of *yes*, and clinical significance classifications of *Category C*

and *Category B* respectively. The following brief description of the fifth case broadly outlines this scenario:

> *A 9 year old female with a history of asthma diagnosed at 3 years of age. She had been admitted to hospital on 6 separate occasions as a result of asthma, 5 within the last 12 months, 1 of which involved admission to the intensive care unit. Her medications prior to admission included salbutamol, prednisolone and fluticasone. Salmeterol had been ceased in the 2 months prior to admission by her parents as she had started the Butako method of breathing. She was admitted to hospital on this occasion with an acute exacerbation of asthma on a background of an URTI. She gradually improved, was resumed on salmeterol, commenced on theophylline and discharged.*

The third scenario was represented by 3 cases in which they refused to be administered the medication in question. The mean age of cases was 4.3 years (median 3.9, ±SD 2.5). The drugs involved were: sodium cromoglycate; fluticasone; and beclomethasone. The *multidisciplinary panel* determined a causality classification of *definite, probable* and *possible* for cases 1 to 3 respectively. All were determined to be preventable by the panel. Cases 1 and 3 were both allocated a clinical significance classification of *Category B*, with a classification of *Category A* being allocated to the remaining case. The scenario involved is best described by the following brief description of the first case:

> *A 3 year old female with a history of chronic persistent asthma was admitted to hospital with an acute asthma exacerbation. Prior to admission she had a 1-day history of cough, wheeze and shortness-of-breath on a background of refusing to take beclomethasone even though her mother had tried very hard to make her. It was stated that the patient was jealous of a new baby in the family and hence was refusing to take the beclomethasone. The acute asthma exacerbation of moderate severity was treated*

with prednisolone, salbutamol and ipratropium. The beclomethasone was resumed and she was discharged with an asthma management plan.

The final asthma-related scenario encompassed 17 cases who were non-adherent with one or more of the following drugs: beclomethasone; budesonide; fluticasone; salmeterol; or sodium cromoglycate. The mean age of cases was 14.1 years (median 14.3, ± SD 2.7). A causality classification of *definite* was determined by the *multidisciplinary panel* for 1 case, *probable* for 4 cases and *possible* for the remaining 12 cases. A total of 12 cases were allocated a preventability classification of *yes*, with the remaining 5 cases allocated a classification of *unable*. Six cases each were allocated a clinical significance classification of *Category A*, 5 cases were allocated a classification of *Category B* with the remaining 6 cases being allocated to *Category C*. The following brief description outlines a case where the causality classification was *probable*, the preventability classification was *yes*, and the clinical significance classification was *Category B*:

> *A 15 year old female with a history of asthma diagnosed at 6 years of age was admitted to hospital. She had been admitted a total of 6 times as a result of exacerbations of her asthma, none of which were to the intensive care unit. Her most recent asthma-related admission was 1-year ago. Her medication prior to admission included salbutamol and beclomethasone. The dose of beclomethasone prescribed was 100mcg twice a day, however, the patient stated that she only used this inhaler once every 4 days because she forgets. She was admitted with an acute exacerbation of asthma on a background of a 2-day history of an URTI. Her asthma exacerbation resolved with appropriate treatment, she was educated regarding the importance of adherence to beclomethasone therapy and was discharged.*

The second disease state associated with a large proportion of cases allocated to Category Seven was diabetes. Two common scenarios were

evident for the cases where diabetic complications lead to the patient's hospital admission.

The first scenario involved 2 cases, with insulin-neutral and insulin-isophane being used inappropriately because of limited knowledge. The *multidisciplinary panel* determined a causality classification of *possible* for the first case and *probable* for the second. Both were allocated a preventability classification of *yes* and a clinical severity classification of *Category C*. The following brief description of the second case outlines the scenario involved:

> *A 10 year old female with a history of insulin dependent diabetes diagnosed at 8 years of age. She self manages her diabetes on a background of issues of non-adherence and a questionable family understanding of diabetes. Prior to presentation at another hospital she had a 1-hour history of symptoms of a febrile illness. The patient was admitted to another hospital with diabetic ketoacidosis (Blood sugar level 48 mmol/L, blood pH 6.9). She was subsequently transferred to the intensive care unit of the hospital in question where she made an unremarkable and steady recovery. The patient and her family were re-educated regarding diabetes because they stated that they had been told a blood sugar level of 15 was "ok" and that less than 5 was "low". Once the patient was stabilised and education had occurred she was discharged.*

The second diabetic scenario involved 3 cases and non-adherence with insulin-neutral, insulin-isophane or insulin-lispro. The mean age of cases was 17.3 years (median 17.5, $\pm$ SD 0.43). The *multidisciplinary panel* determined a causality classification of *definite* for the first of these cases, *probable* for the second and *possible* for the third. Each case was classified as preventable. A clinical significance classification of *Category B* was allocated to 2 cases with a classification of *Category C* allocated to the remaining case. The following brief description of the first case best represents the cases allocated to this scenario:

A 17 year old male with a history of insulin dependent diabetes since 14 months of age was admitted to hospital with mild to moderate diabetic ketoacidosis (blood sugar level 21.8 mmol/L, blood pH 7.23, blood bicarbonate 13.7mmol/L) on a background of having missed 48 hours of insulin. He had been away from home for the last 2 days and at a party on the night prior to admission where alcohol was consumed. He was stabilised on an insulin infusion, and made a gradual recovery. His insulin was changed to insulin-biphasic and he was subsequently discharged.

A diverse range of disease states are evident for the remaining cases allocated to Category Seven. Despite this diversity a scenario common to 2 of the cases can be drawn. The scenario involved non-adherence with trimethoprim or sulphasalazine. The *multidisciplinary panel* determined a causality classification of *possible* for both cases and a preventability classification of *yes* for the first case and *unable* for the second. Clinical significance classification of *Category C* and *Category A* was allocated respectively to the cases. The following brief description of the second case provides an outline of the type of cases allocated to this scenario:

A 16 year old female with a history of Crohn's disease diagnosed at 9 years of age, and a subsequent resection of her terminal ileus was admitted to hospital with a 3-day history of increasing abdominal pain, vomiting and diarrhoea. Drug treatment for her Crohn's disease consisted of sulphasalazine only, however the patient felt that her symptoms were less well controlled upon sulphasalazine and had not taken her doses in the 3 days prior to admission. She was re-hydrated on admission, her sulphasalazine was resumed, and she was discharged with active follow-up planned.

The remaining 4 cases involved flucloxacillin, sodium valproate and co-trimoxazole. A common scenario was not evident for these remaining cases and they will not be explored in further detail.

5.2.4.7.8 Category Eight

The individual drugs specified in Category Eight, where cases had taken a drug for which no valid medical indication existed, are listed in Table 5.16.

Table 5.16 Drugs implicated in Category Eight

Therapeutic Classification*	Drugs within this classification
Cardiovascular System	
- Antihypertensives	clonidine (2)[†], verapamil (1), nifedipine (1), enalapril (1)
- Beta-adrenergic blocking agents	propranolol (2), atenolol (1)
- Antimigraine preparations	pizotifen (1)
Central Nervous System	
- Sedative, Hypnotics	nitrazepam (1), oxazepam (3), temazepam (1)
- Antianxiety agents	diazepam (4) alprazolam (1)
- Antipsychotic agents	thioridazine (1), olanzapine (1)
- Antidepressents	dothiepin (3), sertaline (1)
- Other central nervous system agents	dexamphetamine (1)
- Anticonvulsants	sodium valproate (1)
Analgesia	
- Narcotic analgesics	detropropoxyphene (1)
- Simple analgesics and antipyretics	paracetamol (6)
- Combination simple analgesics	paracetamol / codeine / doxylamine (1), paracetamol / codeine (2)
Musculoskeletal System	
-Nonsteroidal anti-inflammatory agents	naproxen (1), mefenamic acid (1), ibuprofen (1), phenylbutazone (1)
- Muscle relaxants	orphenadrine (1)
Endocrine and Metabolic Disorders	
- Adrenal steroid hormones	prednisolone (1)
- Insulin preparations	insulin (1)
- Hypoglycaemic agents	glibenclamide (1), metformin (1)

Drugs implicated in Category Eight (continued)

Infections and Infestations	
- Antimalarials	chloroquine (1)
Respiratory System	
-Expectorants,antitussives, mucolytics, decongestants	dextromethorphan/pseudoephedrine (1)
- Bronchospasm relaxants	theophylline (4), terbutaline (1), choline theophyllinate (1)
- Bronchodilator aerosols and inhalations	salbutamol (1)
Allergic Disorders	
- Antihistamines	promethazine (1)
Nutrition	
- Anorectics and weight reducing agents	phentermine (1)
Vitamins and Minerals and other Nutritional supplements	ferrous sulphate (1)
Unlisted	calcium carbonate (1), echinacea (1), evening primrose oil (1)
Alcohol, illicit or unidentified substances	alcohol (1), heroin (1), unidentified (3)

*Classification is according to the indexing used by MIMS Annual 2000.[183]
†The number of cases in which the drug was involved is indicated in parenthesis.

A diverse range of drugs were implicated in the 46 cases allocated to Category Eight. A number of common scenarios can be determined when the cases allocated to this category are split into two age groups: those less than or equal to 5 years of age; and those greater than 5 years of age. It should be remembered that a causality classification of *definite* was automatically allocated to each case meeting the criteria for Category Eight. As indicated in Section 3.5, the *multidisciplinary panel* recommended that preventability not be assessed for these cases because the majority involved accidental or intentional poisonings.

Twenty-four cases were in the first age group. Cases had a mean age of 2.2 years (median 1.9, ± SD 0.9) and were predominantly male (75.0%, 18/24). The mean number of drugs taken was 1.5 (median 1.0, ± SD 1.0). Most

(8?.8%, 24/29) of the drugs involved were prescription medications. Dothiepin (3) and propranolol (2) were the only drugs involved in more than 1 case. Three scenarios were common to the cases in this age group:

The first highlights the background on which more than one medication was accidentally ingested. The scenario involved 2 cases and the drugs: chloroquin; prednisolone; clonidine; calcium carbonate; echinacea; evening primrose oil; enalapril; and metformin. A clinical significance classification of *Category A* was allocated to 1 case and *Category C* for the remaining case. The following brief description best outlines this scenario:

> *An 18 month old female with a past history of being born at 30 weeks gestation, presented after an accidental ingestion of chloroquin, prednisolone, clonidine, calcium carbonate, echinacea and evening primrose oil. The tablets were her mother's and were left on the bedside table for her mother to take. The patient was given activated charcoal in the emergency department. When her blood pressure dropped to 60/30 mmHg she was admitted to the intensive care unit. She was monitored overnight without incident and was subsequently discharged.*

The second scenario involved 1 case and the accidental administration of the wrong drug by a parent or guardian. The drug involved was choline theophyllinate. The clinical significance classification for this case was *Category A.*

> *A 21 month old female with no significant past history presented after the accidental ingestion of choline theophyllinate. Prior to presentation she had a 1-day history of an URTI. One of her parents accidentally administered 10mLs of choline theophyllinate mixture to the patient instead of her sibling. Upon presentation the patient was found to be tachycardic and hypertensive and was admitted overnight. Her symptoms had settled by the following morning and she was discharged.*

The final scenario for the younger age group involved instances were only one type of medication was ingested. This scenario involved 21 cases, that is, 87.5% (21/24) of the cases in this age group. The drugs involved in this scenario included: verapamil; propranolol; atenolol; pizotifen; diazepam; alprazolam; dothiepin; olanzapine; dexamphetamine; dextropropoxyphene; phenylbutazone; orphenadrine; glibenclamide; dextromethorphan / pseudoephedrine; theophylline; phentermine; ferrous sulphate; and an unidentified white tablet. Seventeen cases were allocated a clinical significance classification of *Category A*, 1 case *Category B*, with the remainder allocated to *Category C*.

> *A 20 month old male with no significant past history was admitted to hospital after an accidental ingestion of propranolol tablets. He was found with an open bottle of propranolol 40mg tablets. The bottle contained 100 tablets prior to being found by him, 97.5 tablets were counted afterwards and hence a maximum of 2.5 propranolol tablets could possibly have been ingested. The patient did not vomit after the ingestion. He was admitted to hospital where activated charcoal was administered and he was monitored. He remained asymptomatic over an 8-hour period of observation and was subsequently discharged.*

In the older age group, there were 22 cases, of which 18.2% (4/22) were males. Cases had a mean age of 15.2 years (median 15.5, ± SD 1.8). The mean number of drugs taken was 2.1 (median 2.0, ± SD 1.2). Most (68.4%, 26/38) of the drugs implicated were prescription medications. The 5 most common drugs were: paracetamol (6); oxazepam (3); diazepam (3); theophylline (3); and paracetamol / codeine.

A single scenario involving the intentional ingestion of one or more drugs was common to each of the cases in this age group. The drugs involved were diverse with the 5 most common drugs listed above providing the best overview of the drugs implicated. A clinical significance classification of *Category A* was allocated for 10 cases, *Category B* for 7 cases and *Category*

C for 5 cases. The following brief description broadly describes the cases allocated to this scenario:

A 16 year old female with no significant past history presented with an overdose of paracetamol and paracetamol / codeine. The patient ingested 18 paracetamol tablets and 6 paracetamol / codeine tablets 12 hours prior to presentation. She vomited 5 minutes after ingestion but no tablets were seen. Five hours later she began to feel increasingly unwell, with vomiting and abdominal pain and hence presented to hospital. Upon presentation a 12-hour post ingestion paracetamol level of 306mmol/L was recorded and hence acetylcysteine treatment was commenced. Acetylcysteine was ceased upon resolution of blood test abnormalities and the patient underwent a psychiatric review. Pressure at school and fighting with friends were given as reasons for the overdose. She was discharged 2 days after admission.

5.3 Discussion

The results presented for this stream of data collection confirm that hospital admissions are associated with DRPs within the Australian paediatric population. More specifically 4.3% (95% CI 3.5 – 5.1%) of eligible admissions at RCH and 4.3% (95% CI 1.4 – 7.2%) at GH were determined to be associated with a DRP. Data from BH are however not included.

There were no data from BH because the one-week period of data collection was not long enough to enable the detection of cases determined by the *multidisciplinary panel* to have hospital admissions associated with DRPs. However, whilst this lack of data may limit a full analysis of DRPs in the paediatric populations investigated, its impact may be reduced by the following factors. Firstly, significant differences in the frequency of hospital admissions associated with DRPs or the incidence rates calculated were not identified between RCH and GH. Secondly, earlier research had found that there were no significant differences in the frequency of emergency

department attendances associated with DRPs across the three hospital sites (See sections 4.2.1, 4.2.2 and 4.2.3). Finally, by comparing data from RCH, GH and BH it was found that there were no significant differences in terms of age or gender for the eligible patient populations. It is unlikely, therefore, that if data collection had been conducted over a longer period of time at BH that the results obtained would have been significantly different to those reported at RCH and GH. This assumption is further supported by the results reported by Mitchell et al who found no significant differences in the frequency of paediatric ADR admissions between teaching and community hospitals.[61]

The combined data revealed the frequency of hospital admissions associated with DRPs to be 4.3% (95% CI 3.6 – 5.0%). Three previous paediatric studies investigated hospital admissions associated with DRPs,[7, 62, 63] one of which was conducted with the Australian paediatric population[7]. The two overseas studies (Lebanon, Israel) report the frequency of such admissions to range between 7.9% and 17.7%,[62, 63] results that differ markedly from those reported in this thesis. The differences may primarily reflect variances in sample populations, as both studies included oncology patients.[62, 63] However, differences in methodologies were also apparent. For example, the two overseas paediatric studies utilised admission interviews in the process of data collection, a factor thought to contribute to a higher number of DRPs being identified (See Section 4.3).

A more appropriate comparison may therefore be with the preliminary study conducted within the Australian paediatric population by Easton et al.[7, 67] This study was conducted in a comparable patient population utilising a similar methodology to that reported in this thesis, with the main difference being that an interview was undertaken in a selection of patients to further explore issues of adherence.[7] The frequency of hospital admissions associated with DRPs reported in the preliminary study was 3.4% (95% CI 2.5% to 4.3%), a figure that was not significantly different to that reported in this thesis.[7] The lack of a significant difference between the preliminary study, which was conducted in 1996, and the research reported in this thesis

strengthens the level of confidence that can be placed in the findings reported in this chapter. It is proposed that this level of confidence is supported by the fact that, in both instances, a *multidisciplinary panel* determined the cases that met study inclusion criteria.

In terms of comparisons with the adult population, numerous studies investigating drug related hospital admissions within the adult population have been reported.[42-44, 69, 80] However, given the possible influence of different drug utilisation patterns between countries,[58, 103] comparisons will be restricted to studies conducted in Australia. In a review of Australian studies investigating drug related admissions Roughead et al reported the frequency of such admissions to range from 2.4% to 22%.[42] The 4.3% (95% CI 3.6 – 5.0%) of admissions reported in this thesis therefore falls within the range of that reported previously in the adult population.

Analysing the results reported by Roughead et al in greater detail, 2.4% - 3.6% of *all* hospital admissions, 5.7% - 6.4% of *emergency* admissions, 12% of all admissions to *medical wards* and 15 – 22% of all emergency admissions among the *elderly* were drug related.[6, 42] Taking into account confidence intervals, the results presented in this thesis were not significantly different to the studies investigating *all* hospital admissions,[39, 189] or *emergency* admissions[6, 57]. If, however, the adult population is restricted to those admitted to *medical wards* or to the *elderly* population, the frequency of hospital admissions associated with DRPs reported in this thesis was significantly lower than that reported for the adult population.[5, 190, 191]

The finding that the age of cases identified in this thesis was significantly higher than that of the eligible patient population (a finding noted in each hospital data set) raises the prospect of increasing age as a possible risk factor for DRPs. This is not a new concept, as Yosselson-Superstine and Weiss reported the age distribution of patients admitted with ADRs to be unremarkable except for a group of 6 – 10 year old patients who comprised 41.5% of such admissions while they represented only 16.5% of the total number of hospitalisations.[63] A similar finding was reported in two other

paediatric studies investigating hospital admissions associated with ADRs.[60,
192] It is however, important to note that the data referred to in each of these studies relates to ADRs only and that the age of onset of diseases, such as acute leukemia, in the patient population under investigation may have contributed to the pattern seen.[192] Furthermore, in the research reported in this thesis the age of cases allocated to Category Seven was found to be significantly higher than that of cases allocated to Category Five. This finding indicates that the age of patients experiencing ADRs was not the major factor contributing to the age differences noted between cases and the eligible patient population. Instead, it appears that cases allocated to Category Seven had a greater impact on the variance in ages than any of the remaining DRP categories (See Table 5.3). Despite this, increasing age is unable to be confirmed as a risk factor until an analytical study design is utilised to evaluate hospital admissions associated with DRPs.

In contrast to the preliminary Australian paediatric study conducted by Easton et al, Category Eight, where cases had taken a drug(s) for which no valid medical indication exists, was the most common DRP identified in the results presented in this thesis.[7] The preliminary study reported non-adherence to be the most common DRP.[7] There are two possible explanations for this difference. The first being that the preliminary study was conducted at a time when seasonal factors may have influenced the high proportion (70.4%) of cases identified as non-adherent with asthma medications.[7] The impact of seasonal variations may have been reduced in the research presented in this thesis as a result of the longer period of data collection. The second explanation is that the interview undertaken in the preliminary study to further explore issues of adherence may account for the differences in type of DRPs encountered.[7] A situation which would be consistent with the observation made in the preliminary study that the use of an interview enabled verification of non-adherence which was not always clearly documented within a case's medical history. Roughead et al also found that non-adherence was often poorly noted in medical histories and highlighted this as as a factor that needed to be addressed.[4] It is possible, therefore, that the extent of non-

adherence associated with hospital admissions may have been underestimated in the research presented in this thesis.

The finding that the type of DRPs allocated to Category Eight were the most frequent DRPs encountered in the research reported in this thesis was comparable to the findings of a study conducted within the Australian adult population.[191] However, the majority of other studies conducted within the Australian adult population report ADRs to be the most common type of DRP encountered.[5, 6, 39] The scope of definitions utilised could be a factor contributing to these differences. For example, the type of cases that were allocated to Category Eight in this thesis were excluded from the definition of DRPs utilised by one of the studies that reported ADRs to be the most common DRP identified.[6] The different pattern of DRPs detected may also reflect variances in the type of drugs and drug utilisation patterns between the adult and paediatric populations.[61]

The state and national extrapolations of the data presented in this thesis appear to underestimate the frequency of hospital admissions associated with DRPs when compared to data from the Victorian Inpatients Minimum Dataset. While the possibility of underestimating the frequency of hospital admissions associated with non-adherence has already been raised, it is unlikely that the extrapolations presented in this thesis underestimate the frequency of hospital admissions associated with DRPs to the extent suggested by this comparison. This is because data from the Victorian Inpatients Minimum Dataset may be influenced by the reported high degree of inappropriate medication poisoning admissions occurring in regional areas.[31] Hockey and Reith reported that children were admitted to hospital as a result of such problems more than twice as frequently in regional areas as compared to metropolitan areas.[31] The authors suggested that the variance reported arose from disparities in admission policies between regional and metropolitan areas.[31] From the available data in this thesis, the potential effect of this disparity in admission policies between regional and metropolitan hospitals cannot be evaluated.

Given the extent of hospital admissions associated with DRPs it is important to consider the preventability of such admissions. In the current study, 46.9% of cases were considered preventable, a figure apparently lower than the 66.6% reported in the preliminary study.[7] This variation may be as a result of the higher level of non-adherence identified in the preliminary study.[7]

Three studies have investigated the issue of preventability in the Australian adult population, with the frequency of preventable admissions ranging from 32% to 69%.[5, 6, 190] The percentage of preventable admissions associated with DRPs reported in this thesis therefore falls within the range reported in the general adult population. Such results indicate that both the frequency of hospital admissions associated with DRPs and the preventability of such admissions falls within the range of that reported in the general adult population. It is therefore not unreasonable to expect that the issue of DRPs occurring in the paediatric population should be given as much attention as that given to the adult population.

The clinical significance of DRPs has been investigated in two of the three paediatric studies exploring DRPs associated with hospital admissions.[7, 63] However, one study used different criteria than those reported in this thesis, thus reducing the relevance of potential comparisons.[63] The remaining study was the preliminary study conducted by Easton et al which, utilising the same criteria, reported that a higher proportion of cases were allocated to *Category B* and *Category C* in comparison to the results presented in this thesis (27.6% and 36.2% versus 21.3% and 29.1% respectively). It is proposed that the overrepresentation of non-adherent cases in the preliminary study, when compared to the results presented in this thesis, may account for the variance in clinical significance reported. This opinion was based upon the fact that one of the major components to the clinical significance criteria utilised was length of stay, and in Section 5.2.4 the length of stay of cases allocated to Category Seven was significantly higher than that of cases allocated to Category Eight. Unfortunately no comparisons could be made with the studies conducted within the Australian adult population because the issue of clinical significance has not been evaluated in the published studies.

With respect to the number of medications taken, Whyte and Greenan reported that ADRs occurred most frequently in paediatric patients who suffered from serious diseases that presented difficult therapeutic challenges.[58] This observation may reflect the relationship between increasing drug usage and the number of ADRs experienced, a trend that has been reported by a number of studies conducted within both the adult and paediatric populations.[58, 60, 192, 193] This trend was not evident in the results reported in this thesis. In fact the mean and median number of drugs taken by cases allocated to Category Five was the same as those allocated to Category Seven (See Table 5.7). However, comparisons with the mean number of drugs taken by the eligible patient population are required before the existence of this relationship can be discounted. Such data were not available for the eligible patient population investigated in this thesis.

The drugs most frequently implicated in the DRPs identified in this thesis were found to be remarkably similar to those reported within the preliminary Australian paediatric study.[7] In contrast, Roughead et al reported that a substantially different range of drugs were involved in DRPs within the Australian adult population.[42] As the drugs most commonly implicated in DRPs appear to differ between the adult and paediatric populations it can be inferred that the disease states involved also differ between these two populations. This finding has broader implications for the extrapolation to the paediatric population of prevention strategies developed for the adult population.

Through exploring the common scenarios implicated in the DRPs identified, a number of disease states have been highlighted. Problems such as an unrecognised need for therapy, and too little or too much of the correct drug being prescribed, highlight the difficulties in treating such diseases. Limitations in knowledge on behalf of parents or cases, along with the parental decisions to cease therapy, and general non-adherence have been noted to be factors contributing to sub-optimal treatment. Hence, potential strategies aimed at reducing DRPs should take these factors into consideration. Although preventability was not assessed for cases allocated

to Category Eight, where a case had taken a drug for which there was no valid medical indication, the types of drugs implicated and scenarios identified can be used to highlight potential areas to be targeted by prevention strategies.

5.4 Conclusions

The paucity of information on DRPs in the Australian paediatric population has been addressed by this thesis through exploring the frequency and characteristics of hospital admissions associated with DRPs within the paediatric population of three hospitals. The frequency of admissions associated with DRPs was not substantially different either among the three hospitals or when compared with the preliminary study.[7, 67] The finding that, despite the high proportion of admissions deemed preventable in the preliminary study, the frequency of hospital admissions associated with DRPs has not decreased since initially reported, indicates that attention needs to be drawn to addressing the issue of DRPs in the paediatric population.[7, 67] As the drugs implicated in the DRPs identified in this thesis differed to those reported within the adult population, the approach taken to reduce such problems may also differ. It is therefore important that the potential implications for prevention indicated by the results presented in this stream of data collection be explored. These implications for prevention will be discussed in Chapter Eight.

6 Adverse drug reactions occurring within the inpatient population

Shirkey described children as "therapeutic orphans" as he suggested that a lack of clinical trials conducted in this population meant that they were often deprived of useful drugs.[194] The same concept is apparent in the limited epidemiological literature on ADRs in the paediatric population. The issue of whether the full picture on ADRs in this population is understood must therefore be addressed. In an attempt to do so, this chapter discusses the final stream of data collection, one that investigates the frequency and characteristics of ADRs occurring within the inpatient population of three hospitals.

This chapter will commence with the details of data collection within the three hospitals. The methodologies utilised to determine causality, preventability and clinical significance along with the independent panel review process have been described previously (See Chapter Three). In reading this chapter it should be noted that the design strategy employed was an observational retrospective case series using *spontaneous monitoring* and *retrospective intensive monitoring*. The results section of this chapter will detail the nature and extent of ADRs within the inpatient populations investigated. A discussion that highlights the issues pertinent to this stream of data collection will then follow.

6.1 Methods

6.1.1 Eligibility

All paediatric patients admitted to a ward of RCH, GH and BH over the periods of data collection were considered for inclusion. The eligible population was not restricted to paediatric medical patients. However, to

remain consistent with the previous two streams of data collection, oncology patients were excluded (See Section 4.1.1 and Section 5.1.1).

6.1.2 Inclusion criteria

A patient was considered a study case if the reaction in question met the definition for an ADR, a causality classification of *definite*, *probable* or *possible* was established, and if the ADR occurred while the patient was an inpatient of a ward of a hospital.

6.1.3 Data collection

Adverse drug reactions arising in the inpatient population were identified using two methods: *spontaneous monitoring*; and *retrospective intensive monitoring.* Spontaneous monitoring involved using the existing ADR reporting systems operating within the three hospitals, all of which were voluntary systems that received reports from doctors, pharmacists and nurses. At both RCH and BH, posters highlighting the reporting system were present in the hospital wards. The ADR reporting forms used at RCH and BH were separate to the "blue card" of the Australian Adverse Drug Reactions Advisory Committee (ADRAC).[195] Using the hospital specific forms, details of ADRs are filed in the pharmacy departments of RCH and BH regardless of whether or not a report is forwarded to ADRAC. At GH, a separate ADR form is not used, rather an ADRAC blue card is completed if a serious and/or unusual ADR is identified. The blue card is sent to ADRAC and a copy is kept on file in the pharmacy department. Incentives in the form of chocolates or pens, are offered by the pharmacy department to help motivate staff at RCH to report ADRs.

Retrospective intensive monitoring involved reviewing ADR related *International Classification of Diseases, 9th edition, Clinical Modification (ICD-9-CM)*[196] and *International Statistical Classification of Diseases and Health Related Problems, 10th revision, Australian Modification (ICD-10-AM)* codes[197]. The ICD-9-CM codes were used to identify ADRs for patients

admitted up to July 1998 and the ICD-10-AM codes thereafter. Copies of the ICD-9-CM and ICD-10-AM ADR codes can be found in Appendix Eight.

A preliminary review of the medical histories of patients identified by both monitoring methods was then conducted. Details of the ADRs, along with relevant admission information, was then recorded in a specially designed Microsoft Access 97 (Microsoft Corporation, Redmond, WA, USA) database to allow subsequent analysis.

6.1.4 Pharmacy panel review

The *pharmacy panel* reviewed information collected for each patient identified and established the likelihood of an association between drug administration and the reported reaction. When such an association was established, causality (Section 3.4.2), preventability (Section 3.5), and clinical significance (Section 3.6.3) classifications were determined by the *pharmacy panel*.

6.1.5 Data analysis

The data were analysed using the Statistical Package for the Social Sciences (SPSS) for Windows version 10 (SPSS Inc, Chicago, IL, USA). Differences in gender distributions were investigated using a Chi-Square Test. The Mann-Whitney U Test was utilised to establish if significant differences in age existed between cases identified and the eligible population. The Kruskal-Wallis H Test was used to make age related comparisons among the eligible patient populations of the three hospitals. A significance level of 0.05 was selected for all tests. The 95% confidence intervals (95% CI) for frequencies reported were determined using confidence intervals for a proportion[180].

6.2 Results

6.2.1 Royal Children's Hospital

A 29-week period of data collection was conducted at RCH over three separate time periods: 23 March 1998 to 1 May 1998; 11 May 1998 to 13 September 1998; and 28 September 1998 to 30 October 1998. These time periods corresponded to the data collection periods for investigating emergency department attendances and hospital admissions associated with DRPs (See Section 4.2.1 and Section 5.2.1).

Over the data collection periods a total of 17,103 patients were admitted to wards of RCH. Nine hundred and sixteen were oncology patients and hence excluded, leaving a total of 16,187 eligible patients. Eligible patients were predominantly male (60.6%, 9,804/16,187) with a mean age of 7.3 years (median 4.0, ±SD 5.0).

A total of 39 ADR reports were collected utilising *spontaneous monitoring.* Four were excluded because the patients were not admitted over the period of data collection. One was excluded because the patient was over 17 years of age, and 2 were excluded because they involved oncology patients. Three other ADR reports were excluded from this analysis because they referred to reactions that were determined by the *multidisciplinary panel* to have occurred prior to admission to hospital. For 2 reports the medical histories of the patients could not be located by the medical records department, so these reports were excluded. The *pharmacy panel* ultimately reviewed 27 reports, 7 of which were excluded because the ADRs were determined to have not occurred in a ward of the hospital, and a further 3 were excluded due to a lack of information. The net result was that 17 cases identified by *spontaneous monitoring* were considered by the *pharmacy panel* to have experienced ADRs while inpatients of the hospital.

Utilising *retrospective intensive monitoring,* a total of 244 ADR reports were identified over 24 of the 29 weeks of data collection. ICD-10-AM codes were not available for the 5-weeks from 28 September 1998 to 30 October 1998.

Of the 244 reports, 162 were oncology patients and hence excluded. Five others were excluded because the patients were not admitted during the period of data collection. Fifteen reports were excluded because they referred to reactions determined by the *multidisciplinary panel* to have occurred prior to admission. Two other reports were excluded because the ADR had already been identified using *spontaneous monitoring*. Twenty-six reports were excluded because too little information on the ADR was found, and a further 5 were excluded because the coded adverse reaction did not involve a drug. The *pharmacy panel* ultimately reviewed a total of 29 ADR reports. Three of these were excluded because the ADRs did not occur within a ward of the hospital. A further 3 reports were excluded due to a lack of information. The net result was that 23 cases identified by *retrospective intensive monitoring* were determined by the *pharmacy panel* to have experienced ADRs while inpatients of the hospital.

Combining the two methods, a total of 40 cases were determined by the *pharmacy panel* to have experienced ADRs while inpatients of the hospital. Of the 40 cases identified, the proportion of males was significantly less than that of the eligible population (42.5%, $p = 0.0298$). The mean age of cases was 8.7 years (median 9.3, $\pm$SD 5.5). The age of cases was significantly higher than that of the eligible population ($p < 0.001$). One of the 40 cases died whilst in hospital but the extent to which the ADR contributed to the death could not be quantified.

The frequency of ADRs reported to have been experienced while an inpatient of the hospital was determined to be 0.2% (95%CI 0.1 – 0.3%).[*]

6.2.2 Geelong Hospital

An 8-week period of data collection was conducted at GH from 7 June 1999 to 30 July 1999.

---

[*] An incidence rate was not determined for the results presented in this chapter given the similarities in the denominators that would be utilised and the level of under-reporting identified in Section 6.3.5.

Over this period a total of 963 paediatric patients were admitted to a ward of GH. This figure includes 167 singletons[†] born in hospital. Eighteen of the 963 were oncology patients and were hence excluded, leaving a total of 945 patients that were eligible for inclusion. Eligible patients were predominantly male (51.4%, 486/945) with a mean age of 4.5 years (median 2.0, ±SD 5.3).

During the 8-week period no ADR reports for paediatric patients were collected using *spontaneous monitoring*.

Using *retrospective intensive monitoring* a total of 5 ADR reports were identified over the period of data collection. Two involved oncology patients and were excluded. One report was excluded because it referred to an ADR determined by the *multidisciplinary panel* to have occurred prior to admission. One report was excluded, as the ADR did not occur while an inpatient of the hospital. The *pharmacy panel* determined the remaining report to fulfil case inclusion criteria. The single case was an 8 year old female. No valid statistical comparisons can be made between the eligible population and the case identified.

The frequency of ADRs reported to have been experienced while an inpatient of the hospital was determined to be 0.1% (95%CI >0.0 – 0.3%).

6.2.3 Box Hill Hospital

A 4-week period of data collection was conducted at BH from 8 November 1999 to 3 December 1999.

Over this period a total of 302 paediatric patients were admitted to wards of BH. This figure includes 165 singletons born in the hospital. Two of the 302 patients were oncology patients and were excluded, leaving a total of 300 patients that were eligible for inclusion. Eligible patients were predominantly male (58.0%, 174/300) with a mean age of 3.4 years (median 0.5, ±SD 4.9).

[†] Singletons born in hospital include any neonates born within the hospital specified.

During the 4-weeks of data collection no ADR reports for paediatric patients were obtained using *spontaneous monitoring*.

Two ADR reports were identified using *retrospective intensive monitoring* over the period of data collection. One was excluded because the adverse reaction did not involve a drug and the second was excluded as it referred to a case determined by the *multidisciplinary panel* to have experienced an ADR prior to admission.

No ADR reports at BH were reviewed by the *pharmacy panel*.

6.2.4 Combined data for RCH, GH and BH

Combining data from the three hospitals, a total of 18,368 paediatric patients were admitted to wards over the periods of data collection. Of these, 936 were oncology patients and hence excluded, leaving a total of 17,432 patients eligible for inclusion. Eligible patients from the three hospitals were significantly different with respect to gender ($p < 0.0001$), with a significantly lower proportion of males attending GH when compared to RCH ($p < 0.0001$). A significant difference in the proportion of males was not detected between GH and BH ($p = 0.0548$) or BH and RCH ($p = 0.3999$). Eligible patients were significantly different with respect to age ($p < 0.001$), a difference that was significant at an individual hospital level. Despite the statistically significant differences in gender and age it was considered valid to combine data collected from the three hospital sites.

Of the combined data, a total of 41 cases were determined by the *pharmacy panel* to have experienced ADRs while inpatients of the hospitals. Of these cases, the proportion of males was significantly less than that of the eligible population (41.5%, $p = 0.0236$). The mean age of cases was 8.7 years (median 9.0, ±SD 5.4). The age of cases was significantly higher than that of the eligible population ($p < 0.001$).

The frequency of cases identified via the two monitoring methods as having experienced ADRs while inpatients of the hospitals was determined to be 0.2% (95%CI 0.1 – 0.3%).

6.2.4.1   Extrapolation of data

In order to extrapolate data obtained to a state level, information on the number of paediatric hospital admissions was obtained. A total of 144,656 paediatric patients were admitted to Victorian hospitals from 1 July 1998 to 30 June 1999 (Personal communication, Penm R, Canberra: Australian Institute of Health and Welfare, August 2000). A proportion of the patients admitted to hospital over this time period would not have been considered eligible for inclusion if this study was conducted on a state wide basis due to the eligibility criteria outlined in Section 6.1.1. Therefore, an estimate of the number of eligible patients in Victoria was made using the combined data from the three hospitals. The estimate was based on the fact that of the 18,368 paediatric patients admitted to the three hospitals over the period of data collection, 17,432 were considered eligible.   Utilising the same proportions, it was estimated that, at a state level, 137,285 patients would be eligible for inclusion.

To extrapolate the frequency of cases determined to have experienced ADRs while inpatients of the three hospitals to a state wide basis, it was estimated that 0.2% of the 137,285 eligible admissions, or 274 patients, would have experienced ADRs over the one-year time period.

Nationally, there was estimated to be 1,300 paediatric patients who would have experienced an ADR while in hospital during the one-year time period, based on 650,145 paediatric hospital admissions (Personal communication, Penm R, Canberra: Australian Institute of Health and Welfare, August 2000).

It was initially thought that the validity of both the state and national extrapolations could be assessed by comparing with data reported by the Australian Incident Monitoring System (AIMS).[198] However, this approach was not possible because for ADR reports between July 1997 and

September 2000 where age was specified, only 15 related to paediatric patients (Personal communication, Szep S, Adelaide: Australian Patient Safety Foundation, September 2000).

To validate the state extrapolation a comparison was made with the ICD-10-AM ADR codes from the Victorian Inpatients Minimum Dataset for the same period. However, direct comparisons could not be made because the ICD-10-AM codes did not separate ADRs occurring in the inpatient population from those occurring prior to admission. Instead, an indirect comparison was made by obtaining data from the Victorian Inpatients Minimum Dataset on all paediatric patients with an ICD-10-AM ADR code, for comparison with all ICD-10-AM ADR codes noted in the research reported in this thesis for the three hospitals. The ICD-10-AM ADR code Y43 was excluded from both sources of data because the majority of patients falling under this code were oncology patients.

Using this approach a total of 513 patients were identified in the Victorian Inpatients Minimum Dataset over the one-year time period (Personal Communication, Boronvicar D, Melbourne: Acute Health, Department of Human Services, October 2000). In the research reported in this thesis a total of 251 ICD-10-AM ADR codes were identified across the three hospital sites. When Y43 coded episodes were excluded (n=164) a total of 87 cases were identified.

The frequency of admissions coded with an ICD-10-AM ADR code was therefore 0.5% (87/17,432). Extrapolating these results to a state level it was estimated that 0.5% of 137,285 admissions, or 686 paediatric patients, would be coded with an ICD-10-AM ADR code. This figure is higher than the 513 patients reported in the Victorian Inpatients Minimum Dataset.

6.2.4.2   Causality classification

With respect to combined data from the three hospitals, a causality classification of *probable* was determined for 13 cases (31.7%, 13/41), with a classification of *possible* for the remaining 28 cases (68.3%, 28/41).

6.2.4.3 Preventability classification

With respect to preventability, 35 (85.4%, 35/41) cases were determined not to be preventable, 4 (9.8%, 4/41) preventable, and the remaining 2 (4.8%, 2/41) cases were classified as *unsure*.

6.2.4.4 Clinical significance classifications

A clinical significance classification of *mild* was determined for 14 cases (34.2%, 14/41), *moderate* for 20 cases (48.8%, 20/41) and *severe* for 6 cases (14.6%, 6/41). In 1 case (2.4%, 1/41) a clinical significance classification was unable to be determined due to lack of information.

6.2.4.5 Pharmacy panel agreement

Inter-observer reproducibility for the *pharmacy panel* was measured using the Kappa statistic as outlined in Section 3.7.1. Kappa measures the strength of agreement between panel members, taking into account agreement that would occur by chance alone.

The strength of agreement between panel members when allocating a causality classification was found to be *poor*, with a Kappa value of 0.156.

The strength of agreement between panel members when allocating a preventability classification was found to be *fair*, with a Kappa value of 0.395.

The strength of agreement between panel members when allocating a clinical significance classification was found to be *fair*, with a Kappa value of 0.398.

The intra-observer reproducibility results recorded for *pharmacy panel* members are presented in Appendix Six.

6.2.4.6 Drug classes involved in ADRs

A total of 315 drugs were administered to cases during their time in hospital, with a mean of 7.7 drugs (median 7.0, ±SD 4.1) per case. Twenty-six drugs

were specifically implicated in the ADRs identified. Drug products containing multiple ingredients were considered as one entity in this count.

An analysis according to the Therapeutic Classification of the 26 drugs specifically implicated in the ADRs identified is provided in Table 6.1.

Table 6.1 Drugs associated with ADRs by Therapeutic Classification

Therapeutic Classification*	Drugs within classifications
Cardiovascular System	
-Diuretics	frusemide (2)[†]
Central Nervous System	
-Sedatives, hypnotics	midazolam (2)
-Antianxiety agents	diazepam (1)
-Antipsychotic agents	droperidol (1)
-Anticonvulsants	sodium valproate (1)
-Antiemetics, antinauseants	prochlorperazine (1)
Analgesia	
-Narcotic analgesics	codeine (2), morphine (6), pethidine (1)
Musculoskeletal System	
-Nonsteroidal anti-inflammatory agents	ibuprofen (1)
Endocrine and Metabolic Disorders	
-Agents affecting calcium and bone metabolism	disodium pamidronate (2)
Infections and Infestations	
-Penicillins	amoxycillin (1), ticarcillin / potassium clavulanate (1), penicillin G (1)
-Cephalosporins	cefpirome (1), cephazolin (3)
-Macrolides	erythromycin (2)
-Other antibiotics & anti-infectives	co-trimoxazole (1), metronidazole (1)
Respiratory System	
-Bronchodilator aerosols and inhalations	salbutamol (1)
Eye	
-Topical ocular anti-infective preparations	chloramphenicol (1)
Surgical preparations	
-Anaesthetics – local and general	propofol (1), thiopentone sodium (2),
-Neuromuscular blocking agents	atracurium (2), rocuronium (1)
Unlisted	amethocaine cream (4)

*Classification is according to the indexing used by MIMS Annual 2000.[183]
[†]The number of cases in which the drug was involved is indicated in parenthesis.

The 10 drugs most frequently associated with ADRs were: morphine; amethocaine cream; cephazolin; frusemide; midazolam; codeine; disodium pamidronate; erythromycin; thiopentone sodium; and atracurium.

6.2.4.7   Adverse drug reaction scenarios

In contrast to the cases reported earlier in this thesis, few details on the ADRs identified in this chapter were able to be extracted from the medical histories of cases identified. This, in association with the diversity of drugs and types of reactions identified, meant that it was difficult to classify ADRs identified into scenarios with a case description. So, in an attempt to summarise the type of reactions involved, the nature of the ADRs along with the number of cases and the drugs implicated are set out in Table 6.2.

Table 6.2 Characteristics of ADR cases

Nature of the ADR	Number of cases	Drugs implicated
Anaphylaxis	2	cefpirome, rocuronium
Rash	15	cephazolin, metronidazole, penicillin G, morphine, ticarcillin / potassium clavulanate, co-trimoxazole, codeine, amoxycillin, pethidine, sodium thiopentone, atracurium, ibuprofen
Localised application site reactions	5	chloramphenicol, amethocaine cream
Nausea, vomiting or diarrhoea	6	morphine, erythromycin, codeine, propofol
Febrile reactions	2	disodium pamidronate
Hallucinations, dyskinesias, behavioural reactions	4	midazolam, droperidol, prochlorperazine
Seizures	1	prochlorperazine
Electrolyte disturbances	2	frusemide, salbutamol
Respiratory depression	3	morphine, midazolam, atracurium, sodium thiopentone, diazepam
Coagulopathy	1	sodium valproate

6.2.5 Potential level of under-reporting

Under-reporting is one of the major limitations of collecting data via *spontaneous monitoring* or *retrospective intensive monitoring* (See Section 2.2.1.1). To enable the results presented in this stream of data collection to be interpreted appropriately, an estimate of the potential effect of under-reporting is required. Direct comparisons with *prospective intensive monitoring* data for ADRs arising within the inpatient populations were not possible (See Section 2.2.2), so an indirect estimate was made. This was done by comparing the number of ADRs resulting in admission to hospital identified by *prospective intensive monitoring* in the first two streams of data collection (See Table 4.4 and Table 5.3) with the number identified by *spontaneous monitoring* and *retrospective intensive monitoring*.

6.2.5.1 Spontaneous monitoring

In the stream of data collection discussed in this chapter a total of 39 ADR reports were identified via *spontaneous monitoring* for the three hospitals. Three of the 39 ADRs reports referred to reactions determined by the *multidisciplinary panel* to have occurred prior to admission.

A total of 147 ADR cases were determined by the *multidisciplinary panel* to be associated with emergency department attendances or hospital admissions (See Table 4.4 and Table 5.3), 37 of which were admitted to hospital. Three of the cases (8.0%, 3/37) detected via *prospective intensive monitoring* were therefore identified by *spontaneous monitoring*.

6.2.5.2 Retrospective intensive monitoring

Across the three hospitals a total of 251 ADR reports were identified by *retrospective intensive monitoring*. Seventeen of these referred to reactions determined by the *multidisciplinary panel* to have occurred prior to admission.

A total of 147 ADR cases were determined by the *multidisciplinary panel* to be associated with emergency department attendances or hospital admissions (See Table 4.4 and Table 5.3), 37 of which were admitted to

hospital. Six of the 37 cases were admitted over the period of data collection for which ICD-10-AM codes were not available at RCH and hence were excluded from the calculations. Seventeen of the cases (54.8%, 17/31) detected by *prospective intensive monitoring* were therefore identified by *retrospective intensive monitoring*.

6.3 Discussion

This stream of data collection provides the first information on the frequency of ADRs arising within the Australian paediatric inpatient population. The frequency of such reactions was reported to be 0.2% (95% CI 0.1 – 0.3%) at RCH and 0.1% (95% CI >0.0 – 0.3%) at GH. It was not possible to determine a figure for BH.

The fact that no cases were determined by the *pharmacy panel* to have experienced ADRs while inpatients at BH may limit the full analysis of the results presented in this stream of data collection. However, the impact of this is reduced by the finding that there were no significant differences in the frequency of ADRs arising within the inpatient populations at both RCH and GH. It is therefore possible that no significant differences in the frequency of ADRs would have been reported between the three hospitals if the period of data collection had been extended at BH.

The finding that there were significant differences in the age and gender distributions of the eligible patient populations from the three hospitals raises questions as to the logic of combining the data obtained. In contrast to previous discussions in this thesis (See Section 4.3), it cannot be readily argued that the statistically significant age differences reported for the eligible patient populations have no clinical significance. This is because the median age of the three eligible patient populations ranges from 0.5 to 4.0 years. Clinically significant differences in pharmacokinetics and pharmacodynamics would be expected across this age range.[17] It is most likely that the inclusion of singletons born at GH and BH accounts for the age differences seen between the three hospitals. The possible influence of singletons born in

hospital on the differences in ages can be used to argue the validity of combining data from the three hospitals. This is because reports in the literature indicate that neonates are at a high risk of developing ADRs, with the frequency ranging from 10.6 – 30.0%.[71-73] However, all studies reporting this risk have been conducted within neonatal intensive care units, where, due to their medical conditions, neonates are more prone to ADRs.[73] Neither GH or BH provide neonatal intensive care services, so it likely that the subpopulations equivalent to those reported in the neonatal ADR studies are not represented at these hospitals.[71-73] As a result the "healthier neonatal population" at GH and BH (whose risk of developing an ADR may not be higher than that of the remaining eligible population) justifies the combining of data obtained from the three hospitals.

The rationale for combining the eligible patient populations may also be supported by the finding that the gender differences encountered were not consistent across the three hospitals. Furthermore, it is proposed that the differences inherent in the patient populations and services provided by the three hospitals may enable a more representative reflection of ADRs occurring within the inpatient population to be obtained when the results are combined.

When data from the three hospitals were combined it was found that 0.2% (95% CI 0.1 – 0.3%) of eligible patients were identified as having experienced ADRs while inpatients. This finding does not accord well with that reported previously in the literature, where the majority of paediatric studies report the frequency to range from 1.73 to 16.8%.[58-60, 70, 71, 74-79] The frequency is higher if studies that consider only neonatal or oncology patients are included.[66, 72, 73] Although differences in the patterns of drug utilisation and patient populations may have contributed to the variations between the results reported in this thesis and reports in the literature,[58, 77] it is suggested that the major factor contributing to this disparity was the monitoring methods used. *Spontaneous* and *retrospective intensive monitoring* were used to identify potential cases in the stream of data collection reported in this chapter. In contrast, all but one of the 14 paediatric studies utilised

prospective intensive monitoring,[58-60, 66, 70-77, 79] a method that is more effective in detecting cases than *spontaneous* or *retrospective intensive monitoring*[89, 93, 95]. The remaining study used *spontaneous monitoring*, but the number of eligible patients was unknown, and hence the frequency of ADRs was unable to be determined.[78]

Comparisons with the adult population further emphasise the influence of monitoring methods utilised on the frequency of ADRs reported, because the frequency of ADRs reported in this thesis does not concur that reported in adult studies which used *prospective intensive monitoring*.[199] It could be suggested that the variations in the frequencies reported may have arisen as a result of differences in the number and type of drugs utilised in the two populations. This is unlikely however because the Boston Collaborative Drug Surveillance Program reported the number of ADRs per drug orders administered to be comparable between the paediatric and adult populations.[59]

The lower proportion of males experiencing ADRs reported in this thesis is at variance with the majority of studies conducted previously in the paediatric population, as only one study reported significant differences in gender between cases and the eligible population.[79] Similar studies conducted within the adult population have reported females to be more susceptible to ADRs than males.[200, 201] One these studies reported that this difference was still evident after consideration of the duration of hospitalisation, the number of drugs, age and the presence of liver or renal disease.[200] Despite this supporting evidence from the adult population, gender is unable to be confirmed as a risk factor until an analytical study design is utilised to investigate ADRs within the paediatric inpatient population.

A number of the paediatric studies investigating ADRs within the inpatient population have reported ADRs to increase with age.[71, 77-79] In one of these studies the authors noted that drug use increased with age from infancy through to adolescence, and it was therefore not surprising that the rates of reported ADRs also tended to rise with age.[71] In the results presented in this

thesis the trend of ADRs increasing with age was also evident, with the age of cases identified being significantly older than that of the eligible patient population. However, as reported for gender, more conclusive studies employing an analytical epidemiological study design are required before age can be considered a risk factor for ADRs within the paediatric inpatient population. As reported earlier in this thesis (See Section 2.2.2), employing an analytical study design was not feasible for the research presented in this thesis.

The validity of the extrapolations made in this thesis were measured indirectly through a comparison with the Victorian Inpatients Minimum Dataset. In doing so the estimated number of paediatric patients coded as experiencing an ADR in the results presented in this thesis was higher than the number actually reported in the Victorian Inpatients Minimum Dataset. It appears therefore, that the extrapolations may be overestimates. This conclusion is unlikely however, because the frequency of ADRs reported in this thesis was substantially lower than that reported in the literature. Furthermore, the level of under-reporting determined for the monitoring methods used (See Section 6.2.5) indicates that the state and national extrapolations made in this thesis may instead be conservative estimates.

In contrast with the previous two streams of data collection, the majority of cases identified in this one were not considered preventable. However, if the preventability data presented for emergency department attendances and hospital admissions associated with DRPs (See Table 4.6 and Table 5.5) are restricted to Category Five, where an ADR had occurred, a different picture is seen. In these chapters 58.5% and 79.3% of ADRs identified respectively were not considered preventable. The results of these three streams of data collection therefore suggest that a large proportion of ADRs are not preventable, a result which agrees with the findings of the one paediatric study that investigated the issue of preventability.[78] The authors of that study reported that only 7.7 % of ADRs identified were preventable,[78] a figure comparable to the 9.8% reported in this thesis. This issue has broader

implications with respect to the monitoring and prevention of ADRs within the paediatric inpatient population.

The issue of preventability has also been investigated within the adult population, with 19 – 80% of ADRs identified reported as preventable.[128, 202] This range is reduced to 19 – 58.8% if studies with similar ADR definitions and preventability criteria are reviewed only.[128, 130] The results reported for the adult population contrast the findings presented in this thesis and in the paediatric literature. This may indicate that ADR prevention strategies developed in the adult population may not be applicable to the paediatric population.

The clinical significance of ADRs has been investigated in a number of the paediatric studies reviewing ADRs within the inpatient population.[58, 60, 66, 70, 72, 73, 76, 77, 79] In the research presented in this thesis the majority of ADRs were allocated a clinical significance classification of *moderate*, a result that concurs with three of the paediatric studies within the literature.[58, 60, 66] The remainder of paediatric studies investigating the issue of clinical significance reported the majority of ADRs detected to be be *mild* in nature.[70, 72, 73, 76-79] Zilleruelo reported that ADRs classified as *mild* in nature could appreciably influence the frequency of ADRs reported.[132] Hence, it is possible to suggest that the high number of *mild* reactions included in the latter studies may have contributed to the differences in the frequency of ADRs reported between this thesis and previous paediatric studies. This is unlikely however, because the frequencies noted for the three studies that reported the majority of ADRs to be *moderate* in nature were also considerably larger than the frequency reported in this thesis. Therefore, it is instead more likely that the monitoring methods utilised and patient populations investigated accounted for the observed differences.

In the research presented in this thesis, a mean of 7.7 drugs were administered to cases during their hospital admission, a figure that fell within range of that reported within the literature (range: 7.4 – 10 drugs).[60, 66] Four of the 14 paediatric studies reported that patients experiencing ADRs

received a significantly higher number of drugs than patients who did not experience ADRs.[60, 66, 77, 79] A similar correlation was unable to be investigated in the research presented in this thesis because the drug utilisation patterns within the eligible patient population are unknown.

Similar patterns in the type of drugs involved in ADRs identified were not evident when the results presented in this chapter were compared with the paediatric studies identified in the literature.[58-60, 66, 70-79] Differences in the patient populations investigated along with the year in which of a number of the studies were conducted are acknowledged as factors possibly contributing to the inability to identify a common link.

One of the most important findings of this stream of data collection was the degree of potential under-reporting determined for the two monitoring methods employed. This under-reporting may play a major role in the variance in the frequency of ADRs identified in the research presented in this thesis with that reported in both the paediatric and adult literature. It could be argued that, as an indirect method was used to estimate the degree of under-reporting, the estimate determined may not be an accurate reflection of the actual level of under-reporting. However, given the potential level of severity inferred by an ADR associated with a hospital admission it is proposed that these type of ADRs are more likely to be reported than ADRs arising in the inpatient population, and therefore the method utilised was appropriate.[203]

In the research presented in this thesis 8% of ADRs identified via *prospective intensive monitoring* were also identified utilising *spontaneous monitoring*. The level of under-reporting estimated does not represent a new phenomenon. In comparing *spontaneous monitoring* with *prospective intensive monitoring*, Jha et al found that only 4% of adverse drug events detected via the intensive method were reported using *spontaneous monitoring*.[89] Similarly, comparing the same monitoring methods, Bennett & Lipman reported the frequency of ADRs to be 0.08% or 7.2% respectively if spontaneous and prospective intensive monitoring were used.[143] Furthermore, when compared to *spontaneous monitoring* the level of under-

reporting found in this thesis was markedly lower with *retrospective intensive monitoring* (8.0 vs 54.8%). This finding has also been reported previously.[129, 204] These results confirm previous reports of the limited usefulness of *spontaneous monitoring*.[88, 93]

In contrast to reports in the literature, the number of ADRs detected via *retrospective intensive monitoring* in the research presented in this thesis was higher than that reported in a comparable study conducted by Roughead et al.[41] In their study it was reported that, depending upon the hospital, 11 – 31% of ADRs identified via *prospective intensive monitoring* were detected utilising *retrospective intensive monitoring*.[41] These results indicate that the level of under-reporting identified in the research presented in this thesis cannot be considered unique to the hospitals investigated in this thesis. This finding has broader implications for the methods by which ADRs are monitored in the paediatric population.

6.4 Conclusions

The frequency of ADRs arising within the inpatient population reported in this chapter was found to be substantially lower than that reported in previous studies conducted in both paediatric and adult populations. The degree of under-reporting identified with the monitoring methods utilised was considered the primary factor contributing to this difference. However, the level of under-reporting was not unique to the research reported in this thesis, because similar levels are evident in both the literature and the Victorian Inpatients Minimum Dataset. These results have implications for the surveillance of ADRs within the paediatric population, which will be discussed further in Chapter Eight.

7 The economic implications of DRPs in paediatrics

A primary goal in undertaking research investigating the consequences of DRPs in paediatrics is to identify potential areas to target for future prevention strategies. Although the development of such strategies is beyond the scope of the research reported in this thesis, the collection of baseline data pertaining to the economic implications of DRPs in this population is within its scope. The link between the two is an important one, as the economic data presented in this thesis will provide baseline data which may enable the costs and benefits of funding future prevention strategies to be assessed. In order to provide this baseline data, this chapter will report on the direct and indirect costs of emergency department attendances and hospital admissions associated with DRPs in paediatrics using a *cost of illness* approach.

In presenting these data, this chapter is split into three sections. The first outlines the background and methods relating to the determination of the direct costs incurred by the three hospitals as a result of the emergency department attendances and hospital admissions associated with DRPs identified in this thesis. The results are presented separately for these two streams of data collection. The second section relates to the indirect costs incurred as a result of the DRPs identified in the two streams of data collection. This section is split into the methods and results relating to the costing questionnaire, and the methods and results relating to the analysis of the indirect costing information obtained from the questionnaire. The third section combines the results of data presented in the two previous sections to provide the aggregate total for direct and indirect costs of emergency department attendances and hospital admissions associated with DRPs in the paediatric population investigated in this thesis. The results presented in this chapter are then discussed.

7.1 Direct costs incurred by RCH, GH and BH

In the context of this thesis, direct costs are those incurred by the three hospitals in the diagnosis and treatment of the DRPs identified. It was assumed that no lifelong direct costs were incurred as a result of the DRPs.

The direct costs incurred by hospitals may be calculated in a number of ways, with the three most common being the determination of *per diem* costs, the use of *cost modelling* or by utilising *clinical costing*.[205] *Per diem* costs are derived by dividing total hospital expenditure by the number of occupied bed days.[205] The calculated cost per day is then attributed to patients on the basis of recorded length of stay. Patterns of increased resource utilisation over shorter lengths of stay, along with the impact of patient diagnosis on resource utilisation have meant that *per diem* costs often bear little relationship to the use of resources by individual patients.[205] *Cost modelling* aims to improve upon the *per diem* approach by allocating a portion of total hospital expenditure to various "products" of the hospital, such as diagnosis related groups*.[205] This process is referred to as the "top down" allocation of costs.[205] As stated by Jackson et al "the precision of the estimates from a cost model relies upon the extent to which the model is related to actual resource utilisation".[205] A further refinement on the cost modelling approach is that of *clinical costing*, which derives a cost per patient built up from the recorded utilisation of individual products.[205] Put simply, this means that costs are attached to individual products, such as specific laboratory tests or types of drugs, and the number of these individual products used by a patient over the course of their hospital stay are then multiplied by the cost per product. The total costs determined for individual products are then summed to obtain a final hospital cost for a patient. To do so means that individual departments, such as pharmacy or pathology, must be equipped with computerised forms or "feeder systems" to enable costs to be tracked to an individual patient.[205] This approach provides the most accurate individual costing assessment available at this point in time.[205] It is

---

* Diagnosis related groups are a classification system that enables admissions to be allocated to certain groups depending on diagnosis, procedures undertaken, age, sex and discharge status.

for this reason that the *clinical costing* method was utilised in the determination of hospital costs unless otherwise indicated.

7.1.1 Methods for determining direct costs

The clinical costing departments of the three hospitals provided details on the methods by which individual departments allocated costs to each patient. In obtaining this information it was ascertained that BH calculates costs for patients admitted to hospital only. There were, however, no cases identified at BH which had hospital admissions associated with DRPs over the one-week period of data collection, so costing methods will be reported for RCH and GH only.

The data collected were analysed using Microsoft Excel 97 (Microsoft Corporation, Redmond, WA, USA).

7.1.1.1 Hospital overheads

Catering costs were calculated on an individual basis at RCH, with the catering department assigning these costs based upon the resources utilised during a patient's admission. At GH catering costs were based upon length of stay. All catering costs will be included under the heading of *nursing* (See Section 7.1.1.7) as per normal costing procedure at these hospitals.

The costs of domestic services, electricity, gas and administration were not calculated on an individual basis. These costs were allocated to each patient based upon the proportion of weighted floor space occupied and a patient's length of stay. These costs were allocated to the various individual departments listed below (See Section 7.1.1.2 to Section 7.1.1.11)

7.1.1.2 Pharmacy

At RCH medication costs were calculated on an individual patient basis. The individual drugs and doses administered during a patient's admission were recorded. A cost per drug was subsequently calculated based upon the

actual number of doses received multiplied by the market price per unit dose. The pharmacy buying guide of the Victorian Hospitals Association was used to determine the market price per unit dose of medication.[206] At GH drug costs were allocated to patients based upon ward imprest costs and length of stay.

Pharmacy overheads were not calculated on an individual patient basis at either RCH or GH. Such costs were allocated by length of stay to each patient based upon an estimated proportion of time and salary expenses required to service each area.

7.1.1.3   Radiology

Radiology costs at RCH were allocated on an individual patient basis. The numbers of individual procedures undertaken during a patient's hospitalisation were recorded. The final radiology cost for a patient was determined by multiplying the number of procedures performed by the standard cost for each procedure. At GH radiology costs were based upon the rate specified by the Commonwealth Medical Benefits Schedule.[207]

7.1.1.4   Pathology

Pathology costs were allocated on an individual patient basis at RCH. The type and number of procedures undertaken during a patient's hospital attendance were recorded. The costs were obtained by multiplying the number of procedures performed by the standard cost for each procedure. At GH pathology costs were allocated based upon length of stay.

7.1.1.5   Operating theatre

Operating theatre costs were allocated on an individual patient basis at RCH. The average costs associated with the majority of frequently performed procedures had previously been calculated by the hospital. Where a procedure had not previously been costed, the cost was based upon theatre time and nursing resources required. At GH nursing and medical costs,

along with costs for consumables, were based upon theatre time, with the exception of individual prosthesis costs which were allocated separately.

7.1.1.6 Allied health*

Allied health includes services such as those provided by dietitians, occupational therapists, and physiotherapists. The costs associated with these services were allocated on an individual patient basis at both RCH and GH. The time spent and service type was recorded for an individual patient by the allied health professional. A final cost was then obtained by multiplying the time spent with each patient by a standard cost per time period for the service provided.

7.1.1.7 Nursing*

Nursing costs were allocated on an individual patient basis at RCH and GH. A nursing acuity scale was used to determine the intensity with which nursing resources were utilised by a particular patient. This scale was used on a daily basis and nursing costs for the day were allocated to a patient depending on the level of dependency indicated by the scale.

7.1.1.8 Medical*

Medical costs were allocated based upon length of stay at both hospitals. This method assumes that doctors spend the same period of time with each patient, and hence the total medical costs are divided by the total number of patients and the resulting figure was multiplied by a patient's length of stay.

For patients reviewed by doctors working within the emergency department only, medical costs were listed under the heading of emergency department.

7.1.1.9 Emergency department

For patients attending the emergency department or admitted to hospital via the emergency department at RCH, the costs associated with emergency

---

* Classified as a "department" for costing purposes by the clinical costing departments.

department resource use were assigned in the same way as those admitted to hospital, with the exception of nursing costs. Nursing costs were instead assigned using the triage category allocated to the patient.[182] This allowed an individual assessment of the level of nursing resources required. At GH emergency department costs were determined solely on the basis of the triage category allocated to the patient.

7.1.1.10 Cardiac care unit

The cardiac care unit is considered a high dependency unit at both RCH and GH and therefore the costs associated with this unit were listed separately. In this section, medical and nursing costs were allocated to patients based upon the nursing acuity scale outlined in Section 7.1.1.7.

7.1.1.11 Intensive care unit

The intensive care unit is considered a high dependency unit at RCH and GH and hence the costs associated with this unit were listed separately. At RCH, costs associated with the neonatal care unit were also recorded under this heading. Nursing costs in the intensive care unit were based upon the nursing acuity scale outlined in Section 7.1.1.7. The medical costs in the intensive care unit are calculated based upon the length of stay of a patient.

7.1.2 Results regarding the direct costs incurred due to emergency department attendances associated with DRPs

7.1.2.1 Royal Children's Hospital

The *multidisciplinary panel* determined that 244 cases had emergency department attendances associated with DRPs (See Section 4.2.1). Individual costing data was available from the RCH clinical costing unit for 210 of these cases, but not for the remaining 34 cases, 1 of which was admitted to hospital from the emergency department.

To enable costs for these 34 cases to be estimated, the other 210 cases were split into two groups: patients *admitted*; and patients *not-admitted*. For costing purposes the term *admitted* included admissions to the emergency department, with 61 cases meeting this definition. The total costs for cases allocated to these two groups are presented in Table 7.1. The average admitted emergency department cost per patient of $1,454.33 was allocated to the 1 case admitted to hospital from the emergency department. The average *not-admitted* emergency department cost of $164.65 was allocated to the remaining 33 cases. Hence, the total cost incurred by the RCH as a result of the 244 cases identified to have emergency department attendances associated with DRPs was estimated to be $120,134.78.

Table 7.1 Total costs for emergency department cases at RCH

Individual departments	Admitted cases (n = 61)	Not-admitted cases (n = 149)
Pharmacy	$1,892	$0
Radiology	$571	$391
Pathology	$4,403	$1,720
Theatre	$344	$0
Allied Health	$1,284	$272
Nursing	$34,444	$1,677
Medical	$31,302	$5
Emergency Department	$10,013	$20,468
Cardiac Care Unit	$383	$0
Intensive Care Unit	$4,078	$0
Total	$88,714	$24,533

7.1.2.2 Geelong Hospital

The *multidisciplinary panel* determined that 22 cases had emergency department attendances associated with DRPs (See Section 4.2.2). Individual costing data were not available from GH for patients attending over the data collection period (Personal communication, Hose J, Geelong: Barwon Health, Geelong Hospital, June 2000).

To provide an estimate of the costs associated the cases identified, costing data for all patients attending the emergency department or admitted to hospital via the emergency department for the month of May 1999 was obtained from GH. The costing data was unable to be reviewed by age and hence non-paediatric patients were included in the data. Data was obtained

for a total of 13,170 patients, 6,074 of whom were excluded according the criteria outlined in Table 7.2. The remaining 7,096 were then split into *admitted* and *not-admitted* patients. A total of 1,871 met the costing definition of *admitted*. The total costs for cases allocated to these two groups are presented in Table 7.3. The average admitted emergency department cost of $1,175.67 was allocated to the 9 cases admitted to hospital from the emergency department. The average *not-admitted* emergency department cost of $118.58 was allocated to the remaining 13 cases. Hence, the total cost incurred by the hospital as a result of the 22 cases identified as having emergency department attendances associated with DRPs was estimated to be $12,122.57.

Table 7.2 Characteristics of patients excluded from GH costing dataset

Number excluded	Reason for exclusion
2312	No costs were documented for these patients.
3586	Hospital costing information often differs between public patients and those admitted privately.[208] Hence, in an attempt to ensure all costs were included in the data utilised, patients listed as covered by health insurance were excluded.
143	At GH paediatric patients are generally admitted to either the paediatric ward or the intensive care unit depending upon the severity of the illness in question. For this reason it is unlikely that paediatric patients would be admitted to the Cardiac Care Unit of the GH. Hence, patients for which costs were recorded for the Cardiac Care Unit were excluded.
33	The longest length of stay for cases identified as having emergency department attendances or hospital admissions associated with DRPs was 12 days. Hence, patients with a length of stay longer than 12 days were excluded.

Table 7.3 Total costs for emergency department patients at GH

Individual departments	Admitted cases (n = 1871)	Not-admitted cases (n = 5226)
Pharmacy	$74,445	$27,661
Radiology	$85,747	$167,523
Pathology	$98,494	$46,196
Theatre	$375,313	$19,023
Allied Health	$43,428	$4,332
Nursing	$1,056,746	$0
Medical	$343,252	$214,427
Emergency Department	$98,735	$140,542
Cardiac Care Unit	$0	$0
Intensive Care Unit	$23,513	$0
Total	$2,199,673	$619,704

7.1.2.3 Box Hill Hospital

The *multidisciplinary panel* determined 14 cases at BH to have emergency department attendances associated with DRPs (See Section 4.2.3). Individual costing data was not available for patients attending BH emergency department (See Section 7.1.1), so an estimate was determined utilising GH data (See Section 7.1.2.2).

The average *admitted* cost of $1,175.67 was allocated to 3 patients, while the average *not-admitted* cost of $118.58 was allocated to the remaining 11 cases. Hence, the total costs incurred by BH as a result of the 14 cases identified as having emergency department attendances associated with DRPs was estimated to be $4,831.39.

7.1.2.4 Combined hospital costs for emergency department attendances associated with DRPs

The total direct costs incurred by the three hospitals as a result of the 280 emergency department attendances associated with DRPs was $137,088.74, of which $44,555.01 was associated with DRPs determined by the *multidisciplinary panel* to be preventable.

7.1.3 Results regarding the direct costs incurred due to hospital admissions associated with DRPs

7.1.3.1 Royal Children's Hospital

The *multidisciplinary panel* determined 119 cases to have hospital admissions associated with DRPs (See Section 5.2.1). Individual costing data was available from the clinical costing unit of the hospital for 118 of these cases, resulting in a total of $224,624.00. Table 7.4 provides a breakdown of the total cost calculated for the individual departments.

The average hospital admission cost of $1,903.59 was allocated to the 1 case for which costing data was unavailable. Hence, the total cost incurred by the RCH as a result of the 119 cases identified to have hospital admissions associated with DRPs was determined to be $226,527.59.

Table 7.4 Total costs for cases admitted to RCH

Individual departments	Admitted cases (n = 118)
Pharmacy	$5,961
Radiology	$1,587
Pathology	$13,771
Theatre	$1,910
Allied Health	$2,896
Nursing	$87,527
Medical	$75,887
Emergency Department	$15,733
Cardiac Care Unit	$5,823
Intensive Care Unit	$13,529
Total	$224,624

7.1.3.2 Geelong Hospital

The *multidisciplinary panel* determined 8 cases to have hospital admissions associated with DRPs (See Section 5.2.3). Individual costing data was not available for the majority of cases, so the 1,871 patients *admitted* to GH via the emergency department over the month of May 1999 were used to estimate the costs for cases admitted to GH (See Section 7.1.2.2).

The average hospital admission cost of $1,175.67 was allocated to the 8 cases identified at GH. Hence, the total cost incurred by the GH as a result of the 8 cases identified to have hospital admissions associated with DRPs was determined to be $9,405.36.

7.1.3.3　Box Hill Hospital

No cases were determined to have hospital admissions associated with DRPs over the period of data collection, so no costing data are provided in this section.

7.1.3.4　Combined hospital costs for hospital admissions associated with DRPs

The total direct costs incurred by the three hospital sites as a result of the 127 hospital admissions associated with DRPs was $235,932.95, of which $144,250.02 was associated with DRPs determined to be preventable by the *multidisciplinary panel*.

7.1.4 *Combined direct costs incurred as a result of emergency department attendances and hospital admissions associated with DRPs*

In Chapters Four and Five a total of 407 cases were identified by the *multidisciplinary panel* to have either emergency department attendances or hospital admissions associated with DRPs. The total direct and indirect costs incurred by the three hospitals as a result of these cases was calculated by adding the total costs indicated in Sections 7.1.2.4 and 7.1.3.4. The total cost was determined to be $373,021.69, of which $188,805.03 was associated with DRPs determined by the *multidisciplinary panel* to be preventable.

7.2　Indirect costs incurred as a result of DRPs

In the context of this thesis, indirect costs are those incurred by society through lost production as a result of morbidity and premature mortality associated with DRPs.[164] The costs to society included travel costs and time lost from the workforce as a result of emergency department attendances and hospital admissions associated with DRPs. It was assumed that no lifelong indirect costs were incurred as a result of the DRPs identified.

Information on indirect costs was ascertained via a structured questionnaire. The methods and results describing the development and use of the structured questionnaire are presented in Section 7.2.1.

7.2.1 Costing questionnaire

7.2.1.1 Questionnaire development and distribution

The structured questionnaire utilised to collect costing information comprised two sections: the first to collect costing data; and the second to collect data relating to medication use. The medication use component of the questionnaire is not relevant to this chapter and hence is not further discussed.

The costing component was based upon that published by Street, with minor adjustments being made to adapt it to a paediatric setting.[209] A copy of the questionnaire is in Appendix Nine.

The questionnaire was distributed to the parents or guardians of paediatric patients attending the emergency department at the RCH, and to the parents or guardians of paediatric patients admitted to RCH, GH or BH. Emergency department attendance and hospital admission lists were used to select patients, a process which involved selecting each patient listed at a specified interval. This method was undertaken in preference to only distributing questionnaires to identified cases for two reasons. Firstly, distribution could not be undertaken around the clock, hence, some patients had been discharged before consent to send a questionnaire could be requested. Secondly, the *multidisciplinary panel* determined which patients met inclusion criteria, a process that was undertaken over a two-year period. It was therefore not practical to distribute questionnaires after the panel had established if inclusion criteria had been met. Instead, prior to discharge, the parent or guardian of a patient selected from the emergency department or hospital admission list was given a copy of the explanatory statement by the investigator. Parents or guardians from non-English speaking backgrounds

were given the option of receiving the explanatory statement in either Turkish or Vietnamese, or having it explained to them via a hospital interpreter in an appropriate language. Copies of the explanatory statements for each of the three hospitals are in Appendix Ten.

If consent to receive a questionnaire was granted, a questionnaire was sent to the parent or guardian one-week post discharge. If a response was not received after a two-week period, a reminder letter was sent. Then, if a response to the questionnaire was not received after a four-week period, a telephone call was made to give the parent or guardian the option of withdrawing from the study, receiving another questionnaire or answering the questionnaire by telephone if it was convenient to do so.

If assistance with language was required to answer the questionnaire, parents or guardians were given the option of receiving it in either Turkish or Vietnamese or answering the questionnaire via a telephone call involving the investigator and an interpreter.

The data were analysed using the Statistical Package for the Social Sciences (SPSS) for Windows version 10 (SPSS Inc, Chicago, IL, USA). Differences in age were investigated utilising the Mann-Whitney test. Differences in gender were investigated using a Chi-Square test. A significance level of 0.05 was utilised.

7.2.1.2 Results relating to the questionnaire response rate and characteristics of respondents

Questionnaires were distributed within the RCH emergency department from 19 October 1998 to 30 October 1998 and within RCH admitted patient population from 25 January 1999 to 5 February 1999. At GH and BH questionnaires were distributed from 21 June 1999 to 30 July 1999 and 18 November 1999 to 3 December 1999 respectively. The numbers of parents or guardians invited to consent to receive a questionnaire along with response rates are listed in Table 7.5.

Table 7.5 Questionnaire distribution and response rates

Hospital site	Invited to consent	Consent not given	Completed questionnaires	Response rate %
RCH ED*	31	4	18	66.6
RCH	75	5	55	78.6
GH	30	1	23	79.3
BH	24	2	16	72.7
Total	160	12	112	75.7

*Royal Children's Hospital emergency department

There were no significant differences with respect to age ($p = 0.759$) or gender ($p = 0.8271$) between questionnaire responders and non-responders over the three hospitals.

There were no significant differences with respect to age ($p = 0.126$) or gender ($p = 0.5809$) between the cases identified to have emergency department attendances or hospital admissions associated with DRPs, and patients whose parents or guardians received a questionnaire.

7.2.2 Costing information

The methods and results relating to the analysis of the costing information collected via the structured questionnaire are presented in this Section.

7.2.2.1 Methods to determine costing information

Information regarding travel costs and costs associated with caring for an ill child were collected. The methods used to determine and analyse these costs were based upon those published by Street.[209] Although no significant differences in age ($p = 0.126$) or gender ($p = 0.5809$) patterns were detected between cases identified to have emergency department attendances or hospital admissions associated with DRPs, and patients whose parents or guardians received a questionnaire, potential differences in severity of illness

were not as easy to quantify. In an attempt to adjust for possible severity of illness differences, travel costs and costs associated with caring for an ill child were determined on a cost per day spent in the emergency department or in hospital. A length of stay of one day was allocated to patients attending the emergency department for less than 24 hours.

7.2.2.1.1 Travel costs

There were two components to travel costs: the cost of transportation; and the cost of time spent travelling. Information was collected on these areas in the questionnaire by inquiring about the number of trips made to hospital, the distance from home to the hospital, and the mode of transport used.

The cost of transportation was calculated by first determining the mode of transport used to travel to hospital. It was assumed that all trips were made by private vehicle unless public transport was listed as the only option. An average private vehicle operating cost per kilometre was determined using the average private vehicle operating costs per kilometre reported for a range of vehicle types (See Appendix Eleven). Public transport costs were determined using the price of zone one and / or zone two day tickets.[210] The cost of a daily zone two ticket was utilised for distances travelled that were greater than 20km. The distance travelled was then ascertained from each questionnaire, but was capped at 45km. The cost per kilometre for the mode of transport indicated and the distance travelled were then multiplied for each response, and an average cost of transportation was then calculated.

The cost of time spent travelling was calculated using the transport time figures reported by Street.[209] Briefly, travelling 10 or 20km by car required 30 or 45 minutes respectively, and 60 or 90 minutes for public transport. An average time per kilometre was then determined for each mode of transport. To assign a dollar value to the time spent travelling, an average hourly rate for an adult working full-time was calculated.[211] The cost per hour of travelling was based on 40% of the hourly figure determined, a percentage reported by the United Kingdom Department of Transport.[212] The cost per

hour was then multiplied by the estimated time required to travel the distance noted in each questionnaire and an average cost of time spent travelling subsequently calculated.

To calculate travel costs on a daily basis, the average number of trips per day was obtained from the questionnaire. The average figure was then multiplied by the average figures calculated for both the cost of transportation and the cost of time spent travelling, resulting in a total average travel cost per day.

7.2.2.1.2   Costs associated with caring for an ill child

There were a number of issues to be considered when calculating the costs associated with caring for an ill child. The first relates to the indirect costs incurred by society as a result of days lost to paid or unpaid work by parents or guardians due to their child requiring more care than normal.[213-215] The second pertains to the indirect costs incurred by society as a result of days lost from regular leisure activities by parents or guardians due to their child requiring more care than normal.[213] There is considerable debate about appropriate methods to calculate the costs associated with unpaid work and time out of regular leisure activities,[209, 213] so the lead provided by Carlin et al has been followed[213]. That is, average weekly earning estimates have been applied to all time lost to paid or unpaid work or regular leisure activities, whether within or outside the paid work force.

To obtain information on the costs associated with caring for an ill child, parents or guardians were asked how many days they lost to regular leisure and paid activity as a result of their child attending the emergency department or being admitted to hospital. The same information was obtained for the period after discharge. The total number of days reported for each of these questions was then determined for each questionnaire respondent. The total number of days lost was then divided by the length of stay reported in each questionnaire, and an average total number of days lost calculated. To assign a dollar value to the average total number of days

lost, the average daily rate was calculated using the average earnings for an adult working full-time.[211] The daily rate was then multiplied by the average total number of days lost to determine a cost per day spent in the emergency department or hospital.

7.2.2.1.3   Extrapolation of costs

The travel costs and costs associated with caring for an ill child were then extrapolated to the emergency department attendance and hospital admission cases identified in Chapters Four and Five.   This was done by adding these costs to determine a total cost per day spent in the emergency department or in hospital.   The total cost was then multiplied by the length of stay of the cases identified.

7.2.2.2   Calculation of the indirect costs associated with DRPs

7.2.2.2.1   Travel costs

One hundred and twelve questionnaire responses were received over the three hospital sites.   The modes of transport used by patients to travel to hospital on at least one occasion are shown in Table 7.6.   In calculating the costs of transportation it was assumed that 5 patients travelled by public transport, with the remaining travelling by private vehicle.   The average private vehicle operating cost per kilometre was determined to be $0.50 (Appendix Eleven) and the prices of one and two zone day tickets for public transport were $4.60 and $7.40 respectively.[210]   Of the 112 questionnaires recieved, 108 answered the question related to the distanced travelled to hospital (Table 7.7).   The average cost for patients travelling by private vehicle was determined to be $11.04 (median 12.50, ±SD 7.36).   The average cost for public transport was determined to be $4.60 (median 4.60, ±SD 0.00).   The average costs of transportation per trip for patients across both categories was $10.72 (median 7.50, ±SD 7.31).

Table 7.6 Mode of transport used on at least one occasion

Mode of transport	Number (%)
Private vehicle	90 (80.4)
Public transport	5 (4.5)
Other (ambulance, taxi, pedestrian)	17 (15.1)
Total	112 (100)

Table 7.7 Distance travelled to hospital

Distance from hospital	RCHED*	RCH	GH	BH
Less than 10km	6	11	7	8
11 – 20 kms	6	10	4	3
21 – 30 kms	2	7	6	5
31 – 40 kms	3	8	2	0
More than 40km	1	16	3	0
Total	18	52	22	16

*Royal Children's Hospital Emergency Department

It was determined that 2.6 and 5.3 minutes were required for each kilometre travelled using a private vehicle or public transport respectively. The average Australian weekly earnings for an adult working full-time, at the time of this research, was $772.00, or a daily rate of $154.40.[211] Forty percent of the hourly rate was determined to be $7.72. Using these figures the average travel time cost per trip was determined to be $7.33 (median 7.33, ±SD 4.93).

The average number of trips per day was determined to be 2.1 (median 1.4, ±SD 2.3). The average cost of transportation per day was therefore determined to be $22.52, and the average travel time costs per day was $15.36, so the total travel cost per day was calculated to be $37.88.

7.2.2.2.2   Costs associated with caring for an ill child

Of the 112 questionnaire responses, 109 provided answers as to the occupation of the person who normally cared for the child (Table 7.8).

Table 7.8 Occupation of the person who normally cares for the child

Occupation	Number
Home duties	79
Retired / unemployed	1
Paid employment	50
Total	**130***

*The total is greater than 109 as a number indicated more than one option

The average number of days of paid work or regular leisure activity lost due attending the emergency department or being admitted to hospital was 6.6 days (median 4.0, ±SD 9.9). After discharge from the emergency department or hospital, 74.1% (83/112) indicated that their child needed more care than normal. Of the 83 who indicated that more care was required, 74 indicated how many days of paid work or regular leisure activity was lost due to the increased level of care required. The average number of days of paid work or regular leisure activity lost due to the increased level of care required was also 6.6 (median 4.5, ±SD 6.5). Combining these data and adjusting for length of stay resulted in an average of 3.5 days (median 2.4, ±SD 3.3) lost from paid employment or regular leisure activity per day spent attending the emergency department or in hospital. To assign a dollar value to the days lost from paid employment or regular activities, the average Australian weekly earnings were utilised, which reduces to a daily rate of $154.40. Hence, the total costs associated with caring for an ill child were calculated to be $540.40 per day spent attending the emergency department or in hospital.

7.2.2.2.3   *Extrapolation of costs*

The total costs relating to travel and caring for an ill child were determined to be $578.28 per day spent attending the emergency department or in hospital. The length of stay of cases was then multiplied by this figure. The total indirect costs incurred by society as a result of the 407 cases associated with emergency department attendances or hospital admissions was $342,920.04, of which $111,608.04 was associated with DRPs determined to be preventable.

7.3 Estimated direct and indirect costs of DRPs identified

The total direct and indirect costs associated with the 407 cases determined to have emergency department attendances or hospital admissions associated with DRPs was estimated to be $715,941.73. Of the total direct and indirect costs reported, $300,413.07 was associated with DRPs determined by the *multidisciplinary panel* to be preventable.

Extrapolations of these data to either a state or national level were not undertaken because different costing methods exist for different hospitals within Victoria (See Section 7.1.1), and between states thus limiting the validity of such extrapolations.[208]

7.4 Discussion

The primary objective of the research reported in this chapter was to calculate the direct and indirect costs incurred as a result of the emergency department attendances and hospital admissions associated with the DRPs identified in this thesis. The direct and indirect costs were estimated to be $373,021.69 and $342,920.04 respectively, with a total cost of $715,941.73. This finding adds weight to reports that substantial costs are connected to problems associated with drug therapy.[4] Of particular note is the finding that $300,413.07 of the calculated total cost was associated with DRPs deemed preventable by the *multidisciplinary panel*.

While the economic implications of DRPs have been reported in studies conducted overseas, in both the paediatric and adult populations, it is not easy to make comparisons with the costs determined in the research reported in this thesis.[46, 62, 173] This is primarily because of differences in health care systems, currency exchange rates, and the sizes of the population utilising the health care systems.[146, 216] It is for these reasons the results reported in this thesis will be compared with Australian studies only.

There are, however, no Australian paediatric studies investigating the economic implications of DRPs. In contrast, a number of studies conducted within the Australian adult population comment on the direct costs of hospital admissions associated with DRPs.[6, 42, 96, 97, 190] When the average per patient costs associated with DRPs in these adult studies are compared with those reported in this thesis, it appears that the paediatric costs are lower. This conclusion is based on the finding that the average cost per case reported for the adult population ranges from $2634.00 to $5227.00,[6, 190] compared to the $1.175.67 and $1,903.59 reported for GH and RCH respectively (see Section 7.1.3).

However, the *per diem* method of costing utilised in the adult studies,[6, 42, 96, 97, 190] often bears little relationship to the use of resources by patients[205]. It is possible, therefore, that the costs reported in the adult studies may overestimate the actual direct costs associated with DRPs. In addition, hospitalisation patterns have been reported to differ between adult and paediatric populations, with a greater emphasis placed upon discharging children from hospital to home based care sooner.[147, 150] This may in part account for the difference in the average length of stay of hospitalised cases identified in the research presented in this thesis, as compared with that reported in the adult population. For example, the average length of stay reported for hospitalised cases in this thesis was 2.1 days (See Table 5.3) compared to the 8.3 days for adults reported by Dartnell et al.[6]

The reported differences in hospitalisation patterns between the paediatric and adult populations may make it more important to determine indirect costs

in studies conducted within the paediatric population.[147, 150] In the research reported in this thesis the indirect costs incurred by society as a result of the 407 cases was estimated to be $342,920.04. Unfortunately, it is not possible to make any comparisons with other studies, as the indirect costs associated with DRPs have not previously been reported for the Australian paediatric or adult populations.

In the context of this thesis, lifelong direct or indirect costs would primarily arise if a child died or was permanently disabled by a DRP.[165] In determining the economic implications of DRPs in this thesis, it was assumed that no lifelong direct or indirect costs were incurred as a result of illness associated with DRPs. An assumption that concurs with the finding that no paediatric patients died or were permanently disabled by the DRPs identified in this thesis (See Section 4.2.4 and See Table 5.6).

It has been reported that accounting systems for general hospitals such as GH and BH, as compared to specialist paediatric hospitals like RCH, usually do not take into consideration the higher intensity of services required to treat children.[147] The importance of this finding is highlighted by the assumption made in this thesis that the direct costs calculated for emergency department attendances and hospital admissions at GH and BH were representative of the actual direct costs for cases at each hospital. An alternative method to using the GH dataset to determine the costs for GH and BH, would have been to apply the average costs calculated for RCH to GH and BH. However, the differences between the accounting systems of general and specialist paediatric hospitals reported in the literature render this approach inappropriate, and add weight to the assumption made that the approach taken in this thesis was suitable.[147]

As the indirect costs calculated were extrapolated from patients whose parents or guardians received a questionnaire, to the DRP cases identified in this thesis, the finding that there were no significant differences in age and gender patterns between these two groups was of great interest. This interest was primarily focussed on age because, if significant differences in

age were identified, reported age related differences in the costs of care may have led to variances in indirect costs between the two groups.[147] The finding that there were no such differences therefore supports the assumption that the indirect costs reported in this thesis were representative of the actual indirect costs incurred by society as a result of the DRP cases identified. An assumption that is further justified by the fact that adjustments were made to account for potential differences in the distances travelled (by capping the distance travelled at 45km), and severity of illness (by adjusting for length of stay).[209]

In the research presented in this thesis it was assumed that there was a correlation between the indirect costs calculated and length of stay (See Section 7.2.2.1). Although there is no direct evidence to confirm this correlation, it is an assumption that has been suggested previously by researchers undertaking similar studies and hence was considered appropriate for this thesis.[213]

The method by which patients admitted with and without private health insurance are costed has been reported to differ, principally in relation to medical, pathology and radiology costs.[208] Such differences arise because for patients with private health insurance, the costs for medical, pathology and radiology services are met by the patient themselves and later reimbursed by health insurance funds.[208] It is for this reason that these costs may not be included within the hospital costing data, and hence differences the between public and privately insured patients are often adjusted for when calculating direct costs. In the research reported in this chapter no attempt was made to adjust for differences between public and private patients. This was because medical, pathology and radiology costs for private patients were accounted for in the hospital costing data provided, thus negating the need for such adjustments to be made.

The total direct and indirect costs presented in this thesis may be a conservative estimate according to the *cost of illness* approach, as intangible costs were not included in the current study. Furthermore, the indirect costs

included in the study may also be considered conservative because, although the approach taken was based upon that reported in the literature, the indirect costs included were by no means indicative of all possible indirect costs.[209] This point is indicated by the fact that other paediatric *cost of illness* studies investigating particular disease states have included indirect costs such as medications purchased and costs associated with changes in diet due to a child being unwell.[214, 215] However, it is unlikely that the indirect costs determined in this thesis would be substantially increased by the inclusion of these costs, because in the studies that included such costs, their contribution towards the total costs determined was almost negligible.[214, 215]

7.5 Conclusions

The results reported in this chapter provide the first data on the direct and indirect costs of emergency department attendances and hospital admissions associated with DRPs within the Australian paediatric population. The direct costs per case reported here are lower than those reported within the Australian adult population. However, variances in the costing methods utilised along with reported differences in patterns of hospitalisation between the two populations, limit what can be concluded from this difference.

Of great interest was the finding that, of the total direct and indirect costs associated with DRPs ($715,941.73), it was estimated that $300,413.07 was associated with DRPs considered preventable, a finding that will be further discussed in Chapter Eight.

8   Implications of DRPs in paediatrics

There has been much emphasis on the quality of pharmaceutical care within the elderly population,[5, 48, 217, 218] but considerably less attention paid to those at the other end of the age spectrum, the paediatric population.[18] This thesis has investigated QUM issues related to emergency department attendances and hospital admissions associated with DRPs, ADRs arising within the inpatient population, and the economic implications of the DRPs identified. To some extent each of these issues have been discussed, however, the broader implications of the findings reported in this thesis will be discussed here in two sections: methodological implications; and implications for prevention.

8.1 Methodological implications

The major methodological issues to be considered when designing studies to investigate the consequences of DRPs were identified earlier in this thesis. One such issue was the importance of considering the patient population under investigation, because a criticism of DRP and ADR studies conducted in single large academic, tertiary care hospitals was that the results obtained may be biased.[68] This possible shortcoming was addressed in the research presented in this thesis by conducting data collection in a specialist tertiary referral hospital (RCH), a general regional hospital (GH), and a general suburban hospital (BH). In doing so it was found that the frequency of DRPs associated with emergency department attendances and hospital admissions was not significantly different between the three hospitals, a finding similar to that reported by Mitchell et al.[61] This consistency provides a high level of confidence that the frequency of events determined is indicative of what is occurring on a wider basis.

Despite this consistency, the exclusion of both trauma and oncology patients from the emergency department and hospital admission streams of data

collection may mean that it is not possible to generalise the results obtained to the entire paediatric population. However, given that oncology patients have been reported to be four times more likely to experience an ADR, it is likely that the frequency of DRPs reported in the research presented in this thesis is a conservative estimate.[66, 71]

In reviewing the consistency of the frequencies reported, it must be acknowledged that because data collection was not conducted over a full one-year period at any of the hospitals, it is possible that seasonal variations may have influenced the frequency of DRPs reported. This is quite possible for DRPs associated with asthma or respiratory tract infections because the frequency of exacerbations or the occurrence of such disease states are generally greater over the winter months.[219] However, in the research presented in this thesis the data collection periods in the emergency departments of two of the hospitals were unlikely to be affected. Furthermore, the failure to detect a significant difference in the frequency of emergency department attendances between the three hospitals when data collection was conducted over six different months of the year indicates that the influence of seasonal factors may be minimal.

The small number of cases identified in this thesis as having ADRs arising while inpatients limited the ability to conclude that there was consistency in the frequency of such events between the three hospitals. The inability to answer this question does not reflect negatively upon the choice of patient populations, or the periods of data collection, but instead upon the monitoring methods used in this stream of data collection.

In contrast to the first two streams of data collection, ADRs arising within the inpatient populations were investigated using *spontaneous* and *retrospective intensive monitoring*. The results presented in this thesis demonstrated that such methods were associated with a high-degree of under-reporting when compared to *prospective intensive monitoring*. This under-reporting was in agreement with previous studies, hence it is unlikely that it was specific to the three hospitals investigated in this thesis.[41, 89, 143] These findings indicate that

prospective intensive monitoring should, where possible, be undertaken in preference to *spontaneous* or *retrospective intensive monitoring* to enable a more comprehensive analysis of ADRs occurring within the inpatient population.

However, if resources necessitate the use of *spontaneous* or *retrospective intensive monitoring* then these monitoring methods should be used at the same time because in this thesis only two ADRs were common to both methods (See Section 6.2.1). Furthermore, if these monitoring methods are utilised it must be understood that their effectiveness depends upon the adequate documentation of ADRs within medical records. This point was demonstrated in this thesis by a lack of information necessitating the exclusion of three ADR reports identified by *spontaneous monitoring* and 29 detected by *retrospective intensive monitoring*. A very similar conclusion was arrived at by Cantrill and Cottrell who reported that 36% of ADRs were not documented in patients' medical records.[220]

Although an estimate of the level of under-reporting was established for the methods employed to detect ADRs within the inpatient population, a similar estimate was unable to be calculated for *prospective intensive monitoring*. Despite this, a theme highlighted previously in this thesis (See Section 4.3 and Section 5.3) was the possibility of increased case detection if a patient interview was included in the monitoring process. This possibility is supported by a study conducted by McLennan, in which an interview conducted with patients to determine an accurate medication history was found to result in the most frequent detection of DRPs.[221] However, the sheer number of eligible patients screened in the research presented in this thesis makes incorporation of a patient interview unmanageable if it was to be adopted by investigators separate to the everyday clinical management of patients. A more feasible option, with wider quality implications, is to raise awareness among all health care professionals of the importance of documenting DRPs detected in such interviews within patients' medical histories.[41] While this is not a new concept, recent studies indicate that this role has not been comprehensively embraced.[41, 222, 223]

Two *structured algorithms* were used to assess causality in the research presented in this thesis: a modified version of the criteria put forward by Dartnell et al;[6] and the Naranjo algorithm[111]. To enable the effectiveness of these methods to be assessed the desired process would have been to test their reproducibility and validity so that the results could be discussed at this point. The difficulty in doing so, however, is indicated by the fact that none of the *structured algorithms* proposed to date have been validated.[116] This is in spite of these methods being noted as appropriate,[106] and forming the mainstay of causality assessment in this type of research[106, 113, 114].

As discussed previously (See Section 2.4.1), Hutchinson and Lane reported that the primary reasons that algorithms failed to meet the validity and reproducibility criteria they had developed was due to their lack of flexibility and their apparent failure to address aetiological balancing.[105] In the research presented in this thesis it was proposed that these shortcomings may be overcome by the use of a panel of independent evaluators. Unfortunately, the impact of the panels employed was unable to be evaluated. This is because the reproducibility and validity criteria developed by Hutchinson and Lane are unable to test if a method meets these atributes, but instead acts as a conceptual description of the distinct qualities that a method should posess.[105]

Although the reproducibility and validity of the methods used to determine causality in this thesis were unable to be assessed, the inter and intra-observer reproducibility findings are interesting. In reviewing the *moderate* and *fair* inter-observer reproducibility levels reported for the first two streams of data collection, it would be natural to assume that the higher the level of agreement the better the algorithm. However, as indicated by Meyboom et al, in the area of causality assessment, this is not necessarily the case, so it is difficult to draw normal conclusions using the Kappa statistics reported.[116] These statistics are more useful, however, if they are compared with the intra-observer reproducibility figures presented in Appendix Six. The levels of intra-observer reproducibility reported were found to be higher than the levels of inter-observer reproducibility, a finding which may demonstrate the

importance of cases being reviewed by more than one panel member and consensus opinion obtained where disagreements arise. This is because, as reported by Hutchinson, individual evaluators, even when presented with the same information, may mentally process this information differently.[224] If this is indeed the case it is hypothesised that methods, such as those used in this thesis, which allow differences between evaluators to be resolved through discussion and consensus opinion may be considered of greater validity than ones that do not.

While Meyboom et al indicated that higher levels of agreement did not necessarily mean that an assessment was more accurate,[116] the *poor* strength of inter-observer reproducibility between *pharmacy panel* members when using the Naranjo algorithm algorithm requires clarification[111]. In contrast to the results reported in this thesis, using the same algorithm, Naranjo et al reported inter-observer reproducibility to range from *good* to *very good*.[111] This difference may illustrate the importance of information on the ADR under review. This opinion is based upon the fact that Naranjo et al used ADR case reports from the literature to measure inter and intra-observer reproducibility.[111] Such reports provide extensive information on the case in question and must contain sufficient evidence of a causal relationship between the drug and the observed event to be published.[225] In the results presented in this thesis a similar level of information on the ADRs arising in the inpatient population was unable to be extracted from patients' medical histories. Therefore, in agreement with previous reports in the literature, it is proposed that the limited information available was a primary factor influencing the low Kappa values reported in this thesis when using the Naranjo algorithm.[225]

The low level of intra-observer reproducibility reported for the *pharmacy panel* members (See Appendix Six) may further explain the *poor* strength of inter-observer reproducibility found. This is because if the intra-observer crosstabulation tables for the *pharmacy panel* members are examined, it can be seen that the majority of differences relate to whether a case should be allocated to a causality classification of *possible* or *probable*. This difficulty in

being able to distinguish between the two adjacent categories is in agreement with previous reports in the literature.[116, 226] The effects of limited information and the difficulties in differentiating between *possible* and *probable* classifications identified in this thesis, further highlight the importance of having a process that utilises two independent evaluators and consensus agreement.

With respect to the preventability criteria employed in this thesis, examining inter and intra-observer reproducibility highlighted three main issues. Firstly, the finding that the inter-observer reproducibility was *moderate* to *fair* indicates that the criteria proposed by Schumock and Thornton can be modified to encompass the broader concept of DRPs.[82] Secondly, the preventability criteria employed did not appear to be significantly hampered by the restricted information available for the ADR cases. This was indicated by the fact that the Kappa value for ADRs arising within the inpatient population was only slightly lower than that reported for the other two streams of data collection. However, an alternative to this explanation is that data required to answer the preventability criteria were more readily available from patients' medical records. Finally, the higher levels of intra-observer reproducibility in comparison to inter-observer reproducibility may again reflect the opinion of Hutchinson that different evaluators may process information differently.[224] Once again highlighting the importance of cases being assessed by more than one panel member with consensus agreement obtained where differences in opinion arise.

In the research presented in this thesis clinical significance classifications were determined by panel members for ADRs arising within the inpatient population only. The *fair* level of agreement reported in this thesis when reviewing inter-observer reproducibility may illustrate the difficulties of determining clinical significance with the limited information that was available on the ADRs identified. A hypothesis that is supported when the clinical significance crosstabulation table presented for inter-observer reproducibility in Appendix Six is reviewed. In analysing this table it can be seen that the major differences in opinion occurred when allocating cases a

mild or moderate clinical significance classification. The difference between these two classifications primarily relates to whether treatment had been administered for the ADR and the level of impact the ADR had on the patient, information that was not always available for the ADRs identified in this stream of data collection.

A number of methodological implications can therefore be gained by reviewing the methods utilised in the current study. A theme common to almost all areas was the influence of the quality of documentation of DRPs and in particular ADRs within patients' medical histories by health care professionals. In agreement with reports in the literature, the detection of cases via all monitoring methods utilised in the research presented in this thesis may have been increased by an improvement in the quality of the documentation within medical records.[41, 91] The second theme was the importance of having a case reviewed by more than one panel member with consensus agreement obtained were opinions differed. This point should be included as one of methodological issues to be considered when designing a study to investigate the consequences of DRPs.

8.2 Implications for prevention

A primary issue driving research investigating the consequences of DRPs in paediatrics is the quest for prevention. The results presented in this thesis indicate that this quest is possible. They also indicate that this quest is important because the direct and indirect costs associated with the preventable DRPs identified in this thesis were estimated to be $300,413.07.

Prevention strategies aimed at reducing the frequency of emergency department attendances and hospital admissions associated with DRPs were not evident in the paediatric population, although in adults a community based intervention aimed at reducing the frequency of drug related hospitalisations has been reported.[43] That intervention involved educating general medical practitioners about the type of drug related hospitalisations identified.[43] A primary component of this education involved the use of

common drug related hospital admission scenarios identified via a similar process to that reported in the research presented in this thesis.[43] The intervention reported a statistically significant reduction in the frequency of drug related hospitalisations classified as definitely avoidable.[43] Given that the results of the research presented in this thesis indicate the frequency and preventability of DRPs to be similar to that reported within the adult population it is important that the issue of prevention strategies are explored within the paediatric population.

Mitchell et al indicated that the content of prevention strategies developed within the adult population should not simply be extrapolated to the paediatric population due to the different nature of diseases and drug therapies seen between the two populations.[61] Although extrapolating the content of such prevention strategies may be inappropriate, the approach taken to determine the content of the adult community based intervention can be applied to the paediatric population.[43] In applying this approach, common DRP scenarios identified in this thesis should be reviewed and their implications for prevention assessed.

Like the elderly population, paediatric patients may be especially vulnerable to inappropriate medication use.[227] A pertinent example provided in this thesis was the scenario indicating inappropriate prescribing of antibiotics for viral infections (See Section 4.2.4.7.2). This inappropriate prescribing is not a new phenomenon,[228, 229] with a study by Nyquist et al reporting that 44% of paediatric patients received antibiotics for the common cold[11]. However, the finding that the majority of the cases allocated to this scenario in this thesis were determined to be preventable, adds weight to the opinion of Nyquist et al that paediatric patients are important targets for efforts aimed at reducing unnecessary antibiotic use.[11]

Efforts to decrease such unnecessary antibiotic use are important to reduce the spread of bacterial resistance,[230-232] and to prevent unnecessary ADRs[232]. The importance of preventing unnecessary ADRs is highlighted by studies conducted within the paediatric outpatient population which report

antibiotics to be the drugs most frequently prescribed to paediatric patients and the drugs implicated in the largest number of ADRs.[124, 233-235] The results presented in this thesis further highlight the importance of preventing such unnecessary use, as antibiotics were the drugs most frequently implicated in ADRs (See Table 4.14 and Table 5.13). Of particular interest was the finding that antibiotics were involved in 34 of the 36 ADRs associated with emergency department attendances considered preventable. These results therefore concur with the opinion of Schwartz et al that educational interventions must focus on both the optimal approach to diagnosis and management of respiratory tract infections and the negative consequences of unnecessary antibiotic use. [232]

The majority of cases allocated to DRP scenarios that involved similar issues to the inappropriate use of antibiotics for viral infections, were also found to be preventable in the research presented in this thesis (See Section 4.2.4.7.2 and Section 5.2.4.7.2). These scenarios involved the use of medications not considered first line therapy, inappropriate dose forms being used or treatment considered ineffective administered. A diverse range of drugs were implicated in these scenarios making it difficult to highlight a particular drug class or disease state that may be targeted by a prevention strategy. Another approach to prevention may therefore be to focus upon possible barriers to optimal prescribing within the paediatric population. Young reported the scarcity of paediatric drug information as one such barrier.[14] This scarcity is highlighted by the fact that 72% of prescription drugs listed in the 1994 Australian MIMS either provided no information at all, or contained a general or partial disclaimer regarding use in paediatric patients.[20] As stated by Young "without adequate information, prescribers are often reluctant to prescribe potentially beneficial therapies for their paediatric patients".[14] Schwartz indicated that clinician experience may also influence optimal prescribing, because clinicians who see fewer paediatric patients may be less confident in their diagnostic skills with these patients and hence more likely to prescribe inappropriate therapy.[232] Whether or not these barriers affected prescribing can only be speculated on in this thesis, more

information is therefore required to determine what clinicians actually regard as barriers for optimal prescribing in paediatrics.

Another factor to potentially affect prescribing is the influence of parental expectations. Vinson and Lutz reported that in paediatric patients presenting to general medical practitioners with coughs, parental expectation was second only to the presence of rales as influencing the decision to prescribe antibiotics.[236] Parental expectations that a consultation with a general medical practitioner should end with a prescription are highlighted by the results of a study conducted by Australian Health Innovations.[8] The study interviewed parents of paediatric patients and reported that 60% of mothers only take their children to a general medical practitioner when they believe their child requires a prescribed medication.[8] Furthermore, 16% of mothers interviewed admitted to going from one general medical practitioner to another until they find one willing to prescribe medication.[8] It is therefore not surprising that concerns regarding parental satisfaction have been reported to influence a clinicians approach to prescribing.[232] Any approach to preventing inappropriate prescribing must therefore also seek to educate parents on appropriate medication use.[8]

Soumeri reported that paediatric patients are particularly susceptible to receiving too little or too much of a correct drug,[227] a finding which is supported by two community pharmacy intervention studies[237, 238]. The need for routine evaluation and calculation of individual dosages on the basis of patient age, weight or body surface area,[239] has been proposed as a primary reason for the increased susceptibility of paediatric patients to medication errors[27, 240, 241]. Although such medication errors are not common to all cases identified in this thesis, a number of the scenarios presented can be seen to display this characteristic (See Sections 4.2.4.7.3, 4.2.4.7.4, 5.2.4.7.3 and 5.2.4.7.4). Furthermore, the majority of cases allocated to these scenarios were considered preventable.

The importance of preventing medication errors has been highlighted at an international level by the report "To Err is Human",[242] and at a national level

by the "Safety First" report to the Australian Health Ministers Conference[243]. While these reports have been mainly directed towards errors arising within the inpatient population, the results presented in this thesis, along with studies exploring community pharmacists interventions, indicate that consideration should be given to preventing these problems arising in the community setting.[237, 238, 244]

The American Academy of Paediatrics and the Paediatric Advocacy Group have recently published guidelines aimed at reducing medication errors.[245, 246] While these guidelines have been developed primarily for the hospital inpatient setting a number of basic tenets can be extrapolated to the community setting. Recommendations that can be extrapolated include the education of all health care providers regarding the need for accurate dose calculations within the paediatric population.[241] Buck proposed that, in order to do so, a greater emphasis on the teaching of the calculation of paediatric doses at an undergraduate level is required, as well as the development of educational programs for health care professionals already in practice.[241]

The guidelines also highlight the use of technological advances, such as computerised clinician order entry, to reduce errors.[245, 246] In a hospital setting computerised physician ordering systems, with dosage guidelines, have been reported to reduce the frequency of dose errors by 23%.[123] While it can be hypothesised that the implementation of such systems may reduce dosage errors within the paediatric population, their impact may be reduced in paediatrics as a result of the limited amount of drug information available for this population.[14]

Finally, taking a multidisciplinary approach to the prevention of medication errors is a concept that can be extrapolated to the community setting.[246] Community pharmacist intervention studies have demonstrated that pharmacists can play an important role in preventing medication errors and thus form an important component of the multidisciplinary team.[237, 238, 244] However, as indicated by Rupp et al, the ability of pharmacists to act in this capacity is reduced by the limited amount of patient information available to

them.[238] Although attempts to increase the level of information available have been made, they have not been widely implemented.[247] Further attention to this area is therefore required in order to increase the potential role that may be played by community pharmacists in this multidisciplinary team.

The most frequent DRPs associated with emergency department attendances and the third most common DRPs associated with hospital admissions in the research presented in this thesis were ADRs, the majority of which were not considered preventable. This finding can be extended to ADRs arising within the inpatient population, as the majority of such reactions identified in this thesis were considered unpreventable. It is obvious then, that preventative measures to avoid the development of new ADRs would be difficult to implement. Alternative approaches may instead include attempting to prevent re-exposure to drugs noted to have previously caused ADRs, or to facilitate the early detection of ADRs and hence prevent further harm to a patient.[199] The lack of information available on ADRs within medical histories noted in this thesis (See Section 6.3) and also in the literature illustrates the need for strategies aimed at preventing re-exposure to ADRs to improve documentation.[41, 220, 222] Such strategies would potentially aid in both the prevention of re-exposure and in decisions regarding the appropriateness of controlled re-exposure if necessary.

With respect to strategies to facilitate the early detection of ADRs, computer based alert systems which aim to enhance early detection have been developed and tested.[248, 249] Such interventions can, however, only aid in the detection of previously known ADRs.[199] The ability of health care professionals to undertake the role of early detection also appears to be determined by knowledge and awareness of ADRs.[248] Hence, the reported scarcity of drug information may mean that the ability to implement such strategies in the paediatric population are limited.[14, 15, 20] This situation is further complicated by the use of *unlicenced* or *off-label* drugs.[9, 12, 13] It is therefore proposed that before systems enabling the early detection of ADRs

can be implemented, more information is required on ADRs in the paediatric population.

The "Pharmaceuticals for Children" report by the Australian Association of Paediatric Teaching Centres calls for the Australian government to facilitate an increase in the level of ADR surveillance in the paediatric population.[19] In the research reported in this thesis, the degree of under-reporting of the *spontaneous* and *retrospective intensive monitoring* systems (See Section 6.2.5) which are commonly utilised in Victorian hospitals, supports this call.[250] The lack of paediatric ADR data available from a large incident monitoring databases like the Australian Incident Monitoring System further highlights the need for greater surveillance within the paediatric population.[198] Although comparisons with reports in the literature indicate the degree of under-reporting identified in this thesis is not limited to the paediatric population, it is proposed that these findings are of increased importance to the paediatric population. The level of *unlicensed* or *off-label* drug use reported in this population forms the basis of this opinion.[9, 12, 13] Recently, Turner et al reported the frequency of ADRs associated with *unlicensed* or *off-label* drug use to be 6% as compared to 3.9% for drugs licensed for use in children.[70] If the level of under-reporting of ADRs indicated in this thesis correlates to that of ADRs to *unlicensed* or *off-labelled* drugs, it is possible that a false sense of security regarding the safety of these drugs exists. Calls for greater surveillance of paediatric ADRs should therefore be heeded and acted upon by the relevant governing bodies.

With respect to non-adherence, the factors influencing this DRP are complex within the general population,[251] and in the paediatric population these complexities are further compounded by the need for acceptance by, and cooperation of, both parent and child[23]. In this thesis 25 emergency department attendances and 38 hospital admissions were associated with non-adherence, of which 79.4% were considered preventable.

There are a number of implications for prevention that can be drawn from the cases associated with non-adherence identified in this thesis. The first

relates to the provision of adequate information on medication regimens because a scenario common to both streams of data collection was one in which limitations in knowledge lead to inappropriate medication use. The level of knowledge of a medication regimen prescribed has been reported to be one of the major patient characteristics that influences adherence to therapy.[22, 252, 253] While there is an increasing push for the provision of more information on medication regimens,[254, 255] the results of an Australian survey of parents of paediatric patients indicates there is a significant information deficit in prescription medications.[8] That study reported one-half of mothers perceived that they do not receive from either a general medical practitioner or pharmacist the information that they require on prescription medications.[8] While it is unlikely that mothers actually received such a small amount of information, the fact remains that an information deficit is perceived.[8] If, as the report suggests, mothers get more information than they realise, it is possible that the perceived deficit may arise as a result of the information not being provided in manner to enhance adherence. Liptak indicated that in order to enhance adherence, both verbal and written information on medication regimens is required.[24] Alternatively, the language utilised by health care professionals, such as "beta agonist" or "bronchodilator" may be confusing to patients and parents alike, thus heightening the perceived deficit in information.[8] Furthermore, if information is inadequate or confusing, reports indicate that parents are unlikely to initiate a request for further information or clarification.[8] Therefore, in order to enhance adherence, health care professionals need to be pro-active in both providing information both verbally and in writing,[8, 24, 256] and in seeking to clarifying misunderstandings[24].

Despite the importance of providing information on medication regimens, sound knowledge is not consistently associated with good adherence.[257, 258] The parental cessation of therapy scenarios outlined in this thesis highlight that their attitudes are an important factor in paediatric adherence (See Section 4.2.4.7.7 and Section 5.2.4.7.7).[23, 24] It is clear from reports in the literature that many parents report a reluctance to administer medications to their child.[8, 23] Despite adequate information on a medication regimen, part

of this reluctance may stem from a parent's lack of confidence in the diagnosis made, a reluctance that may be addressed by health care professionals seeking to clarify parents' feelings about the diagnosis made.[24] Parental attitudes regarding the severity of a child's illness,[8, 21, 24] and the consequences of not taking medication have also been reported to affect paediatric adherence [259].

In conjunction with parental attitudes, the attitudes of the child are also extremely important when investigating adherence.[24] Refusal of a child to take a medication has been highlighted in this thesis (See Section 4.2.4.7.7 and Section 5.2.4.7.7) and in the literature as a factor contributing to non-ahderence.[21, 23] It has been suggested that health care professionals may help to address this problem by explaining the importance of taking the prescribed medication directly to the paediatric patient.[23] A sentiment echoed in a recent position statement on medication use in paediatrics by the United States Pharmacopoeia.[260]

The attitudes of a paediatric patient to taking a medication have been reported to become of even greater importance as they get older.[24] To this end adolescents have been reported to be at a high risk of non-adherence.[23] However, studies investigating adolescents' adherence to long term medications report conflicting results.[261-264] For example, a study using salicylate levels as an indicator of adherence in juvenile rheumatoid arthritis found that children were less adherent than adolescents.[261] Whereas, studies investigating patients with diabetes,[262] malignancies,[264] and those who had undergone renal transplants,[263] reported the level of non-adherence to be higher in adolescent patients when compared to children. The results reported in this thesis indicated non-adherence to be a problem in adolescents, but reasons why they are non-adherent are complex and were not able to be extracted from the scenarios presented in this thesis.[22, 265] What can be extracted from the scenarios presented, is that asthma and diabetes were the two disease states implicated most frequently. More intensive research using qualitative methods should therefore be undertaken

to extract the non-adherence issues associated with asthma and diabetes in adolescents.

Problems with asthma therapy accounted for 36.0% and 67.6% of emergency department attendance and hospital admission cases associated with non-adherence respectively, making asthma the most common disease state associated with non-adherence in this thesis. Reports in the literature highlight non-adherence with asthma therapy as an area to be addressed in the paediatric population.[33, 55, 259, 266] In their study investigating emergency department attendances associated with DRPs, Schneitman-McIntire identified non-adherence with respiratory agents in paediatric patients as one of the three areas of particular concern.[55] More recently, Ordonez et al reported poor adherence with preventative treatments to be associated with 21% of paediatric asthma admissions identified at a specialist paediatric hospital.[33]

Reasons for non-adherence with asthma medications within the paediatric population are diverse.[259, 266] However, a factor that appears to be common to many of these reasons are deficiencies in knowledge.[259, 266] Such deficiencies in knowledge are evident with respect to the disease state itself, as indicated by an Australian survey of mothers with asthmatic children.[8] The study reported that nearly one-quarter of mothers surveyed admitting to knowing little about the condition.[8] Ordonez et al reported that when parents were tested, 49% were found to have a low level of asthma knowledge.[33] Parental knowledge of asthma may affect their perception of the severity of the disease state, a perception that has been reported to influence the level of adherence.[8, 24] Smith et al reported that perceptions regarding the usefulness of asthma medication also influenced adherence.[259] The authors found that a significant determinant of non-adherence with asthma therapy was the belief that asthma was an unlikely consequence if such medication was not taken.[259] Within the adolescent asthmatic population Bortoletto reported that a large proportion of adherence problems encountered also stemmed from inadequate knowledge of the disease state and its treatment.[267]

Deficiencies in knowledge of this disease state are not, however, limited to patients and their families, as health care professionals have also been reported to often lack adequate knowledge and understanding of various aspects of asthma.[268] This lack of knowledge may be associated with the scenarios reported in this thesis where there was an unrecognised need for the use of preventative treatments. A finding that was not unique to this thesis,[33, 34] as Ordonez et al reported that one-quarter of children admitted with frequent episodic and persistent asthma were not using preventative medications[33].

The possibility that such deficiencies in knowledge exist in spite of extensive educational programs,[33] highlights the need for evaluation of current methods to educate patients, parents and health care professionals about asthma.[8, 269]

Reports in the literature indicate that the medication misuse in the form of accidental or intentional poisonings are common within the paediatric population.[30-32] As a result of such reports the importance of reducing medication related poisonings within the paediatric population has been highlighted at a national level.[10, 270, 271] In this thesis, 93 emergency department attendances and 46 hospital admissions, were allocated to Category Eight, and thus associated with such events, indicating that the national emphasis placed upon reducing the frequency of such DRPs is not misguided. Although the preventability of the cases identified in this thesis was not determined, a number of implications for prevention can be drawn from the results obtained.

Epidemiological studies of medication related poisonings within the paediatric population have demonstrated a clear pattern with respect to the age and sex of patients at risk.[30, 272] Accidental medication poisonings are reported to be predominant in children less than five years of age, with intentional self poisoning common in adolescents.[272] This pattern was also evident in the research reported within this thesis.

With respect to paediatric patients five years of age and below, reports in the literature indicate that there is a peak poisoning incidence at two years of age, with a male predominance in this age group.[30, 31, 272] The results of the research reported in this thesis concur with this patient at risk profile, with a mean age of 2.3 years and 2.2 years reported for emergency department attendance and hospital admission cases respectively. Males predominated in the hospital admission cases, however, the extent of predomination was much less in the emergency department. The developmental stages of paediatric patients between one to three years has been suggested as the primary reason for the peak incidence of poisoning occurring at two years.[30] At these stages children become increasingly mobile, with a drive to explore the environment, and as a consequence are able to search out new objects and put them in their mouth.[30, 272] Given that at this age they have little idea of what is safe to ingest, and that the majority of ingestions occur within the home,[30, 31, 273] the primary focus of prevention strategies in this age group include educating parents to keep medicines out of the reach of children,[30, 274] and reducing the chance of ingestion through child-resistant packaging[30, 31, 274].

The potential degree of under-reporting of medication poisonings in the Victorian Emergency Minimum Dataset found in this thesis and reported in the literature,[32] may mean that studies that have relied upon this database have underestimated the role of non-prescription medicines in medication poisonings in this age group[30, 31]. The results reported in this thesis indicated that these drugs played a substantial role in the medication poisonings associated with emergency department attendances (See Section 4.2.4.7.8). Reports in the literature suggest that a lack of awareness by parents regarding the toxicity of non-prescription drugs may be a factor contributing to the frequency of poisoning with these agents.[8, 30] This lack of awareness, along with a belief that children will not be able to open child-resistant packages, may make parents complacent in their efforts to keep such drugs out of reach of children.[31, 275] As community pharmacies are a primary source of non-prescription drugs, community pharmacists are well placed to

assist in interventions to reduce the frequency of poisonings with non-prescription drugs.

While interventions aimed at decreasing the frequency of non-prescription drug poisonings may reduce the frequency of emergency department attendances, they are unlikely to have a significant impact upon hospital admissions. This opinion is based upon the finding that that 82.8% of the drugs associated with hospital admissions for this age group were prescription drugs. Hence, broader prevention strategies are required to reduce the frequency of hospital admissions associated with medication poisonings. Aside from child-resistant packaging,[30, 274, 276] there is little evidence to indicate the effectiveness of other intervention strategies, such as general education campaigns,[277] or poison warning stickers.[30] The difficulty in implementing effective prevention strategies is indicated by the National Health Priority Areas Report on Injury Prevention and Control, which notes that, despite hospitalisations for child poisonings being one of the stated national priority areas for the last 10 years, there is no evidence to suggest any decline in the frequency of such hospitalisations.[31] As child-resistant packaging has been reported to be the only effective intervention to date, further research in this area may be the way to reduce such admissions.[30]

With respect to children greater than five years of age the pattern of poisoning changes. Poisonings are reported to be less common in children between six and 10 years of age, and then increase in frequency during the adolescent years.[32, 272] The intent of poisoning changes from accidental ingestions to exposures that are more likely to be deliberate, either for the purposes of experimentation or self harm.[278] The gender pattern is the opposite to that seen in cases five years of age and below, with females involved in the majority of cases.[32, 272, 279] The results presented in this thesis concur with these observations because only 4 of the 59 cases in this age group were between six and 10 years of age with the remainder primarily adolescent females.

Paracetamol was the drug most frequently implicated in both the emergency department and hospital admission streams of data collection in this older group, a finding also reported by Routley et al.[32] Gilbertson et al indicated that the use of paracetamol to induce self-harm in this age group may be influenced by a lack of awareness of the severity of toxicity.[280] In their 1996 survey of American and British adolescents, greater than 90% of those surveyed recognised that paracetamol in overdose could be fatal, but overestimated the amount of drug that would be required.[280] This finding indicates that education is required to prevent such poisonings, however, conflicting reports exist on the potential use of education strategies.[281] Instead, other methods such as packaging restrictions which limit the quantities of drug available have been suggested as more appropriate.[32, 282, 283]

Despite paracetamol being the drug most frequently implicated in poisonings within this age group, other drugs were implicated in the cases identified in this thesis. The implementation of interventions such as packaging restrictions is not a practical option for all the drugs implicated in these cases due to diversity of the agents identified.[284] Furthermore, as indicated by Poulin, prevention efforts to reduce the frequency of poisoning in this older age group should not only address the physical means of poisoning but also the nature and cause of the distress underlying these acts.[285] In comparison with patients five years of age and below, there are limited data on the effectiveness of non-packaging means of preventing medication poisonings.[286] Thus, as indicated by Hawton et al, there is an urgent need for large trials of promising interventions to reduce the frequency of poisonings within this patient population.[286]

A pattern common to both age groups of paediatric poisoning patients is that the drugs implicated change over time.[272] It is therefore essential that accurate databases are maintained to allow trends to be detected and targeted with prevention strategies.[32, 284, 287] The Victorian Emergency Minimum Dataset and the Victorian Admitted Episodes Dataset are sources of such information.[32, 279] However, given the potential level of under-

reporting for the Victorian Emergency Minimum Dataset indicated in both this thesis (See Section 4.2.4.1) and in the literature, the ability of these databases to perform this function in their current form must be assessed.[32] Likewise, national databases should be identified and assessed as the importance of the information provided in such databases are recognised in the literature.[30, 32, 279, 284, 287]

In achieving the objectives outlined in this thesis, this research has provided the first extensive information on the consequences of DRPs within the Australian paediatric population. By providing data on the frequency and characteristics of emergency department attendances and hospital admissions associated with DRPs, information that encompasses DRPs occurring at different levels of severity within the community has been provided. The consistency of the results obtained across the three hospitals investigated in each stream of data collection enhances the relevance of the results provided to the broader paediatric population. The finding that there were no significant differences in the frequency of hospital admissions associated with DRPs reported in this thesis when compared to the preliminary study conducted in 1996 indicates that the extent of the problem has not reduced with time.[7]

The high proportion of emergency department attendances and hospital admissions associated with DRPs deemed preventable in the research presented in this thesis indicates that the frequency of such events can be reduced. Areas to be targeted with strategies to prevent or reduce the impact of DRPs were identified in this chapter. Paediatric patients, parents and health care professionals alike need to be the focus of such strategies as each has a unique role to play in reducing the consequences of DRPs in paediatrics.

The review of ADRs arising within the inpatient population highlights an area that requires urgent attention. This level of attention is required as the results presented in this thesis indicate that the potential under-reporting of methods currently utilised to monitor ADRs may significantly hamper appreciation of

the type and frequency of ADRs in the paediatric population. The importance of this finding is heightened by the reported paucity in drug and clinical trial information available within this population resulting in the *unlicensed* and *off-label* use of medications.[9, 12-15]. It is therefore imperative that calls by the Australian Association of Paediatric Teaching Centres for a greater level of surveillance of ADRs within the paediatric population are heeded.

While greater surveillance of ADRs are required it must be recognised that in their current form *spontaneous monitoring* and *retrospective intensive monitoring* do not appear to be suited to the task. If such monitoring methods are to be used, improvements in the information that is obtained will not only depend on addressing the issue of under-reporting, but also the quality of information provided in medical records. The need to improve the quality of information provided in medical records is not isolated to these monitoring methods and ADRs. In fact the results of the research presented in this thesis indicate that improved documentation could potentially enhance the detection of events via all monitoring methods utilised. Improved documentation may increase the capture of such events in state and national databases, thus enabling trends in the type of DRPs occurring to be identified and addressed.[32] It is therefore essential that strategies to improve the documentation of DRPs are undertaken.

The establishment of data relating to the economic implications of DRPs in paediatrics indicates that, like the adult population, substantial costs are associated with problems with medication use in this population.[4] The provision of such data provides an important basis for the economic evaluation of strategies to reduce the impact of DRPs within the paediatric population.

As a result of the research presented in this thesis information is now available on the frequency and characteristics of DRPs and ADRs. Areas to be targeted for prevention strategies have been identified and the economic implications of such problems calculated. This thesis has reported the frequency of DRPs identified to be similar to that reported within the adult

population but the areas to be targeted by prevention strategies differ. Given that the need to prevent DRPs is recognised within the adult population,[4, 6, 43] it is now time to pay attention to the younger end of the age spectrum and act to reduce the consequences of DRPs in paediatrics.

APPENDIX ONE

Operational definitions

Admitted patient*

An admitted patient is a patient who undergoes a hospital's formal admission process and meets one of the following minimum criteria:

Same day patient

That the patient receive Day Only Surgical and Diagnostic Services as specified in bands 1A, 1B, 2, 3 and 4 but excluding uncertified type C Professional Attention Procedures within the Health Insurance Basic Table as defined in s.4(1) of the *National Health Act 1953* (Cwith); or

That the patient receive type C Professional Attention Procedures as specified in the Heath Insurance Basic Table as defined in s.4(1) of the *National Health Act 1953* (Cwlth) with accompanying certification form a medical practitioner that an admission was necessary on the ground of medical condition of the patient or other special circumstances that relate to the patient; or

Overnight stay patient

That the patient, following a clinical decision, receives hospital treatment for a minimum of one night. Note: This includes all babies born in hospital. However, all neonates are further divided into categories of qualified and unqualified. A qualified neonate is nine days old or less and meets at least one of the following criteria:

1) is the second or subsequent live born infant of a multiple birth, whose mother is currently an admitted patient;

2) is admitted to an intensive care facility in a hospital, being a facility approved by the Commonwealth Health Minister for the purpose of the provision of special care;

3) remains in hospital without its mother;

4) remains in hospital with its mother after day nine;

5) is admitted to the hospital without its mother.

---

* National Health Data Committee. National health data dictionary, Version 4. Canberra: Australian Institute of Health and Welfare, 1995.

Newborn babies who do not meet this criteria are classed as unqualified and should be recorded as such. Unqualified babies should not be counted under the Medicare Agreement and are not eligible for health insurance benefit purposes.

Non-admitted patient[*]

A non-admitted patient is patient who does not undergo a hospital's formal admission process.

There are three categories of non-admitted patients:

1) emergency department patient;

2) outpatient;

3) other non-admitted patient.

Attendance

Patients falling into category one of the non-admitted patients definition, that is, a non-admitted patient attending the emergency department.

Non-English speaking patient

A patient flagged as requiring an interpreter in the patient's medical records.

Oncology patient

An oncology patient is defined as any patient that attends or is admitted to hospital with a diagnosis of, complications with or treatment for neoplasms.

Patients with the following ICD-9-DM codes are defined as oncology patients:

140-165	170-176
179-208	210-239

Patients with the following ICD-10-AM codes are defined as oncology patients:

C00-C75	C76-C80
C81-C96	C97
D00-D09	D10-D36

---

[*] National Health Data Committee. National health data dictionary, Version 4. Canberra: Australian Institute of Health and Welfare, 1995.

D37-D48

Paediatric Persons

Paediatric persons are people aged 17 years of age or less residing in a defined area. The actual defined area varies depending on the context in which this term is used. For example in calculations relating to the RCH, the defined area will be the catchment area for the RCH.

Singletons born in hospital

The term singletons born in hospital includes any neonates born within the hospital specified.

Trauma patients

Trauma patients are defined as any patient that attends or is admitted to hospital with an injury caused by:

1)   a motor vehicle (includes driver or passenger);
2)   a motorcycle (includes driver or passenger);
3)   a pedal cyclist (includes rider or passenger);
4)   a pedestrian;
5)   other transport related circumstances;
6)   a fall (low and high);
7)   submersion or drowning ;
8)   other threat to breathing (includes strangulation, asphyxiation);
9)   fire, flames, smoke;
10)   scalds (hot drink, food, water, other fluid, steam, gas or vapour);
11)   a contact burn;
12)   a firearm;
13)   a cutting, piercing object;
14)   an animal or is animal related;
15)   being struck by or in a collision with a person or object;
16)   machinery;
17)   electricity;

18)   cold conditions (natural origin). *

Patients with the following ICD-9-DM codes are defined as trauma patients:

E800-E809	E810-E819	E820-E829	E830-E838
E840-E848	E880-E888	E890-E899	E901-E903
E905-E909	E910-E919	E920-E928	E954-E958
E964-E966	E973-E974	E983-E988	E961, E970

830-838	840-848	850-853	860-861
870-879	880-887	910-919	920-929
930-939	940-949	958-959	991, 993, 994

Patients with the following ICD-10-AM codes are defined as trauma patients:

S00.0	S03.0	S16.0	S38.3	S63.0	S90.0	T050	T200
S00.05	S03.4	S17.0	S38.3	S63.1	S90.1	T051	T210
S00.08	S03.5	S17.8	S40.0	S63.50	S90.2	T051	T220
S00.1	S05.0	S17.9	S40.7	S63.51	S90.3	T052	T230
S00.2	S05.1	S20.0	S40.9	S63.52	S90.7	T053	T240
S00.3	S05.2	S20.11	S41.0	S63.53	S90.88	T054	T250
S00.35	S05.3	S20.2	S41.80	S63.54	S90.9	T055	T260
S00.4	S05.4	S20.7	S43.0	S63.55	S93.0	T056	T270
S00.45	S05.5	S20.31	S43.4	S63.56	S93.1	T057	T280
S00.5	S05.7	S20.41	S43.5	S63.57	S93.3	T058	T290
S00.6	S05.8	S20.81	S43.6	S63.58	S93.40	T059	T300
S00.7	S05.9	S21.0	S43.7	S63.60	S93.41	T090	T310
S00.8	S06.00	S21.1	S46.0	S63.61	S93.42	T0905	T330
S00.85	S06.02	S21.2	S47	S63.62	S93.43	T091	T340
S00.9	S06.04	S21.7	S48.0	S63.68	S93.48	T092	T350
S00.95	S06.05	S21.80	S48.1	S63.7	S93.5	T096	T700
S01.0	S07.0	S21.83	S48.9	S67.0	S93.6	T1105	T750
S01.1	S07.1	S21.9	S50.0	S67.8	S97.0	T111	T790
S01.20	S07.8	S23.3	S50.1	S68.0	S97.1	T116	T791
S01.21	S07.9	S23.4	S50.7	S68.1	S97.8	T1305	T792

---

* Monitoring and Review Subcommittee of the Steering Committee on the Emergency Department Information Systems Project. Victorian emergency minimum dataset, Version 2.0. Melbourne: Department of Human Services, 1997.

S01.22	S08.0	S23.5	S50.88	S68.2	T001	T134	T793
S01.23	S08.1	S26.0	S50.9	S68.3	T002	T141	T794
S01.29	S08.8	S26.88	S51.80	S68.4	T002	T143	T795
S01.30	S09.61	S26.9	S51.9	S68.8	T003	T146	T796
S01.31	S09.9	S27.0	S53.0	S68.9	T003	T150	T797
S01.33	S10.0	S27.1	S53.40	S70.0	T006	T151	T798
S01.34	S10.1	S27.2	S53.41	S70.1	T008	T158	T799
S01.35	S10.2	S27.38	S53.42	S70.7	T009	T159	S02.5
S01.36	S10.3	S29.0	S53.43	S70.88	T010	T16	S14.7
S01.37	S10.4	S30.0	S53.44	S70.9	T011	T170	S38.2
S01.38	S10.5	S30.1	S53.48	S71.7	T012	T171	S61.9
S01.39	S10.6	S30.2	S57.0	S73.0	T013	T172	S87.8
S01.41	S10.7	S30.7	S57.8	S80.0	T0147	T173	T049
S01.42	S10.8	S30.81	S57.9	S80.1	T016	T175	T199
S01.43	S10.9	S30.91	S58.0	S83.0	T018	T178	
S01.49	S10.95	S31.0	S58.1	S80.7	T019	T179	
S01.50	S11.01	S31.1	S58.9	S80.7	T030	T180	
S01.51	S11.02	S31.4	S58.9	S80.88	T033	T181	
S01.52	S11.07	S31.5	S60.0	S80.9	T034	T182	
S01.53	S11.1	S31.7	S60.1	S83.40	T038	T183	
S01.54	S11.21	S31.80	S60.2	S83.41	T039	T184	
S01.55	S11.22	S33.4	S60.7	S83.42	T040	T185	
S01.59	S11.7	S33.50	S60.88	S83.50	T041	T189	
S01.59	S11.80	S33.51	S60.9	S83.51	T042	T190	
S01.7	S11.80	S33.6	S61.0	S83.52	T043	T191	
S01.80	S11.9	S33.7	S61.1	S83.6	T044	T192	
S01.82	S13.4	S38.0	S61.7	S86.0	T047	T193	
S02.5	S13.6	S38.1	S61.80	S87.0	T048	T198	

APPENDIX TWO

Ethics committee approval

On the following pages documentation of approval are provided for four ethics committees:

1)   Royal Children's Hospital Ethics in Human Research Committee;

2)   The Monash University Standing Committee on Ethics in Research on Humans;

3)   Barwon Health, The Geelong Hospital, Research and Ethics Advisory Committee;

4)   Box Hill Hospital Ethics Committee.

Royal Children's Hospital Ethics in Human Research Committee

Royal Children's Hospital
Melbourne, Victoria

Department **ETHICS IN HUMAN RESEARCH COMMITTEE**

APPROVAL

Flemington Road,
Parkville, Victoria, 3052
Australia.
Telephone: (03) 9345 5522
Facsimile: (03) 9345 5789

EHRC REF. No:	97089 A
PROJECT TITLE:	The consequences of drug related problems in paediatrics
INVESTIGATOR(S):	R Linsley, J Brien, K Easton

DATE OF NEW APPROVAL: **25 November 1997**

DURATION: 8 months

SIGNED: 27/.11./97
          COMMITTEE REPRESENTATIVE   DATE

CONDITIONS

ALL PROJECTS

1. Any proposed change in protocol and the reasons for that change, together with an indication of ethical implications (if any), must be submitted to the Ethics in Human Research Committee for approval.
2. The Principal Investigator must notify the Secretary of the Ethics in Human Research Committee of:
   - Actual starting date of project.
   - Any adverse effects of the study on participants and steps taken to deal with them.
   - Any unforeseen events.
3. A progress report must be submitted annually and at the conclusion of the project, with special emphasis on ethical matters.

DRUG TRIALS

4. The investigators must maintain all records relating to the study for a period of 23 years.
5. The investigator(s) must report to the Sponsor and the Ethics in Human Research Committee within 24 hours of becoming aware of any serious adverse event experienced by any subject during the trial

The Monash University Standing Committee on Ethics in Research on Humans

M O N A S H   U N I V E R S I T Y

RESEARCH GRANTS AND ETHICS BRANCH

10 March 1998

Dr Jo-anne Brien   Mr Ross Linsley   Ms Kylie Easton
Pharmacy Practice   Royal Women's and Children's Pharmacy Practice
Parkville Campus   Healthcare Network   Parkville Campus
                          132 Grattan Street
                          Carlton 3053

Project 98/004 - The consequences of drug related problems in paediatrics

I write in reference to the approval procedure of the above project which was considered by the Standing Committee on Ethics in Research on Humans at meeting A1/98 on 10 February 1998.

The items requiring attention have been resolved to the satisfaction of the Committee subject to receipt of confirmation from the Royal Children's Hospital that, as indicated on page 5 of your faxed letter, they will inform the Standing Committee on Ethics in Research on Humans of any complaints received.

Accordingly this research is approved to proceed. The project has been approved as conforming to NH&MRC guidelines. This approval is of the project as submitted and if any changes are subsequently made, the Committee should be advised. Please quote the project number above in any further correspondence.

Institutional Ethics Committees are required by the NH&MRC to monitor research projects until completion to ensure that they continue to conform with approved ethics standards. The Committee undertakes this role by means of annual progress reports and termination reports. Please ensure that the Committee is provided with a brief summary of the outcomes of your project when it has concluded.

The Chief Investigators of approved projects are responsible for the storage and retention of original data pertaining to a project for a minimum period of five years. You are requested to comply with this requirement.

Ann Michael

Ann Michael
Human Ethics Officer
Standing Committee on Ethics in Research on Humans

Barwon Health, The Geelong Hospital, Research and Ethics Advisory Committee

RESEARCH AND ETHICS ADVISORY COMMITTEE

Secretary
Andrew Love Cancer Centre
The Geelong Hospital
70 Swanston Street
GEELONG 3215

Telephone: 03 5226 7978
Facsimile: 03 5226 5857
e-mail: BERNICE@BarwonHealth.org.au

The Geelong Hospital,
Ryrie Street P.O. Box 281
Geelong Victoria 3220
Telephone: 03 5226 7111
Facsimile: 03 5221 3429

ETHICS COMMITTEE APPROVAL STATEMENT

| 99/28 | Ms Easton- Carter | The Consequences of Drug related Problems in Paediatrics |

Thankyou for submitting your application with the Research and Ethics Advisory Committee.

Full approval was granted on   20/05/99

In addition any items approved in support of this project are listed below:

Date Aproved	*Item ID*	*Additional Information*	*Document Date*

I have attached a current list of the REAC Members at the date of the last meeting for your information. The Hospital Human Research and Ethics Advisory Committee is constituted and operates in accordance with the National Health and Medical Research Council's Statement on Human Experimentation and Supplementary Notes (July 1992).
All Research Projects approved by REAC must comply with the guidelines for "Monitoring of Research" listed below and the general conditions in the NHMRC Statement on Human Experimentation and Supplementary Notes.

Monitoring of Research.
Supplementary note 1 of the NHMRC Statement on Human Experimentation and Supplementary Notes, requires Institutional Ethics Committees (IECs) to monitor research projects to which they have given ethical approval in order to ensure that they conform to the protocol approved.
The guidelines detailed below are the current methods and approach used by the REAC to monitor activities of research projects.
1. Provision of relevant reports to the REAC is the responsibility of the principal investigator.
2. Reports shall be provided annually or upon completion of the project, whichever occurs sooner, although the REAC may request more frequent reports. The report should provide details of the following:

Thursday, 20 May 1999   *Coordinator*   *None*   *Page 1 of 2*

Barwon Health, The Geelong Hospital, Research and Ethics Advisory Committee (continued)

2.1 the status of the project (completed/in progress/abandoned) and anticipated date for completion;

2.2 the number of subjects accepted into your study;

2.3 compliance with the general conditions stated in the NHMRC Statement on Human.   Experimentation and Supplementary Notes;

2.4 compliance with any special conditions stated by the REAC as a condition of approval; and

2.5 the security of data collected and the conditions governing access to it.

3. Notwithstanding the above, principal investigators are responsible for notifying the REAC immediately of matters which might affect continued ethical acceptability of the project including:

3.1 adverse affects of the project on subjects and steps, either proposed or taken, to deal with these;

3.2 substantial changes in the research protocol together with an indication of ethical implications.

Should you require any further information concerning the Committee's approval of your research   or have any concerns regarding the Reporting requirements please contact the secretary, Ms Bernice Lamp on 52267978.

In all future correspondence regarding your study please quote your Project No. and full title of your Research
Investigation.

Yours sincerely,

Mr Andrew Hill
Chairperson

Box Hill Hospital Ethics Committee

Box Hill Hospital Ethics Committee
2nd Floor Clive Ward Centre
Telephone (03) 9895 3269
Facsimile (03) 9895 3461

Box Hill Hospital

A Monash University Teaching Hospital
Nelson Road, Box Hill Victoria 3128
PO Box 94, Box Hill Vic 3128 Australia
Telephone: (61 3) 9895 3333
Facsimile: (61 3) 9895 3268
Email: blhhosp.@boxhill.org.au
Website: www.boxhill.org.au

PS:heg

17 November, 1999

Mr Des Meagher
Chief Pharmacist
Box Hill Hospital

Dear Des

36/99   The consequence of drug related problems in paediatrics

The above Protocol referred to in your letter dated 29 September 1999 was considered by the Box Hill Hospital Ethics Committee at its meeting on 28 October 1999.

The Protocol was approved.

For future correspondence please quote Protocol No.36/99 .

Yours sincerely,

Dr Peter Sloan
Chairman - Box Hill Hospital Ethics Committee.

INNER & EASTERN
HEALTH CARE NETWORK

APPENDIX THREE

Drug related problem category allocation guidelines

Cases identified to have DRPs associated with emergency department attendances or hospital admissions were allocated to the DRP categories using the allocation guidelines listed in this appendix.

Category One:

The case has a medical condition that requires drug therapy (a drug indication) but the case is not receiving a drug for that indication.

- The medical condition must have been present for a significant period of time prior to admission and an opportunity existed for omitted therapy to be initiated.
- The case would have been unlikely to be admitted in the presence of the omitted drug.
- The case was treated with the proposed or a similar drug during the admission.

Category Two:

The case has a medical condition for which the wrong drug is being taken.

- The case received a medication where there was a known allergy or contraindication.
- The case received a medication that is considered ineffective for the medication condition or a drug therapy more effective exists.
- An inappropriate dose form or device was prescribed.
- The wrong drug was dispensed or administered by a health professional.

Category Three:

The case has a medical condition for which too little of the correct drug is being taken.

- The dose, frequency or duration of the drug prescribed is considered sub-therapeutic for the cases medical condition according to the Australian Prescription Products Guide[*] and/or the Paediatric Pharmacopoeia[†] and/or the Drug Doses booklet[§].

Category Four:

The case has a medical condition for which too much of the correct drug is being taken.

- The dose, frequency or duration of the drug prescribed is considered to be above therapeutic levels according to the Australian Prescription Products Guide[*] and/or the Paediatric Pharmacopoeia[†] and/or the Drug Doses booklet[§].

- Required therapeutic drug monitoring or other necessary laboratory tests were not preformed resulting in toxicity.

Category Five:

The case has a medical condition resulting from an adverse drug reaction.

- "Any response to a drug that is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis or treatment of disease, or for the modification of physiological function".[‡]

Category Six:

The case has a medical condition resulting from a drug-drug, drug-food, drug-laboratory interaction.

- A drug taken that is known to interfere with the absorption, distribution, metabolism or elimination characteristics of another drug as indicated in

---

[*] Australian Prescriptions Products Guide. In: Thomas J, ed. Hawthorn: Australian Pharmaceutical Publishing Company Limited, 1999.

[†] Paediatric Pharmacopoeia. In: Kemp CA, McDowell JM, Lilley BJ, et al., eds. Melbourne: Pharmacy Department, Royal Children's Hospital, 1998.

[§] Shann F. Drug Doses. Parkville: Intensive Care Unit, Royal Children's Hospital, 1998.

[‡] World Health Organisation. World Health Organisation Technical Report No. 498, 1972

Meyler's Side Effects of Drugs: an Encyclopedia of Adverse Reactions and Interactions[*] and/or Facts and Comparisons News[†] and/or Drug Interactions & Updates[§] or is a drug to drug interaction that has been defined within the literature.

- Food taken that is known to interfere with the absorption, distribution, metabolism or elimination characteristics of the drug taken as indicated in Meyler's Side Effects of Drugs: an Encyclopedia of Adverse Reactions and Interactions[*] and/or Facts and Comparisons News[†] and/or Drug Interactions & Updates[§] or is a drug to food interaction that has been defined within the literature.

- A drug is taken that is known to interfere with the results of a standard laboratory test is known as a drug-laboratory interaction.

Category Seven:

The case has a medical condition that is the result of not receiving the prescribed drug.

- "Any non-trivial deviation from the prescribed medication regimen which can be intentional or unintentional and includes dosage errors (underuse and overuse), interruption of treatment, failure to take drugs at specified times and taking them at incorrect intervals."[‡]

Category Eight:

The case has a medical condition that is a result of taking a drug for which there is no valid medical indication.

- An accidental or intentional overdose had taken place.
- The case was taking illicit drugs.

---

[*] Meyler's side effects of drugs: an encyclopedia of adverse reactions and interactions. In: Dukes MNG, ed. Oxford: Elsevier, 1996.

[†] Drugs facts and comparisons news. St louis: Facts and Comparisons, 1998.

[§] Hansten PD, Horn JR. Drug interactions & updates. Malvern: Lea & Febiger, 1990.

[‡] Col N, Fanale JE, Kronholm P. The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly. Arch Intern Med 1990; 150:841-845.

APPENDIX FOUR

Emergency department coversheet and checklists

Emergency department coversheet

Drug Related Problems Study

IS THIS PAEDIATRIC PATIENT'S ATTENDANCE <u>POSSIBLY</u> ASSOCIATED WITH A <u>DRUG RELATED PROBLEM</u> ?

IF <u>YES</u> ⇒

PATIENTS NAME:_____   UR number:_____

REPORTED BY: _____

WHICH CATEGORY?

☐ **CATEGORY 1:   DRUG INDICATION**

- Patient has sought medical advice for a condition requiring drug therapy. Required drug therapy not initiated.

☐ **CATEGORY 2:   WRONG DRUG TAKEN OR ADMINISTERED**

- Known allergy or contraindication to the medication.
- Medication prescribed is considered ineffective for patients condition (eg. antibiotics for a viral infection)
- Medication prescribed is not recommended as first line treatment. (eg. Ceclor for tonsillitis)
- Inappropriate dose form or device prescribed. (eg. Turbuhaler for a one year old child)
- Wrong drug dispensed or administered by a health professional.

☐ **CATEGORY 3:   SUBTHERAPEUTIC DOSE PRESCRIBED OF CORRECT DRUG**

- Subtherapeutic dose prescribed. (See DRP folder)
- Dose subtherapeutic according to the RCH Pharmacopoeia and/or "Drug Doses" booklet by Frank Shann

☐ **CATEGORY 4:   TOXIC DOSE PRESCRIBED OF CORRECT DRUG**

- Toxic dose prescribed. (See DRP folder)
- Dose toxic according to the RCH Pharmacopoeia and/or the "Drug Doses" booklet by Frank Shann

☐ **CATEGORY 5:   ADVERSE DRUG REACTION**

- A drug reaction that is undesired, unintended, or unexpected in doses recognised in accepted medical practice.

☐ **CATEGORY 6:   DRUG INTERACTION**

- A drug - drug interaction
- A drug - food interaction.
- A drug has interfered with the results of a standard laboratory test.

☐ **CATEGORY 7:   NONCOMPLIANCE**

- More medication given by the parent or guardian than prescribed.
- Less medication given by the parent or guardian than prescribed.
- Medication prescribed not given by parent or guardian.

☐ **CATEGORY 8:   ACCIDENTAL OR INTENTIONAL OVERDOSE**

> **PLEASE OBTAIN THE CHECKLIST CORRESPONDING TO THE APPROPRIATE CATEGORY NUMBER AND COMPLETE DETAILS. CHECKLISTS LOCATED IN THE CLERKS OFFICE.**
> *FOR MORE INFORMATION PLEASE SEE -*
> *KYLIE EASTON-CARTER or DR ANDREW MACLEAN*

Checklist One

```
╔═══════════════════════════════════════════════════╗
║         DRUG RELATED PROBLEMS STUDY               ║
║      CATEGORY 1        DRUG INDICATION            ║
╚═══════════════════════════════════════════════════╝
```

Patient Information/ Hospital Sticker

Surname:	Weight: kg
First name:	
UR No:	

Patient's medication history prior to attendance		
Name / Strength	Dose	Purpose (if known)

CATEGORY 1   DRUG INDICATION.

- How long has the medical condition requiring drug therapy been present?   Day(s) □   Week(s) □   Month(s) □
- Have they seen a medical practitioner for this condition?   Yes □   No □   Unsure □
- Is it unlikely the patient would have attended the emergency department if therapy had been initiated by a medical practitioner?   Yes □   No □   Unsure □
- Patient's attendance required treatment with the same or similar drug omitted   Yes □   No □   Unsure □

Medication (s) omitted associated with the reason for attendance

Name / Strength	Patient discharged from the emergency department on the medication?	
	Yes □	No □
	Yes □	No □

Brief description of the reason for attendance

Checklist Two

```
┌──────────────────────────────────────────────────────────────┐
│               DRUG RELATED PROBLEMS STUDY                     │
│   CATEGORY 2      WRONG DRUG TAKEN OR ADMINISTERED ?         │
└──────────────────────────────────────────────────────────────┘
```

Patient Information / Hospital Sticker		
Surname:	Weight:	kg
First name:		
UR No:		

Patient's medication history prior to attendance		
Name / Strength	Dose	Purpose (if known)

CATEGORY 2   WRONG DRUG TAKEN OR ADMINISTERED ?

• Known allergy to drug	Yes ☐	No ☐	Unsure ☐
• Known contraindication in patient's disease state	Yes ☐	No ☐	Unsure ☐
• Drug known to be ineffective in patient's disease state. (eg. Antibiotics for a viral infection)	Yes ☐	No ☐	Unsure ☐
• Drug prescribed is not recommended as first line treatment. (eg. Ceclor for tonsillitis)	Yes ☐	No ☐	Unsure ☐
• Wrong drug administered by health professional	Yes ☐	No ☐	Unsure ☐
• Wrong drug dispensed by health professional	Yes ☐	No ☐	Unsure ☐

Medication (s) implicated in reason for attendance

Name / Strength	Duration of treatment	
	Day (s) ☐	Week (s) ☐
	Day (s) ☐	Week (s) ☐
	Day (s) ☐	Week (s) ☐

Brief description of the reason leading to attendance

Checklist Three

DRUG RELATED PROBLEMS STUDY
CATEGORY 3   SUBTHERAPEUTIC DOSE OF CORRECT DRUG

Patient Information / Hospital Sticker

Surname:	Weight:	kg
First name:		
UR No:		

Patient's medication history prior to attendance		
Name / Strength	Dose	Purpose (if known)

CATEGORY 3 SUBTHERAPEUTIC DOSE OF CORRECT DRUG			
• Dose of drug **prescribed** is subtherapeutic	Yes ☐	No ☐	Unsure ☐
• Frequency of administration **prescribed** renders the dose subtherapeutic	Yes ☐	No ☐	Unsure ☐
• Duration of therapy less than recommended and hence renders the dose subtherapeutic	Yes ☐	No ☐	Unsure ☐

Medication(s) implicated in the reason for attendance

Name / Strength	Duration of treatment	
	Day (s) ☐	Week (s) ☐
	Day (s) ☐	Week (s) ☐
	Day (s) ☐	Week (s) ☐

Brief description of the reason leading to attendance

_____

_____

_____

_____

_____

_____

Checklist Four

DRUG RELATED PROBLEMS STUDY
CATEGORY 4   TOXIC DOSE OF CORRECT DRUG

Patient Information / Hospital Sticker		
Surname:	Weight:	kg
First name:		
UR No:		

Patient's medication history prior to attendance		
Name / Strength	Dose	Purpose (if known)

CATEGORY 4   TOXIC DOSE OF CORRECT DRUG

• A dose considered toxic was **prescribed**	Yes ☐	No ☐	Unsure ☐
• Frequency of administration **prescribed** renders the dose toxic .	Yes ☐	No ☐	Unsure ☐
• Duration of therapy **prescribed** renders the dose toxic	Yes ☐	No ☐	Unsure ☐
• Required drug monitoring or laboratory tests were not preformed resulting in toxicity	Yes ☐	No ☐	Unsure ☐

Medication (s) implicated in the reason for attendance

Name / Strength	Duration of treatment	
	Day (s) ☐	Week (s) ☐
	Day (s) ☐	Week (s) ☐
	Day (s) ☐	Week (s) ☐

Brief description of the reason leading to attendance

Checklist Five

<table>
<tr><td colspan="2" align="center">DRUG RELATED PROBLEMS STUDY
CATEGORY 5   ADVERSE DRUG REACTION</td></tr>
</table>

Patient Information / Hospital Sticker

Surname:	Weight: kg
First name:	
UR No:	

Patients medication history prior to attendance

Name / Strength	Dose	Purpose (if known)

CATEGORY 5   ADVERSE DRUG REACTION

- The observed reaction was undesired, unintended or unexpected   Yes ☐   No ☐

- The reaction was: Nausea ☐   Vomiting ☐   Diarrhoea ☐
  Other ☐ *(indicate)* _____   Rash ☐ *(type?)* _____

- Reaction improved when the drug was discontinued.   Yes ☐   No ☐   Don't know ☐

- Reaction improved when a specific antagonist was administered.   Yes ☐   No ☐   Don't know ☐

- Reaction reappeared when the drug was readministered.   Yes ☐   No ☐   Don't know ☐

- Reaction was more severe when the dose was increased and/or less severe when the dose was decreased   Yes ☐   No ☐   Don't know ☐

- Patient has had a similar response to drug previously   Yes ☐   No ☐

- Are there any other factors that may explain this reaction? (eg. viral illness, gastroenteritis etc)
  Please specify _____

Medication (s) implicated in the reason for attendance

Name / Strength	Time to onset of reaction		
	minute (s) ☐	hour (s) ☐	day (s) ☐
	minute (s) ☐	hour (s) ☐	day (s) ☐
	minute (s) ☐	hour (s) ☐	day (s) ☐

Brief description of the reason leading to attendance

Checklist Six

```
┌─────────────────────────────────────────────────────────┐
│           DRUG RELATED PROBLEMS STUDY                    │
│        CATEGORY 6        DRUG INTERACTION                │
└─────────────────────────────────────────────────────────┘
```

Patient Information / Hospital Sticker

Surname:	Weight: kg
First name:	
UR No:	

Patient's medication history prior to attendance

Name / Strength	Dose	Purpose (if known)

CATEGORY 6   DRUG INTERACTION

- The drug taken is known to interfere with the absorption, distribution, metabolism or elimination of drug(s) the patient is taking — Yes ☐ No ☐
- Food eaten is known to interfere with the absorption, distribution, metabolism or elimination of drug(s) the patient is taking — Yes ☐ No ☐
- Administration of a drug has interfered with the results from a standard laboratory test — Yes ☐ No ☐

Medication, Food and/or Laboratory test implicated in the reason for attendance

Medication Name / Strength	Food	Laboratory test

Brief description of the reason leading to attendance

Checklist Seven

```
┌─────────────────────────────────────────────────────────┐
│              DRUG RELATED PROBLEMS STUDY                  │
│        CATEGORY 7        NONCOMPLIANCE                    │
└─────────────────────────────────────────────────────────┘
```

Patient Information / Hospital Sticker

Surname:	Weight:	kg
First name:		
UR No:		

Patient's medication history prior to attendance

Name / Strength	Dose	Purpose (if known)

CATEGORY 7   NONCOMPLIANCE

• The patient was taking <u>less</u> than was prescribed of the correct medication(s)	Yes ☐	No ☐
• The patient was taking the dose <u>less</u> frequently than was prescribed.	Yes ☐	No ☐
• The patient was taking <u>more</u> than was prescribed of the correct medication(s)	Yes ☐	No ☐
• The patient was taking the dose <u>more</u> frequently than was prescribed	Yes ☐	No ☐

	Daily	Weekly	Rarely	Never
• How often would the patient miss taking one or more of their medications?	☐	☐	☐	☐

Medication(s) implicated in the reason for attendance

Name / Strength	Time period of the event		
	Day (s) ☐	Week (s) ☐	Month (s) ☐
	Day (s) ☐	Week (s) ☐	Month (s) ☐
	Day (s) ☐	Week (s) ☐	Month (s) ☐
	Day (s) ☐	Week (s) ☐	Month (s) ☐

Brief description of the reason leading to attendance

Checklist Eight

DRUG-RELATED PROBLEMS STUDY
CATEGORY 8   ACCIDENTAL OR INTENTIONAL OVERDOSE

Patient Information / Hospital Sticker		
Surname:	Weight:	kg
First name:		
UR No:		

Patients medication history prior to attendance		
Name / Strength	Dose	Purpose (if known)

CATEGORY 8   ACCIDENTAL OR INTENTIONAL OVERDOSE

- The event was a result of an accidental overdose.   Yes ☐   No ☐

- The event was a result of an intentional overdose.   Yes ☐   No ☐

Medication (s) implicated in the reason for attendance

Name / Strength	Suspected dose taken

Brief description of the reason leading to attendance

APPENDIX FIVE

Incidence calculation

In the calculation of incidence rates the numerator is the number of new events occurring over a defined time period with the denominator being the population at risk of experiencing the event during this time period.[*] Hence the incidence (I) rate is calculated as follows:

I rate = **number of new cases of a disease during a given period of time** (x10^n)

sum of the length of time during which each person in the population is at risk

In general, each person in the study population contributes one person year to the denominator for each year they remained under observation and free of the event in question.[*†]

In this study an I rate was determined for emergency department attendances and hospital admissions associated with DRPs only. An I rate was not calculated for ADRs arising within the inpatient population due to the similarities in the denominators utilised and the level of under-reporting identified in Section 6.2.5.

Emergency department attendances and hospital admissions associated with DRPs

Before an I rate was calculated for each of the three hospitals the total population at risk needed to be calculated. The total population at risk was assumed to be all paediatric persons within the catchment areas of the three hospitals who were taking medications. The first step in this calculation involved determining the catchment areas of the three hospitals. The second step involved estimating the number of paediatric persons within that catchment area who were taking medications. At this point the remaining steps were split into emergency department attendances and hospitals

---

[*] Beaglehole R, Bonita R, Kjellstrom T. Basic epidemiology. Geneva: World Health Organization, 1993.
[†] Hennekens CH, Burning JE. Measures of disease frequency. In: Mayrent SL, ed. Epidemiology in medicine. Boston: Little, Brown and Company, 1987:54-98.

admissions. The third step involved extrapolating data regarding the number of cases identified in Chapter Four and Chapter Five to a one-year period. The fourth step involved calculation of the I rate. The final step involves determining a 95% confidence interval for the I rate. Each of these steps will now be presented for RCH, GH and BH.

Royal Children's Hospital

Step One

An exact definition of the catchment area for RCH does not exist, so an estimate of the catchment area was made utilising paediatric inpatient geographic statistics for 1 July 1998 to 30 June 1999.

Inpatient geographic statistics for RCH

Region	Persons	% total cases
(1) Barwon-South Western	954	3.2
(2) Eastern	4130	13.9
(3) Gippsland	753	2.5
(4) Grampians	658	2.2
(5) Hume	1205	4.1
(6) Loddon	1382	4.7
(7) Northern	9017	30.3
(8) Southern	4028	13.6
(9) Western	6341	21.3
Overseas / interstate / unknown*	1256	4.2
Total	**29724**	**100.0**

*Excluded from calculation and hence not numbered

The number of paediatric persons was then determined for each region using statistics from the books titled: Melbourne in fact: 1996 census statistics for Melbourne's local government areas*; and Regional Victoria in Fact: 1996

---

* Victorian Department of Infrastructure Research Unit. Melbourne in fact: 1996 census statistics for Melbourne's local governement areas. Melbourne: Victorian Department of Infrastructure Research Unit, 1998.

census statistics for Victoria's local government areas˙. The number of paediatric persons per region was then multiplied by the corresponding percentage of RCH admissions to determine the catchment number for each region. The catchment areas for each region were then added to determine an estimated catchment number for the RCH.

Catchment numbers for RCH by region

Region	Local government areas included	No. of persons	Catchment no. for region
(1)	Golden Plains, Surf Coast, Greater Geelong, Queenscliff, Colac-Otway, Southern Grampians, Glenelg, Warrnambool, Moyne, Corangamite	87,928	2,822.5
(2)	Yarra Ranges, Maroondah, Knox, Manningham, Whitehorse, Monash, Boroondara	216,713	30,101.4
(3)	Bass Coast, Baw Baw, La Trobe, South Gippsland, East Gippsland, Wellington	64,837	1640.4
(4)	Ararat, Pyrenees, Ballarat, Hepburn, Moorabool, Hindmarsh, Yarriambiack, West Wimmera, Horsham, Northern Grampions	49,423	1092.3
(5)	Campaspel, Moira, Greater Shepparton, Strathbogie, Mitchell, Murrindindi, Delatite, Wangaratta, Alpine, Towonga, Wodonga, Indigo	77,464	3137.3
(6)	Loddon, Greater Bendigo, Central Goldfields, Mount Alexander, Macedon Ranges, Mildura, Swan Hill, Gannawarra, Buloke	66,701	3101.6
(7)	Hume, Whittlesea, Nillumbik, Moreland, Darebin, Banyule, Yarra	169,876	51,540.4
(8)	Greater Dandenong, Casey, Bayside, Kingston, Frankston, Cardinia, Mornington Peninsula, Glen Eira, Port Phillip, Stonnington	239,032	32,388.8
(9)	Melton, Brimbank, Hobsons Bay, Wyndham, Moonee Valley, Maribyrong, Melbourne	136,445	29,103.7
	Total	1,108,409	154,928.4

˙ Victorian Department of Infrastructure Research Unit. Regional Victoria in fact: 1996 census statistics for Victoria's local government areas. Melbourne: Victorian Department of

The number of paediatric persons within the RCH catchment area was estimated to be 154,928.4.

Step Two

An estimate of the number of paediatric persons within the catchment area for the RCH who were taking medication was determined using the 1995 National Health Survey: Use of Medicines*. This publication reported that 50.5% of people between 0 and 14 years of age had used medications or vitamins in the two weeks prior to interview. The number of paediatric persons in the RCH catchment area was then multiplied by 0.505 (50.5/100). The population at risk for RCH was estimated to be 78,238.8 paediatric persons.

Step Three

Emergency department attendances

Over the 11-week period of data at RCH a total of 244 cases were identified. Extrapolating this data it is estimated that a total of 1153.5 cases would be identified over a 52-week period of data collection.

Hospital admissions

Over the 18-week period of data collection a total of 119 cases were identified. Extrapolating this data it is estimated that a total of 343.8 cases would be identified over a 52-week period of data collection.

Step Four

Emergency department attendances

I rate = 1153.5/78,238.8 (x 100,000)

I rate = 1,474 per 100,000 paediatric persons / year

Hospital admissions

I rate = 343.8/78,238.8 (x 100,000)

I rate = 439 per 100,000 paediatric persons / year

Step Five

If I rate = no of new cases (D)/population at risk (Y)

Then the 95% Confidence interval = D/Exp(1.96/Sqr(D)) to D*Exp(1.96/Sqr(D))[†]

Emergency Department

95% Confidence interval = 1400 to 1551 per 100,000 paediatric persons / year

Hospital Admissions

95% Confidence interval = 400 to 482 per 100,000 paediatric persons / year

Geelong Hospital

Step One

As an exact definition of the catchment area for GH does not exist an estimate of the catchment area was made utilising inpatient geographic statistics. Similar statistics to those provided by the RCH were not available. Instead it was reported that GH served the Barwon-South Western Region with approximately 83% of hospital admissions arising from residents of the City of Greater Geelong (personal communication, Weeks G, Geelong: Geelong Hospital, January 1999). The number of paediatric persons residing within the catchment area was calculated via the same method as that reported for RCH.

Catchment numbers for GH by Local Government Area

Local Government Area	No. of persons 0-17 years	... proportion
Golden plains, Surf Coast, Queenscliff, Colac-Otway, Southern Grampians, Glenelg, Warrnambool, Moyne, Corangamite	42,336	7197.1
Greater Geelong	45,592	37,841.4
Total	87,928	45,038.5

[†] Armitage P, Berry G. Statistical methods in medical research. Boston: Blackwell Scientific Publications, 1994.

The number of paediatric persons within the GH catchment area was estimated to be 45,038.5.

In the remaining steps the same methods as those outlined for RCH will be utilised.

Step Two

The population at risk was estimated to be 22,744.4 paediatric persons.

Step Three

The estimated number of cases over a 52-week period of data collection was determined to be:

Emergency department: 286.0

Hospital admissions: 104.0

Step Four

The I rate was determined to be:

Emergency department: 1257 per 100,000 paediatric persons / year

Hospital admissions: 457 per 100,000 paediatric persons / year

Step Five

The 95% Confidence interval was determined to be:

Emergency department: 1189 to 1328 per 100,000 paediatric persons / year

Hospital admissions: 416 to 500 per 100,000 paediatric persons / year

Box Hill Hospital

Step One

As an exact definition of the catchment area for BH does not exist an estimate of the catchment area was made utilising paediatric inpatients geographic statistics for 1 July 1998 to 30 June 1999. The following steps were undertaken utilising the same methods as those outlined for RCH.

Inpatient geographic statistics for BH

Local Government Area	No. of persons	Percentage
Banyule	24	1.0
Boroondara	268	11.7
Knox	156	6.8
Manningham	319	13.9
Maroondah	267	11.6
Monash	43	1.9
Nilumbik	25	1.1
Whitehorse	702	30.6
Yarra Ranges	390	17.0
Other*	100	4.4
Total	**2294**	**100.0**

*Other was comprised of 38 different local government areas and was excluded from the calculation.

Catchment numbers for BH by Local Government Area

Local Government Area	No. of persons 0-14 years	Catchment population area
Banyule	26,755	280.9
Boroondara	31,059	3,640.1
Knox	38,389	2,618.1
Manningham	23,840	3,325.7
Maroondah	24,201	2,824.3
Monash	31,076	584.2
Nilumbik	17,433	190.0
Whitehorse	28,605	8781.7
Yarra Ranges	39,543	6742.1
Other	0	0
Total	**260,901**	**28,987**

The number of paediatric persons within the BH catchment area was estimated to be 28,987.1.

Step Two

The population at risk was estimated to be 14,638.5 paediatric persons.

Step Three

The estimated number of cases over a 52-week period of data collection was determined to be:

Emergency department: 242.7

Hospital admissions: not able to be calculated

Step Four

The I rate was determined to be:

Emergency department: 1658 per 100,000 paediatric persons / year

Hospital admissions: not able to be calculated

Step Five

The 95% Confidence interval was determined to be:

Emergency department: 1580 to 1740 per 100,000 paediatric persons / year

Hospital admissions: not able to be calculated

Combined data for RCH, GH and BH

The I rates determined for each of the hospitals in this section may be considered conservative estimates. This is because it is possible that not all emergency department attendances or hospital admissions associated with DRPs occurring in paediatric persons residing within the catchment areas presented to the hospitals monitored over the period of data collection. As a complete capture of DRPs is not assured across the three hospital sites a combined I rate was not calculated.

Assumptions made in calculating an incidence rate

A number of assumptions have been made in calculating an I rate for each of the three hospitals listed in this research.

1. The population at risk for emergency department attendances and hospital admissions associated with DRPs was estimated by determining the catchment areas of the three hospitals. As catchment area calculations were based upon inpatient geographic statistics, it was assumed that geographical distribution of paediatric persons attending the

three emergency departments was the same as that of paediatric persons admitted to the three hospitals.

2. The 1995 National Health Survey: Use of Medicines* was utilised to determine the proportion of paediatric persons taking medications. With respect to paediatric persons the data referred to persons 0 to 14 years of age. It was therefore assumed that the frequency of medication use by persons between 15 and 17 years of age was the same as that reported for patients 0 to 14 years of age.

3. Data regarding the number of cases identified at of the hospitals were extrapolated to a one-year period for all three streams of data collection. In doing so it is assumed that the number of cases identified over the data collection periods is representative of the frequency to which they occur over the one-year period and hence not affected by seasonal variations.

---

* Australian Bureau of Statistics. 1995 National Health Survey: Use of Medications. Cat. no. 4377.0, Canberra: ABS, 1999

APPENDIX SIX

Inter and intra-observer reproducibility

Inter and intra-observer reproducibility was measured in order to provide an estimate of the reproducibility of results obtained. Inter-observer reproducibility was measured using the Kappa statistic, which measures the strength of agreement between panel members taking into account agreement that would occur by chance alone.[*] The Kappa statistic is calculated using the following formula:

$$Kappa = \frac{P(A) - P(E)}{1 - P(E)}$$

where

P(A) = the proportion of times that *n* raters agree

P(E) = the proportion of times that *n raters* would be expected to agree by chance.

Inter-observer reproducibility

Emergency Department attendances

---

[*] Seigel S, Castellan NJ. Nonparametric statistics for the behavioral sciences. New York: McGraw-Hill International, 1988.

- ## DRP category

Inter-rater reliability pertaining to allocation of DRP category

Count

		DRP category for 2							
		Category Two	Category Three	Category Four	Category Five	Category Seven	Category 8	No	Total
DRP category for 1	Category Two	8	1		4	2		31	46
	Category Three	1	6			3		4	14
	Category Four			1	1		1		3
	Category Five	6	1	1	103		1	10	122
	Category Seven	1	5	1		9	2	2	20
	Category Eight		1				93	3	97
	No	18	4	1	7	6	2	73	111
Total		34	18	4	115	20	99	123	413

Symmetric Measures

	Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement Kappa	.622	.028	23.981	.000
N of Valid Cases	413			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

- ## Causality

Inter-rater reliability relating to allocation of causality classification

Count

		Causality ranking 2				
		Definite	Probable	Possible	Not applicable	Total
Causality ranking 1	Definite	95	9	6	13	123
	Probable	9	39	20	12	80
	Possible	11	28	40	20	99
	Not applicable	7	16	19	70	112
Total		122	92	85	115	414

Symmetric Measures

	Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement Kappa	.449	.032	15.747	.000
N of Valid Cases	414			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

- **Preventability**

Inter-rater reliability relating to allocation of preventability classification

Count

		Preventablity ranking 2				
		Yes	No	Unable	Not applicable	Total
Preventablity ranking 1	Yes	53	14	7	34	108
	No	9	40	8	3	60
	Unable	20	11	5	6	42
	Not applicable	30	7	7	159	203
Total		112	72	27	202	413

Symmetric Measures

	Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement Kappa	.425	.034	13.422	.000
N of Valid Cases	413			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

- **Clinical Significance**

The investigator determined clinical significance for emergency department attendances associated with DRPs and hence inter-observer reproducibility was not investigated.

Hospital Admissions

- ### DRP category

Inter-rater reliability pertaining to the allocation of DRP category

Count

		DRP category for 2									Total
		Category One	Category Two	Category Three	Category Four	Category Five	Category Six	Category Seven	Category 8	No	
DRP category for 1	Category One	1						4		1	6
	Category Two		1								1
	Category Three	1		3				10		3	17
	Category Four								1		1
	Category Five		1		2	24				2	29
	Category Six						1				1
	Category Seve	1		5				16		6	28
	Category Eight								49		49
	No	5	2	3	1	5		7	2	12	37
Total		8	4	11	3	29	1	37	52	24	169

Symmetric Measures

	Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement Kappa	.545	.043	15.102	.000
N of Valid Cases	169			

[a]. Not assuming the null hypothesis.

[b]. Using the asymptotic standard error assuming the null hypothesis.

- ### Causality

Inter-rater reliability relating to allocation of causality classification

Count

		Cauality ranking 2				Total
		Definite	Probable	Possible	Not applicable	
Causality ranking 1	Definite	52	2			54
	Probable	7	8	11	1	27
	Possible	6	15	20	11	52
	Not applicable	7	11	7	11	36
Total		72	36	38	23	169

Symmetric Measures

	Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement Kappa	.369	.047	8.295	.000
N of Valid Cases	169			

[a]. Not assuming the null hypothesis.

[b]. Using the asymptotic standard error assuming the null hypothesis.

- **Preventability**

Inter-rater reliability relating to allocation of preventability classification

Count

		Preventability ranking 2				
		Yes	No	Unable	Not applicable	Total
Preventablity ranking 1	Yes	27		4	4	35
	No	5	12		1	18
	Unable	13	5	5	8	31
	Not applicable	17	3	3	62	85
Total		62	20	12	75	169

Symmetric Measures

	Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement Kappa	.448	.050	9.556	.000
N of Valid Cases	169			

[a]. Not assuming the null hypothesis.

[b]. Using the asymptotic standard error assuming the null hypothesis.

- **Clinical Significance**

The investigator determined clinical significance for hospital admissions associated with DRPs and hence inter-observer reproducibility was not investigated.

ADRs within the inpatient population

- ### ADR definition

Inter-rater reliability relating to allocation of ADR defintion

Count

		ADR2	
		Yes	Total
ADR	yes	47	47
- y/n	no	1	1
Total		48	48

Symmetric Measures

	Value
Measure of Agreement Kappa	.[a]
N of Valid Cases	48

a. No statistics are computed because ADR2 is a constant.

Note that in 9 cases it was not indicated at this point as to whether a case met the ADR definition.

- ### Causality

Inter-rater reliability relating to allocation of causality classification

Count

		causality			
		Possible	Probable	Not applicable	Total
causality1	Possible	13	12	4	29
	Probable	11	7	1	19
	Not applicable	2		7	9
Total		26	19	12	57

Symmetric Measures

	Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement Kappa	.156	.114	1.611	.107
N of Valid Cases	57			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

- ## Preventability

Inter-rater reliability relating to preventability classification

Count

		PREVENT				
		Yes	No	Unable	Not applicable	Total
PREVE1	Yes	2	1			3
	No	1	31	5	5	42
	Unable	1	2			3
	Not applicable		2		7	9
Total		4	36	5	12	57

Symmetric Measures

		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa	.395	.112	4.362	.000
N of Valid Cases		57			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

- ## Clinical Significance

Inter-rater reliability relating to allocation of severity classification

Count

		SEVERITY				
		Mild	Moderate	Severe	Not applicable	Total
SEVER1	Mild	11	10		3	24
	Moderate	5	9		1	15
	Severe	2		5	1	8
	Not applicable	1	1		7	9
Total		19	20	5	12	56

Symmetric Measures

		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa	.398	.097	4.939	.000
N of Valid Cases		56			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

Intra-observer reproducibility

Multidisciplinary Panel

- **Causality**

REVIEWER ONE

Count

		Cauality ranking 2				
		Definite	Probable	Possible	Not applicable	Total
Causality ranking 1	Definite	8	1	2	1	12
	Probable		1	1	1	3
	Possible		1	8		9
	Not applicable			1	5	6
Total		8	3	12	7	30

Symmetric Measures

		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa	.628	.107	5.711	.000
N of Valid Cases		30			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

REVIEWER TWO

Count

		Cauality ranking 2				
		Definite	Probable	Possible	Not applicable	Total
Causality ranking 1	Definite	5		1		6
	Probable		5	4		9
	Possible		2	4	2	8
	Not applicable			2	4	6
Total		5	7	11	6	29

Symmetric Measures

		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa	.489	.125	4.559	.000
N of Valid Cases		29			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

REVIEWER THREE

Count

		Cauality ranking 2				
		Definite	Probable	Possible	Not applicable	Total
Causality ranking 1	Definite	9	2			11
	Probable	1	5			6
	Possible		2			2
	Not applicable		2	1	7	10
Total		10	11	1	7	29

Symmetric Measures

	Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement Kappa	.609	.109	5.274	.000
N of Valid Cases	29			

[a] Not assuming the null hypothesis.

[b] Using the asymptotic standard error assuming the null hypothesis.

REVIEWER FOUR

Count

		Cauality ranking 2				
		Definite	Probable	Possible	Not applicable	Total
Causality ranking 1	Definite	9				9
	Probable		2	3		5
	Possible			11	1	12
	Not applicable				4	4
Total		9	2	14	5	30

Symmetric Measures

	Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement Kappa	.807	.088	7.165	.000
N of Valid Cases	30			

[a] Not assuming the null hypothesis.

[b] Using the asymptotic standard error assuming the null hypothesis.

REVIEWER FIVE

Count

		Cauality ranking 2				Total
		Definite	Probable	Possible	Not applicable	
Causality ranking 1	Definite	10		1		11
	Probable		5	1		6
	Possible	1		4		5
	Not applicable		1		7	8
Total		11	6	6	7	30

Symmetric Measures

	Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement Kappa	.817	.084	7.599	.000
N of Valid Cases	30			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

REVIEWER SIX

Count

		Cauality ranking 2				Total
		Definite	Probable	Possible	Not applicable	
Causality ranking 1	Definite	9	1	1		11
	Probable		4	4		8
	Possible			2	1	3
	Not applicable	1	1	2	4	8
Total		10	6	9	5	30

Symmetric Measures

	Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement Kappa	.511	.108	5.080	.000
N of Valid Cases	30			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

- ## Preventability

REVIEWER ONE

Count

		Preventablity ranking 2				
		Yes	No	Unable	Not applicable	Total
Preventablity ranking 1	Yes	7		2	2	11
	No	1	4			5
	Unable	1				1
	Not applicable	1			12	13
Total		10	4	2	14	30

Symmetric Measures

	Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement Kappa	.642	.114	5.166	.000
N of Valid Cases	30			

[a]. Not assuming the null hypothesis.

[b]. Using the asymptotic standard error assuming the null hypothesis.

REVIEWER TWO

Count

		Preventablity ranking 2				
		Yes	No	Unable	Not applicable	Total
Preventablity ranking 1	Yes	6	2		1	9
	No		2			2
	Unable	1	4	1	2	8
	Not applicable	1	1		8	10
Total		8	9	1	11	29

Symmetric Measures

	Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement Kappa	.450	.105	4.673	.000
N of Valid Cases	29			

[a]. Not assuming the null hypothesis.

[b]. Using the asymptotic standard error assuming the null hypothesis.

REVIEWER THREE

Count

		Preventablity ranking 2				
		Yes	No	Unable	Not applicable	Total
Preventablity ranking 1	Yes	4				4
	No	3	3			6
	Unable			1		1
	Not applicable	2	1		15	18
Total		9	4	1	15	29

Symmetric Measures

		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa	.659	.113	5.482	.000
N of Valid Cases		29			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

REVIEWER FOUR

Count

		Preventablity ranking 2				
		Yes	No	Unable	Not applicable	Total
Preventablity ranking 1	Yes	7			1	8
	No	1	9	1		11
	Unable			1		1
	Not applicable				10	10
Total		8	9	2	11	30

Symmetric Measures

		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa	.856	.078	7.246	.000
N of Valid Cases		30			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

REVIEWER FIVE

Count

| | | Preventablity ranking 2 | | | Total |
		Yes	No	Not applicable	
Preventablity ranking 1	Yes	6	2		8
	No	1	4		5
	Not applicable	1		16	17
Total		8	6	16	30

Symmetric Measures

	Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement Kappa	.775	.099	5.789	.000
N of Valid Cases	30			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

REVIEWER SIX

Count

| | | Preventablity ranking 2 | | | | Total |
		Yes	No	Unable	Not applicable	
Preventablity ranking 1	Yes	8	2		1	11
	No		1			1
	Unable	1				1
	Not applicable	3		1	13	17
Total		12	3	1	14	30

Symmetric Measures

	Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement Kappa	.544	.127	3.872	.000
N of Valid Cases	30			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

• Clinical Significance

The investigator determined clinical significance for emergency department attendances and hospital admissions associated with DRPs and hence intra-observer reproducibility was not investigated.

Pharmacy Panel

One member of the *pharmacy panel* was not available to complete the cases required to establish intra-observer reproducibility. The following kappa values are therefore for *pharmacy panel* members 1 to 3 only.

- **Causality**

REVIEWER ONE

Count

		causality			
		Possible	Probable	Not applicable	Total
causality1	Possible	9	3	1	13
	Probable	4			4
	Not applicable			3	3
Total		13	3	4	20

Symmetric Measures

	Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement Kappa	.227	.202	1.380	.168
N of Valid Cases	20			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

REVIEWER TWO

Count

		causality			
		Possible	Probable	Not applicable	Total
causality1	Possible	6	3		9
	Probable	5	3		8
	Not applicable		1	2	3
Total		11	7	2	20

Symmetric Measures

	Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement Kappa	.247	.199	1.445	.148
N of Valid Cases	20			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

REVIEWER THREE

Count

		causality			
		Possible	Probable	Not applicable	Total
causality1	Possible	6	8		14
	Probable	5	3		8
	Not applicable			1	1
Total		11	11	1	23

Symmetric Measures

		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa	-.045	.214	-.253	.800
N of Valid Cases		23			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

- **Preventability**

REVIEWER ONE

Count

		PREVENT				
		Yes	No	Unable	Not applicable	Total
PREVET1	Yes	2				2
	No	1	11	1		13
	Unable	1			1	2
	Not applicable				3	3
Total		4	11	1	4	20

Symmetric Measures

		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa	.660	.135	4.592	.000
N of Valid Cases		20			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

REVIEWER TWO

Count

		PREVENT		
		No	Not applicable	Total
PREVE1	No	17		17
	Not applicable	1	2	3
Total		18	2	20

Symmetric Measures

	Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement Kappa	.773	.216	3.549	.000
N of Valid Cases	20			

[a] Not assuming the null hypothesis.

[b] Using the asymptotic standard error assuming the null hypothesis.

REVIEWER THREE

Count

		PREVENT			
		Yes	No	Not applicable	Total
PREVE1	Yes	1	1		2
	No		20		20
	Not applicable			1	1
Total		1	21	1	23

Symmetric Measures

	Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement Kappa	.783	.208	4.956	.000
N of Valid Cases	23			

[a] Not assuming the null hypothesis.

[b] Using the asymptotic standard error assuming the null hypothesis.

- ## Clinical significance

REVIEWER ONE

Count

		SEVERITY			
		Moderate	Severe	Not applicable	Total
SEVER1	Mild	4			4
	Moderate	8			8
	Severe		4	1	5
	Not applicable			3	3
Total		12	4	4	20

Symmetric Measures

	Value
Measure of Agreement Kappa	.[a]
N of Valid Cases	20

[a.] Kappa statistics cannot be computed. They require a symmetric 2-way table in which the values of the first variable match the values of the second variable.

REVIEWER TWO

Count

		SEVERITY				
		Mild	Moderate	Severe	Not applicable	Total
SEVER1	Mild	9	1			10
	Moderate		4			4
	Severe			3		3
	Not applicable		1		2	3
Total		9	6	3	2	20

Symmetric Measures

	Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement Kappa	.852	.097	6.223	.000
N of Valid Cases	20			

[a.] Not assuming the null hypothesis.

[b.] Using the asymptotic standard error assuming the null hypothesis.

REVIEWER THREE

Count

		SEVERITY				
		Mild	Moderate	Severe	Not applicable	Total
SEVER1	Mild	8	5			13
	Moderate	3	5			8
	Severe			1		1
	Not applicable				1	1
Total		11	10	1	1	23

Symmetric Measures

		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa	.395	.188	2.400	.016
N of Valid Cases		23			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

APPENDIX SEVEN

Hospital admissions checklist

DRUG RELATED PROBLEMS STUDY

COULD THE PATIENTS ATTENDANCE POSSIBLY INVOLVE ONE OF THE FOLLOWING DRUG RELATED PROBLEM CATEGORIES

① **CATEGORY 1:   DRUG INDICATION**

- Patient has sought medical advice for a condition requiring drug therapy. Required drug therapy not initiated.

② **CATEGORY 2:   WRONG DRUG TAKEN OR ADMINISTERED**

- Known allergy or contraindication to the medication.
- Inappropriate dose form or device prescribed. (eg. Turbuhaler for a one year old child)
- Wrong drug dispensed or administered by a health professional.

③ **CATEGORY 3:   SUBTHERAPEUTIC DOSE PRESCRIBED OF CORRECT DRUG**

- Subtherapeutic dose prescribed.
- Dose subtherapeutic according to the RCH Pharmacopoeia and/or ICU booklet by Frank Shann

④ **CATEGORY 4:   TOXIC DOSE PRESCRIBED OF CORRECT DRUG**

- Toxic dose prescribed.
- Dose toxic according to the RCH Pharmacopoeia and/or the ICU booklet by Frank Shann

⑤ **CATEGORY 5:   ADVERSE DRUG REACTION**

- A drug reaction that is undesired, unintended, or unexpected in doses recognised in accepted medical practice.

⑥ **CATEGORY 6:   DRUG INTERACTION**

- A drug - drug interaction
- A drug - food interaction.
- A drug has interfered with the results of a standard laboratory test.

⑦ **CATEGORY 7:   NONCOMPLIANCE**

- More medication given than prescribed by parent or guardian.
- Less medication given than prescribed by parent or guardian.
- Medication prescribed not given by parent or guardian.

⑧ **CATEGORY 8:   ACCIDENTAL OR INTENTIONAL OVERDOSE**

IF SO, PLEASE TICK THE APPROPRIATE CATEGORY AND COMPLETE DETAILS ON THE OTHER SIDE OF THIS PAGE.

DRUG RELATED PROBLEMS STUDY

Patient Information / Hospital Sticker		
Surname:	Weight:	kg
First name:	Height:	cm
UR No:	Ward:	

DETAILS OF DRUG OR DRUGS SUSPECTED IN REASON FOR ADMISSION:

DRUG 1. ....

DRUG 2. ....

DRUG 3. ....

DRUG 4. ....

PATIENTS REGULAR MEDICATIONS (NOT IMPLICATED IN THE REASON FOR ADMISSION)

DRUG 1. ....

DRUG 2. ....

DRUG 3. ....

DRUG 4. ....

TREATMENT WITHIN THE HOSPITAL

DRUG 1. ....

DRUG 2. ....

DRUG 3. ....

DRUG 4. ....

BRIEF DESCRIPTION OF THE EVENT LEADING TO ATTENDANCE:

....
....
....
....
....

PATIENT NUMBER _____

APPENDIX EIGHT

Summary of hospital admission codes relevant to adverse drug reactions

ICD-9-CM codes

Under the ICD-9-CM coding system all hospital admissions associated with adverse events are coded with an E-code (or injury code) to identify the cause of the adverse event. E-codes 930 to 949 identify adverse drug reactions due to therapeutic drug use. The codes and the corresponding drug classes are listed below.

E930	Antibiotics
E931	Other anti-infectives
E932	Hormones & synthetic substitutes
E933	Primarily systemic agents
E934	Agents primarily affecting blood constituents
E935	Analgesics, antipyretics & antirheumatics
E936	Anticonvulsants & anti-parkinsonism drugs
E937	Sedatives & hypnotics
E938	Other CNS depressants & anaesthetics
E939	Psychotropic agents
E940	CNS stimulants
E941	Drugs primarily affecting the autonomic nervous system
E942	Agents primarily affecting the cardiovascular system
E943	Agents primarily affecting the gastrointestinal system
E944	Water, mineral & uric acid metabolism drugs
E945	Agents primarily acting on the smooth & skeletal muscles and respiratory system
E946	Agents primarily affecting skin & mucus membrane, ophthalmological, otorhinolaryngological & dental drugs
E947	Other & unspecified drugs & medicinal substances
E948	Bacterial vaccines
E949	Other vaccines & biological substances

ICD-10-AM codes

Under the ICD-10-AM coding system all hospital admissions associated with adverse events are coded with a V, W, X or Y-code, known as an external causes of morbidity and mortality code. Y-codes Y40 to Y59 identify drugs, medicaments and biological substances causing adverse effects in therapeutic use. The codes and the corresponding drug classes are listed below.

Y40	Systemic antibiotics
Y41	Other systemic anti-infectives and antiparasitics
Y42	Hormones and their synthetic substitutes and antagonists, not elsewhere classified
Y43	Primarily systemic agents
Y44	Agents primarily affecting blood constituents
Y45	Analgesics, antipyretics and anti-inflammatory drugs
Y46	Antiepileptics and antiparkinsonism drugs
Y47	Sedatives, hypnotics and antianxiety drugs
Y48	Anaesthetics and therapeutic gases
Y49	Psychotropic drugs, not elsewhere classified
Y50	Central nervous system stimulants, not elsewhere classified
Y51	Drugs primarily affecting the autonomic nervous system
Y52	Agents primarily affecting the cardiovascular system
Y53	Agents primarily affecting the gastrointestinal system
Y54	Agents primarily affecting water-balance and mineral and uric acid metabolism
Y55	Agents primarily acting on smooth and skeletal muscles and the respiratory system
Y56	Topical agents primarily affecting skin and mucous membranes and ophthalmological, otorhinolaryngological and dental drugs
Y57	Other and unspecified drugs and medicaments
Y58	Bacterial vaccines
Y59	Other and unspecified vaccines and biological substances

APPENDIX NINE

Questionnaire

Section One

In this section we are trying to find out about the costs to you and your family as a result of your child's visit to the Royal Children's Hospital.

Please answer each question unless asked not to do so. If you are not sure or cannot remember the exact details please make an estimate.

---

1. When you last took your child to the Royal Children's Hospital, what type of transport was used?

  ☐ Private vehicle

  ☐ Taxi

  ☐ Ambulance

  ☐ Public transport

  ☐ Other *(please specify)* _____

2. How far away from the hospital do you live?

  ☐ Less than 10 kilometres (kms)

  ☐ 11 - 20 kms

  ☐ 21 - 30 kms

  ☐ 31 - 40 kms

  ☐ More than 40 kms *(please specify)* _____

3. How long did your child stay at the Royal Children's Hospital?

  ☐ 1 - 3 hours

  ☐ 3 - 10 hours

  ☐ 10 - 24 hours

  ☐ 2 days

  ☐ More than 2 days *(please specify)* _____

4. During your child's stay how many visits did you and your family make to the hospital and what type of transport was used to get there?
(Please write number of trips using each type of transport in box.)

  Private vehicle
  Taxi
  Public transport
  Other *(please specify)* _____

5. For how many days did you and your family have to change your normal activities because your child was in hospital?
(Please write number in the box)

  Days of paid work
  Days of regular activity (home duties, leisure time, etc)

6. After your child came home from hospital, did he or she need more care than usual?

☐   Yes   If **Yes** please go to **Question 7**

☐   No   If **No** please go to **Question 9**

7. If yes, for how many days did you and your family have to change your normal activities because your child needed extra care?

Days of paid work
Days of regular activity (home duties, leisure time, etc)

8. If your child needed more care than normal after coming home from hospital, was any professional care required? (eg housekeeper, home nursing service, other)

Please specify_____
☐ Number of hours

9. What is the occupation of the person who normally cares for the child?

☐   Home duties

☐   Retired / unemployed

☐   Paid employment *(please specify)*   _____

Section 2

This section looks at medicines and other products that you may have used to treat your child. We are most interested to know about medicines and other products that <u>do not</u> require a prescription from the doctor (non-prescription medications).
Please answer each question unless otherwise indicated.

---

10. Children often need products that <u>do not</u> require a prescription from the doctor to treat minor illnesses. Nine groups of commonly used medications and other products that do not need a prescription are listed below. Please show if you have given your child one or more of these types of medications in either the two weeks before your child's visit to hospital or since your child has left the hospital.

Please give the name of product (s)

☐   Pain relief / Anti-fever medicines   _____

☐   Vitamins, minerals or herbal products   _____

☐   Cough and cold medicines   _____

☐   Creams for the skin   _____

☐   Diarrhoea mixtures   _____

☐   Antacids   _____

☐   Nose sprays   _____

☐   Laxatives   _____

☐   Allergy products   _____

☐   Other non-prescription products   _____

11. Where do you obtain information about how to use / give non-prescription medicines and other products? *(Please show all sources you get information from)*

☐	Relative	☐	Nurse	☐	Product label
☐	Paediatrician	☐	Dentist	☐	Other *(Please specify)*
☐	Family doctor	☐	Pharmacist		_____
☐	Friend (s)	☐	Naturopath		

12. Please show how often, if ever, you use the following people to obtain information on medicines and other products that <u>do not</u> need a prescription. *(Please show a response for each category)*

	Very Often	*Often*	*Sometimes*	*Seldom*	*Never*
Relative	☐	☐	☐	☐	☐
Paediatrician	☐	☐	☐	☐	☐
Family doctor	☐	☐	☐	☐	☐
Friend (s)	☐	☐	☐	☐	☐
Pharmacist	☐	☐	☐	☐	☐
Nurse	☐	☐	☐	☐	☐
Dentist	☐	☐	☐	☐	☐
Naturopath	☐	☐	☐	☐	☐
Other _____	☐	☐	☐	☐	☐

13. When you are choosing a medicine or other product for your child's illness how important is information from the following people to you? *(Please show a response for each category)*

	Very important	*Somewhat important*	*Not very important*	*Not important*
Relative	☐	☐	☐	☐
Paediatrician	☐	☐	☐	☐
Family doctor	☐	☐	☐	☐
Pharmacist	☐	☐	☐	☐
Nurse	☐	☐	☐	☐
Friend (s)	☐	☐	☐	☐
Naturopath	☐	☐	☐	☐
Other _____	☐	☐	☐	☐

14. Where do you normally buy medicines and other products that do not need a prescription?

A regular pharmacy	☐	Different pharmacies	☐
Supermarket	☐	Naturopath	☐
Health food shop	☐	Other _____	

APPENDIX TEN

Explanatory Statements

Royal Children's Hospital

Royal Children's Hospital
Melbourne, Victoria

Department

Flemington Road,
Parkville, Victoria, 3052
Australia.
Telephone: (03) 9345 5522
Facsimile: (03) 9345 5789

HOSPITAL VISITS AND MEDICINE USE IN CHILDREN

This study is being conducted jointly by the Royal Children's Hospital and Monash University. The study is being supervised by Dr Jo-anne Brien (Monash University) and Mr Brian Lilley (Royal Children's Hospital).

Little information is available on travel costs and time lost from normal activities by the families of children who have had to visit hospital. The first aim of this study is to obtain information about these costs to you and your family as a result of your child's visit to the Royal Children's hospital. This information will give us a better understanding of the costs to families involved with caring for an ill child.

The second aim of this study is to find out about the use in children of medicines and other products such as herbal remedies and alternative medicines that do not need a prescription. These products are often used in children to treat minor illnesses. In obtaining this information we hope to understand what type of products are commonly used and where people get advice about these products.

The study involves 10 - 15 minutes of your time to fill out a questionnaire. The questionnaire will ask you about travel costs and time lost from normal activities due to your child being in hospital. There are also questions about medicines and other products, such as herbal therapies and alternative medicines not requiring a prescription that are used to treat children. This study only requires you to fill out this one questionnaire.

If you agree to be involved in this study a questionnaire will be sent to you one week after your child has left the hospital. If we do not receive a response from you we will phone to check that you have received the questionnaire. This call will give you the option of withdrawing from the study, receiving another questionnaire or answering the questionnaire over the phone if it is convenient for you to do so.

Information you provide in the questionnaire will be kept confidential. You are free to withdraw from the study at any time without explanation, and non-participation in this study will not in any way affect access to the best available treatment and care at the Royal Children's Hospital.

If you require a non-English version of this statement, please ask for it to be provided in your language. If required, assistance with language through an interpreter will be made available to help you with this statement and/or to answer the questionnaire.

Thank you for the opportunity to talk with you.

Kylie Easton

For further information contact:
Mr Brian Lilley, Acting Network Director of Pharmacy, Royal Women's and Children's Healthcare Network. or Ms Kylie Easton, Research Pharmacist, Royal Children's Hospital. Tel : (03) 9345 5492

Barwon Health, The Geelong Hospital

Barwon Health

Acute Health

The Geelong Hospital
Ryrie Street   P.O. Box 281
Geelong   Victoria   3220
Telephone   03 5226 7111
Facsimile   03 5221 3429

HOSPITAL VISITS AND MEDICINE USE IN CHILDREN

This study is being conducted jointly by the Geelong Hospital and Monash University. The study is being supervised by Dr Jo-anne Brien (Senior Lecturer in Pharmacy Practice, Monash University) and Mr Greg Weeks (Director of Pharmacy, Geelong Hospital).

Little information is available on travel costs and time lost from normal activities by the families of children who have had to visit hospital. The first aim of this study is to obtain information about these costs to you and your family as a result of your child's visit to the Geelong Hospital. This information will give us a better understanding of the costs to families involved with caring for an ill child.

The second aim of this study is to find out about the use in children of medicines and other products such as herbal remedies and alternative medicines that do not need a prescription. These products are often used in children to treat minor illnesses. In obtaining this information we hope to understand what type of products are commonly used and where people get advice about these products.

The study involves 10 - 15 minutes of your time to fill out a questionnaire. The questionnaire will ask you about travel costs and time lost from normal activities due to your child being in hospital. There are also questions about medicines and other products, such as herbal therapies and alternative medicines not requiring a prescription that are used to treat children. This study only requires you to fill out this one questionnaire.

If you agree to be involved in this study a questionnaire will be sent to you one week after your child has left the hospital. If we do not receive a response from you we will phone to check that you have received the questionnaire. This call will give you the option of withdrawing from the study, receiving another questionnaire or answering the questionnaire over the phone if it is convenient for you to do so.

Information you provide in the questionnaire will be kept confidential. You are free to withdraw from the study at any time without explanation, and non-participation in this study will not in any way affect access to the best available treatment and care at the Geelong Hospital.

If you require a non-English version of this statement, please ask for it to be provided in your language. If required, assistance with language through an interpreter will be made available to help you with this statement and/or to answer the questionnaire.

Thank you for the opportunity to talk with you.

Kylie Easton-Carter
Research Pharmacist

For further information contact:
Mr Greg Weeks, Director of Pharmacy, Geelong Hospital. or Ms Kylie Easton-Carter, Research Pharmacist, Geelong Hospital. Tel : 03 52267556

Box Hill Hospital

Box Hill Hospital

A Monash University Teaching Hospital
Nelson Road, Box Hill Victoria 3128
PO Box 94, Box Hill Vic 3128 Australia
Telephone: (61 3) 9895 3333
Facsimile: (61 3) 9895 3268
Email: bhhosp.@boxhill.org.au
Website: www.boxhill.org.au

HOSPITAL VISITS AND MEDICINE USE IN CHILDREN

This study is being conducted jointly by the Box Hill Hospital and Monash University. The study is being supervised by Dr Jo-anne Brien (Senior Lecturer in Pharmacy Practice, Monash University) and Mr Des Meagher (Director of Pharmacy, Box Hill Hospital).

Little information is available on travel costs and time lost from normal activities by the families of children who have had to visit hospital. The first aim of this study is to obtain information about these costs to you and your family as a result of your child's visit to the Box Hill Hospital. This information will give us a better understanding of the costs to families involved with caring for an ill child.

The second aim of this study is to find out about the use in children of medicines and other products such as herbal remedies and alternative medicines that do not need a prescription. These products are often used in children to treat minor illnesses. In obtaining this information we hope to understand what type of products are commonly used and where people get advice about these products.

The study involves 10 - 15 minutes of your time to fill out a questionnaire. The questionnaire will ask you about travel costs and time lost from normal activities due to your child being in hospital. There are also questions about medicines and other products, such as herbal therapies and alternative medicines not requiring a prescription that are used to treat children. This study only requires you to fill out this one questionnaire.

If you agree to be involved in this study a questionnaire will be sent to you one week after your child has left the hospital. If we do not receive a response from you we will phone to check that you have received the questionnaire. This call will give you the option of withdrawing from the study, receiving another questionnaire or answering the questionnaire over the phone if it is convenient for you to do so.

Information you provide in the questionnaire will be kept confidential. You are free to withdraw from the study at any time without explanation, and non-participation in this study will not in any way affect access to the best available treatment and care at the Box Hill Hospital.

If you require a non-English version of this statement, please ask for it to be provided in your language. If required, assistance with language through an interpreter will be made available to help you with this statement and/or to answer the questionnaire.

Thank you for the opportunity to talk with you.

Kylie Easton-Carter
Research Pharmacist

For further information contact:
Mr Des Meagher, Director of Pharmacy, Box Hill Hospital. or
Ms Kylie Easton-Carter, Research Pharmacist, Box Hill Hospital. Tel : 03 9895 3309

INNER & EASTERN
HEALTH CARE NETWORK

APPENDIX ELEVEN

Average private vehicle operating cost per kilometre

An average private vehicle operating cost per kilometre was calculated utilising the information from the *RACV Vehicle Operating Costs – June 2000* public policy document (Personal communication, Downes J, Melbourne: Royal Automobile Club of Victoria, August 2000).

Private vehicle operating costs for light, small, medium and large cars, people movers along with small and large 4WD'S are provided in the document. The costs calculated are based upon the assumption that privately owned vehicles are owned for 5 years, travel an average annual distance of 15,000 kilometres, and air conditioning is included in each vehicle. Depreciation, interest, vehicle registration, Traffic Accident Commission, insurance, fuel, vehicle maintenance and vehicle purchase costs are included in the costs determined.

Light vehicles							
Daewoo Lanos SE	Daihatsu Charade TS	Ford Festiva Trio	Holden Barina City	Hyundai Excel Sprint	Mazda 121 Metro	Mitsub. Mirage 3D	Toyota Echo 3D
Total costs							
Average cents / km 34.77	35.52	35.44	35.22	32.27	39.09	36.92	35.47

Small vehicles							
Daewoo Nubira SE	Ford Laser GLXi	Holden Astra City	Hyundai Lantra GLE	Mazda 323 Protégé	Mitsub Lancer GLXi	Nissan Pulsar LX	Toyota Corolla Csi
Total costs							
Average cents / km 42.08	46.89	44.64	43.06	47.91	42.18	42.57	42.60

	Medium vehicles				Large vehicles			
	Daewoo Leganza 2.2	Holden Vectra GL	Hyundai Sonata GLS	Toyota Camry Csi 2.2	Ford Falcon Forte	Holden Commdr Exec	Mitsub Magna Exec	Toyota Camry Csi V6
Total costs								
Average cents / km	47.71	47.81	48.98	48.19	53.36	55.41	53.93	56.87

	People movers			
	Chrysler Voyager LE	Honda Odyssey 4cyl	Mitsub Starwagon GLX	Toyota Tarago Gli
Total costs				
Average cents / km	79.68	64.29	66.55	72.67

	Small 4WD'S				Large 4WD'S	
	Honda CRV	Subaru Forester GX	Suzuki Grand Vitara	Toyota RAV4 5D	Holden Jackaroo S	Mitsub Pajero GLX
Total costs						
Average cents / km	52.76	51.96	51.20	51.55	75.44	72.74

An average private vehicle operating cost per kilometre was determined by averaging the costs provided for each type of vehicle listed.

The average private vehicle operating cost per kilometre was therefore determined to be $0.50.

References

1.   Commonwealth Department of Health and Aged Care. National Medicines Policy 2000. Canberra: Publications Production Unit (Public Affairs, Parliamentary and Access Branch), 1999.

2.   Commonwealth Department of Health Housing and Community Services. A policy on the quality use of medicines. Prepared in conjunction with the Pharmaceutical Health and the Rational use of Medicines (PHARM) working party. Canberra: Australian Government Publishing Service, 1992.

3.   Australian Bureau of Statistics. 1995 National Health Survey: use of Medications. Cat. no. 4377.0, Canberra: ABS, 1999.

4.   Roughead E. The nature and extent of drug-related hospitalisations in Australia. J Qual Clin Pract 1999; 19:19-22.

5.   Ng D, Cosh DG, Harris J, Whitehead C. Unplanned medication-related admissions to an acute care general teaching hospital. Aust J Hosp Pharm 1999; 29:84-87.

6.   Dartnell JGA, Anderson RP, Chohan V, et al. Hospitalisation for adverse events related to drug therapy: incidence, avoidability and costs. Med J Aust 1996; 164:659-662.

7.   Easton KL, Parsons BJ, Starr M, Brien JE. The incidence of drug-related problems as a cause of hospital admissions in children. Med J Aust 1998; 169:356-359.

8.   Australian Health Innovations. Educational strategies for the quality use of paediatric medications. Vol. 4. Sydney: Australian Health Innovations Pty Limited, 1995.

9. Turner S. Unregistered and off-label drug use in paediatric inpatients. Aust J Hosp Pharm 1999; 29:165-168.

10. Australian Institue of Health and Welfare and Commonwealth Department of Health and Family Services. First report on National Health Priority Areas 1996. Canberra: AIHW and DHFS, 1997.

11. Nyquist A, Gonzales R, Steiner JF, Sande MA. Antibiotic prescribing for children with colds, upper respiratory tract infections, and bronchitis. JAMA 1998; 1998:875-877.

12. Conroy S, Choonara I, Impicciatore P, et al. Survey of unlicenced and off label drug use in paediatric wards in European countries. BMJ 2000; 320:79-82.

13. Turner S, Longworth A, Nunn AJ, Choonara I. Unlicensed and off label drug use in paediatric wards: prospective study. BMJ 1998; 316:343-345.

14. Young S. Providing pharmaceutical care to the pediatric patient. J Pharm Pract 1996; 1X:3-13.

15. Impicciatore P, Pandolfini C, Bosetti C, Bonati M. Adverse drug reactions in children: a systematic review of published case reports. Paediatr Perinat Drug Ther 1998; 2:27-36.

16. Collier J. Paediatric prescribing: using unlicensed drugs and medications outside their licensed indications. Br J Clin Pharmacol 1999; 48:5-8.

17. Milsap RL, Hill MR, Szefler SJ. Special pharmacokinetic considerations in children. In: Evans WE, Schentag JJ, Jusko WJ, eds. Applied pharmacokinetics: principals of therapeutic drug monitoring. Vancouver: Applied Therapeutics Inc, 1992:10.1-10.32.

18. Zenk KE. Challenges in providing pharmaceutical care to pediatric patients. Am J Hosp Pharm 1994; 51:688-694.

19. Australian Association of Paediatric Teaching Centres. Policies 1997: pharmaceuticals for children. Deakin West: The Australian Association of Paediatric Teaching Centres, 1997.

20. Working Party on Registration of Drugs for Use in Children. Report of the working party on the registration of drugs for use in children. Canberra: Australian Drug Evaluation Committee, 1997.

21. Thatcher Shope J. Medication Compliance. Pediatr Clin North Am 1981; 28:5-12.

22. Litt IF, Cuskey WR. Compliance with medical regimens during adolescence. Pediatr Clin North Am 1980; 27:3-15.

23. Blanchard N, Primovic J, Leff RD. Compliance with pediatric medications. J Pediatr Pharm Pract 1999; 4:181-185.

24. Liptak GS. Enhancing patient compliance in pediatrics. Pediatr Rev 1996; 17:128-134.

25. Heubi JE, Barbacci MB, Zimmerman HJ. Therapeutic misadventures with acetaminophen: hepatoxicity after multiple doses in children. J Pediatr 1998; 132:22-27.

26. Koran G, Haslam RH. Pediatric medication errors: predicting and preventing tenfold disasters. J Clin Pharmacol 1994; 34:1043-1045.

27. Rowe C, Koren T, Koren G. Errors by paediatric residents in calculating drug doses. Arch Dis Child 1998; 79:56-58.

28. Simon HK, Weinkle DA. Over-the-counter medications: do parents give what they intend to give? Arch Pediatr Adolesc Med 1997; 151:654-656.

29. McMahon SR, Rinsza ME, Curtis Bay R. Parents can dose liquid medication accurately. Pediatrics 1997; 100:330-333.

30. Routley V, Ozanne-Smith J, Ashby K. Poisonings in early childhood. Hazard 1996; 27:1-13.

31. Hockey R, Reith D. Childhood poisoning and ingestion. Injury Bull 2000; 60:1-6.

32. Routley V, Ashby K, Lough J. Adult poisoning overview - Victoria. Hazard 1999; 39:1-19.

33. Ordonez GA, Phelan PD, Olinsky A, Robertson CF. Preventable factors in hospital admissions for asthma. Arch Dis Child 1998; 78:143-147.

34. Bauman A, Mitchell CA, Henry RL, et al. Asthma morbidity in Australia: an epidemiological study. Med J Aust 1992; 156:827-831.

35. Roughead EE, Gilbert AL, Primrose JG, Harvey KJ, Sampson LN. Report of the national indicators: evaluating the Quality Use of Medicines component of Australia's National Medicines policy. Canberra: Publications Production Unit (Public Affairs, Parliamentary and Access Branch), 1999.

36. Raschetti R, Morgutti M, Menniti-Ippolito F, et al. Suspected adverse drug events requiring emergency department visits or hospital admissions. Eur J Clin Pharmacol 1999; 54:959-963.

37. Tafreshi MJ, Melby MJ, Kaback KR, Nord TC. Medication-related visits to the emergency department: a prospective study. Ann Pharmacother 1999; 33:1252-1257.

38. Dennehy CE, Kishi DT, Louie C. Drug-related illness in emergency department patients. Am J Health Syst Pharm 1996; 53:1422-1426.

39. Larmour I, Dolphin RG, Baxter H, Morrison S, Hooke DH, McGrath BP. A prospective study of hospital admissions due to drug reactions. Aust J Hosp Pharm 1991; 21:90-95.

40. Strand LM, Morley PC, Cipolle RJ, Ramsey R, Lamsam GD. Drug-related problems: their structure and function. Ann Pharmacother 1990; 24:1093-1097.

41. Roughead EE, Gilbert AL, Primrose JG, Sansom LN. Coding drug-related admissions in medical records: is it adequate for monitoring the quality of medication use? Aust J Hosp Pharm 1998; 28:7-12.

42. Roughead EE, Gilbert AL, Primrose JG, Sansom LN. Drug-related hospital admissions: a review of Australian studies published 1988 - 1996. Med J Aust 1998; 168:405-408.

43. Hallas J, Harvald B, Worm J, et al. Drug related hospital admissions: results from an intervention program. Eur J Clin Pharmacol 1993; 45:199-203.

44. Nelson KM, Talbert RL. Drug-related hosptial admissions. Pharmacotherapy 1996; 16:701-707.

45. Smith KM, McAdams JW, Frenia ML, Todd MW. Drug-related problems in emergency department patients. Am J Health Syst Pharm 1997; 54:295-298.

46. Johnson JA, Bootman JL. Drug-related morbidity and mortality: a cost-of-illness model. Ann Intern Med 1995; 155:1949-1956.

47. Johnson JA, Bootman JL. Drug-related morbidity and mortality and the economic impact of pharmaceutical care. Am J Health Syst Pharm 1997; 54:554-558.

48. Rothschild JM, Bates DW, Leape LL. Preventable medical injuries in older patients. Arch Intern Med 2000; 160:2717-2728.

49. Bootman JL, Harrison DL, Cox E. The health care cost of drug-related morbidity and mortality in nursing homes. Arch Intern Med 1997; 157:2089-2096.

50. Day R. Use of non steroidal anti-inflammatory drugs, Proceedings of the reducing adverse drug events in the Australian health care system conference, Adelaide, 1998. South Australian Department of Human Services and the Australian Department of Health and Family Services.

51. Gallus A. Use of anticoagulants, Proceedings of the reducing adverse drug events in the Australian health care system conference, Adelaide, 1998. South Australian Department of Human Services and the Australian Department of Health and Family Services.

52. Aparasu RR. Drug-related injury visits to hospital emergency departments. Am J Health Syst Pharm 1998; 55:1158-1161.

53. Munoz MJ, Ayani I, Rodriguezsasiain JM, Gutierrez G, Aguirre C. Adverse drug reaction surveillance in pediatric and adult patients in an emergency room. Medicina Clinica 1998; 111:92-98.

54. Stoukides CA, D'Agostino PR, Kaufman MB. Adverse drug reaction surveillance in an emergency room. Am J Health Syst Pharm 1993; 50:712-714.

55.   Schneitman-McIntire O, Farnen TA, Gordon N, Chan J, Toy WA. Medication misadventures resulting in emergency department visits at an HMO medical center. Am J Health Syst Pharm 1996; 53:1416-1422.

56.   Prince BS, Goetz CM, Rihn TL, Olsky M. Drug-related emergency department visits and hospital admissions. Am J Hosp Pharm 1992; 49:1696-1700.

57.   Galbraith K. Is there a role for a clinical pharmacist in the emergency department? Melbourne: Grad Dip Hosp Pharm thesis: Victorian College of Pharmacy, Monash University, 1993.

58.   Whyte J, Greenan E. Drug usage and adverse drug reactions in paediatric patients. Acta Paediatr Scand 1977; 66:767-775.

59.   Boston Collaborative Drug Surveillance Program of the Boston University Medical Center. Drug Surveillance: problems and Challanges. Pediatr Clin North Am 1972; 19:117-129.

60.   McKenzie MW, Stewart RB, Weiss CF, Cluff LE. A pharmacist-based study of the epidemiology of adverse drug reactions in pediatric medicine patients. Am J Hosp Pharm 1973; 30:898-903.

61.   Mitchell AA, Lacouture PG, Sheehan JE, Kauffman RE, Shapiro S. Adverse drug reactions in children leading to hospital admission. Pediatrics 1988; 82:24-29.

62.   Major S, Badr S, Bahlawan L, et al. Drug-related hospitalization at a tertiary teaching center in Lebanon: incidence, associations, and relation to self-medicating behavior. Clin Pharmacol Ther 1998; 64:450-461.

63.   Yosselson-Superstine S, Weiss T. Drug-related hospitalization in paediatric patients. J Clin Hosp Pharm 1982; 7:195-203.

64.   Martinez-Mir I, Garcia-Lopez M, Palop V, et al. A prospective study of adverse drug reactions as a cause of admission to a paediatric hospital. Br J Clin Pharmacol 1996; 42:319-324.

65.   McKenney JM, Harrison WL. Drug-related hospital admissions. Am J Hosp Pharm 1976; 33:792-795.

66.   Collins GE, Clay MM, Falletta JM. A prospective study of the epidemiology of adverse drug reactions in pediatric hematology and oncology patients. Am J Hosp Pharm 1974; 31:968-975.

67.   Easton KL. Incidence of hospital admissions associated with drug related problems in paediatrics. Melbourne: Honours thesis: Victorian College of Pharmacy, Monash University, 1996.

68.   Bates DW. Drugs and adverse drug reactions: how worried should we be? JAMA 1998; 279:1216-1217.

69.   Einarson TR. Drug-related hospital admissions. Ann Pharmacother 1993; 27:832-340.

70.   Turner S, Nunn AJ, Fielding K, Choonara I. Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. Acta Paediatr 1999; 88:965-968.

71.   Mitchell AA, Goldman P, Shapiro S, Slone D. Drug utilization and reported adverse reactions in hospitalized children. Am J Epidemiol 1979; 110:196-204.

72.   Aranda JV, Portuguez-Malavasi A, Collinge JM, Germanson T, Outerbridege EW. Epidemiology of adverse drug reactions in the newborn. Dev Pharmacol Ther 1982; 5:173-184.

73.   Aranda JV. Factors associated with adverse drug reactions in the newborn. Pediatr Pharmacol 1983; 3:245-249.

74.   Choonara IA, Harris F. Adverse drug reactions in medical inpatients. Arch Dis Child 1984; 59:578-580.

75.   Dharnidharka VR, Kandoth PN, Anand RK. Adverse drug reactions in pediatrics with a study of in-hospital intensive surveillance. Indian Pediatr 1993; 30:745-751.

76.   Gill AM, Leach HJ, Barker C, Nunn AJ, Choonara I. Adverse drug reactions in a paediatric intensive care unit. Acta Paediatr 1995; 84:438-441.

77.   Gonzalez-Martin G, Caroca CM, Paris E. Adverse drug reactions (ADRs) in hospitalized pediatric patients. A prospective study. Int J Clin Pharmacol Ther 1998; 36:530-533.

78.   Carleton B, Poole R, Milton J, Travis J, Grinder D. The pediatric adverse drug reaction reporting system. J Pediatr Pharm Pract 1999; 4:284-307.

79.   Martinez-Mir I, Garcia-Lopez M, Palop V, Ferrer JM, Rubio E, Morales-Olivas FJ. A prospective study of adverse drug reactions in hospitalized children. Br J Clin Pharmacol 1999; 47:681-688.

80.   Hallas J, Harvald B, Gram LF, et al. Drug related hospital admissions: the role of definitions and intensity of data collection, and the possibility of prevention. J Intern Med 1990; 228:83-90.

81.   Kramer MS. Difficulties in assessing the adverse effects of drugs. Br J Clin Pharmacol 1981; 11:105S-110S.

82.   Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm 1992; 27:538.

83.   Bates DW, Spell N, Cullen DJ, et al. The costs of adverse drug events in hospitalized patients. JAMA 1997; 277:307-311.

84. Atkin PA, Shenfield GM. Medication-related adverse reactions and the elderly: a literature review. Adverse Drug React Toxicol Rev 1995; 14:175-191.

85. Miller RR. Drug surveillance utilzing epidemiologic methods: a report from the Boston Collaborative Drug Surveillance Program. Am J Hosp Pharm 1973; 30:584-592.

86. Hallas J, Gram LF, Grodum E, et al. Drug related admissions to medical wards: a population based survey. Br J Clin Pharmacol 1992; 33:61-68.

87. Karch FE, Lasagna L. Adverse drug reactions: a critical review. JAMA 1975; 234:1236-1241.

88. Muelhlberger N, Schneeweiss S, Hasford J. Adverse drug reaction monitoring - cost and benefit considerations part I: frequency of adverse drug reactions causing hospital admissions. Pharmacoepidemiology Drug Saf 1997; 6:S71-S77.

89. Jha AK, Kuperman GJ, Teich JM, et al. Identifying adverse drug events: development of a computer-based monitor and comparsion with chart review and stimulated voluntary report. J Am Med Inform Assoc 1998; 5:305-314.

90. Schlienger RG, Luscher TF, Schoenenberger RA, Haefeli WE. Academic detailing improves identification and reporting of adverse drug events. Pharm World Sci 1999; 21:110-115.

91. Stowasser DA, Staatz CE, Stowasser M, Coombes JA, Collins DM. Identifying drug-related readmissions: is there a better way of assessing the contribution of adverse medication events? Aust J Hosp Pharm 2000; 30:47-53.

92. Hennekens CH, Burning JE. Design strategies in epidemiologic research. In: Mayrent SL, ed. Epidemiology in medicine. Boston: Little, Brown and Company, 1987:16-29.

93. Venulet J, Ham MT. Methods for monitoring and documenting adverse drug reactions. Int J Clin Pharmacol Ther 1996; 34:112-129.

94. Stather R. Spontaneous reporting of ADRs - the Australian perspective. React 1996; 615:3-4.

95. Choonara I, Gill A, Nunn A. Drug toxicity and surveillance in children. Br J Clin Pharmacol 1996; 42:407-410.

96. Hewitt J. Drug-related unplanned readmissions to hospital. Aust J Hosp Pharm 1995; 25:400-403.

97. Blackbourn J. Readmission to fremantle hospital. Part II - Drug-related readmissions. Fremantle: Fremantle Hosptial, 1991.

98. Hennekens CH, Burning JE. Descriptive studies. In: Mayrent SL, ed. Epidemiology in medicine. Boston: Little, Brown and Company, 1987:101-131.

99. Hennekens CH, Buring JE. Cohort studies. In: Mayrent SL, ed. Epidemiology in medicine. Boston: Little, Brown and Company, 1987:153-177.

100. Hennekens CH, Buring JE. Case-control studies. In: Mayrent SL, ed. Epidemiology in medicine. Boston: Little, Brown and Company, 1987:132-152.

101. Classen DC, Pestotnik SL, Evans S, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients: excess length of stay, extra costs and attributable mortality. JAMA 1997; 277:301-306.

102. Avorn J. Putting adverse drug events into perspective. JAMA 1997; 277:341-342.

103. Stephens MDB. Introduction. In: Stephens MDB, Talbot JCC, Routledge PA, eds. Detection of new adverse drug reactions. London: MacMillan Publishers, 1998;1-58.

104. Koch-Weser J, Sellers EM, Zaces R. The ambiguity of adverse drug reactions. Eur J Clin Pharmacol 1977; 11:75-78.

105. Hutchinson TA, Lane DA. Assessing methods for causality assessment of suspected adverse drug reactions. J Clin Epidemiol 1989; 42:5-16.

106. Stephens MDB. The diagnosis of adverse medical events associated with drug treatment. Adverse Drug React Acute Poisoning Rev 1987; 1:1-35.

107. Stephens MDB. Detection of new adverse drug reactions. Hampshire: MacMillan Publishers, 1992.

108. Kramer MS. Assessing causality of adverse drug reactions: global introspection and its limitations. Drug Inf J 1986; 20:433-437.

109. Karch FE, Smith CL, Kerzner B, Mazzullo JM, Weintraub M, Lasagna L. Adverse drug reactions - a matter of opinion. Clin Pharmacol Ther 1976; 19:489-492.

110. Hutchinson TA, Leventhal JM, Kramer MS, Karch FE, Lipman AG, Feinstein AR. An algorithm for the operational assessement of adverse drug reactions: demonstration of reproducibility and validity. JAMA 1979; 242:633-638.

111. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30:239-245.

112. Naranjo CA, Shear NH, Lancotot KL. Advances in the diagnosis of adverse drug reactions. J Clin Pharmacol 1992; 32:897-904.

113. Lanctot KL, Naranjo CA. Comparison of the Bayesian approach and a simple algorithm for assessment of adverse drug events. Clin Pharmacol Ther 1995; 58:692-698.

114. Venulet J. Aspects of standardization as applied to the assessment of drug-event associations. Drug Inf J 1984; 18:199-210.

115. Girard M. Testing the methods of assessment for adverse drug reactions. Adverse Drug React Acute Poisoning Rev 1984; 4:237-244.

116. Meyboom RHB, Hekster YA, Egberts ACG, Gribnau FWJ, Edwards IR. Causal or Casual? The role of causality assessment in pharmacovigilance. Drug Saf 1997; 17:374-389.

117. Karch FE, Lasagna L. Towards the operational identification of adverse drug reactions. Clin Pharmacol Ther 1977; 21:247-254.

118. Hutchinson TA, Dawid PA, Spiegelhalter DJ, Cowell RG, Roden S. Computerized aids for probabilistic assessment of drug safety I: a spreadsheet program. Drug Inf J 1991; 25:29-39.

119. Hutchinson TA, Dawid AP, Cowell RG, Roden S. Computerized aims for probabilistic assessment of drug safety II: an expert system. Drug Inf J 1991; 25:41-48.

120. Michel DJ, Knodel LC. Comparison of three algorithms used to evaluate adverse drug reactions. Am J Hosp Pharm 1986; 43:1709-1714.

121. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events: implications for prevention. JAMA 1995; 274:29-34.

122. Cullen DJ, Sweitzer BJ, Bates DW, Burdick E, Edmondson A, Leape LL. Preventable adverse drug events in hospitalized patients: a comparative study of intensive care and general care units. Crit Care Med 1997; 25:1289-1297.

123. Bates D, Leape LL, Cullen DJ, et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. JAMA 1998; 280:1311-1316.

124. Kramer MS, Hutchinson TA, Flegel KM, Naimark L, Contardi R, Leduc DG. Adverse drug reactions in general pediatric outpatients. J Pediatr 1985; 106:305-310.

125. Seeger JD, Kong SX, Schumock GT. Characteristics associated with the ability to prevent adverse drug reactions in hospitalized patients. Pharmacotherapy 1998; 18:1284-1289.

126. Rawlins MD, Thompson JW. Pathogenesis of adverse drug reactions. In: Davies DM, ed. Textbook of adverse drug reactions. Oxford: Oxford University Press, 1977:10-31.

127. Wills S, Brown D. A proposed new means of classifying adverse reactions to medicines. Pharm J 1999; 262:163-165.

128. Pearson TF, Pittman DG, Longley JM, Grapes ZT, Vigliotti DJ, Mullis SR. Factors associated with preventable adverse drug reactions. Am J Hosp Pharm 1994; 51:2268-72.

129. Johnstone DM, Kirking DM, Vinson BE. Comparison of adverse drug reactions detected by pharmacy and medical record departments. Am J Health Syst Pharm 1995; 52:297-301.

130. Gholami K, Shalviri G. Factors associated with preventability, predictability, and severity of adverse drug reactions. Ann Pharmacother 1999; 33:236-240.

131. Schneider PJ, Hartwig SC. Use of severity-indexed medication error reports to improve quality. Hosp Pharm 1994; 29:208-211.

132. Zilleruelo I, Espinoza E, Ruiz I. Influence of the assessment of the severity on the frequency of adverse drug reactions (ADRS). Int J Clin Pharmacol Thera Toxicol 1987; 25:328-333.

133. Horn SD, Chachich B, Clopton C. Measuring severity of illness: a reliability study. Med Care 1983; 21:705-714.

134. Gharaibeh M, Zmeili S, Abu-Rajab A, Daoud Z. Drug-induced admissions to medical wards at Jordan University Hospital. Int J Clin Pharmacol Ther 1998; 36:478-482.

135. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985; 13:818-829.

136. Le Gall J-R, Lemeshow S, Saulnir F. A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. JAMA 1993; 270:2957-2963.

137. Parkerson GR, Broadhead WE, Tse CJ. The duke severity of illness checklist (DUSOI) for measurement of severity and comorbidity. J Clin Epidemiol 1993; 46:379-393.

138. Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. Crit Care Med 1988; 16:1110-1116.

139. Gross PA, Beyt BE, Decker MD, et al. Description of case-mix adjusters by the severity of illness working group of the Society of

Hospital Epidemiologists of America (SHEA). Infect Control Hosp Epidemiol 1988; 9:309-316.

140. Horn SD, Sharkey PD, Buckle JM, Backofen JE, Averill RF, Horn RA. The relationship between severity of illness and hopital length of stay and mortality. Med Care 1991; 29:205-317.

141. Venulet J. Monitoring adverse reactions to drugs. In: Jucken E, ed. Progress in Drug Research. Basle: Berghausen Verlag, 1977.

142. Gardner P, Watson L. Adverse drug reactions: a pharmacist-based monitoring system. Clin Pharmacol Ther 1970; 11:802-807.

143. Bennett BS, Lipman AG. Comparative study of prospective surveillance and voluntary reporting in determining the incidence of adverse drug reactions. Am J Hosp Pharm 1977; 34:931-936.

144. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm 1992; 49:2229-2232.

145. Colodny L, Spillane J. Towards increasing reporting of adverse drug reactions. Hosp Pharm 1999; 34:1175-1189.

146. Australian Institute of Health and Welfare. International comparisons of health expenditure. Health Expenditure Bull 1992; 7:28-29.

147. National Association of Children's Hospitals and Related Institutions. Children's health care needs are different - why one size won't fit all. A NACHRI briefing paper. Alexandria: National Association of Children's Hospitals and Related Institions, 1993.

148. Vertrees JC, Pollatsek JS. Paying for paediatric inpatient care. Final report of the Universal Access for Children Reimbursement Study

Project. Conducted for NACHRI. Alexandria: Solon Consulting Group, 1993.

149. Miller H. Final report of Paediatric Costing Study. Conducted for NACHRI. Alexandria: Center for Health Policy Studies, 1993.

150. Hanson RM, Phythian MA, Jarvis JB, Stewart C. The true cost of treating children. Med J Aust 1998; 169:S39-S41.

151. Schneider PJ, Gift MG, Lee Y, Rothermich EA, Sill BE. Cost of medication-related problems at a university hospital. Am J Health Syst Pharm 1995; 52:2415-2418.

152. Drummond MF, Stoddart GL. Principles of economic evaluation of health programmes. World Health Stat Q 1985; 38:355-367.

153. Robinson R. What does it mean? BMJ 1993; 307:670-673.

154. Robinson R. Costs and cost-minimisation analysis. BMJ 1993; 307:726-728.

155. Drummond MF, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford: Oxford Univeristy Press, 1987:10-13.

156. Weinstein MC. Principles of cost-effective resource allocation in health care organisations. Int J Technol Assess Health Care 1990; 6:93-103.

157. Robinson R. Cost-effectiveness analysis. BMJ 1993; 307:793-795.

158. Donaldson C, Hall J. Economic evaluation of health care: guidelines for costing. Westmead: Centre for Health Economics Research and Evaluation, 1991.

159. Robinson R. Cost-utility analysis. BMJ 1993; 307:859-862.

160. Hall J, Gerard K, Salkeld G, Richardson J. A cost utility analysis of mammography screening in Australia. Soc Sci Med 1992; 34:993-1004.

161. Robinson R. Cost-benefit analysis. BMJ 1993; 307:924-926.

162. Jolicoeur LM, Jones-Grizzle AJ, Boyer G. Guidelines for performing a pharmacoeconomic analysis. Am J Hosp Pharm 1992; 49:1741-1747.

163. Rice DP. Estimating the cost of illness. In: Public Health Service, ed. Health Economics Series No.6. Washington: US Government Printing Office, 1966.

164. Drummond M. Cost-of-illness studies: a major headache? PharmacoEconomics 1992; 2:1-4.

165. Hodgson TA, Meiners MR. Cost-of-illness methodology: a guide to current practices and procedures. Milbank Mem Fund Q 1982; 60:429-461.

166. Koopmanschap MA. Cost-of-illness studies: useful for health policy? PharmacoEconomics 1998; 14:143-148.

167. Shiell A, Gerard K, Donaldson C. Cost of illness studies: no aid to decision making? Health Policy 1987; 8:317-323.

168. Davey PJ. The cost of cost-of-illness studies. Med J Aust 1993; 158:583-584.

169. Scitovsky AA. Estimating the direct costs of illness. Milbank Mem Fund Q 1982; 60:463-491.

170. Rice DP. Cost-of-illness studies: fact or fiction? Lancet 1994; 344:1519.

171. Schumock GT, Meek PD, Ploetz PA, Vermeulen LC, and the Publications Committee of the American College of Clinical Pharmacy. Economic evaluations of clinical pharmacy services - 1988-1995. Pharmacotherapy 1996; 16:1188-1208.

172. Luce BR, Manning WG, Siegel JE, Lipscomb J. Estimating costs in cost-effectiveness analysis. In: Gold MR, Russell LB, Siegel JE, Weinstein MC, eds. Cost-effectiveness in health and medicine. New York: Oxford University Press, 1996:176-213.

173. White TJ, Arakelian A, Rho JP. Counting the costs of drug-related adverse events. PharmacoEconomics 1999; 15:445-458.

174. Marra CA, Lecine M, McKerrow R, Carleton BC. Overview of health-related quality-of-life measures for pediatric patients: application in the assessment of pharmacotherapeutic and pharmacoeconmic outcomes. Pharmacotherapy 1996; 16:879-888.

175. Eisen M, Ware JE, Donald CA, Brook RH. Measuring components of children's health status. Med Care 1979; 17:902-921.

176. World Health Organisation. World Health Organisation Technical Report No. 498, 1972.

177. Col N, Fanale JE, Kronholm P. The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly. Arch Intern Med 1990; 150:841-845.

178. Seigel S, Castellan NJ. Nonparametric statistics for the behavioural sciences. New York: McGraw-Hill International, 1988.

179. Altman DG. Practical statistics for medical researchers. London: Chapman & Hall, 1991.

180. Dawson-Saunders B, Trapp RG. Basic & clinical biostatistics. East Norwalk: Appleton & Lange, 1994:344.

181. Armitage P, Berry G. Statistical methods in medical research. Boston: Blackwell Scientific Publications, 1994.

182. Monitoring and Review Subcommittee of the Steering Committee on the Emergency Department Information Systems Project. Victorian Emergency Minimum Dataset, Version 2.0. Melbourne: Department of Human Services, 1997.

183. The MIMS Annual. Caswell A, Jarvis V, Dalton C, Gagic V, eds. St Leonards: Havas MediMedia, 2000.

184. Writing Group for Therapeutic Guidelines: Antibiotic. Therapeutic Guidelines: Antibiotics. Melbourne: Therapeutic Guidelines Limited, 1998.

185. Writing Group for Therapeutic Guidelines: Gastrointestinal. Therapeutic Guidelines: Gastrointestinal. Melbourne: Therapeutic Guidelines Limited, 1998.

186. National Health and Medical Research Council. The Australian Immunisation Handbook. Canberra: Commonwealth of Australia, 2000.

187. Woolfenden S, Ritchie J, Hanson R, Nossar V. Parental use of a paediatric emergency department as an ambulatory care service. Aust N Z J Public Health 2000; 24:204-6.

188. Malpass A, Helps SC, Runciman WB. An analysis of Australian adverse drug events. J Qual Clin Pract 1999; 19:27-30.

189. Gleeson C. Adverse drug reactions causing hospital admission. Sydney: Dip Hosp Pharm Thesis: Sydney University, 1988.

190. Sarkawi H, Daud T. A study of drug induced illness as a contributor to hospital admissions. Adelaide: Pharmacy Department: Royal Adelaide Hospital, 1995.

191. Stanton LA, Peterson GM, Rumble RH, Cooper GM, Polack AE. Drug-related admissions to an Australian hospital. J Clin Pharm Ther 1994; 19:341-347.

192. McKenzie MW, Marchall GL, Netzloff ML, Cluff LE. Adverse drug reactions leading to hospitalization in children. J Pediatr 1979; 89:487-490.

193. Smith JW, Seidl LG, Cluff LE. Studies on the epidemiology of adverse drug reactions: clinical factors influencing susceptibility. Ann Intern Med 1966; 65:629-640.

194. Shirkey HC. Therapeutic orphans - everybody's business. Drug Intel Clin Pharm 1968; 2:323.

195. Roeser HP, Rohan AP. Post-marketing surveillance of drugs. The spontaneous reporting scheme: role of the Adverse Drug Reactions Advisory Committee. Med J Aust 1990; 153:720-726.

196. US Department of Health and Human Services. The international classification of diseases, 9th revision, clinical modification (ICD-9-CM). In: Bethesda MD, ed. Ann Arbor: Commission on Professional and Hospital Acitivities, 1989.

197. National Centre for Classification in Health. ICD-10-AM Tabular list of procedures (MBS-Extended). Faculty of Health Sciences, ed. Sydney: University of Sydney, 1998.

198. Australian Patient Safety Foundation. Final report of the Australian Incident Monitoring Study. Adelaide: Australian Patient Safety Foundation, 1998.

199. van den Bemt PMLA, Egberts TCG, de Jong-van den Berg LTW, Brouwers JRBJ. Drug-related problems in hospitalised patients. Drug Saf 2000; 22:321-333.

200. Domecq C, Naranjo C, Ruiz I, Busto U. Sex-related variations in the frequency and characteristics of adverse drug reactions. Int J Clin Pharmacol Ther Toxicol 1980; 18:362-366.

201. Bowman L, Carlsted BC, Hancock EF, Black CD. Adverse drug reaction (ADR) occurrence and evaluation in elderly inpatients. Pharmacoepidemiology Drug Saf 1996; 5:9-18.

202. Melmon KL. Preventable drug reactions - causes and cures. N Engl J Med 1971; 284:1361-1368.

203. Moride Y, Harambura F, Requejo AA, Begaud B. Under-reporting of adverse drug reactions in general practice. Br J Clin Pharmacol 1997; 43:177-181.

204. Hanesse B, Legras B, Royer RJ, Guillemin F, Briancon S. Adverse drug reactions: comparison of two reporting methods. Pharmacoepidemiology Drug Saf 1994; 3:223-229.

205. Jackson T. Cost estimates for hospital inpatient care in Australia: evaluation of alternative sources. Aust N Z J Public Health 2000; 24:234-241.

206. Victorian Hospitals Association. Buying Guide. Mulgrave: Hospital Suppliers of Australia, 1998.

207. Commonwealth Department of Health. Medical benefits schedule book. Canberra: Australian Government Publishing Service, 1980.

208. Duckett S. Casemix funding for acute hospital inpatient services in Australia. Med J Aust 1998; 169:S17-S21.

209. Street A. Gallstone disease: the cost of treatment. Melbourne: Centre for Health Program Evaluation, 1993.

210. http://www.victrip.com.au/metcard/ (Accessed May 2000).

211. Australian Bureau of Statistics. Average weekly earnings, states and Australia. Cat. no. 6302.0, Canberra: ABS, 2000.

212. Sharp C. The value of time savings and of accident prevention. J Transport Econ Policy 1988; 32:235-238.

213. Carlin JB, Jackson TLL, Bishop RF, Barnes GL. Cost effectiveness of rotavirus vaccination in Australia. Aust N Z J Public Health 1999; 23:611-616.

214. Ferson MJ, Shen WL, Stark A. Direct and indirect costs of chickenpox in young children. J Paediatr Child Health 1998; 34:18-21.

215. Liddle JLM, Burgess MA, Gilbert GL, et al. Rotavirus gastroenteritis: impact on young children, their families and the health care system. Med J Aust 1997; 167:304-307.

216. Anonymous. The cost of adverse drug reactions. Adverse Drug React Toxicol Rev 1997; 16:75-78.

217. Gurwitz JH, Field TS, Avorn J, et al. Incidence and preventability of adverse drug events in nursing homes. Am J Med 2000; 109:87-94.

218. Thomas EJ, Brennan TA. Incidence and types of preventable adverse events in elderly patients: population based review of medical records. BMJ 2000; 320:741-744.

219. Johnston SL, Pattermore PK, Sanderson G, et al. Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. BMJ 1995; 310:1225-1228.

220. Cantrill JA, Cottrell WN. Accuracy of drug allergy documentation. Am J Health Syst Pharm 1997; 54:1627-1629.

221. McLennan DN. Prospective analysis of ICD-10-AM activities and clinical outcomes codes associated with pharmacits' interventions. Melbourne: Honours thesis: Victorian College of Pharmacy, Monash University, 1998.

222. Stowasser DA, McGuire TM, Petrie GM, Lauchlan RL, Collins DM. Information quality: a major consideration in the development of medication liaison services. Aust J Hosp Pharm 1997; 27:362-366.

223. Sang Lau H, Florax C, Porsius AJ, de Boer A. The completeness of medication histories in hospital medical records of patients admitted to general internal medicine wards. Br J Clin Pharmacol 2000; 49:597-603.

224. Hutchinson TA. Standardized assessment methods for adverse drug reactions: a review of previous approaches and their problems. Drug Inf J 1986; 20:439-444.

225. Louik C, Lacouture PG, Mitchell AA, et al. A study of adverse reaction algorithms in a drug surveillance program. Clin Pharmacol Ther 1985; 38:183-187.

226. Dietz BL, Oberg KC. Judicious evaluation of adverse drug reactions: inaccurate assessment of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor-induced muscle injury. Pharmacotherapy 1999; 19:232-235.

227. Soumerai SB, Ross-Degnan D. Drug prescribing in pediatrics: challenges for quality improvement. Pediatrics 1990; 86:782-784.

228. National Prescribing Service Ltd. Is there still unnecessary use of antibiotics in Australia? Prescribing Practice Review. Vol. 9. Sydney: National Prescribing Service, 2000.

229. McManus P, Hammond ML, Whicker SD. Antibiotic use in the Australian community, 1990-1995. Med J Aust 1997; 167:124-127.

230. Arason VA, Kristinsson KG, Sigurdsson JA, Stefansdottir G, Molstad S, Gudmundsson S. Do antimicrobials increase the carriage rate of penicillin resistent pneumococci in children? Cross sectional prevalence study. BMJ 1996; 313:387-391.

231. Arnold KE, Leggiadro RJ, Breiman RF, et al. Risk factors for carriage of drug-resistant *Streptococcus pneumoniae* among children in Memphis, Tennessee. J Pediatr 1996; 128:757-764.

232. Schwartz B, Mainous AG, Marcy SM. Why do physicians prescribe antibiotics for children with upper respiratory tract infections? JAMA 1998; 279:881-882.

233. Cirko-Begovic A VB, Bakran I. Intensive monitoring of adverse drug reactions in infants and preschool children. Eur J Clin Pharmacol 1989; 36:63-65.

234. Woods CG, Rylance ME, Cullen RE, Rylanace GW. Adverse reactions to drugs in children. BMJ 1987; 294:869-870.

235. Sanz E, Boada J. Adverse drug reactions in paediatric outpatients. Int J Clin Pharm Res 1987; 7:169-172.

236. Vinson DC, Lutz LJ. The effect of parental expectations on treatment of children with a cough: a report from ASPN. J Fam Pract 1993; 37:23-27.

237. Westerlund T, Almarsdottir AB, Melander A. Drug-related problems and pharmacy interventions in community practice. Int J Pharm Pract 1999; 7:40-50.

238. Rupp MT, DeYoung M, Schondelmeyer SW. Prescribing problems and pharmacist interventions in community practice. Med Care 1992; 30:926-940.

239. Pediatric Pharmacy Administrative Group Committee on Pediatric Pharmacy Practice. Pediatric pharmacy practice guidelines. Am J Hosp Pharm 1991; 48:2475-2477.

240. Lesar TS, Briceland L, Stein DS. Factors related to errors in medication prescribing. JAMA 1997; 277:312-317.

241. Buck ML. Preventing medication errors in children. Pediatric Pharmacol 1999; 5: 1-6

242. Committee on Quality in Health Care in America. Institute of Medicine. To err is human: building a safer health system. Kohn LT, Corrigan JM, Donaldson MS, eds. Washington: National Academy Press, 1999.

243. Australian Council for Safety and Quality in Health Care. Safety first: report to the Australian Health Minister's Conference. Canberra: Australian Council for Safety and Quality in Health Care, 2000.

244. Caleo S, Benrimoj S, Collins D, Lauchlan R, Stewart K. Clinical evaluation of community pharmacists' interventions. Int J Pharm Pract 1996; 4:221-227.

245. Anonymous. Prevention of medication errors in the pediatric inpatient setting. American Academy of Pediatrics. Committee on Drugs and Committee on Hospital Care. Pediatrics 1998; 102:428-30.

246. Institute for Safe Medication Practices and Pediatric Pharmay Advocacy Group. Draft guidelines for preventing medication errors in pediatrics. J Pediatr Pharm Pract 1998; 3:189-202.

247. Liddell MJ, Goldman SP. Attitudes to and use of a modified prescription form by general practitioners and pharmacists. Med J Aust 1998; 168:322-325.

248. Evans RS, Petotnik SL, Classen DC, Horn SD, Bass SB, Burke JP. Preventing adverse drug events in hospitalized patients. Ann Pharmacother 1994; 28:523-527.

249. Classen DC, Pestotnik SL, Evans S, Burke JP. Description of a computerised adverse drug event monitor using a hospital information system. Hosp Pharm 1992; 27:776-779.

250. Raymond PM, Robertson MB. Adverse drug reaction reporting in Melbourne teaching hospitals. Aust J Hosp Pharm 1994; 24:237-242.

251. Ley P. Cognitive variables and noncompliance. J Compliance Health Care 1986; 1:171-188.

252. Fotheringham MJ, Sawyer MG. Adherence to recommended medical regimens in childhood and adolescence. J Paediatr Child Health 1995; 31:72-78.

253. Mattar ME, Markello J, Yaffe SJ. Pharmaceutic factors affecting pediatric compliance. Pediatrics 1975; 55:101-108.

254. Pharmaceutical Health and Rational use of Medicines (PHARM) Consumer Sub-Committee. Using Consumer Medicine Information (CMI) effectively: a report of the workshop. Sydney: Commonwalth Department of Health and Aged Care, 1998.

255. Wozitzky K. Patient drug information - what do consumers want from general practitioners and pharmacists? RISK study in general practice. Melbourne: National Health Foundation and Monash University Department of Community Medicine, 1992.

256. Jonville AE, Autret E, Bavoux F, Bertrand PP, Barbier P, Gauchez AM. Characteristics of medication errors in paediatrics. Ann Pharmacother 1991; 25:1113-1118.

257. Becker HM. Patient adherence to prescribed therapies. Med Care 1985; 23:539-555.

258. Dunbar J, Agras W. Compliance with medical instructions. In: Ferguson JM, Taylor CB, eds. The comprehensive handbook of behavioural medicine. Volume 3. Extended applications and issues. Lancaster: MTP Press, 1980:115-145.

259. Smith NA, Seale P, Ley P, Shaw J, Bracs P. Effects of intervention on medication compliance in children with asthma. Med J Aust 1986; 144:119-122.

260. U.S Pharmacopeia (USP) *Ad Hoc* Advisory Panel on Children and Medicines. Guide to developing and evaluating medicine education programs and material for children and adolescents. Rockville: The United States Pharmacopeial Convention, 1998.

261. Litt IF, Cuskey WR. Compliance with salicylate therapy in adolescents with juvenile rheumatoid arthritis. Am J Dis Child 1981; 135:434-436.

262. Johnson SB, Kelly M, Henretta JC, Cunningham WR, Tomer A, Silverstein JH. A longitudinal analysis of adherence and health status in childhood diabetes. J Pediatr Psychol 1992; 17:537-553.

263. Korsch BM, Fine RN, Negrette VF. Non-compliance in children with renal transplants. Pediatrics 1978; 61:872-876.

264. Smith SD. A reliable method for evaluating drug compliance in children with cancer. Cancer 1979; 43:169-173.

265. Jay S, Litt IF, Durant RH. Compliance with therapeutic regimens. J Adolesc Health Care 1984; 5:124-136.

266. Coutts JAP, Gibson NA. Measuring compliance with inhaled medications in asthma. Arch Dis Child 1992; 67:332-333.

267. Bortoletto DA. Adolescents with asthma: barriers to medication adherence and asthma care at secondary schools. Melbourne: PhD thesis: Victorian College of Pharmacy, Monash University, 1999.

268. Henry RL, Fitzclarence CA, Henry DA, Cruickshank D. What do health professionals know about childhood asthma? J Paediatr Child Health 1993; 29:32-35.

269. Pilotto LS, Beilby JJ, Smith BJ. Asthma clinics in general practice: what is the evidence? Med J Aust 2000; 173:144-146.

270. National Injury Prevention Advisory Council. National injury prevention action plan: priorities for 2000-2002. Canberra: Department of Health and Aged Care, 1999.

271. Commonwealth Department of Human Services and Health. Better health outcomes for Australians: national goals, targets and strategies for better health outcomes into the next century. Canberra: Australian Government Publishing Service, 1994.

272. Tempowski J. Epidemiology of poisoning in children. In: Bates N, Edwards N, Roper J, Volans G, eds. Paediatric toxicology: handbook of poisoning in children. London: MacMillan Reference, 1997:1-8.

273. O'Connor P. Epidemiology of accidental poisoning in children. Med J Aust 1983; 2:181-183.

274. Wiseman H. Prevention of poisoning in children. In: Bates N, Edwards N, Roper J, Volans G, eds. Paediatric toxicology: handbook of poisoning in children. London: MacMillan Reference, 1997:40-51.

275. Burton R. Eat, drink and be dead: a study of the accidental ingestions of poisons in young children. Accid Emerg Nurs 1993; 1:14-19.

276. Rodgers GB. The safety effects of child-resistant packaging for oral prescription drugs: two decades of experience. JAMA 1996; 275:1661-1665.

277. O'Connor PJ. Poisoning prevention: results of a public media campaign. Aust Paediatr J 1982; 18:250-252.

278. Rand CS, Wise RA, Nides M, et al. Metered-dose inhaler adherence in a clinical trial. Am Rev Respir Dis 1992; 146:1559-1564.

279. Li L, Ozanne-Smith J. Injury hospitalisation rates in Victoria, 1987-97: trends, age and gender patterns. Aust N Z J Public Health 2000; 24:158-165.

280. Gilbertson RJ, Harris E, Pandey KS, Kelly P, Myers W. Paracetamol use, availability, and knowledge of toxicity among British and American adolescents. Arch Dis Child 1996; 75:194-198.

281. Hawton K, Ware C, Mistry H, et al. Why patients choose paracetamol for self poisoning and their knowledge of its dangers. BMJ 1995; 310:164.

282. Prince MI, Thomas SHL, James OFW, Hudson M. Reduction in incidence of severe paracetamol poisoning. Lancet 2000; 355:2047-2048.

283. Turvill JL, Burroughs AK, Moore KP. Change in occurrence of paracetamol overdose in UK after introduction of blister packs. Lancet 2000; 355:2048-2049.

284. Pond SM. Prescription for poisoning. Med J Aust 1995; 162:174-175.

285. Poulin C. Prevention of paracetamol poisoning. Lancet 2000; 355:2009-2010.

286. Hawton K, Arensman E, Townsend E, et al. Deliberate self harm: systematic review of efficacy of psychosocial and pharmacological treatments in preventing repetition. BMJ 1998; 317:441-447.

287. Buckley NA, Whyte IM, Dawson AH, McManus PR, Ferguson NW. Self-poisoning in Newcastle, 1987-1992. Med J Aust 1995; 162:190-193.