

Investigating chemotherapy adverse events: incidence, costs and consequences

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Certificate of original authorship

I certify that the work in this thesis has not previously been submitted for a degree, nor has it been submitted as part of requirements for a degree except as fully acknowledged within the text.

I also certify that the thesis has been written by me. Any help that I have received in my research work and the preparation of the thesis itself has been acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

Alison Pearce

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Table of contents

Certificate of original authorship	ii
Acknowledgements	iii
Table of contents	iv
List of figures	ix
List of tables	xi
Abbreviations and shortened forms	xiv
Abstract	xvii
CHAPTER 1: INTRODUCTION	1
1.1 Background.....	3
1.1.1 Cancer in Australia.....	3
1.1.2 Adverse events	8
1.1.3 Funding of healthcare and medicines in Australia	13
1.1.4 Economic evaluation	14
1.1.5 Economic modelling	15
1.1.6 Clinical trials and economic evaluation	18
1.2 Aims and objectives.....	20
1.3 Theoretical framework	21
1.3.1 Policy framework.....	22
1.4 Data sources	23
1.4.1 eviQ	23
1.4.2 Australian Government Department of Veterans' Affairs.....	24
1.4.3 Elements of Cancer Care study.....	25
1.5 Overview of research components	25
CHAPTER 2: COSTS AND CONSEQUENCES OF ADVERSE EVENTS IN A SYSTEMATIC REVIEW OF THE LITERATURE.....	27
2.1 Background.....	27
2.1.1 Modelling chemotherapy adverse events	29
2.2 Methods	31
2.2.1 Aims and objective	31
2.2.2 Literature search	32
2.3 Results.....	36
2.3.1 General model design	39
2.3.2 Reason for inclusion of adverse-events in the model	40
2.3.3 Dose modifications	41
2.3.4 Adverse events and utilities	42

2.3.5	Multiple adverse events.....	42
2.3.6	How type and severity affect cost.....	43
2.3.7	Number of concepts of interest included	51
2.4	Discussion	52
2.4.1	Previous research on modelling chemotherapy adverse events	53
2.4.2	Conclusion.....	58
CHAPTER 3: COSTS AND CONSEQUENCES OF ADVERSE EVENTS USING DECISION ANALYTIC MODELLING		60
3.1	Background.....	61
3.1.1	Economic modelling.....	61
3.1.2	Economic modelling of chemotherapy	67
3.2	Modelling methods.....	67
3.2.1	Decision analytic modelling—the Briggs et al approach.....	69
3.3	Models of chemotherapy adverse events	73
3.4	Diarrhoea model.....	79
3.4.1	Background	79
3.4.2	Structure of the decision model.....	85
3.4.3	Synthesising the evidence	89
3.4.4	Modelling the results	94
3.4.5	Assessing uncertainty.....	95
3.4.6	Discussion.....	98
3.4.7	Conclusion.....	101
3.5	Anaemia model.....	103
3.5.1	Background	103
3.5.2	Structure of the decision models	112
3.5.3	Synthesising the evidence.....	118
3.5.4	Modelling the results	126
3.5.5	Assessing uncertainty.....	128
3.5.6	Discussion.....	137
3.5.7	Conclusion.....	141
3.6	Nausea and vomiting	143
3.6.1	Background	143
3.6.2	Structure of the decision models	151
3.6.3	Synthesising the evidence.....	155
3.6.4	Modelling the results	160
3.6.5	Assessing uncertainty.....	162

3.6.6	Discussion	168
3.6.7	Conclusion	171
3.7	Febrile Neutropenia model.....	172
3.7.1	Background.....	172
3.7.2	Structure of the decision model.....	178
3.7.3	Synthesising the evidence	181
3.7.4	Modelling the results.....	184
3.7.5	Assessing uncertainty	185
3.7.6	Discussion	188
3.7.7	Conclusion	191
3.8	Overall discussion of findings from modelling	192
3.8.1	Conclusion	198
CHAPTER 4: THE INCIDENCE AND COSTS OF CHEMOTHERAPY		
ADVERSE EVENTS IN A LARGE ADMINISTRATIVE DATASET..... 201		
4.1	Background.....	202
4.1.1	Australian Government Department of Veterans' Affairs.....	205
4.1.2	Aims and objectives.....	206
4.1.3	Data	207
4.1.4	Demographic variables in the dataset.....	209
4.1.5	Adverse-event variables	211
4.1.6	Summary statistics	213
4.1.7	Data issues.....	216
4.2	Incidence of chemotherapy adverse events in clinical practice	218
4.2.1	Methods	218
4.2.2	Results	223
4.2.3	Discussion	224
4.3	Factors that influence the incidence of adverse events in clinical practice.....	226
4.3.1	Background to regression analysis with correlated data	226
4.3.2	Methods: logistic regression with summary statistic	230
4.3.3	Methods: GEE.....	231
4.3.4	Data	233
4.3.5	Results: logistic regression with summary statistic	235
4.3.6	Results: GEE.....	248
4.3.7	Discussion	262
4.4	Resource-use associated with chemotherapy adverse events in clinical practice.....	264
4.4.1	Methods	264

4.4.2	Issues with cost data	265
4.4.3	Results	270
4.4.4	Discussion.....	286
4.5	DVA Discussion	288
4.5.1	Conclusion.....	293
CHAPTER 5: INCIDENCE AND CONSEQUENCES OF CHEMOTHERAPY ADVERSE EVENTS IN A PROSPECTIVE COHORT STUDY		295
5.1	Background.....	296
5.1.1	Aims and objectives	298
5.1.2	Data	299
5.2	Analysis.....	302
5.2.1	Demographics and clinical characteristics	304
5.3	Frequency of common adverse events.....	307
5.3.1	Methods.....	307
5.3.2	Results.....	307
5.3.3	Discussion.....	313
5.4	Validate use of an adverse-event treatment proxy	315
5.4.1	Methods.....	315
5.4.2	Results.....	316
5.4.3	Discussion.....	321
5.5	Explore the management of adverse events	323
5.5.1	Methods.....	323
5.5.2	Results.....	324
5.5.3	Discussion.....	326
5.6	Compare rates of adverse events in standard practice to clinical trials	326
5.6.1	Methods.....	327
5.6.2	Results.....	327
5.6.3	Discussion.....	328
5.7	Overall discussion of Elements of Cancer Care	329
5.7.1	Conclusion	333
CHAPTER 6: DISCUSSION.....		334
6.1.1	Conclusion.....	343
APPENDICES 345		
Appendix A: PRISMA Checklist		346
Appendix B: Search strategies for literature review		349
Appendix C: NHS EED annotated abstract		351

Appendix D: Graves checklist (49)	353
Appendix E: Tables of all studies in the literature review, shown by adverse-event type or cancer type	354
(i) Adverse-event treatment studies of neutropoenia	354
(ii) Adverse-event treatment studies of anaemia, thrombocytopenia and multiple events	355
(iii) Adverse-event treatment studies of nausea and vomiting.....	356
(iv) Chemotherapy cost-effectiveness studies of early or primary breast cancer	357
(v) Chemotherapy cost-effectiveness studies of metastatic or advanced breast cancer	360
(vi) Chemotherapy cost-effectiveness studies of cancers other than breast.....	361
Appendix F: Principles of Good Practice for Decision Analytic Modelling in Health Care	
Evaluations	363
Appendix G: Search strategies for adverse event models	367
Appendix H: Previous studies that included a cost of diarrhoea	375
Appendix I: Diarrhoea TreeAge model	379
Appendix J: Previous studies that included a cost of anaemia	381
Appendix K: Anaemia TreeAge model	387
Appendix L: Previous studies that included a cost of nausea and vomiting	389
Appendix M: Nausea and vomiting TreeAge model	393
Appendix N: Previous studies that included a cost of neutropoenia	395
Appendix O: Neutropoenia TreeAge model	403
Appendix P: DVA dataset size	405
Appendix Q: Elements of Cancer Care patient questionnaires	407
REFERENCES	410

List of figures

Figure 1.1: Ten most commonly diagnosed cancers in Australia, 2007 (21)	4
Figure 1.2: Ten most common causes of death from cancer in Australia, 2007 (21)	5
Figure 1.3: Age-specific incidence rates for all cancers combined, Australia 2007 (21)	6
Figure 2.1: Flowchart of study inclusion	37
Figure 2.2: Proportion of studies addressing each Graves criteria.....	39
Figure 2.3: Adverse-event costs (in 1999 International \$) by grade of adverse event (classified as mild, moderate, severe or life threatening).....	45
Figure 2.4: Percentage of Grade IV cost for each adverse event in Ojeda (98) and Capri studies (99)	50
Figure 2.5: The contribution of each adverse-event type to the total cost of adverse events in the Ojeda (98) and Capri studies (99).....	51
Figure 3.1: Sample decision tree showing pathway through decision node and chance nodes for the treatment of lung cancer (119)	62
Figure 3.2: Example of a Markov model for adjuvant breast cancer treatment (87)	64
Figure 3.3: Decision-tree model for chemotherapy-induced diarrhoea	87
Figure 3.4: One-way sensitivity analysis—diarrhoea model	97
Figure 3.5: Decision-tree model for chemotherapy-induced anaemia associated with chemotherapy of curative intent.....	114
Figure 3.6: Decision-tree model for chemotherapy-induced anaemia associated with palliative chemotherapy	115
Figure 3.7: One-way sensitivity analysis of curative anaemia model—all parameters	133
Figure 3.8: One-way sensitivity analysis of anaemia model—EPO three times weekly	134
Figure 3.9: One-way sensitivity analysis of anaemia model—EPO weekly	135
Figure 3.10: One-way sensitivity analysis of anaemia model—darbepoetin weekly	136
Figure 3.11: One-way sensitivity analysis of anaemia model—darbepoetin three- weekly	137
Figure 3.12: Decision-tree model of nausea and vomiting	152
Figure 3.13: Sensitivity analysis—low-emetogenic-risk chemotherapy	164
Figure 3.14: Sensitivity analysis—moderate-emetogenic-risk chemotherapy....	165
Figure 3.15: Sensitivity analysis—anthracycline/cyclophosphamide chemotherapy	166
Figure 3.16: Sensitivity analysis—high-emetogenic-risk chemotherapy	167
Figure 3.17: Decision-tree model for chemotherapy-induced neutropoenia	179
Figure 3.18: One-way sensitivity analysis of neutropoenia model	187
Figure 4.1: Visual representation of dataset merge (using mock data).....	220
Figure 4.2: Distribution of total costs for the first six months of a new chemotherapy treatment	270
Figure 4.3: Distribution of log-costs associated with adverse events in the first six months of a new chemotherapy treatment	271

Figure 4.4: Distribution of cost variables—mean raw cost vs. standard deviation of raw cost per person by age group and gender	272
Figure 4.5: Pattern of residuals—actual with 20 simulations.....	280
Figure 4.6: Pattern of residuals—actual with 20 simulations.....	286
Figure 5.1: Cumulative frequency of self-reported adverse events during Elements of Cancer Care study period	312

List of tables

Table 1.1: Comparison of the relative severity of adverse events in two studies .	10
Table 1.2: Clinical characteristics of four selected chemotherapy adverse events	12
Table 2.1: Characteristics of included studies.....	38
Table 2.2: Modelling methods used by included studies	40
Table 2.3: Studies reporting cost per QALY	44
Table 2.4: Two studies in literature review reporting adverse events at four grade levels	46
Table 2.5: Studies in literature review with two grades of adverse event.....	49
Table 3.1: Clinical characteristics of adverse events to be modelled	69
Table 3.2: CTCAE v4.03 diarrhoea grading (31)	80
Table 3.3: Summary of loperamide, octreotide and antibiotic dose recommendations for diarrhoea.....	86
Table 3.4: Assumptions in the economic model of diarrhoea.....	90
Table 3.5: Costs used in economic model of diarrhoea	94
Table 3.6: Base-case costs of managing chemotherapy-induced diarrhoea.....	95
Table 3.7: Parameters and values tested in the sensitivity analysis of diarrhoea model.....	96
Table 3.8: NCI CTCAE volume 4.03 anaemia grading (31) (page 3).....	104
Table 3.9: FDA Erythropoietic agent dosing recommendations (148).....	106
Table 3.10: Assumptions in the curative economic model of anaemia.....	120
Table 3.11: Assumptions in the palliative economic model of anaemia.....	122
Table 3.12: Costs used in (both) economic models of anaemia.....	125
Table 3.13: Base-case results for curative model of anaemia	126
Table 3.14: Base-case results for palliative model of anaemia—costs.....	127
Table 3.15: Base-case results for palliative model of anaemia—utilities.....	128
Table 3.16: Parameters and values tested in the sensitivity analysis of the curative model of anaemia	130
Table 3.17: Parameters and values tested in the sensitivity analysis of the palliative model of anaemia	131
Table 3.18: NCI CTCAE version 4.03 nausea and vomiting grading (31).....	144
Table 3.19: Comparison of recommendations for nausea and vomiting prophylaxis (adapted from Jordan 2007 (181)).....	148
Table 3.20: Assumptions used in the economic model of nausea and vomiting	156
Table 3.21: Costs used in the economic model of nausea and vomiting	160
Table 3.22: Base-case results—low-emetogenic-risk chemotherapy	161
Table 3.23: Base-case results--moderate-emetogenic-risk chemotherapy.....	161
Table 3.24: Base-case results—anthracycline and cyclophosphamide chemotherapy	161
Table 3.25: Base-case results—high-emetogenic-risk chemotherapy	161
Table 3.26: Parameters and values tested in the sensitivity analysis for nausea and vomiting model	162
Table 3.27: NCI CTCAE v4.03 neutropenia grading (31).....	173
Table 3.28: Assumptions used in the economic model of chemotherapy-induced febrile neutropenia	182
Table 3.29: Costs used in the economic model of chemotherapy-induced febrile neutropenia.....	184

Table 3.30: Results of low-risk neutropoemia management model	185
Table 3.31: Parameters and values tested in sensitivity analysis for chemotherapy-induced neutropoemia model.....	186
Table 4.1: Datasets linked for the analysis of adverse events in DVA clients	208
Table 4.2: Resources identified as treatments for each adverse event	212
Table 4.3: Demographic and clinical characteristics of the DVA cohort.....	214
Table 4.4: Types of cancers—DVA cohort	215
Table 4.5: Ten most administered anti-neoplastic drugs—DVA cohort.....	215
Table 4.6: Variables used to create the analysis dataset of the DVA cohort.....	218
Table 4.7: Variables in DVA adverse-event dataset for calculating incidence...	221
Table 4.8: Incidence of adverse events by dose and by person in the DVA cohort	223
Table 4.9: Rates of treatments in DVA non-cancer cohort, and at 3 and 10 days post-chemotherapy.....	224
Table 4.10: Variables in the DVA adverse-event regression dataset	235
Table 4.11: Model fit statistics—diarrhoea	236
Table 4.12: Analysis of maximum likelihood estimates—diarrhoea	238
Table 4.13: Model fit statistics—nausea and vomiting	239
Table 4.14: Analysis of maximum likelihood and odds ratio estimates—nausea and vomiting.....	241
Table 4.15: Model fit statistics—anaemia	242
Table 4.16: Analysis of maximum likelihood and odds ratio estimates—anaemia	244
Table 4.17: Model fit statistics—neutropoemia	245
Table 4.18: Analysis of maximum likelihood and odds ratio estimates—neutropoemia	247
Table 4.19: Comparison of GEE correlation structures—diarrhoea	248
Table 4.20: Comparison of model structures—diarrhoea	249
Table 4.21: GEE results—diarrhoea.....	250
Table 4.22: Comparison of GEE correlation structures—nausea and vomiting .	252
Table 4.23: Comparison of model structures—nausea and vomiting	254
Table 4.24: GEE results—nausea and vomiting.....	255
Table 4.25: Comparison of GEE correlation structures—anaemia	256
Table 4.26: Comparison of model structures—anaemia	257
Table 4.27: GEE results—anaemia	258
Table 4.28: Comparison of GEE correlation structures—neutropoemia.....	259
Table 4.29: Comparison of model structures—neutropoemia.....	260
Table 4.30: GEE results—neutropoemia.....	261
Table 4.31: Summary of GEE results	262
Table 4.32: Variables included in the DVA models of costs associated with adverse events.....	269
Table 4.33: Results of simple linear regression of costs and each adverse event	274
Table 4.34: Results of linear regression with log-costs and each adverse event.	276
Table 4.35: Results of gamma model of the additional cost associated with each adverse event	278
Table 4.36: GLM results with exponential values.....	279
Table 4.37: Results of gamma model with main effects and interaction terms...	283
Table 4.38: Results of gamma model with interaction terms—exponentiated ...	285

Table 5.1: Adverse-event variables in the Elements of Cancer Care analysis....	303
Table 5.2: Demographic and clinical characteristics of the Elements of Cancer Care cohort.....	306
Table 5.3: Highest grade of adverse event experienced during Elements of Cancer Care study period.....	308
Table 5.4: Self-reported adverse events—any adverse event during the Elements of Cancer Care study period.....	308
Table 5.5: Self-reported adverse events—worst grade reported during Elements of Cancer Care study period.....	310
Table 5.6: Haematological adverse events—worst grade during Elements of Cancer Care study period.....	310
Table 5.7: Comparison of incidence of adverse events in Elements of Cancer Care study with Henry et al. 2008 (87).....	314
Table 5.8: Incidence of adverse events by dose identified using proxy in the Elements of Cancer Care dataset and the DVA dataset.....	316
Table 5.9: Self-reported diarrhoea compared with proxy-diarrhoea.....	317
Table 5.10: Self-reported nausea and vomiting compared with proxy- nausea and vomiting.....	317
Table 5.11: Blood-test-identified anaemia compared with proxy-anaemia.....	317
Table 5.12: Blood-test-identified neutropoenia compared with proxy-neutropoenia.....	318
Table 5.13: Self-reported diarrhoea by grade compared with proxy-identified diarrhoea.....	318
Table 5.14: Self-reported nausea and vomiting by grade compared with proxy-identified nausea and vomiting.....	318
Table 5.15: Blood-test-identified anaemia by grade compared with proxy-identified anaemia.....	319
Table 5.16: Blood–test-identified neutropoenia by grade compared with proxy-identified neutropoenia.....	319
Table 5.17: Proxy-identified diarrhoea treatments compared with self-reported diarrhoea by grade.....	320
Table 5.18: Proxy-identified nausea and vomiting treatments compared with self-reported nausea and vomiting by grade.....	320
Table 5.19: Proxy-identified anaemia treatments compared with laboratory-test-identified anaemia by grade.....	321
Table 5.20: Proxy-identified neutropoenia treatments compared with laboratory-test-identified neutropoenia by grade.....	321
Table 5.21: Proxy-identified diarrhoea treatments compared with self-reported diarrhoea by grade.....	324
Table 5.22: Proxy-identified nausea and vomiting treatments compared with self-reported nausea and vomiting by grade.....	325
Table 5.23: Proxy-identified anaemia treatments compared with blood-test-identified anaemia by grade.....	325
Table 5.24: Proxy-identified neutropoenia treatments compared with blood-test-identified neutropoenia by grade.....	326
Table 5.25: Comparison of trastuzamab adverse events—Cobleigh et al (290) and Elements of Cancer Care study.....	328

Abbreviations and shortened forms

ACAS	Australian Cancer Anaemia Survey
ACT	Australian Capital Territory
ADL	activities of daily living
AE	adverse event
AIC	Akaike's Information Criteria
ANC	absolute neutrophil count
APDC	Admitted Patient Data Collection (NSW)
AR-DRGs	Australian Refined Diagnosis Related Groups
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
ATC	Anatomical Therapeutic Chemical
BCCA	British Columbia Cancer Agency
bid	twice per day
CADTH	Canadian Agency for Drugs and Technology in Health
CCR	Central Cancer Registry (NSW)
CHeReL	Centre for Health Record Linkage
CI	confidence interval
CPT-11	irinotecan
CTCAE	Common Terminology Criteria for Adverse Events
DRG	diagnosis related group
DVA	Australian Government Department of Veterans' Affairs
ECAS	European Cancer Anaemia Survey
EDDC	Emergency Department Data Collection (NSW)
EMCaP	Economic Models for Cancer Protocols
EORTC	European Organisation for Research and Treatment of Cancer
EPO	erythropoietin
ESA	erythropoiesis stimulating agent
ESMO	European Society of Medical Oncology
FDA	US Food and Drug Administration
5-FU	5-fluorouracil
5-HT3RA	5-HT3 receptor antagonists
g/dL	grams per decilitre
GEE	generalised estimating equations
GLM	generalised linear modelling
GP	general practitioner
G-CSF	granulocyte colony-stimulating factor
Hb	haemoglobin
hrs	hours
ICER	incremental cost-effectiveness ratio

ICU	intensive care unit
IM	intramuscular
inpt	inpatient
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IVT	intravenous therapy
lab.	Laboratory
MASCC	Multinational Association of Supportive Care in Cancer
max.	maximum
MBS	Medicare Benefits Schedule
MATES	Medicines Advice and Therapeutics Education Services
MeSH	medical subject heading
mg	milligram
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHCDC	National Hospital Cost Data Collection
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute of Health and Care Excellence
NS	not specified
NSCL	non-small-cell lung cancer
NSW	New South Wales
OOP	out-of-pocket
OLS	ordinary least squares
outpt	outpatient
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PICO	population / intervention / comparison / outcome
PLD	pegylated liposomal doxorubicin
PPN	unique patient identifier
QALY	quality adjusted life year
QIC	quasi-likelihood under the independence model criterion
QICu	simplified quasi-likelihood under the independence model criterion
RBC	red blood cell
RDI	relative dose intensity
RPBS	Repatriation Pharmaceutical Benefits Scheme
SA	sensitivity analysis
SC	Schwarz Criterion
SQ	subcutaneous

SESAHS	South Eastern Sydney and Illawarra Area Health Service
TGA	Therapeutic Goods Administration
tid	three times per day
TTO	time trade-off
U	units
µg	microgram
UK	United Kingdom
US	United States
v.	versus

Abstract

Background: In Australia, economic evaluation is an important tool in prioritising healthcare spending. Adverse events of chemotherapy affect patients' physical health and quality of life; however, they are often excluded from chemotherapy economic evaluations. This thesis explores the incidence, costs and consequences of chemotherapy adverse events and the implications for cost-effectiveness.

Key Objectives:

1. Examine how adverse events are incorporated into models of chemotherapy cost-effectiveness.
2. Develop Australia-based models of costs and consequences of four common adverse events.
3. Estimate incidence of adverse events in clinical practice.
4. Estimate costs of adverse events in clinical practice.
5. Compare rates of adverse events in clinical practice with rates reported in clinical trials.

Methods: There are four components to this research. The first is a systematic review examining how adverse events are incorporated into existing models of chemotherapy cost-effectiveness (Objective 1). The second is the use of decision analytic modelling to develop models of the costs and consequences of diarrhoea, nausea/vomiting, anaemia and neutropenia. These can then become standard components of future models of chemotherapy cost effectiveness (Objective 2). The third is the use of regression to estimate the incidence and costs of adverse events (Objectives 3 and 4) in an administrative dataset linked to routinely collected data on pharmaceutical and medical service use. Finally, an analysis of a prospective cohort of 482 individuals undergoing chemotherapy examines the frequency of adverse events (Objective 3) in comparison with those reported in clinical trials (Objective 5).

Results: The systematic review revealed that adverse events are not included in models of chemotherapy cost-effectiveness in any rigorous way. The models developed demonstrate that rigorous, systematic consideration of the key costs

and consequences of adverse events is possible, and provide a standard way to include adverse events in future models. Older or sicker individuals in the administrative dataset were more likely to experience adverse events, although incidence was low. Mean healthcare costs significantly increased with treatment for nausea, anaemia or neutropoenia but not diarrhoea. The prospective cohort study identified higher rates of adverse events than reported in clinical trials, with low-severity events particularly common.

Conclusions: In exploring the incidence, costs and consequences of chemotherapy adverse events, this thesis demonstrates that it is possible to model the key costs and consequences of chemotherapy adverse events, and that clinical practice data may reduce bias in these models. This is a significant contribution to determining true chemotherapy costs and consequences.