Investigating chemotherapy adverse events: incidence, costs and consequences

Alison Pearce

Centre for Health Economics Research and Evaluation

Faculty of Business

University of Technology, Sydney

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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.

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Alison Pearce

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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

SESIAHS	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 neutropoenia. 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.

Chapter 1: Introduction

Chapter Summary

In providing an introduction and background to this thesis, this chapter focuses on cancer in Australia, chemotherapy, adverse events of chemotherapy and economic evaluation. In addition to providing the reader with an understanding of the basic issues covered in this thesis, this chapter introduces the data sources used throughout the thesis and describes the aims and objectives of this research. These are presented in such a way as to map the structure of the thesis. Overall, the work presented in this thesis contributes to better information for decision-makers about the true incidence, costs and consequences of chemotherapy adverse events.

Pharmaceutical expenditure has been the fastest-growing component of the healthcare system over the last ten years (1, 2), and anti-cancer drugs represent a significant proportion of this expenditure (3). They constitute nearly one third of new medicines (4, 5) and provide hope to patients and the community. Therefore, it is not surprising that cancer patients and their families expect timely and equitable access to these new medicines (6).

However, the incremental benefits provided by these new treatments are small. A study by Australian oncologists found that the overall contribution of chemotherapy to the 5-year survival of adults with cancer was 2.3 per cent (7).

In addition, cancer treatments are expensive (8-10). Although the newer biological therapies provide opportunities for effective treatment, they are among the most-expensive drugs available, and the market is growing (11-13). For example, the biological therapies trastuzumab and cetuximab cost more than $1,500 per patient per week and may be required weekly for up to 12 months (14).

These high costs can be attributed to a number of factors, including the complex manufacturing processes involved, the increasing costs of research and development as drug trials become larger and more complex, the perceived high value of anti-cancer drugs to patients, and the reducing market competition (1, 11). In addition, many anti-cancer treatments require the provision of additional

health services for assessing treatment eligibility, monitoring treatment outcomes, and managing treatment adverse events (15).

The community perceives cancer as a hidden, insidious and feared disease with few treatment options (16). In addition, some economists suggest that the community may value the final years of life more highly than earlier years (17). The implication is, therefore, that the population is generally willing to treat at all cost with little consideration of the economic effects on the healthcare system (16, 17). This was evidenced in the intense public lobbying on behalf of the introduction of trastuzumab to Australia for use in women with cancer that had progressed even though it provides little additional benefit and is estimated to cost the Australian Government close to $150 million per year (18).

One of the biggest challenges facing healthcare systems is how to provide patients with access to these new agents while ensuring the sustainability of funding (8-10). Meeting this challenge requires new policies and healthcare practices that must be developed based on sound clinical and economic evidence, such as the work described in this thesis.

Economic evaluation is a useful way to inform healthcare decision makers about the costs and benefits of new healthcare interventions. These economic evaluations are often based on *models* – mathematical representations of the consequences of alternative options.

This thesis addresses the use of models to address the challenge of funding new cancer treatments in a number of ways. First, the methods used in existing economic models to address adverse events are reviewed (Chapter 2). Four decision-analytic models demonstrating that it is possible to consider all of the relevant costs and consequences of chemotherapy adverse events in chemotherapy cost-effectiveness modelling are presented (Chapter 3). Analyses of two observational data sets are then described (Chapters 4 and 5), which confirm the difference between reports of adverse events in clinical trials and the experience in clinical practice. This highlights the importance of using data that are reflective of clinical practice when populating models of chemotherapy cost-effectiveness.

1.1 Background

1.1.1 Cancer in Australia

Cancer has a significant impact on the Australian community, affecting individuals, families and the healthcare system (19). More than 114,000 new incidences of cancer were diagnosed in Australia in 2009, and in 2010 there were 42,844 deaths from cancer (20). These figures continue to rise annually due to Australia's ageing population (19). With improvements in survival rates over time due to improved treatments for almost all types of cancer, there is a corresponding increase in the prevalence of cancer in the community. More than 774,674 people with a previous diagnosis of cancer were alive at the end of 2007 (20).

The ten most common cancers in Australia in 2007 are shown in Figure 1.1, and the ten most common causes of death from cancer in Australia in 2007 are shown in Figure 1.2. Similar cancers appear in both figures, however the most common cancers do not necessarily cause the most deaths. Figure 1.3 shows the age-specific incidence rates of cancer in Australia in 2007, with a clear pattern of cancer increasing with age and more prevalent in males.

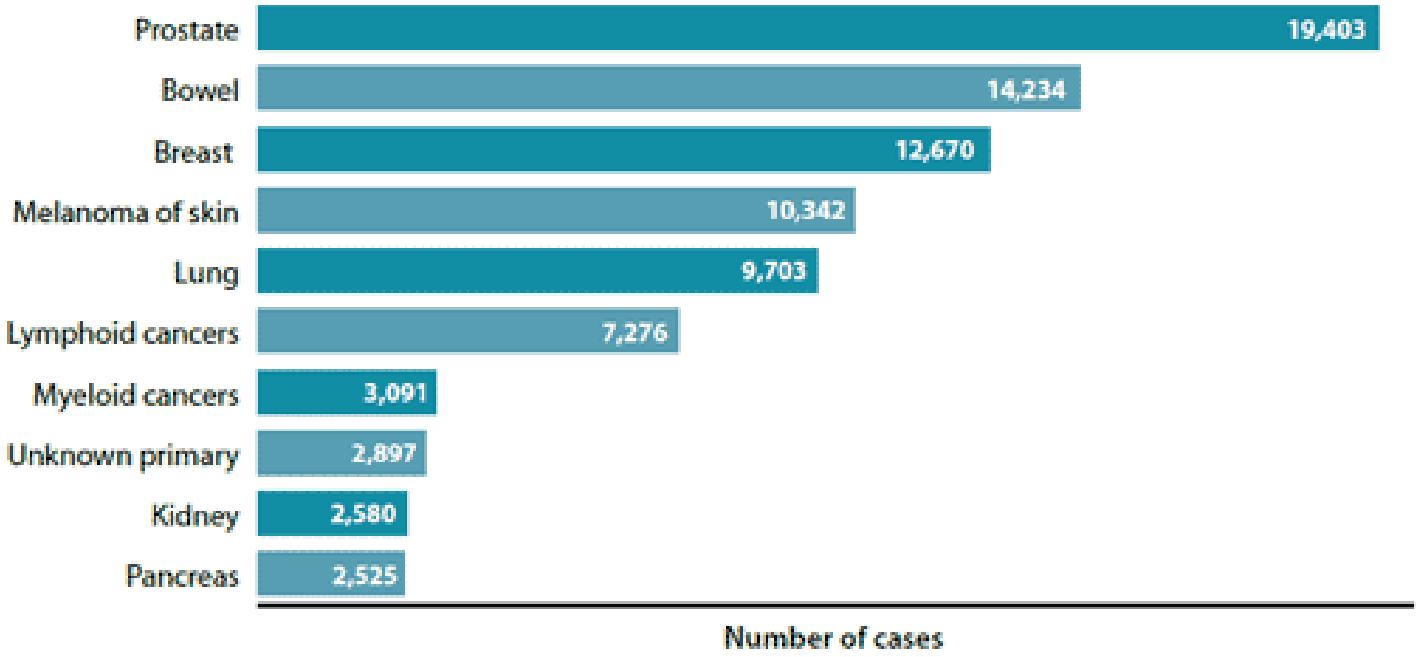


Figure 1.1: Ten most commonly diagnosed cancers in Australia, 2007 (21)

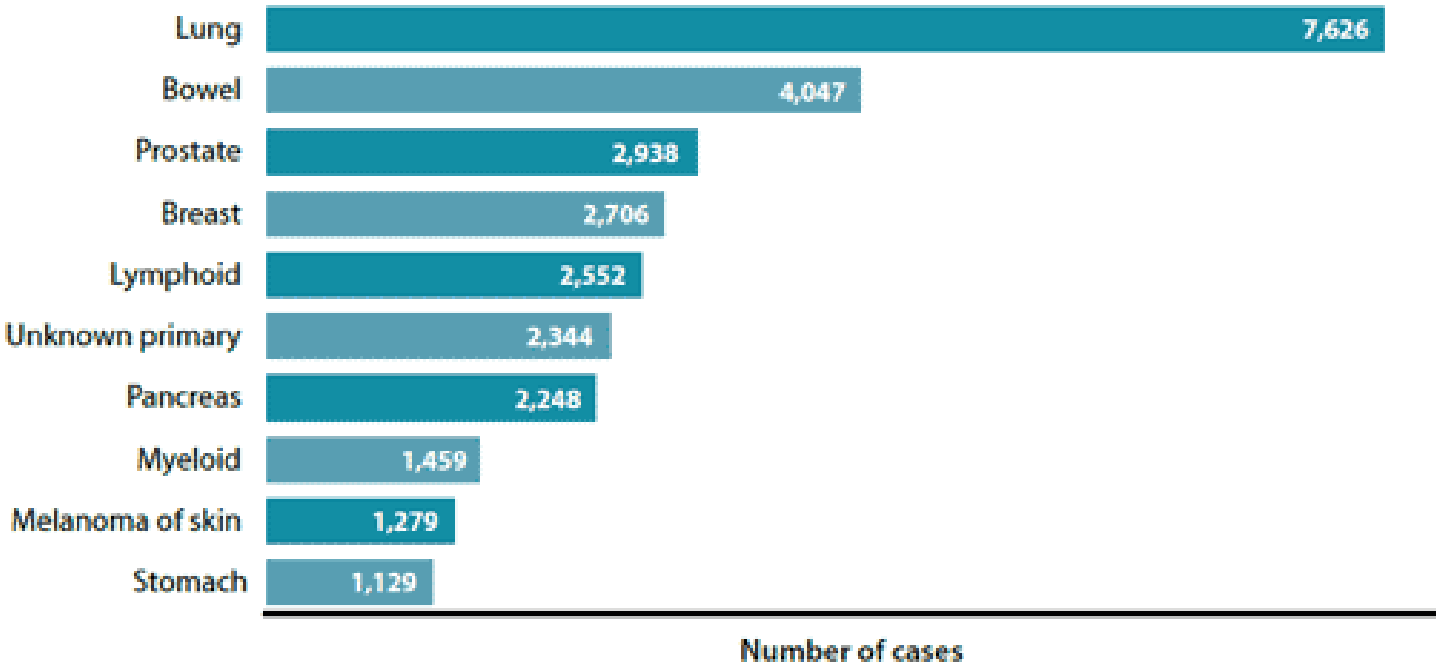


Figure 1.2: Ten most common causes of death from cancer in Australia, 2007 (21)

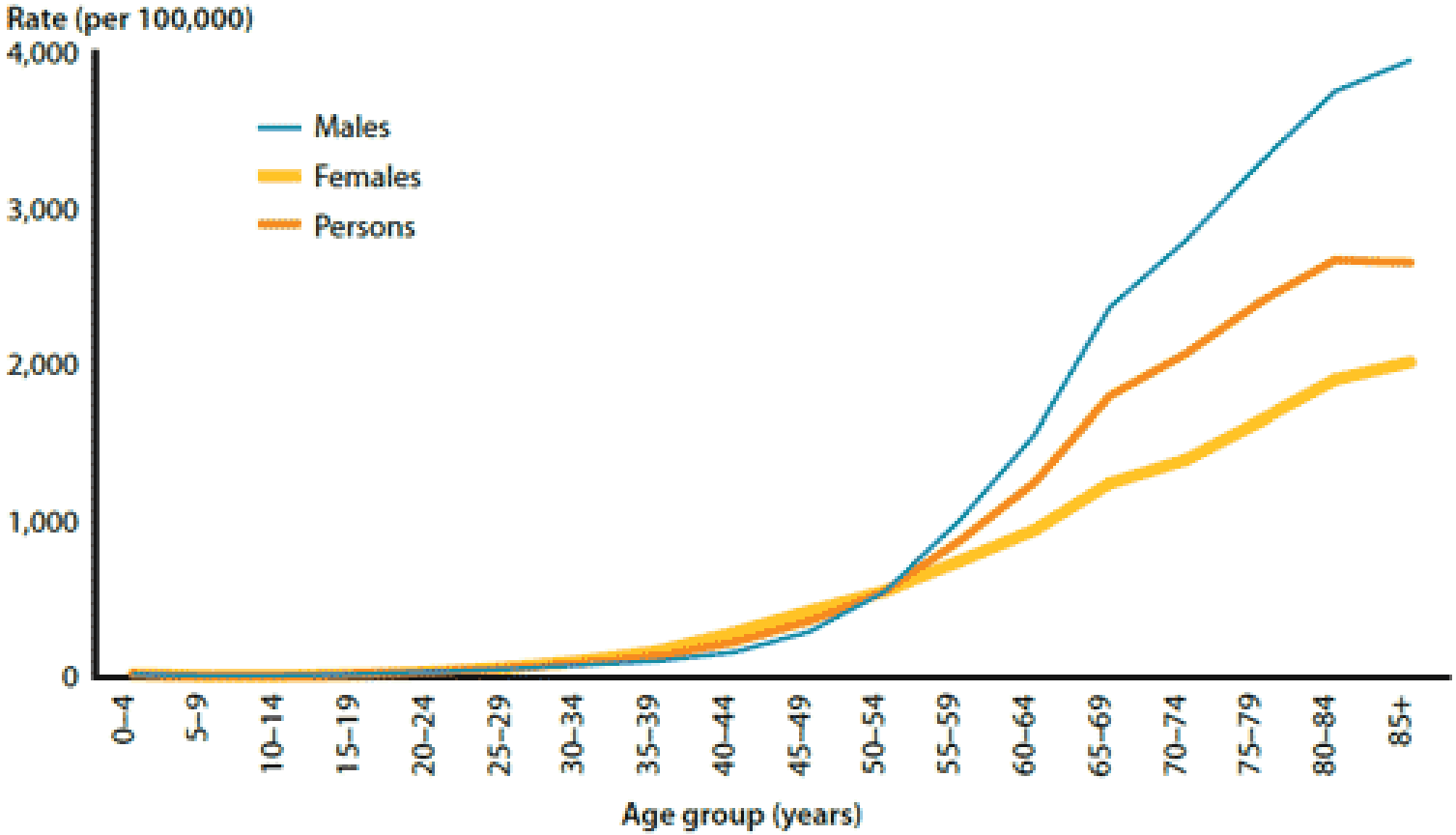


Figure 1.3: Age-specific incidence rates for all cancers combined, Australia 2007 (21)

For the healthcare system, cancer represents a significant component of burden (illness, impairment, injury or premature death) and cost (19). Cancer was estimated to be the largest contributor to the total burden of disease in Australia in 2012, accounting for 19 per cent of the total (20). Approximately ten per cent of all hospital separations (single continuous stay in hospital) in 2010–11 were related to cancer (20).

Cancer results from uncontrolled growth of abnormal cells in the body (22). Most cancers start in a specific organ or location in the body, such as the breast, colon or lung, though some cancers such as leukaemia are in the blood and therefore circulate through the body (22). As cancer cells reproduce, they form a tumour (22). Over time, cancer cells can metastasise (spread) to different organs of the body through the vascular system (22).

In general, cancer is treated in one or more of three ways: surgery, radiotherapy and systemic treatments (22). Surgery is usually the only option for a cancer cure, by completely removing all cancer cells before they spread (22). Even when a cancer has spread, surgery is often used to remove as much cancer as possible to extend survival and improve quality of life (22). Although radiotherapy is effective in killing cancer cells, they must be within a defined tumour area (22). Radiotherapy may be used in isolation or in combination with surgery (22). Unlike with surgery and radiotherapy, systemic therapies, such as chemotherapy or targeted biological agents, can circulate throughout the body and in so doing can kill cancer cells that have spread beyond the original tumour (22).

Chemotherapy is given orally or via injection and is delivered in cycles, with a period of treatment followed by a period of rest (22). The cycle is determined by the type of chemotherapy; some treatments involve one day of chemotherapy followed by a number of weeks of rest, while others involve chemotherapy every day for a period of weeks with only a short break between cycles (22). Chemotherapy often causes adverse events, which may be both uncomfortable and distressing to patients. Common adverse events include nausea and vomiting, diarrhoea, fatigue and hair loss (22). The majority of patients receive chemotherapy in the outpatient setting and manage adverse events at home (23).

Recent advances in systemic therapies have seen the introduction of new, targeted biological treatments designed to interfere with the specific molecules responsible for the growth of tumours (24). These therapies allow for improved tailoring of treatment to tumour type to maximise effectiveness. Given that biological treatments are highly selective in terms of the cells they destroy, the associated adverse events differ from those associated with traditional chemotherapy (24).

New cancer treatments are tested through a series of clinical trials designed to test the safety and efficacy of the treatments. The outcomes of cancer treatments are usually reported by using measures of progression and survival. Overall survival is considered to be the gold-standard outcome measure for cancer studies; however, it is not often used as an outcome measure in clinical trials (25). This may be because of the time and expense involved in following up all patients to death, or because there is a clinical belief that previous or subsequent treatments may influence overall survival, thus clouding the effect of the specific treatment under investigation (25). Five-year survival (the proportion of patients alive five years after diagnosis) is often used to describe cancer mortality (19).

The term *progression* refers to the situation when the tumour has increased in size. Progression, which is usually expressed as a percentage, indicates that the treatment is no longer effective. To determine the existence of progression, the size of the tumour is assessed at baseline and then regularly throughout treatment. In clinical trials, these measurements may be done more often than in standard clinical practice. Progression is used for outcome measures such as progression-free survival (PFS, the time from treatment initiation to disease progression or death) or time to progression (TTP, PFS excluding death as an event) (25).

1.1.2 **Adverse events**

Anti-cancer treatments result in toxicities. Surgery may result in transfusion reactions associated with anaesthesia, or lead to infections (26). Hospital stays can also be associated with pressure ulcers, hip fractures and complications from supportive care such as catheters (26). The adverse events of radiotherapy can be immediate, such as dermatitis at the site of radiation or radiation induced vomiting, or it may be delayed, such as cardiovascular disease (27).

In chemotherapy, these toxicities are referred to as *adverse events*. An *adverse event* is 'any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment' (28, p.2). This thesis is primarily focussed on the sub-category of adverse events known as Adverse Drug Reactions ('A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function' (28, p.2). However, outside of formal regulatory or clinical trial settings the term *adverse event* is more commonly used, and will be used throughout this thesis.

Adverse events occur because as chemotherapy moves through the body it damages healthy cells as well as cancer cells (29). A questionnaire conducted in 2004 found that among Australian patients the ten most common adverse events were constipation, nausea and vomiting, fatigue, alopecia (hair loss), drowsiness, myelosuppression, skin reactions, anorexia, mucositis and diarrhoea (30).

However, there are nearly 250 adverse events commonly related to chemotherapy (31), and each of these can affect an individual's physical and psychosocial health. These adverse events may be mild or severe and can be simple or affect multiple organ systems. Adverse events are managed through a combination of treatments, including preventative strategies such as pharmaceutical products or lifestyle changes and acute treatments such as drugs or medical intervention. The majority of adverse events are managed at home or in the outpatient setting (23). In addition, the chemotherapy dosage can be modified to reduce the chances of an adverse event or to minimise its severity. These dosage modifications could consist of skipped doses, reduction in the dosage or the complete cessation of chemotherapy.

Adverse events have a significant effect on the patient experience of chemotherapy. Adverse events affect quality of life, function, work and relationships and can be very distressing to patients. In a pivotal study of patient perceptions of chemotherapy, Coates et al. identified that in a cohort of Australian patients, vomiting, nausea, hair loss, thoughts of treatments and having needles

were considered to be the most severe adverse effects of chemotherapy treatment (32). An update of Coates et al.'s paper ten years later with a French cohort of cancer patients found some perceptions were different, with effects on family or partner, hair loss, fatigue and effects on work, home and social activities most important (33). Table 1.1 compares the relative severity of side effects for the entire group in the two studies (Coates et al 1983 and Carelle et al 2002). Similarly, studies of patient preferences for adverse event health states have confirmed that adverse events are associated with decreased utility (34).

Table 1.1: Comparison of the relative severity of adverse events in two studies

Relative severity of side effects for the entire group		
	Coates et al 1983 (32)	**Carelle et al 2002 (33)**
Rank	**Side effect**	**Side effect**
1	Being sick (vomiting)	Affects my family or partner
2	Feeling sick (nausea)	Loss of hair
3	Loss of hair	Constantly tired
4	Thought of coming for treatment	Affects my work, home duties
5	Length of time treatment takes at clinic	Affects my social activities
6	Having to have a needle	Loss of sexual feeling
7	Shortness of breath	Giddiness on standing up
8	Constantly tired	Diarrhoea
9	Difficulty sleeping	Weight gain
10	Affects family or partner	Shortness of breath
11	Affects work/home duties	Emesis
12	Trouble finding somewhere to park	Feeling low (depression)
13	Feeling anxious or tense	Irritability / bad temper
14	Feeling low / miserable (depression)	Numbness in fingers or toes
15	Loss of weight (equal rank 14)	Loss of appetite

To maximise the reliability of reporting of adverse events for clinical trials and regulatory monitoring, the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) is used to document chemotherapy adverse events. The CTCAE classifies adverse events on the basis of clinical and laboratory evaluation according to a scale of five grades, ranging from I (*mild symptoms*) to V (*death related to adverse event*) (31).

The emergence of biological treatments has changed the typical pattern of adverse events. For example, the most common adverse event of the biological agent

cetuximab is a rash, experienced by more than 88 per cent of patients (35). These low-severity high-incidence events are changing the profile of adverse events, and this has implications for the patterns of resource-use associated with treating cancer and the results of cost-effectiveness analyses.

It has been suggested that the CTCAE may not reflect this new profile of adverse events. With an increasing number of chemotherapy drugs available in oral form that are taken over extended periods, adverse events may occur at low grades but persist for extended periods (36). The current CTCAE classifies mild diarrhoea in the same way, whether it occurs over one day or one month; however, the difference between these two experiences for patients could be significant (36).

The emerging issues associated with biological anti-cancer therapies provide an additional rationale for the importance of accurate and transparent consideration of chemotherapy adverse events. However, this thesis focuses specifically on chemotherapy, acknowledging that some of the work may be applicable across treatment types such as chemotherapy, hormonal treatments and biological agents.

For the focus of this research, four specific adverse events were selected: 1) diarrhoea, 2) nausea and vomiting, 3) anaemia and 4) neutropoenia. These adverse events were selected based on a number of factors, summarised in Table 1.2.

All of the selected events are common across a range of chemotherapy treatments, occur immediately during or after chemotherapy and are short-term events. This timeframe was deliberately selected as longer-term events are rare, tend to be chemotherapy regimen specific, and can be more difficult to model. Adverse events associated with varying levels of patient distress were selected, with distress classified as low for events that have little effect on day-to-day life and high for events that either have a significant negative effect on day-to-day functioning or are serious enough to cause hospitalisation. The typical amount of resource-use associated with each adverse event ranges from simple medications or lifestyle treatments, to high resource-use events, such as those requiring hospitalisation. A range of management strategies are used for the selected events, including prevention, treatment or a combination of both.

Table 1.2: Clinical characteristics of four selected chemotherapy adverse events

	Anaemia	Neutropoenia	Diarrhoea	Nausea & vomiting
Definition (31)	Reduced Hb in the blood	Reduced neutrophils in the blood	Frequent and watery bowel movements	Queasy sensation, urge to vomit, or vomiting
Clinical implications	Paleness, shortness of breath, cardiac palpitations, fatigue	Increased susceptibility to infection	Dehydration	Dehydration, malnutrition, distress, pneumonia
Patient distress	Low	Low to high	High	High
Rank in Coates study	n/a (constantly tired ranked 8)	n/a	n/a	Vomiting = 1 Nausea = 2
Rank in Carelle study	n/a (constantly tired ranked 3)	n/a	8	Emesis = 8
Timing	Immediate	Immediate	Immediate	Immediate
Term	Short	Short	Short	Short
Management	Prevent & treat	Treat	Treat	Prevent
Resource-use	Moderate	Moderate to high	Low to moderate	Low to moderate

Note: Hb = haemoglobin

1.1.3 Funding of healthcare and medicines in Australia

Australia aims to provide universal access to health services to all Australians. This is primarily achieved through the taxation-funded Australian Government Medicare system (37). Medicare provides subsidised pharmaceutical products and medical services, such as consultations with general practitioners (GPs) and medical specialists, and funding to states and territories to provide free access to public hospitals (37).

The Commonwealth, state and territory governments of Australia share the responsibility for funding and coordinating healthcare services and have some areas of responsibility that overlap, including joint funding of public hospitals and community care (37). In general, the Commonwealth manages national health policy activities and funds most community medical services and health research (37). The state and territory governments manage delivery of healthcare services, such as public hospitals, community health centres and public health programs (37).

There is also a private health sector, which is considered an essential component of the Australian healthcare system (37). The Commonwealth provides incentives to individuals to take up private health insurance, which covers services such as private hospital charges (or charges to be treated as a private patient in a public hospital), as well as allied health services and other health services not covered by Medicare, such as dental care (37).

The Pharmaceutical Benefits Scheme (PBS) is a Commonwealth-funded program which provides affordable access to medicines to those covered by the Medicare system (37). Individuals pay the cost of a dispensed medicine up to a maximum amount (based on whether the individual is a general or concessional patient) (37). Subsidies for any price above this threshold (co-payment) are paid direct to the dispensing pharmacy (37). Medicines are PBS-listed on the basis of their safety, effectiveness, cost-effectiveness and overall cost to the system (38).

Local decision-makers, including clinicians, administrators and patients, also play a vital role in the efficient and equitable distribution of medicines. Once a drug is

PBS-listed, local decision-makers exert control over prescribing patterns and are instrumental in determining whether medicines are used cost-effectively. However, there is often limited economic evidence available to local decision-makers. For example, trastuzumab can be administered to patients on either a weekly or 3-weekly schedule with no clinical difference in the benefits (39). However, the weekly regimen results in significantly more drug wastage, due to the unused portions of opened vials being discarded. If unaware of this, decision-makers may choose the weekly regimen for ease of patient scheduling.

When data are available, they are rarely fully applicable to the local context and their use in decision-making is often ad hoc (40). For example, the pivotal trial of cetuximab recruited patients from both Australia and Canada and included the collection of extensive resource-utilisation data. However, the economic evaluation of cetuximab was published two years after the efficacy data and was analysed from the Canadian healthcare perspective, making interpretation in the Australian clinical context difficult (41).

Local healthcare delivery systems, such as regional health services and hospitals are under considerable pressure to fund medicines that have been rejected, restricted or are pending approval by the PBAC. However, local decision-makers face genuine budget constraints that affect their ability to fund medicines. It is not surprising, therefore, that cancer clinicians are increasingly called upon to discuss not only the clinical aspects of a proposed treatment plan but also the economic aspects at the hospital or health-service level.

To assist such local decision-makers, readily accessible economic models are required. These should be in a format that can easily integrate local circumstances, such as disease incidence, treatment pathways and local resource constraints. They will also need to take into account the effects on local resources of any new treatment.

1.1.4 Economic evaluation

Economics is concerned with the allocation of scarce resources between competing demands (42). Those working in healthcare often find it hard to see

how economics influences their core work providing care to those who are unwell. However, the healthcare system is a market like any other that is subject to the forces addressed in economics (42). Extensive market failure within the healthcare system due to factors such as externalities, uncertainty, information asymmetry and the need for equity means that the community cannot rely on a market system to allocate health resources efficiently and effectively (42). Therefore, a mechanism is needed to provide information to decision-makers about the use of health resources to maximise social welfare.

Economics provides a framework for considering how health services can be distributed to maximise social welfare. Social welfare is typically defined as some aggregate of individual well-being. Economic evaluation is a tool to provide this information, through the systematic comparison of alternatives in terms of their costs and benefits (16). The information generated about the costs and benefits can be used to inform and aid decision-making at a range of levels within the healthcare system (16).

Economic evaluation has two features: it deals with the costs and consequences of activities, and it is concerned with choices. Economic evaluation provides decision-makers with information about the costs and benefits of alternative choices through the use of systematic comparison (16). This is particularly relevant in situations where decision-makers are making collective choices due to market failure (42), such as in the case of the healthcare system.

Economic evaluation allows the estimation of opportunity costs associated with health decisions; that is, it takes into account not only the financial cost but also the potential benefits achievable through alternative uses of resources.

Typically, economic evaluation uses cost effectiveness analysis to produce an Incremental Cost Effectiveness Ratio (ICER). The differences in costs and effects for an intervention and a comparator are calculated and presented as a ratio.

1.1.5 **Economic modelling**

Modelling is a frequently used strategy for representing complex real-world situations in a simpler form (43). In the area of health economics, models are

commonly used to synthesise the best available data from a variety of sources, such as clinical trial data, observational studies, and patients preferences studies. In rare cases, individual data sources, such as clinical trials, may be adequate for economic evaluations; however, more commonly an evaluation will require data beyond those provided in clinical trials. The ability of decision analytic modelling to consider all of the relevant options and the full range of evidence available is beyond the scope of a randomised controlled trial, or even a meta-analysis (43, 44). Economic analysis may require intermediate endpoints to be linked to final endpoints and extrapolation of outcomes, which can be achieved using decision analytic modelling (43-45). Finally, the use of decision analysis allows outcomes to be applied to the specific decision-making context (43, 44). With theoretical foundations in statistical decision theory, expected utility theory and a close association with Bayesian statistics, decision analysis has been used in areas such as engineering and business (44, 46) and has been used in health to inform clinical decision-making (44, 46, 47).

There are concerns about the trade off between external and internal validity when using economic modelling techniques (48). When economic evaluations are conducted purely within a randomised clinical trial, the chance of bias resulting in differences between the study groups is minimised through the use of randomisation (48). This *internal validity* extends to the economic data which is obtained and analysed in the same way as the clinical data (48). Modelling, with its multiple data sources, including non-randomised data such as observational studies, does not control for potential bias in the data, and so may produce biased results (48). However, clinical trials do not necessarily reflect clinical practice. Clinical trials often run with stringent protocols, in high quality centres with experienced clinicians. This reduces *the external validity*, or generalisability, of the study and its results (48). Further discussion of internal and external validity in economic evaluations of chemotherapy can be found in Chapter 4.

In the case of chemotherapy, decision analytic modelling is an appropriate approach to economic evaluations. This is due to the need to consider the full

range of evidence with appropriate consideration of uncertainty, and to assess all relevant alternatives (46). Decision analytics uses mathematical relationships between options and their potential consequences to define probabilities for each consequence, along with the cost and outcomes of each option evaluated (46). There are a number of different approaches to decision analytic modelling, including decision tree analysis, Markov modelling and microsimulation.

Decision trees show patient pathways through various treatment decisions and alternative events, and are populated with information on resource-use and outcomes. Epidemiological studies are generally required to provide the outcomes or the probabilities of different arms of the decision tree, but identification of the associated resource-use is often more difficult. A Markov model assumes that individuals are in one of a predetermined set of health states, with each health state assigned a cost, effectiveness and utility (in cost-utility analysis). Individuals then move through the health states over predetermined periods of time, called cycles. Finally, microsimulation models track individual patients, rather than patient cohorts, through different health states over time, offering flexibility not possible in decision trees or Markov models. Further discussion of the different types of economic modelling techniques and their strengths and limitations is in Chapter 3.

The models developed in this thesis have been designed to provide a common method for the inclusion of adverse events in models of chemotherapy cost effectiveness. By providing a standard plug-in to economic evaluations, the transparency and reproducibility of chemotherapy cost effectiveness analyses will be improved.

In developing a decision-analysis model, information about the costs and outcomes of treatments for cancer is required, including relevant data on the incidence of adverse events, the types and quantities of resources used to treat adverse events and the unit costs of these resources. These data can be collected in a number of ways. A bottom-up approach identifies, measures and costs individual-level resources and then aggregates these results to obtain an overall cost for a health service. This ensures that variations in local requirements and

practice can be accounted for in model design (49, 50). Alternatively, top-down approaches assign total costs of a healthcare system to individual services. These are more appropriate for models that are designed for generalising across a range of settings (49, 50). In selecting the most appropriate approach and data for the model, the analyst must also take into account the availability of data.

It is also common for decision analytic models to use a combination of clinical trial data, administrative data and some bottom-up costing information. However, the influence of these different sources of data has received relatively little attention in the literature (49, 50). The comparison of adverse events reported in clinical trials and clinical practice described in Chapter 5 examines this issue.

1.1.6 Clinical trials and economic evaluation

Randomised controlled trials (clinical trials) are considered the gold-standard method for determining the efficacy and effectiveness of new medical treatments (51, 52), including of chemotherapy drugs. The strength of clinical trials comes from the minimisation of bias within the design of clinical trials, and this results in high levels of internal validity (52). However, this internal validity may come at the price of low external validity, meaning generalisation of the results to clinical practice may be limited (52). Rothwell (52) provides a comprehensive list of the issues that may affect the external validity of clinical trials, including the trial setting, patient selection, outcome measures and follow-up protocols.

Rothwell also notes that the way in which adverse events are managed in clinical trials may often differ from their management in clinical practice. For example, patients who are at risk of complications are often excluded from clinical trials (52). Safety procedures may also be significantly more intensive in clinical trials than in clinical practice (52).

In addition, the reporting of chemotherapy adverse events in clinical trials is often poor (53, 54). There is no standard method for eliciting from patients the symptoms and, therefore, adverse events they are experiencing (55). There is evidence that different elicitation methods can result in the identification of different adverse events (56).

These issues have implications for the clinical applicability of trial results to practice, but they also have implications for economic evaluation. Cost-effectiveness analyses often use the results of clinical trials to populate models (57). For inputs related to treatment efficacy, the results of clinical trials provide data that has minimal bias and is generally appropriate (57). However, for the reasons listed above, the costs and consequences of adverse events captured in clinical trials may not reflect clinical practice.

The primary purpose of most health economic evaluations is to inform decision-makers about the costs and consequences of treatments or services. Decision-makers are therefore interested in information that provides a picture of how the treatment or service will influence the health of the individuals in the population for whom they are making a decision. If the data used as inputs for economic models do not reflect the particular population, or have low external validity, the results of the economic evaluation may not be replicated when implemented in clinical practice.

This tension between internal and external validity is a primary issue in economic evaluations. With clinical trials designed to maximise internal validity, the treatment efficacy results are based on the 'best-case scenario'. Economic evaluation is designed to inform real world decision making and thus requires greater external validity. In addition, the data required for economic evaluation is not always available from clinical trials. Constraints on the amount of data able to be collected and the length of follow up mean the data in clinical trials is insufficient for the time-horizon and information needs of economic models. Economic evaluation typically addresses this tension by using both types of data – where clinical trial data is available and appropriate this is used, with data from other sources such as observational studies or administrative datasets completing the model and evaluation. This approach maximises the benefit of internal validity while minimising problems of external validity.

1.2 Aims and objectives

This research examined the incidence, costs and consequences of chemotherapy adverse events, with a focus on economic evaluation. The three aims of this research were to explore:

1. the incidence of chemotherapy adverse events
2. the costs of chemotherapy adverse events
3. the consequences of chemotherapy adverse events.

These aims were addressed with a series of research objectives, listed below according to the thesis chapter in which each is discussed.

Chapter 2

Research objective 1: Assess how adverse events are incorporated into models of chemotherapy cost-effectiveness

Chapter 3

Research objective 2: Develop Australia-based models of the costs of best-practice management of four common chemotherapy adverse events.

Chapter 4

Research objective 3: Explore the incidence of chemotherapy adverse events in clinical practice through administrative data.

Research objective 4: Explore the factors that influence the incidence of chemotherapy adverse events in clinical practice.

Research objective 5: Explore the resource-use associated with chemotherapy adverse events in clinical practice.

Chapter 5

Research objective 6: Identify the frequency of common adverse events in a sample of people with cancer being treated with chemotherapy in a clinical practice setting.

Research objective 7: Validate the use of adverse event treatments in administrative data as a proxy for experiencing adverse events.

Research objective 8: Explore the management of diarrhoea, vomiting, neutropoenia and anaemia in a standard-practice sample.

Research objective 9: Compare rates of adverse events in standard practice with rates in clinical trials.

1.3 Theoretical framework

This research is based on the technique of economic evaluation, with decision analytic modelling and regression analyses used as methods for economic evaluation.

Economic evaluation aims to inform decision-makers about the efficient, effective and equitable distribution of resources in the face of market failure. As such, it explicitly targets the decision-maker's perspective. There are differing views within economics about the implications of this in terms of the relationship between economic evaluation and the theoretical foundations of economics. Various frameworks have been adopted, including welfarism, extra-welfarism and the decision-makers approach (58).

The decision-makers approach places emphasis on the information needs of decision-makers. This pragmatic approach can be applied within either a welfarist or extra-welfarist framework. It defines the outcome function as the one identified by the decision-maker commissioning the analysis in comparison to the outcome functions in extra-welfarist economics, which are need and health, or in welfare economics where they are demand and utility. For the decision-maker, choices are often complex, with multiple perspectives, data sources and incomplete information available. The use of a framework such as decision analytic modelling therefore provides a useful structure for modellers to inform decision-makers in a meaningful way.

In the case of chemotherapy, decision makers are often interested in outcomes such as survival (such as progression free survival or 5-year survival) and quality of life, both of which may be influenced by adverse events. Resource utilisation associated with adverse events such as emergency department presentations,

prescriptions, and staff time may also be of interest. This interest in both the costs and the benefits of treatments makes economic evaluation an excellent methodology to address decision makers needs.

The work described in this thesis uses the decision-maker approach for economic evaluation, and it could be considered within a social perspective focusing on health-service resource-use and outcomes. Although this research focuses on undertaking original applied health-services research, these theoretical underpinnings are important in understanding the assumptions underlying the methods used in economic evaluation.

1.3.1 Policy framework

This research contributes to the understanding of modelling for chemotherapy cost-effectiveness and aims to produce evidence useful to decision-makers. It is therefore important that the research also be considered within a policy framework.

A number of national organisations, such as the National Institute of Health and Care Excellence (NICE) in the United Kingdom (UK) and the PBAC in Australia, have identified the use of economic evaluation as a key component of the decision-making framework used to determine the reimbursement of new pharmaceuticals in the healthcare system. For decision-makers, decision modelling allows the identification of an optimal decision on the basis of evidence relating to costs and benefits, but it also considers the various types of uncertainty relating to the evaluation (44).

Although this approach has many positives, economic evaluation is often undertaken in an ad hoc manner. Submissions for reimbursement to national bodies differ in regard to their methods, objectives and outcomes. Whereas each research question will require appropriate methods, and each submission has the overall aim of obtaining approval, these inconsistencies make comparison between submissions difficult and may mean that inconsistent decisions are unintentionally taken. It is also noted that the objectives of the model (obtaining approval) may differ to those of the healthcare decision-makers using the model,

who are likely to be looking for efficient and equitable care for patients. This highlights the importance of transparency in the reimbursement submission process.

The aim of this research was to develop a benchmark approach for the inclusion of the costs and consequences of chemotherapy adverse events into economic analyses and thus streamline the modelling process for economic evaluators by providing transparent models that can be adapted to their setting. In addition, the consistent application of robust modelling techniques would improve consistency for evaluators allowing comparison across applications.

1.4 Data sources

Three primary data sources were used in this research. The first, eviQ, a source of information about best clinical practice recommendations for chemotherapy treatments, contributed to the modelling described in Chapter 3. The remaining two, observational cohorts which provided an opportunity to examine chemotherapy adverse events in a clinical practice setting, are described in Chapters 4 and 5.

1.4.1 **eviQ**

The source eviQ is a website hosted by the Cancer Institute NSW and provides information about the Standard Cancer Treatment protocols for clinicians, patients and carers (59). These protocols include information about chemotherapy drugs and radiotherapy, including clinical evidence, drug-dose calculation and administration, and adverse events (59).

The Cancer Institute NSW provides the governance structure and support for the eviQ program. Detailed treatment protocols are developed by a core team of project officers as well as two specialist reference groups with representative multidisciplinary membership including consumer representatives. The information, which is published on a dedicated website (eviQ), is updated in real time and available to health professionals and consumers.

Pharmacological agents are typically evaluated for safety, effectiveness and adverse events using randomised controlled trials. The results of such trials form

the basis of information provided on eviQ regarding effectiveness and adverse events. This information provides best-practice recommendations for chemotherapy use as a treatment for cancer. This information can be used as high-quality Australia-specific inputs to modelling of chemotherapy and adverse events.

1.4.2 Australian Government Department of Veterans' Affairs

Australia's universal healthcare system provides significant potential to use administrative data for epidemiological research and to evaluate health services and policies. However, there are few Australian peer-reviewed studies investigating the use of person-level data.

The Australian Government Department of Veterans' Affairs (DVA) provides services to over 230,000 people, including veterans as well as the spouses, widows, widowers and dependants of veterans in Australia (60). These services include a broad range of healthcare and social supports, and holders of a DVA gold card are entitled to the full range of eligible healthcare services at DVA's expense, including medical, dental and optical care (61). In addition, the Repatriation Pharmaceutical Benefits Scheme (RPBS) provides access at a concessional rate to all items on the Schedule of Pharmaceutical Benefits available to the general community under the PBS, as well as an additional list contained in the RPBS, which is available at subsidised cost to veterans only (62).

The use of DVA data enables epidemiological and policy research in the area of pharmaceuticals. The DVA data can be expanded by using a data linkage system established in New South Wales (NSW) in 2006 by the Centre for Health Record Linkage (CHeReL). This allows the key records from both NSW and the Australian Capital Territory (ACT) data collections to be linked to the PBS and the Medicare Benefits Schedule (MBS) data collections. Access to this linked data was made available for this research through the principal investigators of the research program, 'Investigating the use and impact of cancer medicines in real world clinical practice'.

1.4.3 Elements of Cancer Care study

The Economic Models for Cancer Protocols (EMCaP) study is part of a program of work supported by a health-services research grant funded by the National Health and Medical Research Council (NHMRC). The purpose of the EMCaP program is to develop and disseminate evidence about the cost-effective use of cancer medicines in clinical practice.

One of the central components of the EMCaP program is the prospective study Elements of Cancer Care, which collected data from 482 individuals undergoing chemotherapy treatment for cancer in NSW over a two-year period. Data were collected through interviews and medical-record reviews about the chemotherapies used, the adverse events experienced and the costs associated with treatment. For secondary data, Medicare Australia provided data for individuals in the Elements of Cancer Care study from the PBS and the MBS, and the CHeReL performed a linkage with the NSW Central Cancer Registry (CCR), the NSW Admitted Patient Data Collection (APDC), the NSW Emergency Department Data Collection (EDDC) and the NSW Registry of Births, Deaths & Marriages (63). These linked data provide an ideal opportunity to examine the real-world experience of chemotherapy adverse events and the associated costs.

1.5 Overview of research components

There are four inter-related components to this research. First, a systematic review of the methods used in existing models to incorporate the costs and consequences of chemotherapy adverse events is presented in Chapter 2.

Second, Chapter 3 presents four models based on decision analytic techniques, which identify the Australian costs and consequences of managing diarrhoea, nausea and vomiting, anaemia and neutropoenia. These models, which address the deficiencies in modelling noted in the existing models in Chapter 2, are based on published data from clinical trials and are designed to be applied within future, larger models of chemotherapy cost effectiveness.

Third, a large administrative dataset is used to explore the incidence and cost of chemotherapy adverse events in a standard-practice cohort. These results are

described in Chapter 4. Last, analysis of a prospective cohort study examines the incidence and consequences of self-reported chemotherapy adverse events and is presented in Chapter 5. These data are also used to validate the proxy measure of adverse events developed in Chapter 4.

Chapter 6 provides an overview of the work undertaken, and extends this to highlight the contribution made to the literature in the area of chemotherapy economic evaluation in relation to model structure and inputs relating to the incidence, costs and consequences of chemotherapy. The implications of the results for decision-makers, modellers, clinicians and patients are considered as well as the opportunities for future research in this area.

This thesis explores the incidence, costs and consequences of chemotherapy adverse events, and the ways in which they are modelled for cost-effectiveness analyses. This chapter has provided background to the primary topic areas, such as cancer, chemotherapy and economic evaluation. In addition, the available data sources and the aims and objectives of the research were described. These concepts will be extended in Chapter 2, which presents a review of methods to address adverse events in existing models of chemotherapy cost-effectiveness.

Chapter 2: Costs and consequences of adverse events in a systematic review of the literature

Chapter summary

Cost-effectiveness analysis is an important tool for government policymakers when determining which new treatments will be subsidised. This is particularly so in the case of expensive treatments, such as many new chemotherapy drugs. However, in order for cost-effectiveness analysis to be useful, it must be based on accurate information and include all of the relevant costs and consequences of treatment.

This chapter explores the inclusion of the costs and consequences of chemotherapy adverse events in models of chemotherapy cost-effectiveness. It focuses on the ways in which existing studies have modelled the adverse events of chemotherapy. The key elements of chemotherapy adverse events that need to be considered in cost-effectiveness analyses and how these are addressed in existing studies are explored. In particular, the selection of adverse events for modelling, the influence of dose modifications on cost and survival, the effect of adverse events on quality of life, and the ways in which multiple adverse events are dealt with are discussed. The way in which these issues are currently modelled is examined through a systematic review of the literature.

This chapter argues that there are specific aspects of chemotherapy adverse events that are important for decision-making, in both a clinical and policy setting. In many existing models of chemotherapy cost-effectiveness, these aspects are not considered adequately, and this may lead to bias in the model outcomes. It is proposed that a methodology is needed for these aspects of adverse events to be incorporated into models of chemotherapy cost-effectiveness.

2.1 Background

Economic evaluation is increasingly being used to provide information to decision-makers in the healthcare system about the relative value of alternative treatment strategies (16). Although such evaluations can be conducted as part of a

clinical trial, economic modelling is often used to estimate costs and benefits in the longer term and to take into account different endpoints and comparators (46).

Economic evaluation requires consideration of both the costs (resources used) and net benefits (health outcomes) of a treatment, with data used to populate these costs and benefits in the model referred to as *inputs*. Typically, chemotherapy includes three broad cost components: purchasing the chemotherapy products, time and resources involved in administering chemotherapy, and resources required to manage adverse events. On the outcomes side, disease outcomes, such as cancer progression and survival, are commonly measured, with quality-of-life measurement required for cost-utility analyses. Inputs to economic evaluations for chemotherapy outcomes are often readily available through clinical trials, while product purchase costs can be obtained from pricing lists. Less information is available for estimating the costs of administration (64) and adverse events related to chemotherapy (65).

Incorporating adverse events in models of chemotherapy is important, because these events can influence both sides of the economic evaluation equation. Many economic evaluations of chemotherapy are conducted for the purpose of reimbursement. In this case, not only are the impact of model structure and inputs important but awareness of the cost-effectiveness threshold also becomes an issue. Equal treatment of both arms is critical, and all relevant costs and consequences need to be accounted for so that total costs can be considered.

As the use of economic evaluation by decision-makers has increased in recent years, the number of cost-effectiveness analyses of chemotherapy has also grown. These analyses provide a rich source of information about the way chemotherapy adverse events have been considered and included in chemotherapy cost-effectiveness analyses.

The objective of the review was to examine the literature of cost effectiveness analyses of chemotherapy to identify how the costs and consequences of adverse events are considered.

2.1.1 Modelling chemotherapy adverse events

The clinical literature of chemotherapy adverse events is extensive, and raises questions of how adverse events are treated, and the implications of adverse events for patient outcomes and quality of life. However, the way these clinical issues are incorporated into economic evaluations is unclear. This is despite there being potential for these issues to influence either the costs, benefits or both of chemotherapy.

The clinical issues which may influence the outcomes of economic evaluation are the selection of adverse events for inclusion in models of chemotherapy cost-effectiveness, the influence of adverse events on the dose of chemotherapy, the impact of adverse events on patient quality of life, and the impact of multiple adverse events. Each of these is discussed in more detail below.

The selection of adverse events for inclusion in models

The inclusion of adverse events in models of chemotherapy is important as these events can influence costs and consequences. Many economic evaluations of chemotherapy are conducted for the purpose of reimbursement (66). In this case, not only is the impact on model structure and inputs important but also awareness of any defined cost-effectiveness threshold. The equal treatment of both arms is critical to ensure comparable estimates, and all relevant costs and consequences need to be accounted for so that total costs can be considered. It is commonly the case that only high grade adverse events are considered in models. This is based on the assumption that more-serious events have higher resource utilisation associated with them. Although this is an assumption used in much of the literature, there may be a number of reasons why this may not be the case in clinical practice. For example, low-grade events which occur in a high proportion of individuals may be associated with high overall resource utilisation.

The influence of adverse events on dose of chemotherapy

The experience of an adverse event can change the way a patient receives further chemotherapy treatment, as well as having impacts on costs and outcomes. In many cases, when a patient experiences an adverse event, their chemotherapy

dose is either delayed or reduced until they have recovered from the adverse event (39). The chemotherapy may then continue at the reduced dose to lessen the chance of the adverse event re-occurring (39). This influences the amount of chemotherapy the patient receives (67), and therefore the amount of chemotherapy product purchased.

The amount of chemotherapy drug received by a patient can also affect the outcomes of their chemotherapy treatment. The relative dose intensity of chemotherapy is the ratio of the delivered chemotherapy to the planned chemotherapy dose over a specified period (68). There is evidence that patients who receive a relative dose intensity of less than 85 per cent have significantly reduced survival rates (67, 69-75). Retrospective studies have found that up to 55.5 per cent of people have a relative dose intensity less than 85 per cent due to dose adjustments in response to adverse events (76).

The impact of adverse events on quality of life

Adverse events differ between individuals. However, almost all patients on chemotherapy will experience at least one adverse event (77), with many patients reporting these events to be very distressing and their quality of life significantly affected by the experience of chemotherapy-related adverse events (32, 33, 78). It is therefore important to consider that there may be additional utility decrements associated with having an adverse event in addition to those already associated with having cancer and receiving chemotherapy.

The impact of multiple adverse events

The final consideration when including chemotherapy-related adverse events into economic evaluation models is that of multiple events. Patients may experience multiple adverse events in two ways: either the same event occurring multiple times over a course of chemotherapy, or as multiple different adverse events happening simultaneously. If a patient experiences the same event repeatedly, the management of the adverse event in terms of prevention, treatment and chemotherapy dose modifications may change, resulting in differences in costs and outcomes for the model (39). The occurrence of more than one adverse event

at the same time affects the management of the adverse event in terms of treatment, prevention and chemotherapy dose (39), and may also change the quality-of-life impact of an event.

Adverse events have the potential to have a significant impact on models of chemotherapy cost-effectiveness through not only the cost of managing the event itself but also its impact on the quantity of chemotherapy products used, patient quality of life and survival outcomes. It is therefore important that adverse events be taken into account when conducting economic evaluations of chemotherapy to ensure accurate estimates of cost-effectiveness are obtained.

2.2 Methods

The literature review was conducted with reference to the PRISMA statement for the reporting of systematic reviews. The completed PRISMA checklist for systematic reviews is presented in Appendix A.

2.2.1 Aims and objective

The objective of the review was to examine the methods used in the clinical and economic literature to model the costs and consequences of chemotherapy adverse events and identify options for modelling these in future local cost-effectiveness analyses.

The aim was to identify how existing models manage potentially problematic areas specific to chemotherapy adverse events. The review examined published economic evaluations that included a cost for adverse events of chemotherapy.

The primary areas of interest were model structure and inputs related to:

- the selection of adverse events for inclusion in models
- the influence of dose modifications
    - on chemotherapy product quantity
    - on survival outcomes
- the influence of adverse events on quality of life
- the influence of multiple adverse events

- the same event occurring multiple times during a course of chemotherapy
- multiple events occurring at the same point in time

- the influence of severity of an event on cost.

2.2.2 Literature search

Inclusion criteria

The research questions were broken down using the PICO criteria into the following components:

Population: Adults with solid tumour cancers
Intervention: Chemotherapy or systemic therapy resulting in an adverse event
Comparison: Not specified as treatment is not search focus
Outcome: Cost of treatment measured as monetary units or resources

Non-solid tumours were excluded as they have very different treatment approaches and therefore different adverse-event profiles. Similarly, cancers and their management in children differ from in the adult population; therefore, to maximise the comparability of studies reviewed it was decided to exclude paediatric cancers. For the purpose of the review, no specific definition of the term *adult* was used; the definition used by each individual study was used to determine eligibility.

An *adverse event* was defined as an event related to the systemic therapy being undertaken; therefore, adverse events related to the cancer itself were not included in the review. The management of adverse events was not limited to treatment, but also included measures to prevent adverse events occurring, as well as monitoring implemented for early detection.

Cost was broadly defined to include resources with a dollar value, such as the cost to purchase a drug or to pay a salary, or non-financial costs such as unpaid time. The usage of dollar figures (including for non-financial costs, which can still have a dollar value attached to them) as well as resource-use measures such as hours, bed days and so forth were acceptable. Studies had to provide a method for

obtaining the cost of the adverse event; those papers which used an unreferenced or unexplained cost were excluded. The search did not limit the perspective of the studies.

Search strategy

A systematic literature search was conducted in August and September 2009 to identify relevant papers addressing the inclusion criteria. The search was conducted in the following electronic databases:

- Medline
- EMBASE
- PubMed
- EBM Reviews
- CINAHL
- Cochrane Library
- Business Source Premier
- Academic Search Premier
- Cancer Lit Bibliographic database
- EconLit
- National Health Service Economic Evaluation Database (NHS EED)

Searches combined key terms that described the PICO criteria for all research questions. The searches were limited to studies conducted in humans that were published in the English language from January 1999 to September 2009. The search strategies for Medline, NHS EED and York HTA are presented in Appendix B.

In addition to the above databases, government agency websites were searched for relevant information. The search term 'cancer' was used in the search function within each website. The websites were:

- NICE, AHRQ, ASCO, NHMRC and York HTA
- TUFTS CEA Registry (79)

The reference lists of included papers were hand-searched. Conference abstracts were not included as the information within them was too limited for the purposes of this review.

Exclusion criteria

Papers were excluded if they met any of the following exclusion criteria:

- not an original study, such as non-systematic reviews, editorials, letters and opinion pieces
- published in a language other than English
- published prior to 1999.

Studies prior to 1999 were excluded as it was felt that for many cancers, chemotherapy treatment and management of adverse events may have changed since then.

Review process

After removal of duplicates, the titles and abstracts of all citations were assessed by a single reviewer based on the eligibility and PICO criteria. For citations that either appeared to be eligible or that provided insufficient information to assess eligibility, the full text was retrieved for further assessment. For studies where eligibility was unclear, a second opinion was sought.

Data extraction

Data extraction of the characteristics, methodology and outcomes of each eligible study was conducted by one reviewer using the NHS EED annotated abstract form (see Appendix C). For the primary areas of interest, information was extracted on how adverse events were identified for inclusion in the model, whether or not dose modifications were considered, whether the quality of life impact of adverse events were included, and whether multiple adverse events were considered.

To aid comparison of study results, the reported cost for each adverse event was converted to 1999 International dollars, using country of study origin purchasing power parity (80).

Data analysis

For studies where adverse event costs were specified for different grades of the event (for example, mild and moderate compared to severe and life threatening events), linear regression was used to determine if increasing severity of an event is associated with increasing cost. Cost (in 1999 International dollars) was regressed against categorical variables for the study, event grade and the resources used in the study.

Papers which presented adverse event at four grade levels were also used to assess the increase of cost with grades, by calculating cost of each AE grade as a proportion of the grade IV cost for that event. This allowed assessment of the hypothesis that increasing grade would lead to increasing cost.

Quality assessment

Quality assessment using a structured methodology to assess study quality and applicability is an important part of the systematic review process (81). A number of checklists for the quality assessment of economic evaluations in systematic reviews have been developed (44, 49, 82-84).

The Graves checklist, which was selected for use in this review, covers four aspects of study quality (see Appendix D) (49, 85). Although there are a number of such critical appraisal tools available (44, 83), Graves was selected as suitable for the types of economic evaluations anticipated in the review, flexible enough to be applicable to the range of economic evaluation methodologies expected, and easy to complete. The Graves checklist consists of four categories. Category 1 queries general costing issues, such as the perspective used, and uses these questions to assess transparency (49, 85). Category 2 examines the methods used to determine the quantities of resources used and is looking for high-quality studies that include a complete allocation of resources in the costing analysis (49, 85). Category 3 examines the methods used to determine the value of resources consumed, such as how prices are estimated and the use of third-party costs (49, 85). Finally, in Category 4 the reporting of data is considered, with issues such as the use of a common base year and the use of discounting examined (49, 85).

The focus of the review was not on evaluating the quality of research methodology for research studies. However, it is important to note that flaws in clinical research methodology may lead to inaccuracies in economic assessments and results. In order to compare the strength of the evidence base of each study, the Graves checklist was used to generate a quality score, with one point awarded for each criteria fulfilled. The maximum possible score was therefore twelve, and the minimum zero. Although this is not a validated scoring system, it allows a simplistic summary of study quality which can then be explored further through examination of specific study methods.

2.3 Results

Twenty-six studies were eligible for inclusion in the literature review, from 4985 citations and 479 full text articles reviewed, as seen in Figure 2.1. The characteristics of the included studies are summarised in Table 2.1.

The papers were either designed to determine the costs and effectiveness of antineoplastic therapy (n=16) or the costs of a specific treatment for an adverse event (n=10). The aims of these types of studies results in different methodologies and complexities. However, as both provide different an important approaches to answering the questions relevant to this review, it was decided to include both study types, but to consider them separately.

Generally, studies were of moderate quality. They had a mean Graves score of seven and a range of three to nine. Figure 2.2 displays a summary of the proportion of studies that fulfilled each of the 12 Graves criteria, illustrating the areas commonly done well. Six studies included multiple cancer types; the remainder focused on a specific cancer, the most common being breast cancer (12 studies). More than half of the studies were based in the United States (US), with no studies from Asia or the Pacific Region. Studies from the UK were considered separately to those from Europe, due to the UK's unique health care system. For full details of all included studies, see Appendix E.

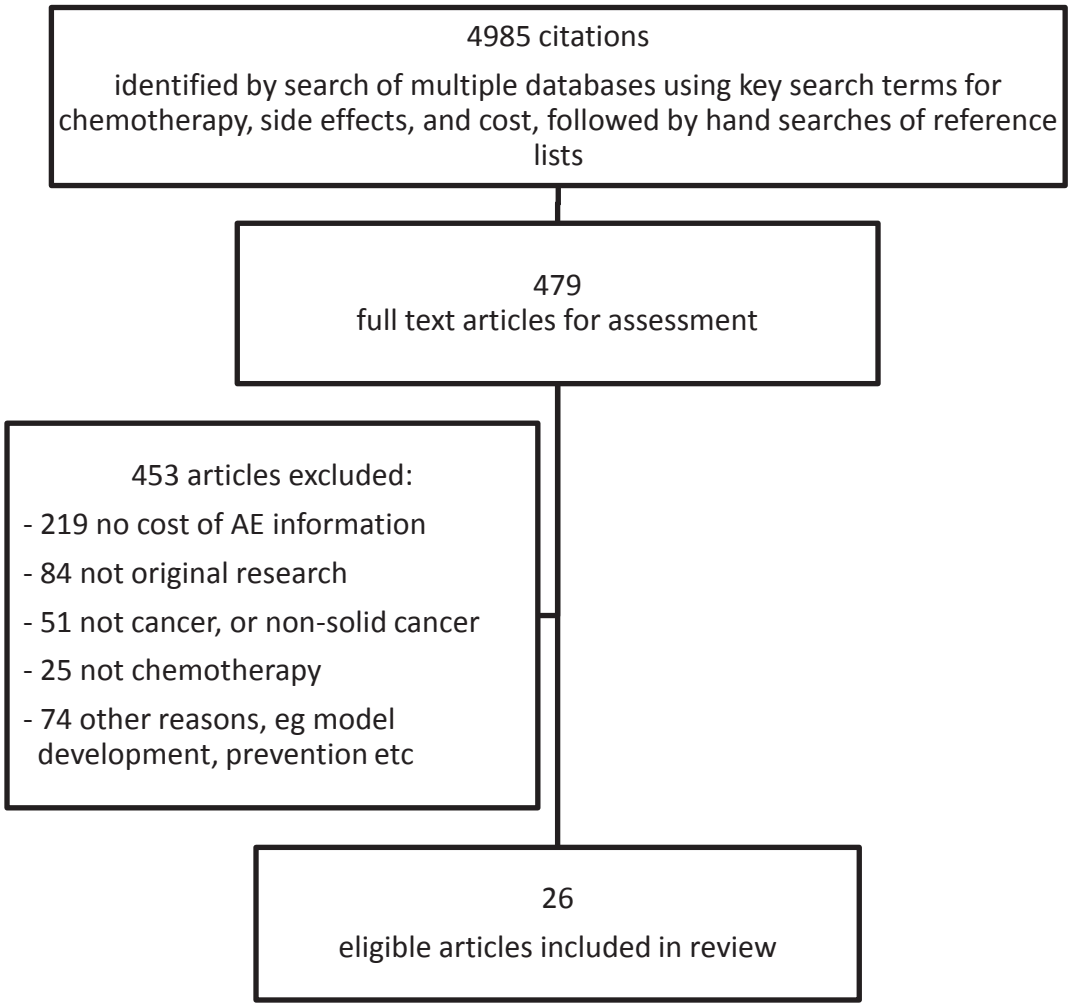
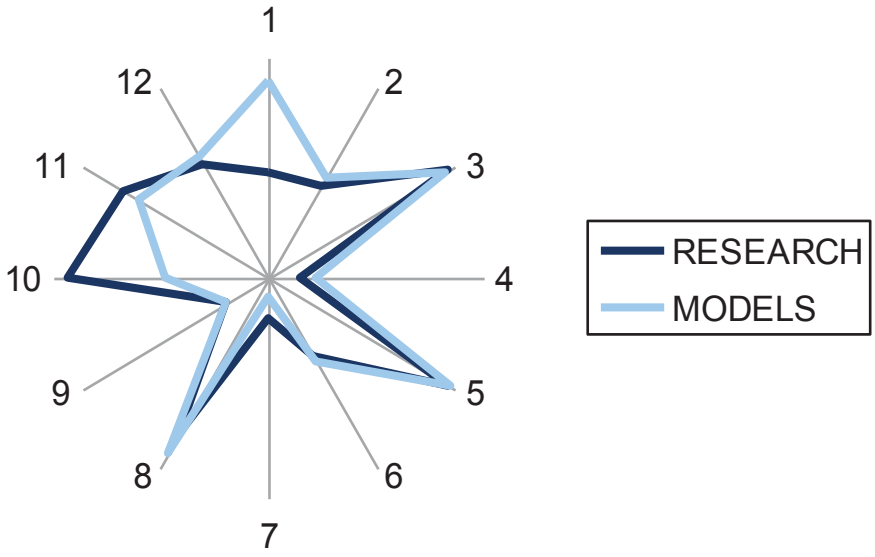


Figure 2.1: Flowchart of study inclusion

Table 2.1: Characteristics of included studies

	Studies of chemotherapy costs and effectiveness (n = 16)	Studies of adverse-event treatments (n=10)	Total (n=26)
Cancers			
Breast	10	2	12
Any	0	6	6
Colorectal	2	0	2
Ovarian	2	1	3
Lung	1	1	2
Head and neck	1	0	1
Cancer stage			
Any stage / stage not specified	0	7	7
Locally advanced / metastatic	9	1	10
Early	7	2	9
Country			
Europe (not UK)	5	4	9
US	8	6	14
UK	2	0	2
Canada	1	0	1
Asia	0	0	0
Industry involvement			
Yes: funded or authorship	11	8	19
No, or none specified	5	2	7



Note 1: Axis of the star graph represents one question of the Graves criteria, with increasing distance from the centre representing a greater proportion of studies which address that criteria.

Note 2: Questions 1 -4: General costing issues, Questions 5 – 7: Methods to determine quantities of resources, Questions 8-9: Methods to determine the value of resources consumed, Questions 10-12: Reporting of data

Figure 2.2: Proportion of studies addressing each Graves criteria

2.3.1 General model design

Table 2.2 shows the modelling methods used by the included studies. Eighty-five per cent of studies used a cost-effectiveness or cost-consequence analysis. The perspective taken was classified according to each study's stated methods. Based on the costs included in the models, the three studies with unspecified perspective appear to have used a societal perspective in two cases (86, 87) and a hospital perspective in the other (88). Chemotherapy studies primarily used Markov models, while decision trees were used in studies of the costs of treating adverse events. For most models the cost of adverse events was a simple input, and therefore adverse events were rarely included in sensitivity analyses.

Table 2.2: Modelling methods used by included studies

	Studies of chemotherapy costs and effectiveness	Studies of adverse event treatments	Total
n =	**16**	**10**	**26**
Economic analysis			
Cost effectiveness / consequence	11	11	22
Total cost	1	1	2
Cost minimisation	1	1	2
Cost utility	1	1	2
Cost of illness	0	0	0
Cost benefit	0	0	0
Cost effectiveness and cost utility	2	2	4
Perspective			
Health care system / hospital	6	7	13
Third party payer	4	0	4
Society	4	2	6
Not specified	2	1	3
Model			
Decision tree	2	7	9
Markov model	11	2	13
Other models	3	1	4
Costs included			
Direct	12	7	19
Indirect	0	0	0
Direct and indirect	4	3	7
Sensitivity analysis			
Univariate	15	8	23
Multivariate	6	2	8
Probabalistic	10	3	13

2.3.2 Reason for inclusion of adverse-events in the model

The 26 studies examined 21 types of adverse events. Eleven studies, mostly adverse-event treatment studies, considered a single adverse event. Of the remaining 15 studies, nine included between two and five adverse events and six

studies each looked at more than five. The highest number of adverse events costed in a single study was 15 (89).

Six did not specify on what basis the specific adverse events had been selected for inclusion in the models. Five studies cited as a reason the presence of a significant difference (based on various definitions) in incidence rates of the event between different treatment arms in the literature. Other reasons included a significant incidence in any treatment arm (usually at the one per cent or five per cent level), potential to impact on cost, or the potential to affect patient quality of life. Eleven studies included any grade of the event, five restricted inclusion to only Grade III/IV events (high-cost/low-volume events), and two additional studies considered only events resulting in hospitalisation.

2.3.3 Dose modifications

The impact of adverse events on the individual's dosage of chemotherapy was specifically included in five studies, all of which were chemotherapy evaluations with access to individual patient data regarding dose modifications during treatment. This allowed researchers to include in the models the actual dose received. An additional five chemotherapy evaluations indirectly included the impact of dose modifications on total dose received by using average dose given from clinical trials, which should have included patients who had dose reductions or delays. The remaining six chemotherapy evaluations and all of the adverse-event treatment studies assumed patients received 100 per cent of the planned dose, regardless of the experience of adverse events. In one study, this was justified as being a conservative estimate of chemotherapy cost (90).

Although early cessation of chemotherapy was sometimes considered in terms of amount of drug delivered, the impact of dose reduction and delays on survival were not. Two studies, both based on the same neutropoenia treatment model, included the scenario where improved adverse-event management resulted in a lower probability of receiving less than 85 per cent of relative dose intensity, with resulting long-term survival benefits (91, 92). In this model, the impact of relative dose intensity on long-term survival was modelled using a Markov process, in which the patient was followed until death (91, 92). Long-term survival was

modelled as a function of patient age, cancer stage and relative dose intensity (RDI) (91, 92). Inputs for the proportion of patients who received less than 85 per cent RDI, and the associated relative risk of death for those with an RDI < 85 per cent (compared with those with more than 85 per cent) were based on data in the literature (91, 92).

2.3.4 Adverse events and utilities

Utility estimates were included as an outcome measure in 18 of the 26 studies (six adverse-event treatment studies and 12 chemotherapy evaluations). Thirteen of these studies included a utility decrement associated with chemotherapy adverse events (six adverse-event treatment studies and seven chemotherapy evaluations). Some of these estimates included unique decrements for adverse events at different grades, or for requiring different treatment, such as hospitalisation instead of outpatient management.

Utility estimates for cancer and chemotherapy health states were usually obtained from previously published studies in the same or similar clinical areas. In contrast, a number of utilities for adverse-event health states were based on assumptions, rather than on empirical evidence (88, 93, 94). For example, Lidgren et al. simply reduced the utility value by 50 per cent for six months in those experiencing symptomatic heart failure (93).

2.3.5 Multiple adverse events

While most models (n=14) allowed for people to experience the same event multiple times during the model time horizon, only two studies (both were adverse-event treatment evaluations) specifically considered multiple events over time. These studies, both based on the same febrile neutropoenia treatment model, added the cost of subsequent care for febrile neutropoenia to the cost of initial hospitalisation. This was based on the assumption that having experienced one episode of febrile neutropoenia, an individual is at increased risk of developing febrile neutropoenia in the future (91, 92).

There were two models that allowed multiple events to occur at the same time; one was a chemotherapy evaluation and the other was an adverse-event treatment

evaluation. Touchette modelled febrile neutropoenia, anaemia and thrombocytopenia, and allowed for any combination of the three to be experienced in each cycle of the Markov model (95). The costs and incidences of adverse events associated with chemotherapy were averaged using a simple decision tree prior to being entered into the model (95). However, the incidence and cost of each adverse event do not appear to differ based on the combination of events experienced.

Delea et al. created a model in which health states were characterised by all combinations of adverse events (90). The model included endometrial cancer, venous thromboembolism, myocardial infarction, unstable angina, heart failure, hip fracture, other fractures, arthralgia and hypercholesterolemia (90). Again, although the model allowed multiple adverse events to be experienced within a cycle, a simple additive model was used and, as such, the incidence and cost of each adverse event did not appear to change with the experience of multiple events.

2.3.6 How type and severity affect cost

In order to assess the effects of adverse-event type and adverse-event severity on the cost of an adverse event, those studies that provided a comparable outcome measure with cost-utility analysis were extracted. Table 2.3 lists the three studies that provided this information, two modelling papers and one research paper.

Although it is logical for there to be differences between the costs per QALY of different adverse events, there are too few studies to determine whether this difference is consistent or due to study methodology, treatments and resources included, or chance. It is assumed that the treatment under observation can have a significant effect on the cost obtained, and many of the studies in this review were designed to test new and innovative treatments, potentially biasing the cost results towards higher estimates.

Table 2.3: Studies reporting cost per QALY

Ref.	Cancer Type	Adverse event	Grade	Adverse-event treatment (resources)	Cost	Currency	International$ (1999)	Units
Borg 2008 **(94)**	Any	Anaemia	Any	RBCs +/– erythropoietin; medication, hospitalisation	24,700	Euro	2,702	per QALY
					870	Euro	95	Increase in total costs
					0.0353	QALYs		*Gain in QALY
Martin 2003 **(96)**	Breast	Anaemia	NS	Epoetin alpha vs. placebo; diagnostic tests, radiotherapy, drug therapy, surgical procedures, inpt & outpt services, palliative care, monitoring, transfusions	6,741	Pounds	10,585	Cost-effectiveness ratio per life year
					8,851	Pounds	13,899	Cost-utility ratio per QALY
Lordic 2007 **(97)**	Any solid	Chemotherapy -induced nausea and vomiting	Any	5HT3 receptor antagonist & dexamethasone +/– aprepitant	73.38	Euros	82	ICER drug cost per patient per cycle
				5HT3 receptor antagonist& dexamethasone +/– aprepitant	28,891	Euros	32,248	Cost/ QALY

Note: ICER = incremental cost-effectiveness ratio; inpt = inpatient; NS = not specified; outpt = outpatient; RBCs = red blood cells; Ref. = reference

In most studies it was assumed that higher grades of an adverse event would increase the cost of management, primarily due to the inclusion of hospitalisation costs. Two studies (98, 99) provided costs of adverse events at each of four levels, and these are presented in Table 2.4. An additional three studies (100-102) provided adverse-event costs at two levels (see Table 2.5).

In general, the results from the five studies above indicate that an increase in grade level led to a corresponding increase in cost, as seen in Figure 2.3. Overall, the mean Grade 3 costs were 46% of the mean Grade IV costs. Grade I or mild adverse events were generally allocated zero or minimal cost, and the variation in cost increased as the grade of the event increased. However, there were some exceptions; in one study, the cost associated with moderate anaemia was higher than for severe or life-threatening anaemia (98) due to the use of epoetin at the moderate level being replaced by blood transfusions at the more-severe levels. On one occasion, thrombocytopenia had no associated cost until it reached Grade IV (99). One study had the same associated cost for sepsis Grades II to IV and no associated cost for sepsis Grade I (98).

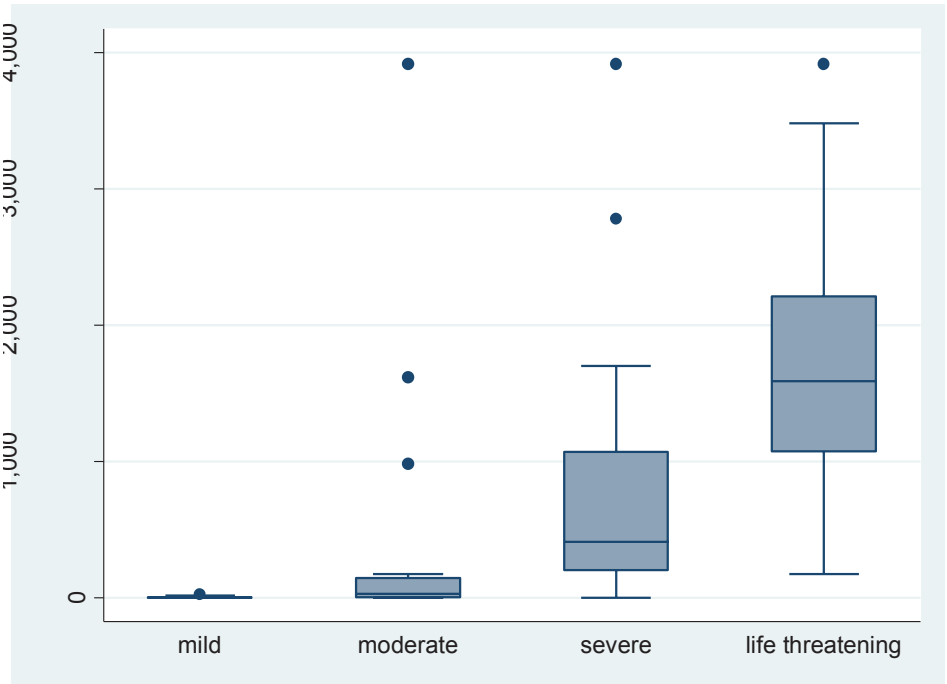


Figure 2.3: Adverse-event costs (in 1999 International $) by grade of adverse event (classified as mild, moderate, severe or life threatening)

Table 2.4: Two studies in literature review reporting adverse events at four grade levels

Ref.	Adverse event	Grade	Adverse-event treatment (resources)	International$ (1999)	Percentage change	Percentage of Grade IV cost	Units
Ojeda 2003 **(98)**	Anaemia	Mild	NS	0		0	Management of each adverse event
		Moderate	NS	983	N/A	134	
		Severe	NS	490	–50	67	
		Life-threatening	NS	734	50	100	
Capri 2003 **(99)**	Anaemia	Grade I	Outpt visit, lab. tests, ambulatory care visits, hospitalisation days, medications	25		1	Mean per patient
		Grade II		1620	6424	47	
		Grade III		2781	72	80	
		Grade IV		3481	25	100	
Ojeda 2003 **(98)**	Neutropoenia	Mild	NS	0		0	Management of each adverse event
		Moderate	NS	1	N/A	0	
		Severe	NS	202	37308	37	
		Life-threatening	NS	554	174	100	
Ojeda 2003 **(98)**	Nausea / Vomiting	Mild	NS	0		0	Management of each adverse event
		Moderate	NS	1	2050	0	
		Severe	NS	482	82833	32	
		Life-threatening	NS	1513	214	100	
Capri 2003 **(99)**	Nausea / Vomiting	Grade I	Outpt visit, lab. tests, ambulatory care visits, hospitalisation days, medications	12		1	Mean per patient
		Grade II		84	610	7	
		Grade III		96	14	8	
		Grade IV		1184	1136	100	

Ref.	Adverse event	Grade	Adverse-event treatment (resources)	International$ (1999)	Percentage change	Percentage of Grade IV cost	Units
Ojeda 2003 **(98)**	Diarrhoea	Mild	NS	0		0	Management of each adverse event
		Moderate	NS	69	N/A	5	
		Severe	NS	655	846	46	
		Life-threatening	NS	1438	120	100	
Capri 2003 **(99)**	Diarrhoea	Grade I	Outpt visit, lab. tests, ambulatory care visits, hospitalisation days, medications	12		1	Mean per patient
		Grade II		26	120	2	
		Grade III		1089	4086	76	
		Grade IV		1442	32	100	
Ojeda 2003 **(98)**	Stomatitis /pharyngitis	Mild	NS	0		0	Management of each adverse event
		Moderate	NS	145	N/A	8	
		Severe	NS	979	578	54	
		Life-threatening	NS	1799	84	100	
Capri 2003 **(99)**	Stomatitis	Grade I	Outpt visit, lab. tests, ambulatory care visits, hospitalisation days, medications	17		1	Mean per patient
		Grade II		32	100	2	
		Grade III		1074	3143	66	
		Grade IV		1638	53	100	
Ojeda 2003 **(98)**	Thrombocytopenia	Mild	NS	0		0	Management of each adverse event
		Moderate	NS	18	N/A	6	
		Severe	NS	262	449	34	
		Life-threatening	NS	766	192	100	

Ref.	Adverse event	Grade	Adverse-event treatment (resources)	International$ (1999)	Percentage change	Percentage of Grade IV cost	Units
Capri 2003 **(99)**	Thrombocytopenia	Grade I	Outpt visit, lab. tests, ambulatory care visits, hospitalisation days, medications	0		0	Mean per patient
		Grade II		0	N/A	0	
		Grade III		0	N/A	0	
		Grade IV		2212	N/A	100	
Ojeda 2003 **(98)**	Sepsis	Mild	NS	0		0	Management of each adverse event
		Moderate	NS	3917	N/A	100	
		Severe	NS	3917	0	100	
		Life-threatening	NS	3917	0	100	
	Fever	Mild	NS	0		0	Management of each adverse event
		Moderate	NS	178	N/A	17	
		Severe	NS	192	8	18	
		Life-threatening	NS	1078	461	100	
Capri 2003 **(99)**	Fever	Grade I	Outpt visit, lab. tests, ambulatory care visits, hospitalisation days, medications	4		0	Mean per patient
		Grade II		6	67	0	
		Grade III		1461	24600	92	
		Grade IV		1589	9	100	
	Sepsis	Grade I		0		0	Mean per patient
		Grade II		27	N/A	2	
		Grade III		1703	6161	99	
		Grade IV		1714	1	100	

Note: lab. = laboratory; N/A = not appropriate; NS = not specified; outpt = outpatient

Table 2.5: Studies in literature review with two grades of adverse event

Reference	Adverse event	Grade	Adverse-event treatment (resources)	International$ (1999)	Percentage change	Percentage of Grade IV cost	Units
Annemans 1999 **(103)**	Anaemia	Moderate	Clinician discretion; medications, tests, interventions, consultations	73			Cost of one episode
		Severe		345	373		
		Moderate		89			
		Severe		300	237		
		Moderate		33			
		Severe		561	1600		
Main 2006 **(100)**	Neutropoenia	Grade III	Outpt visit, ciprofloxacin	81		4	Value (assumed)
		Grade IV	Inpt stay, ciprofloxacin, G-CSF	2246	2684	100	
Main 2006 **(100)**	Stomatitis / pharyngitis	Grade III	Outpt visit, paracetamol mouthwash, sucralfate, Oramorph®	228		7	Value (assumed)
		Grade IV	Inpt stay, fluconazole, intravenous saline, paracetamol mouthwash, sucralfate, Oramorph	3186	1300	100	
Tampellini 2004 **(102)**	Mucositis	Grade III	Medications and hospitalisation	12		7	Per event
		Grade IV		176	1400	100	

Note: G-CSF = granulocyte colony-stimulating factor; Inpt = inpatient; iv = intravenous; outpt = outpatient

The five studies mentioned above, which include multiple grades of adverse events, can be examined further using simple regression analysis. A regression of cost (in 1999 international dollars) against categorical variables for the study and the event grade shows that increasing grade is significantly associated with increasing cost (P > F = < 0.001), with approximately 35 per cent of cost being attributed to grade (R-squared = 0.3536). Further regression of cost, study and grade with the resources included in the studies finds no significant effect (cost Prob > F = 0.5065, R-squared = 0.0719; grade Prob. > F = 0.3369, R-squared = 0.0918).

Figure 2.4 shows the proportion of Grade IV costs for each adverse event in the two studies that provided a cost for each of the four grades for each event. With the exception of outliers, there was a trend for costs to increase exponentially in line with increases in grades of severity of adverse events. When the two additional studies, providing two grades of severity of adverse event (including Grade IV), were included, the same pattern continued, although it did become more variable (data not shown).

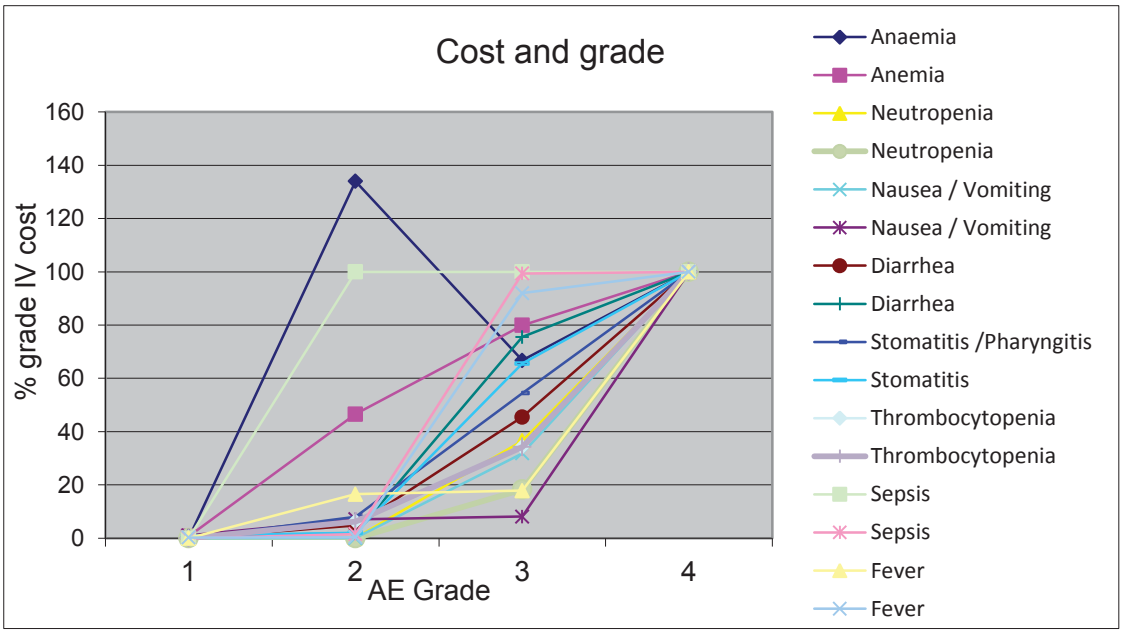


Figure 2.4: Percentage of Grade IV cost for each adverse event in Ojeda (98) and Capri studies (99)

Figure 2.5 shows the proportion of total cost contributed by each type of adverse event in the two studies that provided a cost for each of the four grades of each adverse event. The figure illustrates that the contribution of each event is not consistent between the two studies; this could be due to the different treatments and/or resources considered by the studies.

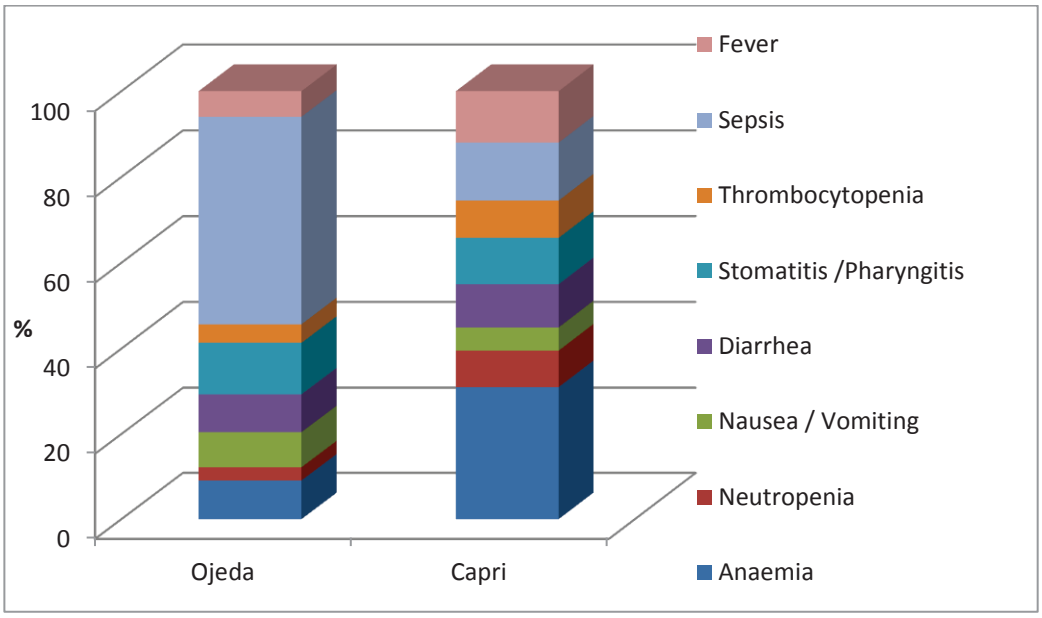


Figure 2.5: The contribution of each adverse-event type to the total cost of adverse events in the Ojeda (98) and Capri studies (99)

It should be noted that the outcome measures used differ between the studies, for example, cost per event and cost per person. For this reason, the costs themselves are not comparable; however, the following analysis is based on the relationships and proportions between costs, rather than on the figures themselves.

2.3.7 Number of concepts of interest included

The concepts of interest were how adverse events were included for selection in the models, the influence of dose modifications on drug quantitiy and survival outcomes, the influence of adverse events on quality of life and the consideration of multiple simultaneous or recurring adverse events. No study reviewed included in their model all of the concepts of interest. Three studies included none of the

concepts of interest in their models. Most commonly included were the potential for an individual to experience the same event multiple times during the time horizon and the impact of adverse events on patient quality of life.

The two studies that included the most concepts of interest were those by Danova (92) and Lui (91). These two studies used the same model for management of neutropoenia using granulocyte colony-stimulating factors (G-CSFs) in women with breast cancer (91, 92). The model includes the impact of dose modifications on survival, the impact of neutropoenia and its treatment on quality of life, and the potential for one episode of neutropoenia to increase risk of future, multiple episodes of neutropoenia (91, 92). As this was a model of neutropoenia management, the cost of chemotherapy was assumed the same in both arms (91, 92). This means that the influence of dose modifications on total dose of chemotherapy purchase was not accounted for and may bias the results. However, this model demonstrates that many of the important components of chemotherapy-related adverse events can be incorporated into a cost-effectiveness model.

2.4 Discussion

This review of the literature identified two types of economic studies that considered the costs of chemotherapy-related adverse events: 1) cost-effectiveness analyses of alternative chemotherapy treatments and 2) assessments of the costs or cost-effectiveness of treatments for chemotherapy-related adverse events. Although there was variation across the studies in terms of methods used, a number of elements were consistent. Most studies were cost-effectiveness analyses undertaken from the perspective of a healthcare system or hospital, with only direct costs included. Selection of adverse events for inclusion in models was based on incidence, cost or impact on quality of life.

The research question appears to be the primary determinant of model structure (Markov model or decision tree) and this makes it difficult to determine if there are systematic differences between the results of the two types of models. The consistency seen in the model structure selected for research questions of similar nature suggests that there are aspects of the research question which guide modellers to a particular type of model. In the case of chemotherapy cost

effectiveness studies, the complexity of cancer treatments and the need to include time dependent events may guide modellers towards Markov models. In contrast, studies of the costs associated with treating adverse events tend to be simpler, and have a relatively short time horizon, indicating the appropriateness of decision tree analysis. There does not appear to be any systematic difference in the magnitude of costs associated with adverse events, or the way adverse events are considered within the different model structures.

A high proportion of the studies included in the review were studies of breast cancer. This may reflect both a high incidence of this cancer generally as well as a number of advances in systemic treatments for breast cancer over the last ten years, many of which would have required economic evaluation for registration.

The review identified a striking variability in the units of measurement used for adverse events in cost effectiveness analyses of chemotherapy. Cost per adverse event was common, as was cost per person, cost per cycle, and cost per month. This variation makes comparison across studies difficult and influences the interpretation of model outcomes.

2.4.1 Previous research on modelling chemotherapy adverse events

Although there are generic guidelines for the development of economic evaluation models (104), these do not consider cancer-specific issues (65). A review of methods used for cost-effectiveness analysis of cancer treatments found common problems in the areas of defining the decision problem; choosing the health outcomes; modelling effectiveness of different types of treatment; modelling quality of life; modelling resource-use, including for adverse events; and discounting and assessing uncertainty (65). However, there are no published reviews of the modelling techniques used specifically for evaluating the costs and consequences of adverse events associated with chemotherapy.

A Health Technology Assessment by the National Health Service (NHS) Health Technology Assessment Programme reviewed economic evidence from four studies of topotecan, doxorubicin and paclitaxel for ovarian cancer (100). The four eligible studies included in the review used similar clinical evidence in their

estimates of chemotherapy effectiveness, supplemented with estimates of resource-use and costs from sources such as expert opinion, patient questionnaires and practice audits (100). The review concluded that different model assumptions about adverse-event management had the potential to overestimate costs through the inclusion of specialised treatment of high-volume / low-cost events, and to underestimate chemotherapy adverse event incidence and costs through the assumptions regarding multiple hospital admissions per cycle (100).

An economic evaluation of erythropoietin agents for the treatment of chemotherapy-related anaemia provided estimates of the cost of anaemia when treated using a specified clinical pathway, modelled in a variety of ways and by a range of researchers (105). The different models produced marked variations in results, ranging between £190,000 and £9,000 per quality adjusted life year (QALY) gained (105). This variation in results highlights the influence that model design and assumptions can have on the outcomes of economic evaluation.

Finally, a number of cost-of-illness studies have examined the costs associated with chemotherapy-induced neutropoenia, diarrhoea, anaemia and infusion reactions. Many of these used methods such as retrospective surveys or cohort record reviews to build a bottom-up estimate of the costs of specific adverse events (106-112). Some studies have used the information available from hospital and health-insurance databases to determine the additional cost of healthcare attributable to treating a specific adverse event (113, 114). Again, these different modelling approaches and variation in model inputs result in a significant variation in model outcomes. Adverse events related to chemotherapy are complex to manage and to model, and their consideration in economic evaluation is vital to ensuring accurate models are developed. The current modelling techniques have a number of limitations that restrict our understanding of the true impact of adverse events on chemotherapy cost-effectiveness. The results of this review suggest that many published models that include information regarding adverse events associated with chemotherapy underestimate the incidence, costs and flow-on effects of adverse events.

Adverse-event selection

The selection criteria used by studies in this review to identify which adverse events to include in models may lead to underestimating the base rate of adverse events. Although including only those events with different rates between arms may not have an impact on the incremental cost-effectiveness ratio for particular chemotherapy intervention alternatives, the overall cost of adverse events (and therefore the impact on the relevant budget) may be higher than that implied by the results. This influences whether the alternative interventions are considered cost-effective according to the nominated threshold level.

This also applies to adverse events that are considered low cost or low severity and may therefore be excluded from the analysis. Whereas a low incidence of these events may not influence cost-effectiveness, a high incidence may have a significant impact on overall costs. This pattern of high incidence of low-grade events can be seen in the new class of biological targeted chemotherapy agents, such as cetuximab for colorectal cancer. The pivotal study of cetuximab found 88 per cent of patients experienced a rash, including 76.8 per cent at the less-serious Grade I or II (35). The economic analysis of that study excluded any adverse events lower than a Grade III severity, because they were not thought to contribute significantly to resource-use (41).

A non-significant difference in incidence between treatment arms for a specific adverse event does not necessarily indicate that there is no difference in overall adverse-event profiles. It may be that a series of non-statistically significant differences in adverse events between arms results in a clinically important difference between treatment arms in terms of the overall toxicity profile. Exclusion of adverse events from modelling of chemotherapy on the basis of a non-significant difference between arms may result in underestimation of the impact of adverse events.

Dose modifications

While some studies did consider the effect that dose modifications would have on the total dose of chemotherapy received, many assumed all patients received 100

per cent of the recommended dose. In the context of a cost-effectiveness evaluation, this would result in an overestimation of the costs of chemotherapy, because some cost savings would be ignored. In the area of cancer treatments, where new chemotherapy drugs are increasingly expensive, the cost of purchasing the chemotherapy drugs may be a significant contributor to costs and therefore overall cost-effectiveness. Intravenous chemotherapy treatments may have the additional complexity of wastage; this is because once a vial has been opened it must often be used immediately or be discarded. When a patient is on a reduced dose, they may not receive the whole vial, but costs in the model will still need to reflect that the entire contents of the vial have been used.

Only two studies considered the impact of dose modifications on survival. With survival often being considered as the primary outcome of effectiveness in cost-effectiveness studies, changes to survival due to adverse events and dose reductions could affect the cost-effectiveness ratio, particularly if adverse events occur unevenly across treatment arms. As identified in this review, many economic evaluations of chemotherapy select adverse events for inclusion based on any significant difference in incidence between treatments.

It is interesting that although there is a body of literature examining the cost-effectiveness of treatments for neutropoenia in relation to the ability to maintain chemotherapy dose intensity (115), there appears to be little transfer of this information into models of chemotherapy cost-effectiveness, despite many of these models including neutropoenia and the costs of its management.

Adverse events and quality of life

The quality-of-life impacts of cancer and chemotherapy are generally well considered in cost-effectiveness studies of chemotherapy and new adverse-event treatments. It is less common for the additional utility decrements associated with adverse events to be included, although a number of studies did this. Part of the difficulty in including additional utility decrements (or improvements) associated with adverse events is how these should be added to those applicable to having cancer and chemotherapy. There are studies that have developed utility decrements for adverse events independent of treatment (116); however, in many

cases the decrement associated with chemotherapy may include a component related to adverse events. If this were the case, the addition of a decrement associated with an adverse event would lead to double counting. It is therefore important that the original source of utility scores for both chemotherapy and adverse events be understood before they are incorporated into an economic evaluation.

Multiple adverse events

The outcome measure selected for the inclusion of adverse events in models of chemotherapy may influence the ability to consider multiple adverse events in the model. For example, a cost per event may enable sequential episodes of the same event to be considered, while a cost per patient may not.

Given that the data inputs for adverse events are usually the results of clinical trials, which report adverse events separately and very rarely give patterns of multiple adverse events, it is not unusual for models of chemotherapy to include each adverse event as an independent event. However, this is not reflective of real life. Multiple simultaneous adverse events are complex to model. It is often unclear which adverse event has caused which resources to be used (such as hospitalisation) and which outcomes (such as reduced quality of life) and therefore their impact on cost-effectiveness is difficult to gauge.

Comorbidity has been identified as a priority research area, and there has been significant interest in developing quantitative methods to account for comorbidities when assessing health interventions (117). In studies of cancer, single-health states for various adverse events of treatment are common; however, the high prevalence of joint states, where more than one adverse event is present simultaneously, are increasingly recognised as important (118). Although direct elicitation of the utility of these joint states through techniques such as standard gamble and time trade-off are possible, the time, resources and respondent burden to collect utilities for more than a few joint states makes conducting these assessments impractical (118). Modelling approaches have therefore been investigated. The original additive approach to modelling combined utilities has

been identified as overly simplistic, but techniques such as multiplicative and minimum modelling are now being studied and used (117, 118).

Limitations of the review

As is possible with any literature review, there may be published economic models incorporating chemotherapy-related adverse events that were not identified by the search strategy. In addition, the decision to exclude papers in languages other than English and conference abstracts may have biased the types of models included. Given that many economic evaluations are conducted for the purpose of policy decision-making, it is also possible that there are economic evaluations of chemotherapy that have been developed but are not currently available in the economic literature. These evaluations may differ systematically from those identified in this review, which may have resulted in bias in the results.

For many of the economic evaluations identified, particularly those assessing chemotherapy cost-effectiveness, the adverse events of chemotherapy were not the primary aim of the analysis. Conducting an economic evaluation is a difficult and time-consuming task, the aim of which is to provide information to decision-makers. Despite the best efforts of model-builders, the results of analyses are not designed to represent real life but rather to provide information about the likely outcomes of a decision. This means that although there may be many aspects of the disease pathway, treatment choices and patient characteristics that may influence the outcomes of a decision, they may not all be incorporated. It may be that for some of the models included in this review, detailed modelling of adverse events was considered a lower priority than other areas of the treatment pathway.

2.4.2 **Conclusion**

This literature review systematically searched for all relevant articles that provided a model of costs and consequences of chemotherapy adverse events. Components were identified as being important to the rigorous modelling of chemotherapy adverse events: the selection of all relevant events; the impact of adverse events on chemotherapy dose, survival and quality of life; and the consideration of multiple adverse events. No models incorporated all of these components. Two models addressed all but one of the components, and these two

models provided an indication of how adverse events can be incorporated into chemotherapy economic evaluations in a rigorous way. Given that there were at least two examples of papers that considered all components when developing their model, it appears it is possible to build a model of chemotherapy cost-effectiveness that considers each of these adverse-event components.

The adverse events related to chemotherapy are complex, however their consideration in economic evaluation is vital to ensuring accurate models are developed. Current modelling techniques have a number of limitations, which restrict our understanding of the true impact of adverse events on chemotherapy cost-effectiveness, and it appears that many published models may underestimate the incidence, cost and flow-on effects of adverse events. Given that modelling adverse events with appropriate consideration of the inclusion and impact of both single and multiple adverse events appears feasible, future models of chemotherapy adverse events should be encouraged to consider these components.

This chapter examined how adverse events are included in models of chemotherapy cost-effectiveness. Of particular interest were the components considered particularly important to adverse events and the ways in which they are managed. These components include the selection of adverse events for inclusion in the models, the influence of dose modifications on cost and survival, the impact of adverse events on quality of life, and the impact of multiple adverse events. Through a systematic review of the literature, it was identified that many existing models of chemotherapy cost-effectiveness fail to consider many of these issues and, as a result, may provide biased or inaccurate results of the cost-effectiveness of chemotherapy.

This raises the need for the development of a rigorous methodology for the costing of chemotherapy adverse events to ensure that all necessary issues are addressed. A demonstration of the development of models that consider the important components of chemotherapy adverse events is described in Chapter 3.

Chapter 3: Costs and consequences of adverse events using decision analytic modelling

Chapter summary

This chapter demonstrates how the existing methods of modelling chemotherapy adverse events can be improved. New models were developed for four common chemotherapy adverse events: diarrhoea, nausea and vomiting, anaemia and neutropoenia. The focus was not only on providing standardised costs for specific adverse events but also on developing high-quality methods for obtaining those costs, which could then be used by others in building models of chemotherapy cost-effectiveness.

Costs and consequences can be assessed in a number of ways. For the purposes of this thesis, decision analytic modelling was used. In justification of this decision, an introduction to modelling in general and to decision analytic modelling in particular is provided. Four models were developed according to best-practice modelling guidelines, with the Briggs et al approach (46) employed to structure both the process of model-building and this chapter.

This thesis demonstrates that the specific aspects of chemotherapy adverse events that are important for decision-making can be incorporated into many models of chemotherapy cost-effectiveness. This thesis argues that these models represent a best-practice example of how the costs and consequences of chemotherapy should be modelled in the future. However, there is a need to recognise that there are potential downsides with using data from clinical trials to populate models of chemotherapy cost-effectiveness. This recognition leads to the research that draws on observational data to examine the incidence, costs and consequences of chemotherapy adverse events, as described in Chapter 4 and Chapter 5.

3.1 Background

3.1.1 Economic modelling

Decision modelling evaluates options using mathematical relationships to define the possible consequences of each option (46). By giving each consequence a cost, an outcome and a likelihood, the expected cost and outcome of each option under evaluation can be determined by summing the costs and outcomes weighted by the probability of that consequence (46).

Typically in economic evaluation, decision analytic modelling is applied when a specific decision between two or more options is to be made. However, this research applied the framework of decision analytic modelling to the development of general models, which could later be incorporated into more-traditional decision analyses. These models formed a theoretical and empirical structure to inform the parameter uncertainty associated with the cost of adverse events in economic models of chemotherapy.

There are two common methods for decision analytic modelling: decision trees and Markov models. Decision trees are a simple and common form of decision analysis (44, 46). An example is given in Figure 3.1, which shows a decision tree used in a decision analytic model built by Carlson et al. to compare three chemotherapy treatments for lung cancer (119).

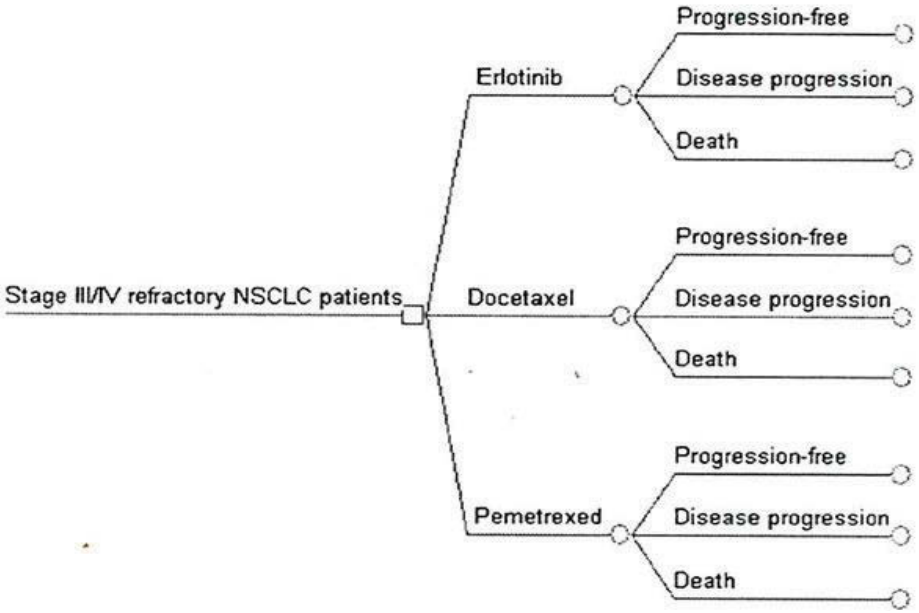


Figure 3.1: Sample decision tree showing pathway through decision node and chance nodes for the treatment of lung cancer (119)

Decision trees show a range of possible patient pathways through various treatment decisions and alternative events (46). Typically, a decision tree starts with a *decision node* (46). In Figure 3.1, the decision node is the choice of one of three chemotherapy treatments for lung cancer: erlotinib, docetaxel or pemetrexed. The effects of each decision are then represented as a series of pathways leading from the decision node (46). These each lead to a chance node, which represents a probabilistic outcome in the pathway (46). In the case of the example shown in Figure 3.1, these outcomes include the patient remaining progression-free, the cancer progressing, or the patient dying. Each pathway is mutually exclusive and exhaustive (46). Each branch extending from a chance node is given a probability of that event occurring, as well as a cost. These are then used to calculate an expected cost for each treatment and to form the basis of a cost-effectiveness analysis (46).

Although relatively easy to conceptualise, decision trees are limited in that they can become highly complex when modelling long-term diseases or conditions that have many possible treatments or outcomes. In addition, decision trees do not contain an explicit time variable. This can make the modelling of time-dependent variables, such as the changing survival rate over time, difficult.

An alternative that overcomes these limitations is a Markov model, which assumes that individuals are in one of a set number of predefined health states (46). Each of these health states can be allocated a utility score and, in cost-effectiveness analysis, a cost. Individuals move through the health states once per cycle (a predetermined length of time), resulting in an incremental utility and, in cost-effectiveness ratios, an incremental cost (46). An example of a Markov model for adjuvant breast cancer treatment developed by Lundkvist et al. (87) is displayed in Figure 3.2. Markov models are particularly useful when clinical events can be repeated or when the timing is uncertain. These situations are difficult to represent in a decision tree but are easily incorporated into a Markov model (46). However, Markov models are unable to account for anything that occurred in earlier cycles—these models have no memory for previous cycles (46).

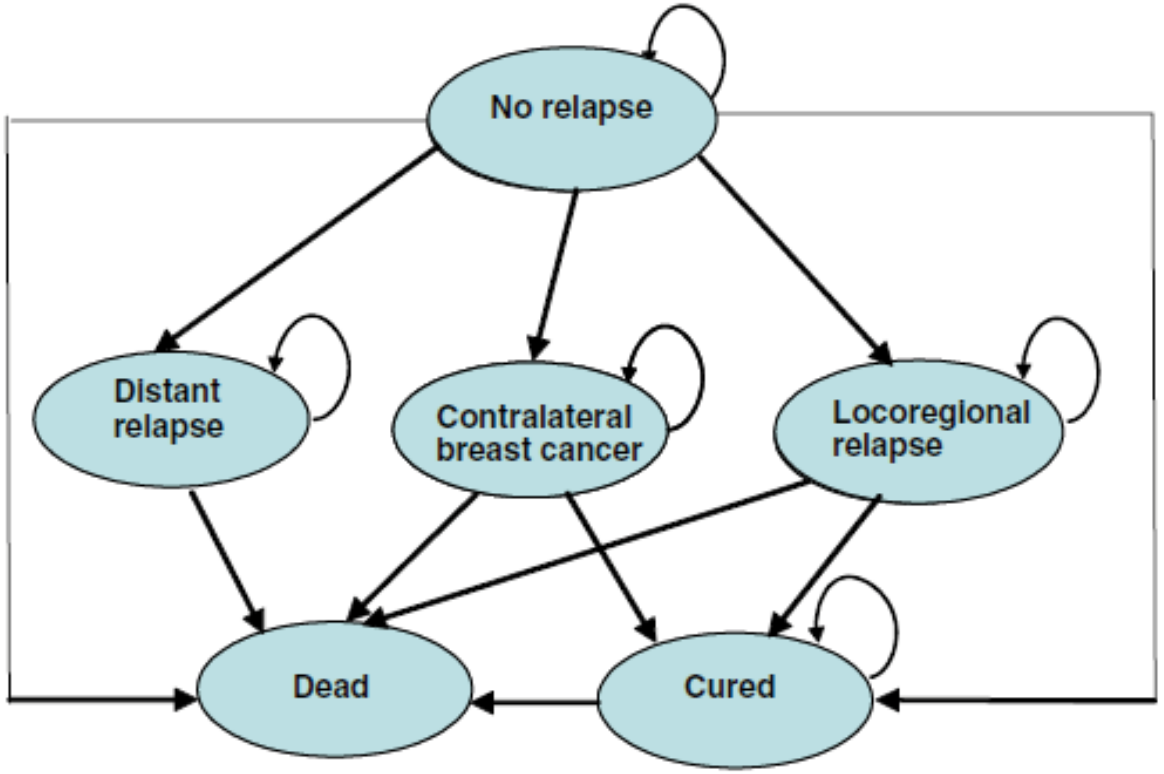


Figure 3.2: Example of a Markov model for adjuvant breast cancer treatment (87)

It is possible to combine the two types of models: a decision tree to determine short-term outcomes and a Markov model to calculate long-term costs and outcomes (46). This allows long-term modelling with time-dependent variables and accounts for conditional probabilities based on the events experienced in the decision tree (46). An alternative to these cohort models are micro-simulation models. By tracking individual patients through the different states over time, these models offer a level of flexibility not offered by cohort models by allowing the future prognosis of a patient to vary according to their history (46). They also have advantages in being more easily able to model multiple subgroups, account for the distribution of outcomes (rather than simply using the mean) and don't have the danger of the number of health states becoming unfeasible (120). However, it is not always possible to take advantage of this extra flexibility because the data required to adjust the prognosis based on history are often not possible at this level (46). These models are also computationally intensive to run (46).

The literature review presented in Chapter 2 identified that studies of treatments for adverse events predominantly used decision trees, while chemotherapy cost effectiveness analyses used Markov models. This is likely due to the differences in the clinical decision problems being addressed leading to alternative model structures being chosen. Treatments of adverse events tend to be short term in nature, with limited health states under consideration. This lends these types of decision problems to modelling with decision trees. In contrast, the models of chemotherapy cost effectiveness tended to use Markov models, perhaps because of the ability to follow patients long-term to assess survival, as well as the ability to model the complex movements between health states seen in the treatment of cancer. The modelling of adverse events for this research involves events that can occur multiple times and have uncertain timing, making decision trees the preferred option. In particular, for those events with a relatively short time horizon (such as the duration of chemotherapy treatment), a recursive tree model can be used to address the ongoing risk and unpredictable timing of changes in the grade of a particular adverse event. Decision trees also allow decisions about the

management of adverse events to take into account previous experiences and treatment of that adverse event.

The need to account for multiple adverse events and the potential role of adverse event treatment history means microsimulation models were also considered. The good research practice guidelines for state transition modelling, which includes microsimulation methods, suggests that the number of health states is key in determining the appropriate model type, and that model structure should be considered in terms of clear specification of the interventions being modelled, the starting cohort and the health states to be included (120). In this case, the number of health states is limited, and thus the loss of transparency, efficiency and ease of debugging associated with simulation methods is not warranted. In addition, consideration of the model structure suggests that while additional validity may be obtained from the use of microsimulation techniques, the data available to complete a microsimulation is unlikely to be available and thus the assumptions required to populate a microsimulation model may introduce additional bias, without changing the results of the simpler decision tree models.

In contrast to typical decision-tree models, the modelling of adverse events here did not start with a decision node. This is because the models were designed to form part of a larger project evaluating the overall costs of chemotherapy. Therefore, the models of adverse events are purely based on chance nodes, and can as such be added into models of chemotherapy cost-effectiveness that commence with a decision node regarding the initial choice of chemotherapy treatment undertaken. Alternatively, the models can also function as stand-alone models of the costs of chemotherapy adverse events at a given profile of adverse-event incidence rates. Thus, it would also be possible for model developers to choose to use the results from this research simply to include the average cost per adverse event into a model of chemotherapy cost-effectiveness rather than to choose to utilise the full model structure itself.

Each adverse event was therefore modelled with the initial chance node being the grade of the event, and the branches of the tree were based on the best-practice management techniques for that event. The costs associated with these treatments,

and their probability of success, were then used to populate the tree, with the outcome of the tree being a cost per event, which could be calculated overall or by grade of event.

3.1.2 Economic modelling of chemotherapy

Economic evaluation requires consideration of both the costs and benefits of a treatment. The data used to populate the model with these costs and benefits are referred to as inputs. Typically, chemotherapy includes three broad cost components, or inputs, to the overall cost: purchasing the chemotherapy products, time and resources for administering the chemotherapy, and managing adverse events. On the benefits side, disease outcomes such as cancer progression and survival are commonly measured, with quality-of-life measurement required for cost-utility analyses to produce QALYs. Information about outcomes is often readily available through clinical trials, while product purchase costs can be obtained from pricing lists. Less information is available about the costs of administration (64) and adverse events related to chemotherapy (65).

3.2 Modelling methods

Decision analytic modelling is a decision-making framework that meets a number of the objectives of economic evaluations (44). These include the need for a structure that reflects the range of individuals, their prognoses and the effects of interventions, as well as the requirement that all relevant evidence be considered (44).

The process of developing decision-analysis models has been described in multiple sources, including in best-practice Principles for modelling developed by ISPOR, which was adhered to in this research (104). Appendix F presents a summary of how the models presented in this chapter address these Principles for Good Research Practice for Decision Analytic Modeling in Health Care Evaluations. The practical methods described by Briggs et al. (46) was followed as a structure for approaching the task of building the models of chemotherapy adverse events. This approach comes from a textbook which reflects a collective view of decision analysts that have developed the methods for use in the evaluation of healthcare programs based on a number of years experience and

published research. The five stages described by Briggs et al. (46) for developing a decision analytic model as they were applied here are summarised below.

It should be noted that the modelling undertaken in this research does not address the type of decision problems typically addressed using decision trees. In general, decision-tree modelling is used to compare two or more options in terms of costs and outcomes. This research uses the decision-tree structure and assumptions to model the outcomes of an adverse event. The grades of severity are the alternative choice nodes in the model. Rather than outcomes that compare two methods of managing adverse events, these models produce outcomes that can be incorporated into models of overall chemotherapy cost-effectiveness, which include chemotherapy purchase costs, administration costs and the costs of adverse events.

Models were developed for the four adverse events described in Chapter 1, and summarised in Table 1.1: diarrhoea, nausea and vomiting, anaemia and neutropoenia. These adverse events provide a range of factors to consider in modelling, which are summarised in Table 3.1. All of the selected events are relatively common across a range of chemotherapy treatments, occur immediately during or after chemotherapy and are short-term. Adverse events that cause varying levels of distress to patients were selected, with distress classified as *low* for those events that have little impact on day-to-day life, and *high* for those events that either have a significant negative impact on day-to-day functioning or are serious enough to cause hospitalisation. The typical amount of resource-use associated with each adverse event ranges from *low*, indicating simple medications or lifestyle treatments, to *high*, such as those requiring hospitalisation. Finally, a range of management strategies is used for the selected events, including prevention, treatment or both.

Table 3.1: Clinical characteristics of adverse events to be modelled

	Anaemia	Neutropoenia	Diarrhoea	Nausea and vomiting
Patient distress	Low	Low to high	High	High
Timing	Immediate	Immediate	Immediate	Immediate
Term	Short	Short	Short	Short
Management	Prevent & treat	Treat	Treat	Prevent
Resource-use	Moderate	Moderate to high	Low to moderate	Low to moderate

3.2.1 Decision analytic modelling—the Briggs et al approach

Defining the decision problem

Defining the decision problem involves specifying the question to be addressed, with particular focus on defining the patient population and the treatment options being compared. In the case of this research, the decision problem for each adverse event was defined using a clinical treatment pathway approach. This approach describes the sequence of therapies that may be used when an adverse event occurs or becomes more severe, and the related changes to chemotherapy dose and schedule. These clinical pathways have been mapped using best-practice guidelines for the adverse events—diarrhoea, nausea and vomiting, anaemia and neutropoenia—and are described later in this chapter.

Defining the boundaries of the model

This step relates to the general issues of economic evaluation as well as to the specific implications of the intervention under consideration. The general considerations are the perspective, measure of effect or benefit and time horizon, all of which have been selected for this study based on the literature review described in Chapter 2. Given the grounding of the model within the decision-makers' approach, a health-service perspective is taken. This perspective includes the costs incurred by the healthcare service. Cost per event may be a more fitting outcome measure than cost per patient, because patients can experience more than

one episode of an adverse event during chemotherapy. The time horizon for each event depends on the event in question. The selected events are short term, and stop with the cessation of chemotherapy. Thus, the duration of chemotherapy treatment is the model time horizon.

The additional considerations that need to be addressed during modelling include the influence of multiple simultaneous adverse events or adverse-event clusters, and the cumulative influence of adverse events over time on adverse event costs. The inclusion of dose and schedule changes on chemotherapy efficacy means that survival may also be an appropriate outcome measure for inclusion in the models. The impact of adverse events on quality of life for patients is also an important potential outcome.

Structuring a decision model

The structure of a decision model is based on consideration of a number of issues relating to the input parameters and how they are related, and the way in which the clinical events are characterised. This leads to a schematic representation of the relationships between parameters in a mathematical series. Based on the relatively short time horizon and the need to account for previous experience in the models, the decision-tree structure was selected as the most appropriate structure for modelling resources associated with adverse events.

Software specifically designed for the construction and analysis of decision analytic models, TreeAge (121), was used.

Identifying and synthesising evidence

The next step is to identify and synthesise available data to populate the model through a systematic process. For effectiveness data, the use of systematic literature reviews and meta-analysis are standard. However, the same rigorous methods are often not available for the other types of inputs to decision models, such as the frequency of adverse events, the consumption of resources and the information about quality of life impacts and estimates of utility weights.

There are two approaches available for the collection of cost data: top-down and bottom-up. A top-down approach assigns total costs for a healthcare system to individual services. A bottom-up approach determines the amount and cost of each individual resource used to produce a service, and aggregates these to an overall cost for a healthcare system. It has been argued that bottom-up approaches are more accurate and detailed, but data collection is significantly more complex and therefore the bottom-up approach is less commonly used than the more-traditional top-down approach. Cost-effectiveness studies can be particularly sensitive to the approach taken to data collection, and of importance to this study is the finding that bottom-up approaches generally produce higher cost estimates for outpatient care and lower cost estimates for inpatient care (50).

The selection of a top-down or a bottom-up approach for data collection in modelling should be based on the decision problem and the purpose of the modelling. A top-down approach will be suitable if accounting for local variation is not as important as being able to generalise results across multiple sites, because local idiosyncrasies are smoothed out in a top-down approach (50). However, if there is a need to examine local variation across sites, or to compare two methods of care at a single site, a bottom-up approach will be more appropriate (50). It is also possible, and often highly practical, to combine top-down and bottom-up approaches to data collection. This common approach allows different methods to serve different purposes and for pragmatic decisions to be made based on data availability.

Given that the objective of these models is to provide generalisable models of chemotherapy adverse events which can be incorporated into models of chemotherapy cost effectiveness, the ability to generalise results across multiple sites was of high importance. Therefore, a top-down approach is used primarily, with data from nationally recognised sources.

Recommendations for managing specific adverse events in terms of the types and quantities of resources used can be obtained through clinical guidelines, such as those available on the eviQ website(39). Following such guidelines would result in models based on the assumption of best practice. However, this may not be reflective of the management of patients that occurs in standard practice.

The unit costs of resources are not available using a bottom-up approach, given the centralised nature of Australia's universal healthcare system. The exception to this is patient out-of-pocket costs, which can be collected in a bottom-up manner. Given that the models were developed to reflect the health-service perspective, reimbursement data (top-down) such as that from the MBS (administered by Medicare, the federal government agency that provides a level of reimbursement for medical services) and the PBS (administered by the Australian Department of Health and Ageing, which provides a level of reimbursement for some pharmaceutical products) are used.

Dealing with uncertainty

Economic evaluation in general is associated with a number of types of uncertainty, including structural, methodological and parameter uncertainty (122). Structural uncertainty recognises that the model structure influences the results. For example, the selection of one care pathway over another, or the use of best practice guidelines rather than observational research to guide model structure influences the resources considered and the outcomes (122). Most commonly this is addressed through qualitative methods such as the description of assumptions made in model development, however analytic approaches such as alternative scenario development and model discrepancy evaluation are emerging (122).

Methodological uncertainty is the uncertainty raised by the lack of consensus among economist in the best way to conduct economic evaluations, and can be addressed through the use of sensitivity analysis, and increasingly the presentation of a standardised 'reference case' for decision makers (122).

Parameter uncertainty is critical to decision modelling and relates to the variation around estimation of inputs to the model, because these data have been collected

from a sample. Traditionally, this uncertainty has been addressed through sensitivity analysis in which one parameter at a time is varied to assess the implications of uncertainty in that parameter. This may be difficult in models that have a large number of parameters or where parameters are related, and care needs to be taken in communicating the meaning of these varied results to decision-makers. With recent advances in computing, the use of probabilistic sensitivity analysis has become more common (46) . This type of analysis allows the probability distribution of a parameter to be defined, rather than a simple range, and can account for the correlation of parameters by using multivariate distributions. Simulation such as the Monte Carlo method is then used to vary the values of all parameters simultaneously to develop estimates of mean overall cost and effect. These can then be presented to decision-makers in the form of cost acceptability curves to aid decision-making.

The models presented in this chapter are not typical decision tree models. They have been designed to fit within larger models of chemotherapy cost effectiveness, and therefore do not have a decision node as the primary node. This means that a probabilistic sensitivity analysis is not possible. This has implications for the interpretation of the results, however, the one-way sensitivity analyses undertaken provide important information to decision makers about the relative uncertainty related to the model parameters. In addition, it should be noted that once incorporated into larger models of chemotherapy cost effectiveness, the parameters in the models of chemotherapy adverse events will presumably be subject to additional sensitivity analysis, which may be probabilistic.

3.3 Models of chemotherapy adverse events

Models are presented for four adverse events: diarrhoea, nausea and vomiting, anaemia and neutropoenia. These models demonstrate that when modelling for assessment of the cost-effectiveness of chemotherapy treatments, it is possible to account for the complexities of chemotherapy adverse events.

Modelling methods: the Briggs et al approach (46)

The **defined decision problem** for each adverse event model was 'What is the cost of treating this adverse event in Australian adults, based on best clinical practice?' The specific components of the research question, including the **model boundaries are defined** below.

Population:	Adult cancer patients (any solid tumour, any cancer stage), receiving chemotherapy
Sub-populations:	Different cancers and chemotherapy regimens will result in different incidence rates of adverse events. However, it is assumed that once an adverse events has occurred, its management will be the same, regardless of which chemotherapy regimen has caused it.
Location and setting:	Australian public hospital inpatient or outpatient setting
Intervention(s):	Treatment of adverse events based on best-practice clinical pathways
Entry and exit:	Individuals enter the model at the commencement of an adverse event, and they exit with the cessation of the adverse event, through either resolution or death.
Perspective:	Health service or hospital

The health service perspective was selected as it is policy makers within the health care system (such as the PBAC) who are the primary audience for many of the chemotherapy cost effectiveness analyses conducted in Australia. The implications of broadening the perspective to the societal would be significant for both the structure and outcomes of the model. Additional modelling of the impacts of adverse events on individuals indirect healthcare costs, such as travel time, productivity losses etc would need to be accounted for. In addition, healthcare costs incurred by individuals or organisations outside the health care system, such as patient out of pocket costs, would need to be modelled. The outcomes of these models would be far higher than those of the models presented.

While this information would be valuable, it would make the models less easily incorporated into cost effectiveness analyses of chemotherapy treatments, and thus the health care system perspective was selected.

It was necessary to **identify the evidence** for a number of aspects of each model. A systematic review of the literature was conducted to identify previous studies that included a cost of each adverse event. Full details of the methodology were described in Chapter 2; however, in summary, a search was conducted in 2009 using multiple databases in both the health and economics literature, such as Medline, EMBASE, Business Source Premier and EconLit. Searches combined key terms that described the research question over the ten years preceding the search. Additional papers were identified through hand-searching. All articles were reviewed for eligibility by a single reviewer, and the quality of each eligible article was assessed using the Graves quality assessment checklist (49). The characteristics, methodology and outcomes of each eligible study were extracted using a modified NHS EED annotated abstract form.

This methodology resulted in the systematic review results presented in Chapter 2, but was also used to identify studies that simply reported a cost of a chemotherapy adverse event. These costs could then be used to provide a comparison with the costs developed through modelling presented in the current Chapter. The structure of the model is based on clinical pathways identified through best-practice guidelines for the management of chemotherapy adverse events. The use of a biological or clinical process to drive a model allows well-understood definitions and high levels of evidence to be incorporated into the model structure, improving both the performance of the model and the interpretations by decision-makers (46). The use of best practice guidelines may not reflect adverse events in clinical practice; however, they provide a relatively simple structure for each model and a strong evidence for the causal links between variables.

Additional literature reviews to identify best-practice guidelines for the management of each adverse event were conducted in January 2012. These reviews were required in addition to the systematic review presented in Chapter 2 because clinical practice guidelines would not have addressed the research

question posed by the systematic review and thus would have been excluded. The medical literature was searched to identify relevant studies published from 2000 to the present. Searches were conducted via the electronic databases Cochrane Library, Medline and the National Guidelines Clearinghouse using a search strategy based on the key elements of the decision problem. Appendix G shows the search strategies used to identify the best-practice guidelines for each adverse event and the search results. Guidelines specific to the Australian setting were prioritised for use in the models, however if these were not available then guidelines from other countries were selected. In cases where guidelines varied in their recommendations and no Australian specific guideline was available, the most common recommendations across multiple guidelines were selected as the basis for the model structure.

In order to **populate the model**, evidence was identified for each of the required input parameters (46). As per the Principles of Good Research Practice, relevant data sources were included regardless of whether they reached generally accepted thresholds of statistical significance. Clinical evidence, such as treatment efficacy, impact of adverse events on chemotherapy dose and quality of life, was obtained through literature reviews conducted in January 2012. Again, these reviews were required in addition to the systematic review presented in Chapter 2 because the previous search was not designed to identify studies of chemotherapy dosage or quality of life. The medical literature was searched to identify relevant studies published in the period 2000 to the present. Searches were conducted via the electronic databases the Cochrane Library and Medline. Appendix G shows the search strategies used to identify the inputs for each adverse event and the search results. For both clinical inputs and inputs related to quality of life, where a number of research studies, each with the study population required for the model, were available the study judged to have the highest methodological quality was selected as the input source. A record of alternative inputs was kept and these values were used as values in the sensitivity analyses conducted.

Inputs relating to costs of treatment were obtained from standard sources, such as administrative data and government guidelines. PBS prices were used for

pharmaceutical products. This is the price at which products are available to the general public in Australia, with the dosage price based on the price for the maximum quantity dispensed. Similarly, the schedule fee for MBS medical services was used, as this is the price at which medical services are charged to the health service.

All of the models were structured to allow quality of life, chemotherapy dose and multiple adverse events to be considered. In cases where sufficient evidence was not available, these components were not populated within the model. Future work could be done to extrapolate potential values for these components, or use expert opinion to estimate values for these components. Sensitivity analyses would then be required to determine the impact of these estimations. Similarly, relatively few subgroups within the population of individuals receiving chemotherapy have been identified as impacting the experience of adverse events, and therefore the disaggregation of the modelled population according to these subgroups was not done. However, future work could extrapolate estimates for differing subgroups and provide estimates based on differential experiences of chemotherapy adverse events.

The structure of the decision model, synthesis of the evidence, model results and assessment of uncertainty for each adverse event model are specific to that adverse event, and are described Section 3.4, Section 3.5, Section 3.6 and Section 3.7.

General assumptions for all models

A number of generic assumptions are implicit to each of the adverse-event models described in this chapter. The first is that best-practice treatment methods were chosen as the basis for the model structure. This provided a common basis for resource-use, which should be consistent across treatment settings. However, it is recognised that clinical practice does not always reflect best-practice guidelines, and this is addressed in the analysis of clinical practice data described in Chapter 4 and Chapter 5. Second, one of the most significant assumptions for the models is that an adverse event is managed equally, regardless of the chemotherapy that

may have caused the event. As discussed in the assumptions of each model, this is supported by the best-practice guidelines for the treatment of each event, with very few guidelines specific to a type of chemotherapy (although this is not unheard of). Again, this assumption has the effect of maximising the generalisability of the models and their outcomes, and will allow them to be used by model-builders producing any model of chemotherapy cost-effectiveness in adults with solid tumours.

Each model is specific only to solid tumours in an adult population. This is designed to maximise the generalisability of the model outcomes, because children and adults with non-solid tumours often have very different disease and treatment patterns from adults with solid tumours.

Model validation

The models were tested for internal validity through review of TreeAge models and use of extreme input values to test key parameters. Calibration of the models against national data was not done, but in future work may be possible. For ongoing validation the models will be made available for peer review purposes as required. In relation to between-model validity, each model was developed independent of the others, and the model outcomes were compared to previous estimates of adverse event costs, with potential reasons for any discrepancies noted.

As noted in the Principles for Good Research Practice, models should never be considered complete. Regular and consistent updating to account for new information regarding model structure or parameter estimates should be considered and incorporated where possible.

3.4 Diarrhoea model

3.4.1 Background

Diarrhoea is a common adverse event of chemotherapy, and one that is often included in models of chemotherapy cost-effectiveness. However, the literature review presented in Chapter 1 found that the inclusion of diarrhoea-related resource-use and outcomes is often not reported in a systematic or rigorous way. This section describes the development of a model of the costs and outcomes of chemotherapy-induced diarrhoea based on best-practice guidelines and using Australia-based cost data. The results of this model can be used to populate cost-effectiveness analyses of any chemotherapy treatment(s) that may result in diarrhoea, with the aim that using a high-quality standard model of diarrhoea will improve the quality and comparability of cost-effectiveness analyses.

Chemotherapy-induced diarrhoea

Diarrhoea is a common condition characterised by frequent and watery bowel movements (31). When diarrhoea is severe, dehydration can result. In vulnerable individuals, such as children, the malnourished or those with impaired immunity, diarrhoea and its consequences can be life-threatening (123).

Diarrhoea in people with cancer can have many causes, including the cancer itself, other cancer treatments, such as antibiotics, chemotherapy or surgery, or decreased physical performance (124). Appropriate management of diarrhoea in cancer patients requires careful analysis of the cause of the diarrhoea, and this is particularly important in the case of chemotherapy-induced diarrhoea (124). This chapter is focused exclusively on chemotherapy-induced diarrhoea.

There are some chemotherapy agents that are known to cause diarrhoea by altering the way the small bowel absorbs and secretes (125). In general, however, chemotherapy-induced diarrhoea is thought to be a multifactorial process (124). Depending on the type of chemotherapy treatment, the incidence of diarrhoea can be as high as 80 per cent (124, 126), and it is one of the most common adverse events in cancer patients (30). In addition, diarrhoea has been identified in surveys

of patients as one of the most distressing adverse events that patients experience (33).

The chemotherapy agents 5-fluorouracil (5-FU), capecitabine and irinotecan are associated with especially high rates of diarrhoea, and these are primarily used in patients with colorectal cancer (124). Colorectal cancer patients are particularly susceptible to chemotherapy-induced diarrhoea, due to their already compromised digestive tract. A recent review of trials for the Saltz regimen (irinotecan plus high-dose fluorouracil and leucovorin) in advanced colorectal cancer identified a life-threatening gastrointestinal syndrome of which diarrhoea is a significant component, and which requires significant monitoring and aggressive treatment (124). Regardless of the causative chemotherapy agent or underlying cancer, the consequences of diarrhoea, such as malnutrition, dehydration and cardiac compromise, can be serious (124). The occurrence and treatment of diarrhoea may also impact on chemotherapy effectiveness by interfering with cancer treatments via dose delays or reductions (124).

Chemotherapy-related diarrhoea can be graded according to the number of stools per day compared to a usual day, as seen in Table 3.2 (31). Grade I and Grade II diarrhoea are commonly considered as *mild*, while Grades III and IV are categorised as *serious*. This is the grading criteria referred to throughout this thesis, unless otherwise specified.

Table 3.2: CTCAE v4.03 diarrhoea grading (31)

Diarrhoea grade (for patients without a colostomy)				
Grade I	**Grade II**	**Grade III**	**Grade IV**	**Grade V**
Increase of < 4 stools per day over baseline	Increase of 4–6 stools per day over baseline	Increase of ≥7 stools per day over baseline; incontinence; hospitalisation indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

Note: ADL = Activities of daily living

In general, treatment of chemotherapy-induced diarrhoea includes non-pharmacological interventions such as diet modification and increased fluid intake along with pharmacological interventions (124). To date, there are only three drugs that are recommended for the treatment of chemotherapy-induced diarrhoea based on evidence: loperamide, octreotide and tincture of opium (124).

Previous studies of diarrhoea cost

Twenty-one studies that included a cost of diarrhoea were identified (see Appendix H). Nine of these were studies of treatments for adverse events, with the remaining 12 being based on models of chemotherapy cost-effectiveness. It is common for studies to combine Grade III and Grade IV events into a single category of *serious adverse events,* labelled *Grade III/IV events.* Most diarrhoea studies included only Grade III/IV events, although some (98, 127) included multiple grades of each event. In most cases, the costs of outpatient visits, medications and, in some cases hospitalisation, were included as the resources to determine costs; however, the management of diarrhoea within the studies was often not specified and varied significantly.

One of the striking features of these results is the variation in estimates of the costs of chemotherapy-induced diarrhoea. This variation could be a result of the differing methodologies used by different studies. The model structure, resources included and local practice variations may all contribute to variation in the results. Although this is understandable, it highlights one of the key issues in the modelling of chemotherapy. Even when adverse events are included, the variation in the way adverse events are considered can have an important effect on the overall results.

Best practice treatment pathway

The search strategy identified five guidelines for the management of chemotherapy-induced diarrhoea. None of these was Australian. In addition, the evi-Q website provided recommendations for Australian management of late onset diarrhoea associated with irinotecan. All guidelines recommended the use of dietary management for very mild diarrhoea (not requiring any other treatment) or

as background supportive therapy for more-serious cases, with the aim of avoiding exacerbation and preventing dehydration. Dietary management includes increasing the intake of clear fluids, avoiding substances that may contribute to diarrhoea, such as dairy products, high-fat foods, caffeine and alcohol, and encouraging frequent small meals of foods in the BRAT diet: bananas, rice, apples and toast.

eviQ provides online guidelines for late-onset diarrhoea associated with irinotecan (128). These guidelines recommend that loperamide be commenced immediately, and if diarrhoea continues for more than 48 hours after commencing loperamide, then octreotide should be commenced and specialist advice sought. The recommended treatment for patients with severe diarrhoea is admission to hospital and management with fluid and electrolyte replacements as required.

Canadian guidelines (2007) (126): The Canadian guidelines were developed by a working group of medical oncologists in 2001 and published in a peer-reviewed journal. The recommendations use a consensus of experts to expand upon guidelines developed by Cancer Care Ontario. The population to whom the recommendations apply is limited to patients with colorectal cancer experiencing chemotherapy-induced diarrhoea. The Canadian guidelines include recommendations on the grading of chemotherapy-induced diarrhoea and investigations for potential causes of chemotherapy-induced diarrhoea, as well as patient management for both prevention and acute treatment of diarrhoea. In the acute setting, low-grade diarrhoea (National Cancer Institute [NCI] Grade I/II) should be treated initially with dietary strategies. If after 24 hours this has been ineffective, loperamide should be given. If this is successful, dietary management should be continued, but if unsuccessful, high-dose loperamide should be commenced. If this is not effective after 24 hours, hospitalisation and octreotide is recommended, along with antibiotics, fluids and electrolyte replacements. Patient with de novo Grade III/IV diarrhoea should be treated with octreotide, and if the patient does not respond, the dose should be escalated until the diarrhoea resolves.

American Society of Clinical Oncology (ASCO) guidelines (2004) (129): In 2002, the practice guidelines that were first published in 1998 were reviewed

along with recent literature by a multidisciplinary expert panel and published in a peer-reviewed journal. Both the recommendations and what they refer to as the *treatment algorithm w*ere revised, and changes were made by panel consensus. A literature review was conducted, although the details of the search were not described. The primary aim of the revision was to take into account the recently identified additional mortality associated with the Saltz regimen. These guidelines recommend categorising individuals with chemotherapy-induced diarrhoea as either *uncomplicated* or *complicated*, with risk factors such as cramping, nausea and vomiting, decreased performance status, fever, sepsis, neutropoenia, bleeding or dehydration contributing to a complicated status. Patients with mild-to-moderate uncomplicated diarrhoea should be treated with dietary modifications and loperamide. If this is ineffective, the dose of loperamide should be increased and antibiotics commenced. If diarrhoea persists after 48 hours of treatment, loperamide should be replaced with octreotide. The potential for budesonide or tincture of opium as second-line treatment is raised, although supported by little evidence. More-aggressive management is recommended for patients with complicated diarrhoea, more severe diarrhoea (Grade III/IV), or those receiving irinotecan plus high-dose fluorouracil and leucovorin. This involves fluids given via intravenous therapy (IVT), octreotide given in increasing doses until diarrhoea is controlled, and antibiotics.

Nursing guidelines (2009) (130): A team of specialist nurses and dieticians conducted an extensive literature review to identify evidence-based interventions for chemotherapy-induced diarrhoea and radiotherapy-induced diarrhoea. Both the literature review and the recommendations were published in a peer-reviewed journal. Based on the evidence, the recommended interventions for chemotherapy-induced diarrhoea are the use of loperamide as first-line therapy, or high-dose loperamide for irinotecan-associated diarrhoea. It is also noted that octreotide at standard dose has been found to have good efficacy. Interventions found likely to be effective include long-acting octreotide or high-dose octreotide for those patients for whom loperamide has failed. The long-standing practice of using tincture of opium was considered useful according to expert opinion; however, a lack of high-quality evidence means this could not be recommended for practice.

According to these guidelines, there is emerging evidence that probiotics and soluble-fibre supplements are likely to be effective; however, further research into these treatments is required to identify the types of diarrhoea most responsive to these therapies.

Novartis guidelines (2000) (131): Following the release of octreotide (a Novartis product), Novartis supported a closed roundtable meeting of oncology clinicians to develop recommendations for the management of chemotherapy-induced diarrhoea. The recommendations, published in a peer-reviewed journal, were for treatment to commence with standard-dose loperamide. For Grade I/II cases that do not resolve, this should be followed by high-dose loperamide. If this is unsuccessful, but diarrhoea remains Grade I/II, octreotide should be commenced in the outpatient setting. If at any stage, the diarrhoea is Grade III or IV, the patient should be admitted to hospital and commenced on octreotide. These guidelines recommend that antibiotics be commenced on admission to hospital, as needed.

National Cancer Institute (NCI) guidelines (2011) (125): On its website, the NCI provides a review of evidence of alternative strategies to manage chemotherapy-induced diarrhoea. The evidence suggests that for patients with uncomplicated diarrhoea symptoms, the use of glutamine is ineffective whereas loperamide and other opioids are effective, although less so in patients with Grade III or IV diarrhoea. No supporting evidence is provided for the role of octreotide in uncomplicated diarrhoea. For those with complicated symptoms, octreotide is considered best-practice management, although the optimal dose is not yet supported by strong evidence. A number of additional pharmacologic strategies with evidence from small case series are presented, along with emerging evidence of the potential role of probiotics in symptom relief.

A summary of the dosing schedules recommended in each of these guidelines is shown in Table 3.3.

3.4.2 Structure of the decision model

A decision-tree model was developed to estimate the costs and benefits of best-practice management for chemotherapy-induced diarrhoea. The structure of the model was based on similar clinical pathways to those described in the guideline documents prepared by ASCO, the Canadians, the British Columbia Cancer Agency (BCCA) and Novartis, and is shown in Figure 3.3. The full TreeAge model is in Appendix I.

The model was designed to be adaptable to any type of chemotherapy, with varying proportions of diarrhoea occurring at each grade. In order to demonstrate the model, a chemotherapy example was required to provide inputs for the proportion of diarrhoea at each grade. The Evi-Q website was used to select a chemotherapy regimen commonly associated with chemotherapy induced diarrhoea. 5-FU + leucovorin was selected as an appropriate case study to demonstrate the roll-back of the model. The rates of diarrhoea at each grade level for individuals receiving 5-FU + leucovorin were obtained from one of the pivotal studies of 5-FU + leucovorin listing on the Evi-Q website, and used to populate the probability parameters within the model.

Table 3.3: Summary of loperamide, octreotide and antibiotic dose recommendations for diarrhoea

Guidelines	Novartis (131)	NCI (125)	Nursing (130)	Canadian (126)	ASCO (129)	eviQ (128)
Loperamide						
Loading dose	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg
Standard dose	2 mg every 4 hrs or after each unformed stool	2 mg after every unformed stool (max. 12 mg daily)	2 mg every 4 hrs	2 mg after each loose stool (max. 16 mg daily)	2 mg every 4 hrs or after every unformed stool	2 mg every 2 hrs
High dose	2 mg every 2 hrs	–	2 mg orally every 2 hrs (4 mg every 4 hrs at night) for up to 48 hrs	4-mg loading + 2 mg every 2 hrs	2 mg every 2 hrs	NS
Octreotide						
Standard dose	100–150 µg SQ tid	100–150 µg SQ tid or 25–50 µg per hour, IVT	100–150 µg SQ tid or 20–30 mg monthly IM injection	100–150 µg SQ tid	100–150 µg SQ tid or 25–50 µg per hour, IVT	NS
High dose		Up to 500 µg tid	Up to 500 µg tid	300–500 µg SQ tid until resolved	Up to 500 µg tid	NS
Antibiotics						
When	On admission to hospital, start antibiotics as needed	NS	NS	Patients treated in hospital should receive antibiotics	In complicated cases, or if mild-to-moderate diarrhoea persists after loperamide	NS
What	NS	NS	NS	e.g. fluoroquinolone	e.g. fluoroquinolone	NS

Note: BCCA = British Columbia Cancer Agency; bid = twice per day; hrs = hours; IM = intramuscular; NS = not stated; SQ = subcutaneous, tid = three times per day; µg = microgram

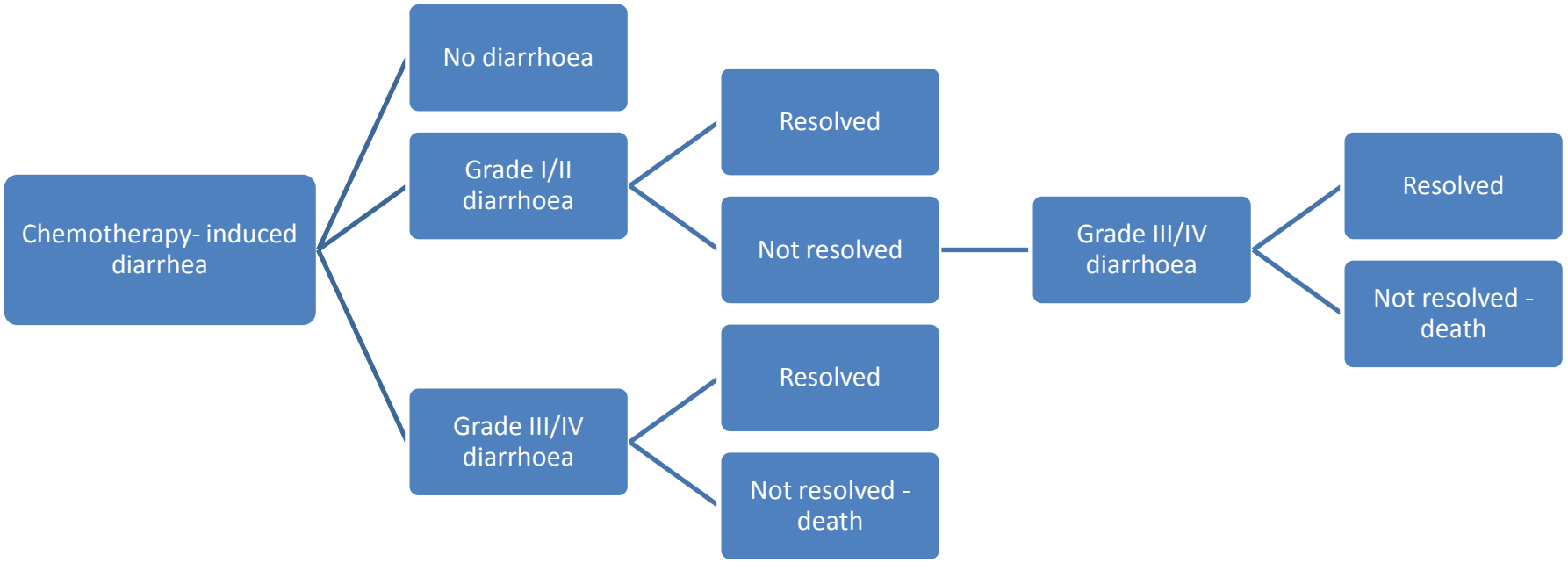


Figure 3.3: Decision-tree model for chemotherapy-induced diarrhoea

The assumptions underlying the structure of the model are as follows:

- Diarrhoea is limited to chemotherapy-induced diarrhoea. All other causes of diarrhoea have been excluded and/or treated appropriately.
- Chemotherapy-induced diarrhoea is managed in the same way, regardless of causative chemotherapy. This is based on the guidelines, all of which (except ASCO) recommend the same management pathway for all chemotherapy-induced diarrhoea.
- Some guidelines introduce consideration of additional patient factors which can complicate the management of chemotherapy induced diarrhoea. This has been excluded from the model, because the aim is to produce a model that provides an estimate independent of patient factors. Given the additional resource intensity associated with managing these complications, disregarding them may result in a model that underestimates outcomes.
- Dietary management of diarrhoea has been excluded from the model, because it is assumed that dietary management is recommended as background supportive care for all grades and treatments of diarrhoea. It is unlikely that the uptake of dietary management would influence the transition probabilities within the model, and dietary management imposes minimal costs on the healthcare system.
- Grade I/II diarrhoea is treated initially with loperamide 4-mg loading-dose, followed by 2 mg every four hours, up to a total of 16 mg per day. This limit was used because it is the limit specified in the Consumer Medicines Information Sheet for loperamide hydrochloride (Imodium®) (132). This treatment would continue for 24 hours, at which time an assessment of resolution would take place.
- If standard-dose loperamide is unsuccessful after 24 hours, the dose would be escalated to 2 mg every two hours, which would continue for up to 24 hours (132).
- Octreotide would not be used for mild diarrhoea or in an outpatient setting. Although this is inconsistent with many of the guideline recommendations,

octreotide is not approved in Australia for use in chemotherapy-induced diarrhoea and is rarely used.

- If diarrhoea remains unresolved after 24 hours of high-dose loperamide, or diarrhoea commences at Grade III/IV, octreotide would be given at a starting dose of 100 μg three times per day. This would continue for 24 hours.
- If diarrhoea remains unresolved, the octreotide dose would be escalated up to 500 μg three times per day. Clinically, this dose could be maintained indefinitely until diarrhoea resolves; however, in the model this dose is continued for the average admission length of 4.56 days, before either the diarrhoea is resolved or the patient is dead.
- If octreotide were being used for serious diarrhoea (Grade III/IV), it would be given in an inpatient setting.
- Antibiotics would commence with hospitalisation (126, 131).

3.4.3 Synthesising the evidence

The probabilities for managing diarrhoea were estimated from a variety of sources, as shown in Table 3.4. Although the best available Australian evidence was sought, in many instances Australia-based data were not available. In this case, the best available international evidence was used. Grade I/II diarrhoea that is unresponsive to loperamide at both low and high dose, as well as to standard-dose octreotide, was considered to be managed in the same way as diarrhoea that commences at Grade III/IV, and therefore the same inputs were used. Utility values were based on the highest-quality Australian data available, and international data in other cases. Utility decrements and overall utility values were considered for inclusion in the model; however, for consistency in model calculations, only one type was selected for inclusion. In the case of diarrhoea, the highest-quality available evidence was provided as a utility decrement, and therefore this was included in the model.

Given the short-term nature of diarrhoea, and therefore the model, no discounting was applied.

Table 3.4: Assumptions in the economic model of diarrhoea

Assumptions	Value*	Source	Justification for source
Transitions	***Probability***		
Resolution of Grade I/II diarrhoea following standard-dose loperamide	0.8400	Cascinu 2000 (133)	Small cohort study of 5-FU-related diarrhoea
Resolution of Grade I/II diarrhoea following high-dose loperamide	0.0600	Abigerges 1994 (134)	Small study of high-dose irinotecan with high-dose loperamide. Value inferred from 17 patients on loperamide protocol, one with uncontrolled diarrhoea
Resolution of Grade I/II diarrhoea following standard-dose octreotide	0.9000	Cascinu 1993 (135)	Cascinu uses a lower dose and Grades II/III, but a more appropriate reference not identified
Resolution of Grade III/IV diarrhoea following hospitalisation, standard-dose octreotide and antibiotics	0.6100	Goumas 1998 (136)	Goumas is an outpt study, but no hospitalised study identified
Resolution of Grade III/IV diarrhoea following hospitalisation, high-dose octreotide, and antibiotics	0.9032	Goumas 1998 (136)	Goumas is an outpt study, but no hospitalised study identified
Dose changes	***Percentage***		
Percentage of patients with Grade I/II diarrhoea who have a dose reduction	4	Arbuckle et al. 2000 (110)	Retrospective review of 100 patients with colorectal cancer who experienced CID. Values are percentage of patients who had specified grade of diarrhoea and who had changes in treatment.
Percentage of patients with Grade I/II diarrhoea who have a dose delay	10		
Percentage of patients with Grade I/II diarrhoea who have a dose discontinuation	8		
Percentage of patients with Grade III/IV diarrhoea who have a dose reduction	38		
Percentage of patients with Grade III/IV diarrhoea who have a dose delay	6		
Percentage of patients with Grade III/IV diarrhoea who have a dose discontinuation	21		

Assumptions	Value*	Source	Justification for source
Health utility decrements	***Utility decrements***		
Grade I/II diarrhoea	–0.11	Szabo et al. ISPOR 2008 poster (137)	Standard gamble utility values for toxicity health states in melanoma patients
Grade III/IV diarrhoea	–0.11	Szabo et al. ISPOR 2008 poster (137)	Standard gamble utility values for toxicity health states in melanoma patients
Treatment duration	***Hours/days***		
Duration of low-dose loperamide prior to assessment of success	24 hrs	As per guidelines	Recommended by multiple clinical practice guidelines
Total duration of low-dose loperamide if assessed successful (includes time (24 hrs) prior to assessment of success, and time following success for any ongoing diarrhoea)	2 days	Consumer Medicines Information Sheet (132)	Although a number of sources suggest that diarrhoea, and therefore its treatment, continues beyond 2 days (eg Gebbia et al 1993: 6 days (145)), the consumer medicines information for loperamide is very clear that it should not be taken for more than 48 hrs in total
Duration of high-dose loperamide prior to assessment of success	24 hrs	As per guidelines	Recommended by multiple clinical practice guidelines
Total duration of high-dose loperamide if assessed successful (includes time (24 hrs) prior to assessment of success, and time following success for any ongoing diarrhoea)	48 hrs	Abigerges 1994 (134); Nursing guidelines (130)	The average duration of diarrhoea was 20 hours in a study of high-dose loperamide (Abigerges 1994) (139). The Nursing guidelines state that the dose should not be given for more than 48 hrs
Duration of standard-dose octreotide prior to assessment of success	24 hrs	As per guidelines	Recommended by multiple clinical practice guidelines
Total duration of standard-dose octreotide if assessed successful	2.5 days	Goumas 1998 (136)	Average day of response to therapy for octreotide 100 µg tid
Duration of high-dose octreotide prior to assessment of success	24 hrs	As per guidelines	Recommended by multiple clinical practice guidelines
Duration of high-dose octreotide if assessed successful	2.75 days	Goumas 1998 (136)	Average day of response to therapy for octreotide 500 µg tid

Assumptions	Value*	Source	Justification for source
Duration of high-dose octreotide if unsuccessful and leads to death	5 days	Goumas 1998 (136)	Treatment failure was defined if no improvement was observed after 5 days of therapy with octreotide
Duration of antibiotics	4.56 days	NHCDC (138)	Duration of hospitalisation
Duration of hospitalisation	4.56 days	NHCDC (138)	As per average in DRG
Pharmaceutical product doses	***Dosage***		
Loperamide loading-dose	4 mg	Consumer Medicines Information Sheet (132)	Consumer medicines information sheet, and as per guidelines
Loperamide low-dose	16 mg daily (2 mg every 4 hrs)	Consumer Medicines Information Sheet (132)	Consumer medicines information sheet, and as per guidelines
Loperamide high-dose	24 mg per day (2 mg every 2 hrs)	As per guidelines	Recommended by multiple clinical practice guidelines
Octreotide standard-dose	300 µg (100 µg tid)	As per guidelines	Recommended by multiple clinical practice guidelines
Octreotide high-dose	1500 µg (500 µg tid)	Richardson et al. 2007 (139)	The BCCA recommends increasing the dose to 300 or 500 µg after 24 hrs if no improvement is evident. The Cancer Care Ontario guidelines suggest increasing every 8 hrs by 50–100 µg until diarrhoea is controlled (to max. 500 µg tid)
Ciprofloxacin (oral antibiotic) during hospitalisation	500 mg every 12 hrs	Consumer Medicines Information Sheet (132)	Consumer medicines information sheet, and as per guidelines

* Probabilities and utilities are expressed in the range 0 to1

Note: BCCA = British Columbia Cancer Agency; CID = chemotherapy-induced diarrhoea; DRG = diagnosis related group; hrs = hours; µg = micrograms; mg = milligrams; tid = three times per day.

Costs are estimated based on the best available evidence from reliable Australian sources in 2012 Australian dollars. High-quality evidence traditionally includes well-designed randomised controlled trials or meta-analyses published in peer-reviewed literature. However, where this is not available, or not appropriate, data from well-conducted observational studies, national policy documents or guidelines for clinical best practice may also provide high-quality evidence. The costs associated with managing diarrhoea events were limited to the cost of pharmaceutical products, administration costs associated with pharmaceutical products, GP visits and inpatient hospital stays. These costs and their sources are shown in Table 3.5.

Pharmaceutical costs are derived from the PBS price for the maximum quantity prescribed. The average price of the drug for the maximum quantity was calculated using all available brands. The impact of using the highest- and lowest-price brands is tested in the sensitivity analysis. To calculate costs associated with different doses, the cost of the drug was divided to find the cost per drug-specific unit (e.g. per capsule or per 50 μg), and used to calculate the cost per dose of the drug. This calculated cost does not account for bulk purchasing (resulting in savings) or wastage by the dispenser (resulting in additional cost).

Table 3.5: Costs used in economic model of diarrhoea

Resource	Cost (A$)	Source	Notes
GP visit for loperamide script	$34.90	MBS	MBS Item 23 (Level B GP consultation in rooms)
Loperamide	$0.745 per 2-mg capsule	PBS	Dispensed price for max. quantity (12 x 2-mg capsules) $8.50–$9.41, $0.71–$0.78 per 2-mg capsule; average = $0.745
Octreotide	$7.18 per 50 µg	PBS	Dispensed price for max. quantity $7.02–$7.34 per 50 µg; average = $7.18
Outpt administration of octreotide, IVT	$21.00	MBS	MBS Item 53 (standard consultation at consulting rooms)
Ciprofloxacin (oral antibiotic)	$7.24 per 24 hrs	PBS	Price per max. quantity dispensed (14 x 250-mg tablets) $25.33 (25.33 ÷ 14 = 1.81 x 4 = 7.24))
Hospitalisation due to diarrhoea with complications	$4,482.00	NHCDC 2006–07	DRG G70A. Given all patients have cancer, assume that all patients would be coded as *with complications*

Notes: DRG = diagnosis related group; GP = general practitioner; IVT = intravenous therapy; max. = maximum; MBS = Medicare Benefits Schedule; mg = milligram NHCDC = National Hospital Cost Data Collection; PBS = Pharmaceutical Benefits Scheme

3.4.4 Modelling the results

The decision-tree model provides a cost for each branch of the tree, based on the inputs. In order to calculate these, a chemotherapy example was required, so that a proportion of patients with each grade of diarrhoea could be entered. The example of 5-FU + leucovorin was selected as a commonly used chemotherapy treatment that is known to frequently cause diarrhoea.

The probability of 5-FU + leucovorin chemotherapy resulting in diarrhoea of each grade level was obtained from one of the pivotal papers of 5-FU + leukovorin reported on the evi-Q website. This paper reported diarrhoea occurring at grade I in 36% of patients, at grade II in 12% of patients, at grade III in 12% of patients and at grade IV in 2% of patients (140). Therefore, the model was populated with

48% of individuals having grade I/II diarrhoea and 14% of individuals having grade III/IV diarrhoea.

Using the base case of 5-FU + leucovorin (140), the average cost of managing one episode of chemotherapy-induced diarrhoea according to best-practice guidelines in Australia was $688. Grade I/II diarrhoea had a cost of $19 per episode, while Grade III/IV diarrhoea cost $4,847 per episode (see Table 3.6). The most-expensive scenario was death from diarrhoea, following progression from Grade I/II to Grade III/IV, which cost $5,650 per episode.

Table 3.6: Base-case costs of managing chemotherapy-induced diarrhoea

Tree branch	Probability	Cost (A$)
No diarrhoea	0.26	0
Grade I/II diarrhoea	0.37	19
Grade III/IV diarrhoea	0.14	4,847

Using the base case of 5-FU + leucovorin (140), both Grade I/II diarrhoea and Grade III/IV diarrhoea resulted in utility decrements of 0.11. Each branch of the tree which ended in resolution of chemotherapy induced diarrhoea included a sub-tree to specify the proportion of individuals with dose delays and reductions, allowing specific survival 'costs' to be incorporated into the model once it is compiled within a larger chemotherapy cost effectiveness model.

3.4.5 Assessing uncertainty

To explore the source and impact of any uncertainty in the model, one-way sensitivity analyses were undertaken to establish which estimates have the greatest effect on the average cost of managing chemotherapy-induced diarrhoea. All parameters were tested in the sensitivity analysis and the values used are shown in Table 3.7. The sensitivity analysis values selected for the probability of diarrhoea at each grade level were taken from a review of the incidence of diarrhoea caused by chemotherapy for colorectal cancer in the Canadian Guidelines (126). The full results of the sensitivity analysis displayed as a tornado diagram in Figure 3.4.

Table 3.7: Parameters and values tested in the sensitivity analysis of diarrhoea model

Transition/Utility/Cost item	Values used in sensitivity analysis	Source
Probabilities	***Probabilities***	
Probability of Grade I/II diarrhoea	0.380–0.600	Lower value from Maroun (126), upper value is point estimate + 25%
Probability of Grade III/IV CID	0.060–0.370	Lower value Maroun table (126), upper value from
Probability that diarrhoea resolves following standard-dose loperamide	0.700–0.910	Range of non-responders in Richardson et al. (139)
Probability that diarrhoea will not resolve following loperamide dose escalation	0.020–0.075	+/– 25%
Probability that diarrhoea resolves after loperamide followed by octreotide	0.600–0.950	Maroun (126)
Probability that diarrhoea will resolve following hospitalisation and octreotide and antibiotics	0.148–0.960	Cascinu 1992 (135)
Probability that diarrhoea will resolve following octreotide dose escalation	0.800–1.000	Gebbia (141), + 25% (limited to 100%)
Costs	***A$***	
Cost of loperamide (per 2-mg capsule)	0.53–0.98	25% +/– high and low prices in cost range
Cost of octreotide (per 50 µg)	5.27–9.18	25% +/– high and low prices in cost range
Cost of octreotide administration	15.75–26.25	25% +/– high and low prices in cost range
Cost of antibiotics	5.43–9.05	25% +/– high and low prices in cost range
Cost of GP visit	26.18–43.63	25% +/–
Cost of hospitalisation for CID with complications	3,361.50–5,602.50	25% +/–

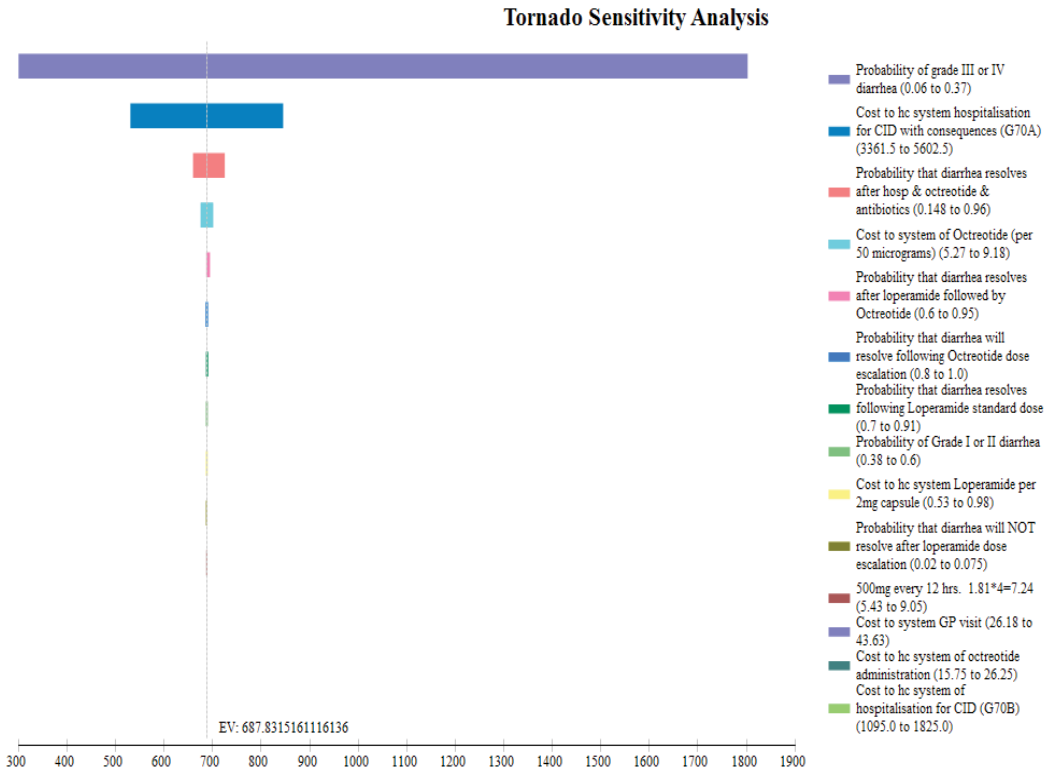
Note: CID = chemotherapy-induced diarrhoea; GP = general practitioner; µg = micrograms; mg = milligrams

The parameters to which the model was most sensitive were:

- probability of Grade III/IV chemotherapy-induced diarrhoea
- cost of hospitalisation for chemotherapy-induced diarrhoea
- probability that diarrhoea will resolve following hospitalisation, and octreotide, and antibiotics

The model was moderately sensitive to:

- cost of octreotide.



Note: x-axis represents cost; CID = chemotherapy induced diarhhoea; EV = expected value;

Figure 3.4: One-way sensitivity analysis—diarrhoea model

For model-builders or decision-makers using this model within an economic evaluation of chemotherapy, these results indicate that an accurate profile of diarrhoea in patients undergoing the chemotherapy treatment of interest is important. This is because uncertainty in the probabilities associated with the parameters for having severe diarrhoea, being hospitalised and having a

chemotherapy dose reduction due to diarrhoea all impact on the cost of managing chemotherapy-induced diarrhoea.

3.4.6 Discussion

Many previous models or studies of the costs of chemotherapy-induced diarrhoea have not specified how diarrhoea was managed. This model utilises evidence-based best-practice guidelines for the management of chemotherapy-induced diarrhoea. These guidelines were developed to cover diarrhoea caused by any chemotherapy regimen and were therefore a highly suitable source of information for generating the structure of the decision analytic model used here. This model is also applicable to diarrhoea caused by any chemotherapy treatment.

The inclusion of dose modifications within the tree structure, and quality of life as a 'payoff' within the model means this model is more detailed than previous models. The costs included in the model were all those applicable according to the perspective of the healthcare system: pharmaceuticals, GP visits, outpatient visits and hospitalisation. This is a more thorough collection of costs than many of the previously published studies or models of the costs associated with chemotherapy-induced diarrhoea.

Previous models that have included a cost of diarrhoea have primarily included only the cost of Grade III/IV (serious) events. Although this analysis found the cost of low-grade diarrhoea is substantially less than for more-serious events, the high probability of diarrhoea in this scenario (46 per cent) indicates that low-grade diarrhoea is still a significant event of interest in terms of cost. This indicates that diarrhoea at all grades should be included in models of chemotherapy-induced diarrhoea costs.

It is challenging to compare the estimates of the costs and consequences of chemotherapy induced diarrhoea from this model with the costs identified in previous studies of diarrhoea (see Appendix H) due to variation in the structure, assumptions, and inputs of the various models.

The majority of the previous identified studies provide a cost only for the more serious grade III/IV diarrhoea. However, Ojeda (98) estimated mild diarrhoea to

have no cost, while moderate diarrhoea cost Int$69.20 per event, and Capri (99) gave a cost of Int$11.83 for grade I diarrhoea and Int$26.02 for grade II diarrhoea. The estimate from this model of AUD$19 (Int$15) are relatively consistent with these estimates, both of which come from cost-minimisation studies of the same two chemotherapy treatments for ovarian cancer. The studies which provided a cost for treating one episode of grade III/IV diarrhoea ranged from Int$49 for a case treated in the ambulatory setting (142) to Int$6713 (143). The results of this study, with a cost of AUD$4821 (Int$3826) per grade III/IV diarrhoea event are towards the high end of these estimates. This may be due to the routine recommendation of the use of Octreotide, which is relatively expensive on the PBS, for all high grade diarrhoea episodes. In addition, a number of previous models either did not include the cost of hospitalisation, or only included the cost of hospitalisation, both of which may have underestimated the true cost of chemotherapy induced diarrhoea in comparison to this model.

Selection of adverse events for inclusion

When taken as a cost-of-illness estimate, the results of this model show that diarrhoea is an adverse event that can be associated with a significant cost. This cost is particularly high for individuals who have more-serious events; however, the relatively large proportion of individuals experiencing diarrhoea during chemotherapy means that even the less-serious, less-expensive diarrhoea events can influence overall costs. This implies that the chemotherapy adverse event of diarrhoea should be included in all chemotherapy cost-effectiveness analyses where diarrhoea is a potential side effect.

Impact of adverse events on quality of life

The impact of the adverse event diarrhoea on quality of life appears to be poorly understood, and there is limited rigorous evidence for use as an input to this component of the model. The model presented here used the same utility decrement for all grades of diarrhoea, which may not reflect the true patient experience. In order to populate the model with the required detail, it would be necessary to obtain utility decrements that are specific to the experience of diarrhoea during chemotherapy, excluding the utility values associated with

cancer and chemotherapy. This is because it is assumed that if this model is used as an input to a larger model of chemotherapy cost-effectiveness, there will be utility values associated with the experience of having cancer and of undergoing chemotherapy already included, and therefore, to avoid double counting, they should be separate from the experience of having an adverse event. The model is structured around the severity of diarrhoea occurring at two levels (low or high); therefore, the decrement associated with each of these should be estimated separately.

Influence of adverse events on dose of chemotherapy

There is moderately rigorous evidence indicating that a high proportion of individuals who experience chemotherapy-induced diarrhoea have dose modifications as a result. These reported high proportions highlight the importance of including the influence of adverse events on the dose of chemotherapy. These dose modifications affect both the total quantity of chemotherapy product(s) received, and the efficacy of the treatment. However, chemotherapy quantity and chemotherapy efficacy are beyond the scope of this model.

A model-builder wishing to incorporate this model of chemotherapy-induced diarrhoea into a model of chemotherapy cost-effectiveness could use these rates of dose modifications to include their impact on chemotherapy quantity and chemotherapy efficacy. By adjusting the total quantity of chemotherapy drug(s) received, the influence on the total cost of treatments through reduced product and fewer clinic visits would be accounted for. The proportion of individuals who have dose modifications should also be included in the estimates of survival for each treatment to account for the evidence that receiving a lower than planned dose of chemotherapy reduces rates of chemotherapy response and overall survival. It is unclear whether this type of information will be available from all clinical trials for all chemotherapy treatments; however, the results of this model demonstrate the importance of considering this as a consequence of the chemotherapy adverse event diarrhoea.

Consideration of multiple adverse events

The decision-tree structure allows recurrent episodes of diarrhoea to be included in a model of chemotherapy effectiveness. In reviewing the literature, there was little to indicate that the management of diarrhoea is adjusted when multiple episodes of diarrhoea are experienced over time, and therefore to use the same model for each episode would appear to be appropriate.

By modelling chemotherapy-induced diarrhoea as a stand-alone event, it is not possible to explore whether the management and resources associated with chemotherapy-induced diarrhoea are altered when it occurs in combination with another adverse event. Little literature was identified about this, neither for diarrhoea specifically, nor for adverse events in general. This will be explored further in Chapter 4 and Chapter 5.

Influence of the severity of adverse events on cost

The results of this model indicate that the presumed relationship between increased severity of an adverse event and increased cost is the case with chemotherapy-induced diarrhoea. Given that this model categorises the severity of chemotherapy-induced diarrhoea as either low or high, the model does not allow for a detailed examination of the relationship. It should also be noted that because octreotide is not approved for use in Australia for chemotherapy-induced diarrhoea and is rarely used outside the inpatient setting, this model includes the use of octreotide for serious diarrhoea only, which is inconsistent with many of the guidelines. This has resulted in a model that is applicable to the current Australian decision-making context that may need to be adjusted if the approval of octreotide changes in Australia or if the model is to be applied to a different setting.

3.4.7 **Conclusion**

The objective was to answer the question, ‘What is the cost of treating chemotherapy-induced diarrhoea in Australian adults, based on best clinical practice?’ A decision-tree model was developed to represent best practice in the management of chemotherapy-induced diarrhoea. Inputs included costs,

effectiveness, health utilities and dose modifications obtained from reviews of the literature. Based on a number of estimates and assumptions:

- In the base case of 5-FU + leucovorin, the average cost of managing chemotherapy-induced diarrhoea according to best-practice guidelines in Australia is $1,793 per adverse event.
- The model is most sensitive to changes in the probability of Grade III/IV diarrhoea, the cost of hospitalisation, and the probability that hospitalisation and octreotide dose escalations will be effective in addressing the diarrhoea.

The cost of managing chemotherapy-induced diarrhoea can be significant, particularly when the diarrhoea is serious (Grade III/IV) and/or it results in hospitalisation. Both low- and high-severity diarrhoea should be included in economic evaluations of chemotherapy cost-effectiveness. This model demonstrates how the Australia-based costs and consequences of chemotherapy-induced diarrhoea, including the impact on quality of life and the dose of chemotherapy, can be estimated.

3.5 Anaemia model

3.5.1 Background

Anaemia is a common adverse event of chemotherapy, and one that is often included in models of chemotherapy cost-effectiveness. However, the inclusion of anaemia-related resource-use and/or outcomes is not reported in any systematic or rigorous way. This section describes the development of a model of the costs and outcomes of chemotherapy-induced anaemia based on best-practice guidelines and using Australia-based cost data. The results of this model can be used to populate cost-effectiveness analyses of any chemotherapy treatment(s) that may induce anaemia, with the aim that the use of a high-quality, standard model of anaemia will improve the quality and comparability of cost-effectiveness analyses.

Chemotherapy-induced anaemia

Anaemia is defined by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE) as 'a disorder characterised by a reduction in the amount of hemoglobin in 100 mL of blood' (31, p3). Symptoms of anaemia can include skin paleness, shortness of breath, cardiac palpitations, tiredness and fatigue (31). It is estimated that between 30 and 90 per cent of patients with cancer experience anaemia at some point (144). This anaemia may be related to the cancer itself, such as through the infiltration of the cancer into the bone marrow, or to cancer treatments such as chemotherapy, which may impair the production process of red blood cells (RBCs), causing anaemia (145). Patients may experience multiple causes of anaemia at the same time, and although the consequences of different types of anaemia are the same, treatments differ (146). Therefore, it is important to identify the underlying cause of anaemia to identify the appropriate treatment (146). This work relates only to chemotherapy-related anaemia in solid tumour cancers.

Individuals with lung and gynaecologic cancers have been identified as having particularly high rates of chemotherapy-induced anaemia (144). This is partially due to the common usage of platinum agents (also used in ovarian and head and

neck cancers), which are well known to induce anaemia (147). Incidences of Grade III/IV anaemia have been found to be as high as 75 per cent with some traditional chemotherapy regimens such as CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone) for lymphoma (147). Other regimens commonly associated with anaemia include cisplatin, docetaxel, 5-FU, paclitaxel, vinorelbine and topotecan (147).

Anaemia usually develops slowly and may present as a delayed adverse event of treatment (148). The effects of chemotherapy may accumulate over time, so repeated cycles of chemotherapy may result in a steady increase in the rate of anaemia (149). It often presents as fatigue, and although this may be seen as a less-serious adverse event in terms of survival and treatment outcomes, it may have a significant effect on quality of life (150). Patients report that fatigue during cancer treatment can have a large impact on function and in younger people is related to a reduced ability to work (151).

Normal haemoglobin (Hb) levels are defined as above 12 g/dL for females, and 13 g/dL for males (152). Anaemia can be graded for severity into five levels, defined in the NCI CTCAE version 4.03 (31).

Table 3.8: NCI CTCAE volume 4.03 anaemia grading (31) (page 3)

Anaemia Grade				
I	**II**	**III**	**IV**	**V**
Hgb < LLN–10.0 g/dL; < LLN–6.2 mmol/L; < LLN–100 g/L	Hgb < 10.0–8.0 g/dL; < 6.2–4.9 mmol/L; < 100–80 g/L	Hgb < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death

LLN = Lower Limit of Normal; Hgb = Hemoglobin

Management

Anaemia can be managed with one or a combination of blood transfusions, erythropoiesis stimulating agents (ESAs) and iron supplementation.

RBC transfusions are blood products derived from blood donations that are processed and enhanced before being transfused into a new patient (149). RBC transfusion has the advantage of working to immediately correct anaemia, with transfusion of one unit (300 cc) of RBCs into an adult resulting in an average 1 g/dL (gram per decilitre) improvement in Hb (149). However, there are risks associated with RBC transfusions, including congestive heart failure, bacterial or viral contamination and iron overload (149). In addition, blood is in limited supply, making reliance on RBC transfusions potentially difficult (149). Until the 1990s, blood transfusions were the only treatment options for anaemia; however, increasing concerns about infections, quality of life and limitations in supply have resulted in alternative treatments being sought (148, 150).

Erythropoietin, which is produced in the body by the kidneys, controls the production of RBCs. ESAs are synthetic versions of erythropoietin that stimulate the production of RBCs (149). ESAs take time to improve Hb, with most patients requiring administration over a number of weeks. Once a response is achieved, ongoing administration is effective in maintaining a target Hb level (149).

This first ESA to be approved was epoetin alpha, originally approved for the management of anaemia related to renal disease, but it has since been investigated for use in other fields, such as HIV, surgery and anaemia related to cancer or chemotherapy (148, 150). There are now two ESAs available for use with cancer patients: epoetin alfa and darbepoetin alfa. Treatment with ESAs is considered safer than RBC transfusions and provides a more sustained correction of anaemia as well as being more convenient for patients (153). Known adverse events of ESAs for patients with cancer include thromboembolism, hypertension and pure red cell aplasia (149). ESAs are expensive, and during the peak of their use they accounted for 17 per cent of all Medicare Part B spending in the US for individuals with cancer (154).

The use of ESAs has reduced significantly in recent years due to new evidence that led the FDA to revise the regulations and the label information. These changes were based on randomised controlled trials and meta-analyses that showed reduced overall survival and/or increased rates of locoregional disease

control when ESAs were used in patients with a variety of cancers, including patients receiving chemotherapy (155). In response to this evidence, the FDA changed the ESA recommendations, which now state that in those cases where chemotherapy is being given with a curative intent, ESAs are not recommended (155). The FDA dosing recommendations for erythropoietic agents is displayed in Table 3.9.

Table 3.9: FDA Erythropoietic agent dosing recommendations (148)

Dose and modification	Epoetin alfa		Darbepoetin alfa	
Initial dose	150 U/kg SQ tiw	40,000 U SQ weekly	2.25 µg/kg SQ weekly	500 µg SQ q3w
Dose increase	Increase dose to 300 U/kg tiw if no reduction in transfusion requirements or increase in Hb after 4 weeks of therapy to achieve and maintain lowest Hb level sufficient to avoid need for Hb transfusion	Increase dose to 60,000 U SQ weekly if no increase in Hb by ≥ 1 g/dL after 4 weeks of therapy, in the absence of a RBC transfusion to achieve and maintain the lowest Hb level sufficient to avoid need for RBC transfusion	Increase dose up to 4.5 µg/kg if there is < 1 g/dL increase in Hb after 6 weeks of therapy	NA
Dose reduction	Decrease dose by 25% when Hb reaches a level needed to avoid transfusion, or Hb increase > 1 g/dL in 2 weeks		Decrease dose by 40% of previous dose when Hb reaches a level needed to avoid transfusion or Hb increases > 1 g/dL in 2 weeks	
Dose withholding	If Hb exceeds a level needed to avoid transfusion, restart dose at 25% below previous dose when Hb approaches a level where transfusion may be required		If Hb exceeds a level needed to avoid transfusion, restart dose at 40%below previous dose when Hb approaches a level where transfusion may be required	
Discontinue	After completion of chemotherapy or if no response after 8 weeks of therapy (measured by Hb levels or continuing need for transfusions)			

Note: ESA = erythropoiesis stimulating agent; Hb = haemoglobin; NA = not applicable; q3w = every three weeks; SQ = subcutaneous; tiw = three times per week; µg = micrograms; U = unit

Iron supplementation can be used on its own or in combination with ESAs and may be delivered either intravenously or orally. Research suggests that although oral iron is commonly used, IVT methods are more effective in managing functional iron deficiency (149). However, IVT iron is associated with adverse events, such as hypotension, hypertension, nausea, vomiting, diarrhoea, pain, fever, dyspnoea, pruritus, headaches and dizziness (149).

Previous studies of anaemia cost

Twenty-three studies that included a cost of anaemia were identified, with the majority being studies of ESAs (see Appendix J). Five of these were research-based papers, with the remaining based on models. Most studies included only Grade III/IV events, although some (94, 105, 113, 156-162) included all events regardless of grade, and three included multiple grades of each event (96, 98, 99). In most cases, the cost of pharmaceuticals was the primary cost included, although the cost of RBCs, hospitalisation and outpatient visits were included in many cases. Given that most studies were designed to assess the effectiveness and/or cost of ESAs, ESAs were the most commonly recommended management strategy in the studies, and it was usually described in detail. Similarly, RBC transfusion was also commonly used and well described.

The costs of managing anaemia differed significantly between studies. Many studies used different units of measurement, such as cost per event, cost per episode, cost per patient, cost per month, cost per cycle, or cost per QALY. Those studies that used the same units of measurement still had very different results. For example, the cost per anaemia event ranged from $269.37 (102) to $3,973.79 (157) (1999 International$) depending on the resources included, the anaemia management strategies assessed, and the source of cost inputs. These differences in methodologies and outcome measures mean that results were unable to be compared across studies.

One of the striking features of these results is the variation in estimates of the costs of chemotherapy-induced anaemia. This variation could be a result of the differing methodologies used by different studies. The model structure, resources included and local practice variations may all contribute to the variation in the

results. Although this is understandable, it highlights one of the key issues in the modelling of chemotherapy. Even when adverse events are included, the variations in the way they are considered can have an important impact on the overall results of the model.

Best practice treatment pathway

The search strategy identified five clinical practice guidelines developed for chemotherapy-related anaemia. None of these guidelines was Australian; however, the Australian Cancer Anaemia Survey asked about the treatments that adults with cancer-related anaemia received.

American Society of Clinical Oncology and American Society of Hematology (ASCO–ASH 2010) (148)

These guidelines are focused on the use of ESAs for the treatment of anaemia resulting from cancer or cancer treatments. Literature and data were selected and synthesised in a systematic and rigorous way as the basis for developing the clinical practice guidelines. The original guidelines were published in 2002 based on an evidence review conducted from 1997 to 2001. The guidelines were updated in 2007 and again in 2010 to take account of new information about the increased risks of morbidity and mortality associated with ESA therapy. For each update, a panel of independent experts in clinical medicine, clinical research, health-services research and related disciplines was convened to turn the evidence review into clinical practice guidelines.

The current guidelines include the following recommendations:

- Epoetin or darbepoetin should be considered for chemotherapy-associated anaemia where Hb has decreased to less than 10 g/dL, with the aim of reducing or avoiding RBC transfusions. RBC transfusion alone could be considered for this group.
- Unless specific clinical circumstances require it, the use of ESA therapy for patients with Hb levels between 10 g/dL and 12 g/dL is not recommended, as per the FDA labels. The use of RBC transfusion should be considered.

- The starting dose and dose modifications of ESA therapy should follow the FDA guidelines (see Table 3.9).
- Although the updated FDA label warning that ESA therapy is not indicated for patients who are having chemotherapy with the goal of cure is acknowledged, these guidelines stress that this is not a recommendation based on comparative clinical trials but on minimising the risk of increased mortality due to ESAs in individuals who might otherwise expect to be cured of their cancer. The recommendation is not that ESAs should be avoided in patients for whom chemotherapy has a curative intent, but that ESAs should be carefully considered for each patient based on treatment goals and the need for anaemia management.
- It is generally recommended that iron supplementation be used to augment response for ESA recipients; however, evidence for the optimal timing, dose and administration of supplemental iron is inconclusive.

Cancer Care Ontario (2010) (163)

The Cancer Care Ontario Program in Evidence-based Care produced a guideline for the treatment of anaemia with erythropoietic agents in patients with cancer based on the 2007 ASCO–ASH Guidelines. A rigorous approach was used to adapt the guidelines using the AGREE instrument and an expert panel. The AGREE instrument is a standardised tool to adapt clinical guidelines from one setting to another, taking account of local practice variations (164). The ASCO–ASH guidelines were updated the same year in which Cancer Care Ontario published their amended version, and Cancer Care Ontario incorporated the additional information from the FDA black box warnings into their guidelines.

The Cancer Care Ontario guidelines recommend that treatment with transfusion or ESAs be considered when Hb falls below 10 g/dL. The two ESA products are considered comparable, and the recommended dosages are taken from the product monograph. ESA is not recommended for individuals with cancer who are not receiving chemotherapy or who are receiving chemotherapy with curative intent.

Canadian Cancer and Anemia Guidelines Development Group (2001) (150)

These guidelines are based on a meta-analysis of 19 randomised controlled trials conducted between 1985 and 1999, which compared the effectiveness of epoetin alfa in reducing transfusion requirements to a suitable control group. The primary focus of the review was on the correction of anaemia as a way to maximise quality of life, noting that the Hb levels that correspond to optimal quality of life are generally higher than the levels that would ordinarily trigger transfusions.

Recommendations are presented in the form of a flow chart. It is recommended that patients start treatment if they have symptomatic anaemia that is affecting their functional capacity or quality of life, regardless of their Hb level. Alternatively, patients with a Hb level of less than 10 g/dL at commencement of chemotherapy, or with a drop of 1–2 g/dL per chemotherapy cycle should also commence treatment.

Treatment with ESAs is recommended in line with the FDA ESA dosing schedule.

European Organisation for Research and Treatment of Cancer (2007) (153)

The European Organisation for Research and Treatment of Cancer **(**EORTC) conducted a literature search to update a previous systematic review of the use of ESAs for individuals with chemotherapy-induced anaemia. Specific questions were identified with the aim being to maintain the completeness and accuracy of the current guidelines rather than to generate new guidelines. Studies were limited to clinical studies where ESAs were used with adult anaemic patients with cancer.

The EORTC guidelines suggest that treatment for anaemia be considered once Hb levels reach 9–11 g/dL. At this level, asymptomatic patients should be considered for ESAs, and those with symptoms should have ESA treatment initiated. Treatment should be continued until Hb reaches 12–13 g/dL, and should then be individualised to maintain Hb levels with minimal treatment. For patients who have Hb levels below 9 g/dL, a transfusion should be considered along with the possibility of ESA treatment. Once Hb reaches 12–13 g/dL, ESA treatment should

be individualised to maintain this target with minimal treatment. The concomitant administration of iron with ESAs is not recommended, based on a lack of evidence. These guidelines, which were published in 2006, make no mention of the potential impact of ESA treatment on cancer survival.

National Comprehensive Cancer Network (2011) (149)

The National Comprehensive Cancer Network (NCCN) guidelines include a risk assessment of patients identified as having chemotherapy-related anaemia in order to identify the initial management strategy. Rather than being based on the usual Hb-based grading of anaemia, the guidelines are based on the symptoms and comorbidities experienced by the patient. There are three groups of risk categories: 1) asymptomatic without significant comorbidities, 2) asymptomatic with comorbidities and 3) symptomatic. The recommended initial management to consider is RBC transfusion; this is not required for Group 1, but transfusion should be considered for Group 2 and is recommended for Group 3. Following initial management, patients should be considered for suitability for treatment with ESAs. The NCCN guidelines follow the FDA recommendation that patients receiving myelosuppressive chemotherapy with curative intent not be treated with ESAs. However, for those patients undergoing palliative treatment with ESAs should be considered as per the FDA guidelines, although a series of alternative regimens are also outlined. For those patients who receive ESAs, consideration of IVT iron supplementation is also recommended.

National Institute for Health and Clinical Excellence (2008) (165)

An appraisal committee reviewed the evidence on the clinical effectiveness and cost-effectiveness of ESAs for people with treatment-induced anaemia, from an updated Cochrane review. Based on the evidence, the review concluded that the realistic incremental cost-effectiveness ratio (ICER) value was unlikely to fall within the range normally considered a cost-effective use of the NHS resources. However, for the specific cases of women with ovarian cancer who had Hb levels below 80 g/dL, or for people who have profound anaemia but are unable to receive blood transfusions, ESA therapy in conjunction with IVT iron is

recommended. The developers of the guidelines were aware that their recommendations were significantly different from the existing guidelines in the US (ASCO–ASH) and Europe (EORTC); however, they felt that their inclusion of cost-effectiveness as well as clinical effectiveness gave them a different perspective and therefore a different set of recommendations for practice.

However, it should be noted that these guidelines were produced in 2008, and the cost-effectiveness analysis was based on ESA treatment being associated with a possible survival advantage. Therefore, these guidelines do not take into account evidence of ESA treatments having a potential detrimental effect on tumour progression.

Australian Cancer Anaemia Survey (166)

Although not guidelines for clinical practice, the results of the Australian Cancer Anaemia Survey are presented here. Given that there were no Australia-based guidelines identified, the results of this survey provide a picture of the frequency and management of chemotherapy-induced anaemia in Australia.

The Australian Cancer Anaemia Survey was a 6-month observational prospective multi-centre study, which recruited 694 patients in mid-2001 (166). Patients had solid or haematological cancers, and were receiving or had received chemotherapy, radiotherapy or both (166). Thirty-five per cent of patients had anaemia at baseline, and 57 per cent of individuals either had anaemia at baseline or developed it during the 6-month follow-up period (166). Only 41 per cent of the patients received treatment for their anaemia: 36 per cent with transfusion, five per cent with iron and two per cent with erythropoietic agents (166). This is markedly different from the practice recommendations in the international guidelines described above, although it should be noted that this survey was done in 2001, before the use of erythropoietic agents became standard.

3.5.2 Structure of the decision models

Two decision-tree models were developed to estimate the costs and benefits of best-practice management for chemotherapy-induced anaemia. The first model was for treatment of anaemia in individuals receiving chemotherapy with curative

intent who would not receive ESA therapy. The second model, which included ESA therapy, was for those receiving palliative chemotherapy. The structure of each model was based on the clinical pathways described in the guideline documents prepared by ASCO–ASH (148), the NCCN (149), EORTC (153), the Canadian Cancer and Anemia Guidelines Development Group (150), and Cancer Care Ontario (163), and is shown in Figure 3.5 and Figure 3.6. The full TreeAge model is in Appendix K.

The model was designed to be adaptable to any type of chemotherapy, with varying proportions of anaemia occurring at each grade. In order to demonstrate the model, a chemotherapy example was required to provide inputs for the proportion of anaemia at each grade. The Australian Cancer Anaemia Survey provides bottom-up data on the prevalence of anaemia in Australian chemotherapy patients. Given the country-specific nature of this data, along with the quality of the observational study used to collect it, this data was considered most appropriate as a case study to demonstrate the model. The rates of anaemia at each grade level for individuals in the Australian Cancer Anaemia Survey were used to populate the probability parameters within the model.

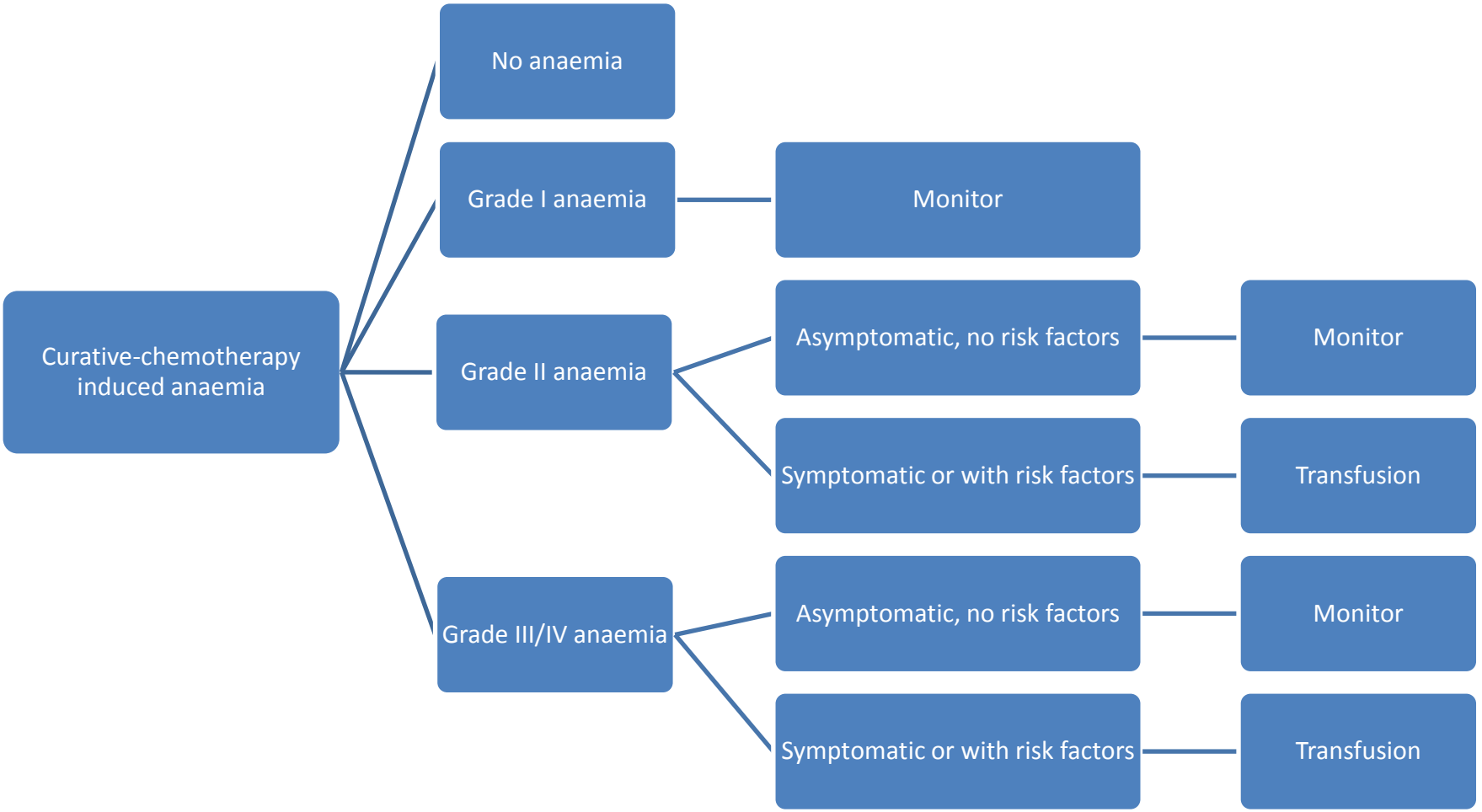


Figure 3.5: Decision-tree model for chemotherapy-induced anaemia associated with chemotherapy of curative intent

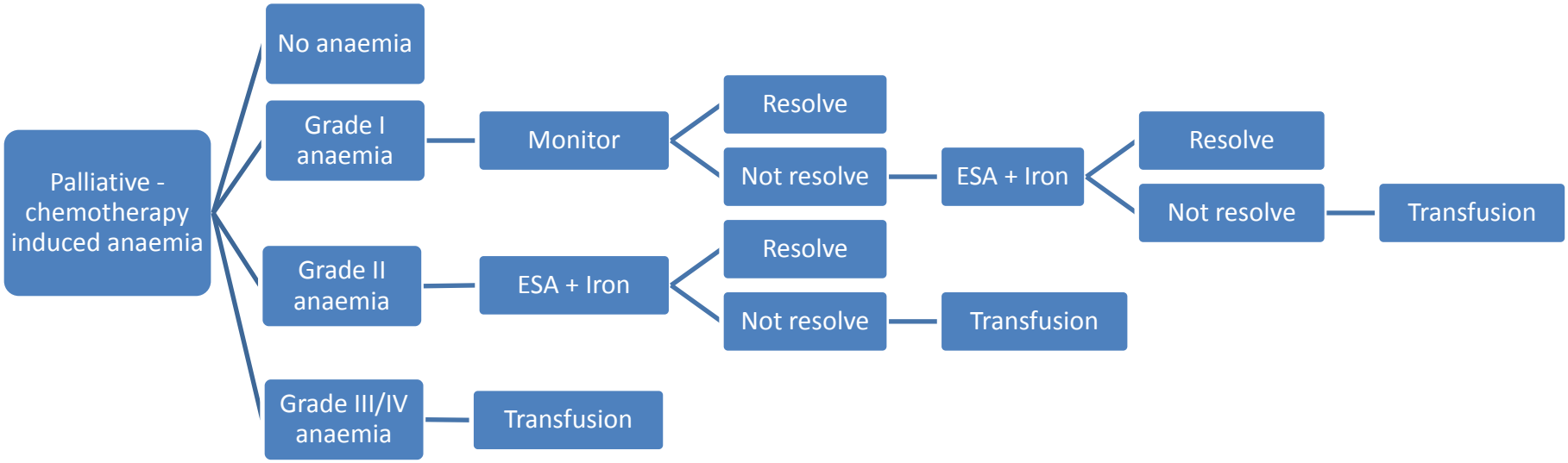


Figure 3.6: Decision-tree model for chemotherapy-induced anaemia associated with palliative chemotherapy

The assumptions underlying the structure of the models are as follows:

General assumptions

- Anaemia is limited to chemotherapy-induced anaemia. All other causes of anaemia have been excluded and/or treated appropriately.
- Chemotherapy-induced anaemia is managed in the same way, regardless of the causative chemotherapy. This is consistent with the clinical practice guidelines reviewed, none of which makes a distinction in anaemia management based on causative chemotherapy.
- Grading of events is according to the NCI CTCAE version 4.1.

Assumptions for chemotherapy-induced anaemia caused by chemotherapy with curative intent

- Several guidelines classify chemotherapy-induced anaemia as being *complicated anaemia* or *uncomplicated anaemia* based on additional patient risk factors. These risk factors include cardiac, lung or vascular disease. The presence of anaemia symptoms is another factor associated with a complicated anaemia diagnosis. Where evidence was available to differentiate the proportion of patients who were symptomatic (and therefore had a complicated anaemia) compared to non-symptomatic, this was included in the model. However, the proportion of patients with risk factors, such as heart, lung or vascular disease, will only be known once the population for the model is identified. This has therefore not been included in the model. This may result in the model underestimating costs, because some patients who may be experiencing complicated anaemia due to health risk factors may be asymptomatic and would therefore be treated more conservatively in the model.
- Grade I anaemia is monitored only.
- Grade II anaemia is considered for iron supplementation.
- Grade III symptomatic anaemia should be considered for transfusion. Asymptomatic patients should be considered for iron supplementation.
- Grade IV anaemia should be treated with an urgent transfusion.

- A one-unit transfusion of RBCs will result in 1 g/dL improvement in Hb, with a goal Hb level of 10 g/dL.
- Additional units of RBCs incur additional blood purchase costs, but do not incur additional administration costs.

Assumptions for chemotherapy-induced anaemia caused by palliative chemotherapy:

- Grade I anaemia is monitored only. If it does not resolve, then erythropoietic agents in combination with IVT iron are used. If these are not effective and anaemia continues, a transfusion is given.
- For Grade II anaemia, erythropoietic agents in combination with IVT iron are used. If these are not effective, a transfusion is given.
- For Grade III/IV anaemia, a transfusion is given.
- Dosage is based on the FDA erythropoietic agent dosing recommendations. The majority of studies specified that these dosage modification recommendations were followed, and therefore the drug efficacy is based on this practice. However, no data were identified to specify the proportion of individuals who have dose escalations or reductions based on these recommendations. It was therefore not possible to amend drug quantities based on dosage, and all patients were assumed to take the starting dose throughout ESA treatment. It is unclear whether this will result in an underestimate or overestimate of resource-use, because it is unknown whether more patients receive dose escalations or more receive dose reductions.

Model construction

The choice of a specific ESA regimen to treat chemotherapy-induced anaemia is primarily based on local practice. It was therefore decided to develop the model for anaemia related to palliative chemotherapy in such a way that a specific ESA could be selected as the local practice, and 100 per cent of patients requiring ESA therapy would be treated using that drug and regimen. Initially, this was achieved using a linked Microsoft Excel spreadsheet, which allowed the selection of a

specific ESA regimen in order to identify the appropriate input data for the model. Dynamic linking of Excel spreadsheets and TreeAge models is used when there are complex cost or utility calculations required in a model (121). However, sensitivity analysis was unable to be conducted on this linked model (TreeAge Support personal communication, 27 Aug 2012) and therefore four separate models were generated.

3.5.3 Synthesising the evidence

The probabilities for managing chemotherapy-induced anaemia were estimated from a variety of sources as indicated in Table 3.10 (curative chemotherapy model) and Table 3.11 (palliative chemotherapy model). Although the best available Australian evidence was sought, in many instances, Australia-based data were not available and best available international evidence was used.

As no high-quality Australian data were identified for the utility values associated with anaemia, the results of a study determining preferences and utility scores for anaemia related to cancer treatment in the UK was used (167). The study obtained utility values from both a sample of the general population (using standard gamble techniques) and from a patient population currently undergoing chemotherapy (using the time trade-off technique). The results found that, compared with patients, members of the general population consistently underestimated the impact of anaemia-related fatigue on utility, particularly with regard to the more-severe grades of anaemia. The reason for these differences in the valuations of anaemia health states could be because for patients, the valuation includes an implicit decrement in utility associated with having cancer and chemotherapy treatment. However, members of the general population may value the disutility of anaemia as separate from that associated with the effects of cancer and its treatments on quality of life. This distinction has implications for the selection of utility values for the model. If the larger model to which this model ultimately becomes an input already contains a utility decrement associated with having cancer and undergoing chemotherapy treatment, the additional decrement associated with anaemia needs to be independent of these factors to avoid double counting. However, if the utility value is related only to having anaemia, including

a more-accurate utility value that also accounts for the impact of cancer and chemotherapy would improve accuracy. The societal values (i.e. those values independent of the effects of cancer and chemotherapy) were selected for use in this model to reduce the potential for double counting.

The literature was searched to identify utility decrements associated with anaemia or overall utility values for having cancer with chemotherapy-induced anaemia. When selecting inputs for the model, papers that provided consistency in the model by providing only utility decrements or only overall utility values were preferred. In addition, preference was given to papers that provided a utility decrement specific to having chemotherapy-induced anaemia. This was because the overall purpose of the model was to provide an input for larger models of cost-effectiveness, and a utility decrement is more easily combined with other effects on utility and minimises the possibility of double counting. However, in the case of anaemia, the highest-quality available evidence was provided as a utility score, and no studies providing a utility decrement for anaemia were identified; therefore, utility was included in the model in this way.

No information was available about the influence of anaemia on chemotherapy dose modifications, and so these impacts were not able to be included in the model.

Given the short-term nature of anaemia, and therefore the model, no discounting was applied.

Table 3.10: Assumptions in the curative economic model of anaemia

Assumptions	Value	Source	Justification for source
Transitions	***Probabilities***		
Proportion of patients with Grade I chemotherapy-related anaemia	0.385	Ludwig et al (2004) (168)	Incidence of anaemia (all causes) in a large observational cohort
Proportion of patients who develop Grade II chemotherapy-related anaemia	0.138		Incidence of anaemia (all causes) in a large observational cohort
Proportion of patients who develop Grade III/IV chemotherapy-related anaemia	0.014		Incidence of anaemia (all causes) in a large observational cohort
Proportion of patients with Grade II anaemia who are symptomatic or have additional anaemia risk factors	0.400		Percentage of people at enrolment who had poor performance status. Assumes if anaemia affects PS, then must be symptomatic
Proportion of patients with Grade III/IV anaemia who are symptomatic or have additional anaemia risk factors	0.507		Percentage of people at enrolment who had poor performance status. Assumes if anaemia affects PS, then must be symptomatic
Dose changes			
Chemotherapy dose changes due to anaemia	No information identified, and therefore not included in the model		
Health utility scores	***Utility scores***		
Utility at Grade III anaemia (Hb 7.0–8.0 g/dL)	0.583	Lloyd et al. (2008) (167)	Societal utility values derived using standard gamble techniques
Utility at Grade II anaemia (average Hb of 8.0–9.0 g/dL and 9.0–10.0 g/dL)	0.624		
Utility at Grade I anaemia (average Hb of 10.0–	0.669		

Assumptions	Value	Source	Justification for source
10.5 g/dL and 10.5–11.0 g/dL and 10.5–11.0 g/dL)			
Utility at no anaemia (Hb 12.0 g/dL +)	0.708		
Treatment duration	***Time***		
Duration of monitoring	1 week	Assumed	Treatment is either monitoring or transfusion, which has an immediate effect; therefore, the model time horizon is one week
Pharmaceutical product doses	***Dosage***		
Grade II anaemia	1.5 U	Calculated	Based on Grade II anaemia being Hb 8–10 g/dL, with a goal of 10 g/dL, and assuming half of Grade II anaemia is 8 g/dL and half 9 g/dL, average of 1.5 g/dL required to gain, and therefore average 1.5 units of blood required for transfusion
Grade III/IV anaemia	3 U	Calculated	Based on Grade III/IV anaemia being Hb < 8 g/dL, with a goal of 10 g/dL Hb, average of 3 g/dL required to gain, and therefore average 3 units of blood required for transfusion

Notes: g/dL = grams per decilitre; Hb = haemoglobin; PS = performance status; U = units

Table 3.11: Assumptions in the palliative economic model of anaemia

Assumptions	Value	Source	Justification for source
Transitions	***Probabilities***		
Proportion of patients with Grade I chemotherapy-related anaemia	0.385	Ludwig et al (2004) (168)	Incidence of anaemia (all causes) in a large observational cohort
Proportion of patients who develop Grade II chemotherapy-related anaemia	0.138	Ludwig et al (2004) (168)	Incidence of anaemia (all cause) in a large observational cohort
Proportion of patients who develop Grade III/IV chemotherapy-related anaemia	0.014	Ludwig et al (2004) (168)	Incidence of anaemia (all causes) in a large observational cohort
Proportion of patients whose anaemia resolves with monitoring alone	0.36	Kim et al. 2007 (169)	Proportion of patients randomised to a no-iron control group who required a transfusion
Proportion of patients whose anaemia resolves with iron supplementation alone	0.6	Kim et al. 2007 (169)	Proportion of patients randomised to an IVT iron control group who required a transfusion
Proportion of patients whose anaemia resolves with epoetin three times per week	0.56	Ludwig et al (2009) (170)	No direct study of this regimen identified, therefore used overall rate from ACT observational study
Proportion of patients whose anaemia resolves with epoetin three times per week plus iron supplementation	0.69	Estimation	No direct study of this regimen identified, so used additional benefit of 0.13 for addition of iron supplementation, based on average additional benefit in other regimens
Proportion of patients whose anaemia resolves with epoetin weekly	0.55	Estimation	Loss of benefit of 0.13 for addition of iron supplementation, based on average additional benefit in other regimens
Proportion of patients whose anaemia resolves with epoetin weekly plus iron supplementation	0.68	Auerbach 2004 (171)	Study of any cancers and any chemotherapy with 6-week follow-up. Response defined as > 12 g/dL or > 2 g/dL
Proportion of patients whose anaemia resolves with darbepoetin weekly	0.618	Pedrazzoli et al. 2008 (172)	Randomised trial of darbepoetin weekly +/- IV iron supplementation – results of control arm
Proportion of patients whose anaemia resolves with darbepoetin weekly plus iron supplementation	0.767	Pedrazzoli et al. 2008 (172)	Randomised trial of darbepoetin weekly +/- IV iron supplementation – results of experimental arm

Assumptions	Value	Source	Justification for source
Proportion of patients whose anaemia resolves with darbepoetin three-weekly	0.73	Bastit 2008 (173)	Randomised trial of darbepoetin every 3 weeks +/- IV iron supplementation – results of control arm
Proportion of patients whose anaemia resolves with darbepoetin three-weekly plus iron supplementation	0.86	Bastit 2008 (173)	Randomised trial of darbepoetin every 3 weeks +/- IV iron supplementation – results of experimental arm
Dose changes			
Chemotherapy dose changes due to anaemia	No information identified, and therefore not included in the model		
Health utility scores	***Utility scores***		
Utility at Grade III anaemia (Hb 7.0–8.0 g/dL)	0.583	Lloyd et al. 2008 (167)	Societal utility values derived using standard gamble techniques
Utility at Grade II anaemia (average Hb of 8.0–9.0 g/dL and 9.0–10.0 g/dL)	0.624		
Utility at Grade I anaemia (average Hb of 10.0–10.5 g/dL and 10.5–11.0 g/dL and 10.5–11.0 g/dL)	0.669		
Utility at no anaemia (Hb 12.0 g/dL +)	0.708		
Treatment duration	***Time***		
Duration of ESA treatment if response achieved	20 weeks	Calculated	
Duration of ESA treatment if no response achieved	8 weeks	NCCN (149)	NCCN guidelines state that if no response is achieved in 8–9 weeks, ESA should be discontinued
Duration of IVT iron supplementation	20 weeks	Calculated	
Other assumptions			
Average patient weight	70 kg	Assumed	Average used in drug dosing models

Note: ECAS = European Cancer Anaemia Survey; ESA = erythropoiesis stimulating agent; g/dL = grams per decilitre; Hb = haemoglobin; IVT = intravenous therapy; kg = kilograms; NCCN = National Comprehensive Cancer Network

Costs are based on Australian sources and are estimated based on the highest-quality evidence available from reliable sources in 2012 Australian dollars. High-quality evidence traditionally includes well-designed randomised controlled trials or meta-analyses published in peer-reviewed literature. However, where this is not available or not appropriate, data from well-conducted observational studies, national policy documents or guidelines for clinical best practice may also provide high-quality evidence. The costs associated with managing anaemia and their sources are described in Table 3.12.

Pharmaceutical costs are derived from the PBS cost for the maximum quantity prescribed. The average cost of the drug for the maximum quantity was calculated using all available brands. The impact of using the highest- and lowest- cost brands is tested in the sensitivity analysis. To calculate costs associated with different doses, the cost of the drug was divided to find the cost per drug-specific unit (e.g. per capsule or per 50 μg), and used to calculate the cost per dose of the drug. This calculated cost does not account for bulk purchasing (resulting in savings) or wastage by the dispenser (resulting in additional cost).

Blood product administration costs are derived from the MBS full fee for a service. As there is an agreement between individual health services and the National Blood Authority, the purchase price of blood products is unclear. Blood products are generally supplied free of charge to end users such as public hospitals and private practitioners (174). The cost to the Government is set by the National Blood Authority based on price and volume, as is in the National Product and Supply List, however list this is not publically available (174). In lieu of an actual cost being available, the estimated cost was determined by using the cost of collecting blood from an individual has been used as a proxy. It is suspected that this is an underestimate of the cost of blood products.

Table 3.12: Costs used in (both) economic models of anaemia

Resource	Cost (A$)	Source	Notes
GP or specialist visit for anaemia assessment or treatment	$34.90	MBS	Item 23 (Level B GP consultation in rooms)
Blood test	$50.60	MBS	Items 65070 & 66596, cost of CRC with indices and blood smear morphology
IVT iron purchase cost	$27.80	PBS	Item 8807M, iron sucrose,
RBC purchase cost	$46.60	MBS	Item 13709. Unclear how this is costed, as health services have agreement with National Blood Authority to provide blood. In lieu of actual cost, the estimated cost of collecting blood from an individual has been used (MBS item 13709). 1 unit (300 cc) of RBCs estimated to increase Hb by 1 g/dL. Transfusion aim is to maintain Hb levels of 7–9 g/dL
RBC administration	$80.20	MBS	Item 13706
Epoetin three times per week: cost for one week	$583.33	PBS	Point estimate cost is mean of price per 1,000 units for all EPO-A drugs on PBS. Low estimate is item 5718Y; high estimate is item 6251B
Epoetin weekly: cost for one week	$740.00	PBS	Point estimate cost is mean of price per 1,000 units for all EPO-A drugs on PBS. Low estimate is item 5718Y; high estimate is item 6251B
Darbepoetin weekly: cost for one week	$552.60	PBS	Point estimate cost is mean price per 10 µg for all DPO-A drugs on PBS. Low estimate is item 5650J; high estimate is item 6320P
Darbepoetin three-weekly: cost for one week	$584.17	PBS	Point estimate cost is mean price per 10 µg for all DPO-A drugs on PBS. Low estimate is item 5650J; high estimate is item 6320P

Note: CRC = colorectal cancer; DPO-A = darbepoetin alpha; EPO-A = epoetin alpha; g/dL = grams per decilitre; GP = general practitioner; Hb = haemoglobin; IVT = intravenous therapy; RBC = red blood cell; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme

3.5.4 Modelling the results

The decision-tree model provides a cost for each branch of the tree, based on the inputs. In order to calculate these, the incidence of anaemia overall in the European Cancer Anaemia Survey (ECAS) was used to determine the proportion of patients who would experience anaemia at each grade. Although there is an Australian Cancer Anaemia Survey (166), the results of the Australian survey describe the overall incidence of anaemia in individuals receiving chemotherapy, divided into Grade I vs. Grades II-IV. The results do not provide sufficient detail to be used as an input to the model.

Curative model

Based on the overall rates of anaemia from the ECAS, the average cost of managing chemotherapy-induced anaemia in individuals according to best-practice guidelines in Australia was $37 per event. The most-expensive anaemia to manage was that which required a transfusion. The utility value for each grade of adverse event was also included in the model (see Table 3.13).

Table 3.13: Base-case results for curative model of anaemia

Grade	Probability*	Cost (A$)	Utilities*
No anaemia	0.463	0	0.71
Grade I anaemia	0.385	51	0.67
Grade II anaemia	0.138	111	0.62
Grade III/IV anaemia	0.014	162	0.58

* Probabilities and utilities are presented with values ranging from 0 to 1

Palliative model

The base case cost results for the models of anaemia related to palliative chemotherapy are shown in Table 3.14.

Epoetin weekly: Based on the overall rates of anaemia from the ECAS and the local practice of using epoetin weekly for ESA treatment, the average cost of managing chemotherapy-induced anaemia over a 12-week chemotherapy regimen according to best-practice guidelines in Australia was $6,838. The most-expensive

anaemia to manage was that which required both ESA treatment and a transfusion, which cost on average $17,192 per person.

Epoetin three times per week: Based on these overall rates of anaemia from ECAS and the local practice of using epoetin three times per week for ESA treatment, the average cost of managing chemotherapy-induced anaemia over a 12-week chemotherapy regimen according to best-practice guidelines in Australia was $5,633. The most-expensive anaemia to manage was that which required both ESA treatment and a transfusion, which cost on average $14,059 per person.

Darbepoetin weekly: Based on these overall rates of anaemia from ECAS and the local practice of using darbepoetin alfa weekly for ESA treatment, the average cost of managing chemotherapy-induced anaemia over a 12-week chemotherapy regimen according to best-practice guidelines in Australia was $5,393 . Grade I anaemia, which required only monitoring, had a cost of $1,710, which was consistent across all the models because Grade I anaemia does not require ESA therapy. The most-expensive anaemia to manage was that which required both ESA treatment and a transfusion, which cost on average $13,444 per person.

Darbepoetin three-weekly: Based on these overall rates of anaemia from ECAS and the local practice of using darbepoetin three-weekly for ESA treatment, the average cost of managing chemotherapy-induced anaemia over a 12-week chemotherapy regimen according to best-practice guidelines in Australia was $5,632. The most-expensive anaemia to manage was that which required both ESA treatment and a transfusion, which cost on average $14,076 per person.

Table 3.14: Base-case results for palliative model of anaemia—costs

Grade	Probability	Epoetin 3 times per week (A$)	Epoetin weekly (A$)	Darbepoetin weekly (A$)	Darbepoetin three-weekly (A$)
No anaemia	0.463	0	0	0	0
Grade I anaemia	0.385	9,564	11,564	9,158	9,555
Grade II anaemia	0.138	13,972	17,107	13,348	13,967
Grade III/IV anaemia	0.014	1,837	1,837	1,837	1837

The utility values for each grade of event were also modelled, and are presented in Table 3.15. The quality of life decreases with increasing severity of anaemia, however there is no difference between utilities for different anaemia treatments.

Table 3.15: Base-case results for palliative model of anaemia—utilities

Grade	Probability	Epoetin 3 times per week	Epoetin weekly	Darbepoetin weekly	Darbepoetin three-weekly
No anaemia	0.463	0.71	0.71	0.71	0.71
Grade I anaemia	0.385	0.63	0.63	0.64	0.64
Grade II anaemia	0.138	0.61	0.61	0.62	0.62
Grade III/IV anaemia	0.014	0.58	0.58	0.58	0.58

3.5.5 Assessing uncertainty

To explore the source and impact of uncertainty in the model, one-way sensitivity analyses were undertaken to establish which estimates have the greatest effect on the average cost of managing chemotherapy-induced anaemia. All parameters were tested in the sensitivity analysis and the values used are shown in Table 3.16 (curative model) and Table 3.17 (palliative model). The full results of the sensitivity analysis, presented as tornado diagrams, are shown in Figure 3.7, Figure 3.8, Figure 3.9, Figure 3.10, and Figure 3.11.

The curative model was most sensitive to:

- probability of Grade I chemotherapy-induced anaemia
- probability of Grade II chemotherapy-induced anaemia
- cost of evaluation for chemotherapy-induced anaemia
- probability of Grade IV chemotherapy-induced anaemia.

The curative model was moderately sensitive to:

- probability of Grade II anaemia being symptomatic
- cost of administering RBC transfusions

- cost of purchasing RBC
- probability of Grade III/IV anaemia being symptomatic.

The parameters to which the palliative models were most sensitive were consistent across the four models:

- probability of Grade II anaemia
- probability of Grade I anaemia
- cost of the eruthropoietin or darbepoetin treatment
- probability of anaemia despite monitoring.

The palliative models were moderately sensitive to:

- cost of a blood test
- cost of a GP visit
- probability of Grade III/IV anaemia
- cost of IV iron supplementation.

Table 3.16: Parameters and values tested in the sensitivity analysis of the curative model of anaemia

Transition/Utility/Cost item	Values used in sensitivity analysis	Source
Probability of Grade I anaemia	0.19–0.58	Low value is Grade I anaemia prevalence in head and neck cancer, regardless of treatment in ECAS. ACAS point estimate used for high value
Probability of Grade II anaemia	0.04–0.20	Low value is Grade II anaemia prevalence in breast cancer in ECAS. ACAS point estimate is 19%; high value is prevalence of Grade II anaemia in leukaemia in ECAS
Probability of Grade III/IV anaemia	0.00–0.06	High value is Grade III/IV anaemia prevalence in leukaemia patients (regardless of treatment); low value is 0 because no specific value given except < 1%, both from ECAS
Probability anaemia Grade II will be symptomatic or with additional risk factors	0.3–0.5	+/– 25% used, because no range found
Probability anaemia Grade III/IV will be symptomatic or with additional risk factors	0.4–0.6	+/– 25% used, because no range found
Cost of RBCs	$34.95–$58.25	25% +/– list price
Cost of transfusion	$60.15–$100.25	25% +/– list price
Cost of GP visit	$26.18–$43.63	25% +/– list price
Cost of blood test	$37.95–$63.25	25% +/– list price
Utility at Grade III/IV	0.297–0.650	Lower value is mean patient TTO utility from Lloyd et al. (2008) (168)—these were consistently lower than societal preference values. High value is highest end of societal value 95% confidence interval
Utility at Grade II	0.360–0.700	
Utility at Grade I	0.446–0.759	
Utility with no anaemia	0.611–0.765	

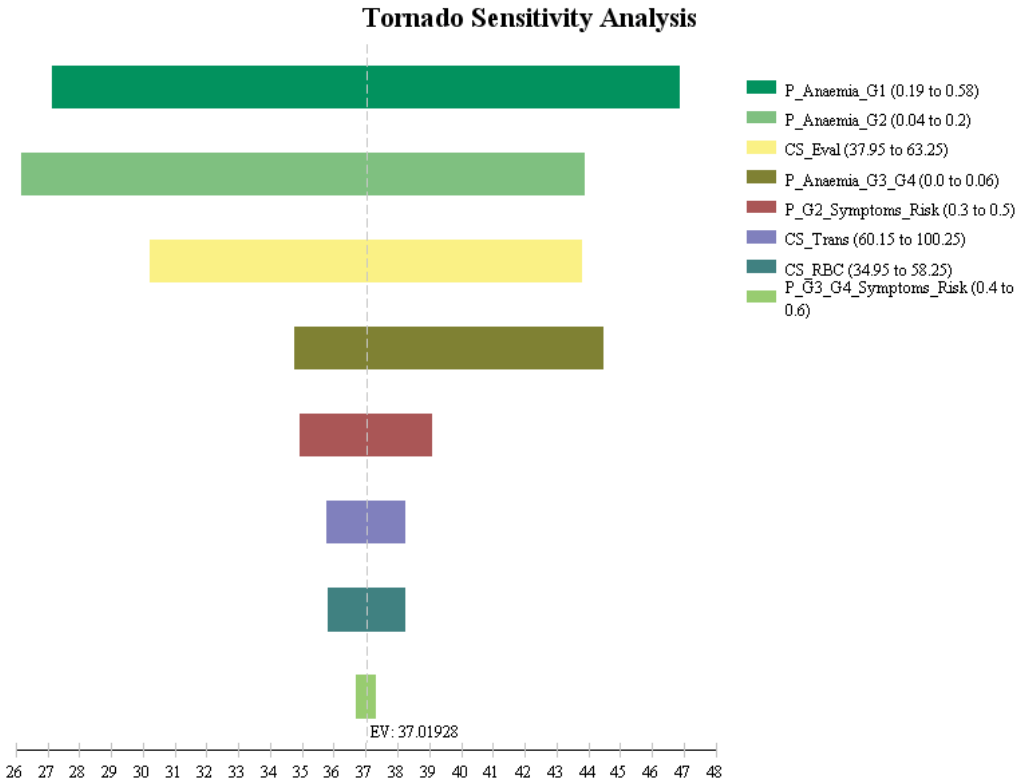
Note: ACAS = Australian Cancer Anaemia Survey; ECAS = European Cancer Anaemia Survey; TTO = time trade-off.

Table 3.17: Parameters and values tested in the sensitivity analysis of the palliative model of anaemia

Transition/Utility/Cost item	Values used in sensitivity analysis	Source
Transitions	***Probabilities***	
Probability of Grade I anaemia	0.23–0.607	Low estimate is from ACAS; high estimate is any anaemia frequency in ECAS.
Probability of Grade II anaemia	0.002–0.32	
Probability of Grade III/IV anaemia	0.00–0.072	
Probability anaemia does not resolve with monitoring alone	0.48–0.80	+/– 25% used, because no range found
Probability anaemia resolves with epoetin three times weekly & iron	0.7075–0.5125	+/– 25% used, because no range found
Probability anaemia resolves with epoetin weekly & iron	0.53–0.73	Henry et al.'s 2007 (173) study of solid cancers and any chemotherapy with 8-week follow-up. Low rate is response rates in ITT analysis; high rate is response rate in only evaluable patients. Response defined as > 12 g/dL.
Probability anaemia resolves with darbepoetin weekly & iron	0.654–0.979	Pedrazzoli et al.'s 2008 (175) study of solid cancers and any chemotherapy. Low estimate is lower 95% CI boundary for ITT analysis. High estimate is upper 95% CI boundary for patients with at least 4 x EPO doses. Response defined as Hb > 12 g/dL or an increase of > 2 g/dL.
Probability anaemia resolves with darbepoetin three-weekly & iron	0.79–0.82	Basitt's 2008 (173) study of solid cancers and any chemotherapy. High and low estimates are upper and lower boundaries of 95% confidence interval. Response defined as Hb > 12 g/dL or an increase of > 2 g/dL
Probability anaemia resolves with transfusion	1.0	Transfusion is 100% effective, but number of units of blood required may vary. This is captured in the SA for cost of RBC.

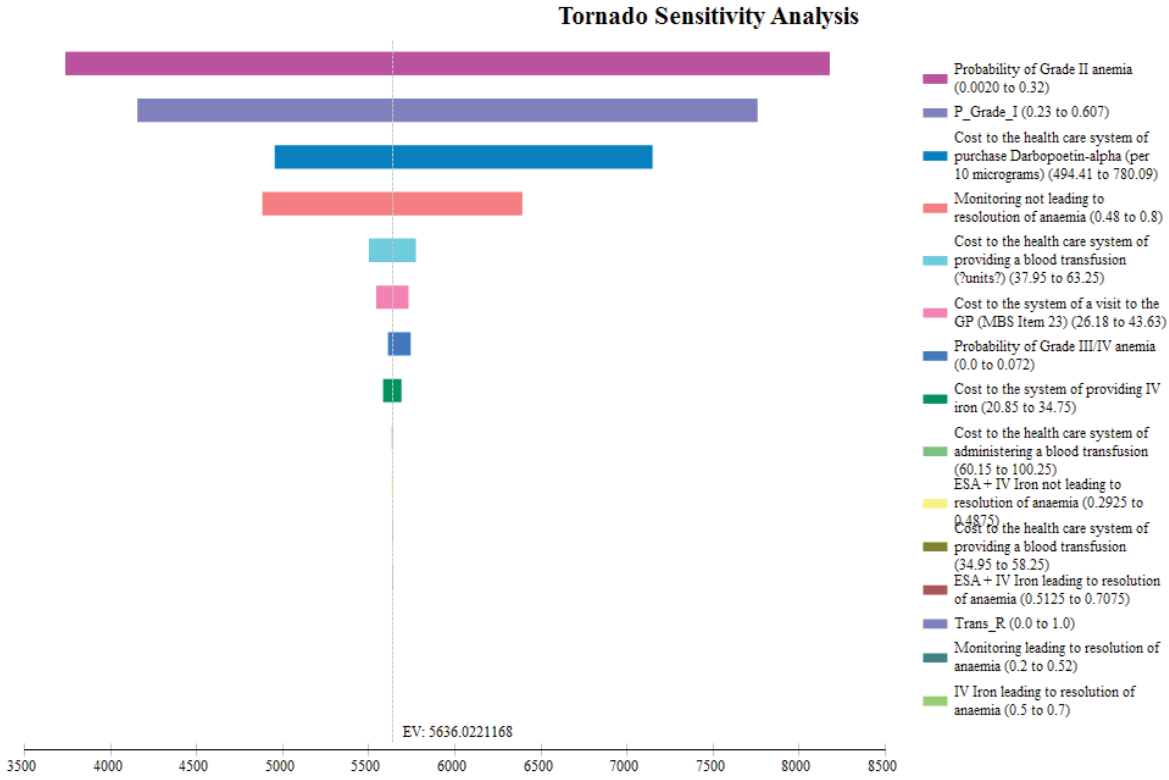
Transition/Utility/Cost item	Values used in sensitivity analysis	Source
Costs	***A$***	
Cost of EPO	$11.76–$30.93	25% +/– the highest and lowest list price
Cost of darbepoetin	$24.40–$58.86	
Cost of iron	$20.85–$34.75	
Cost of RBCs	$34.95–$58.25	
Cost of transfusion	$60.15–$100.25	
Cost of GP visit	$26.18–$43.63	
Cost of blood test	$37.95–$63.25	
Utilities	***Utility values***	
Utility at Hb 7.0–8.0 g/dL	0.297–0.650	Lower value is mean patient TTO utility from Lloyd et al. (2008) (168). These were consistently lower than societal preference values. High value is highest end of societal value 95% confidence interval.
Utility at Hb 8.0–9.0 g/dL	0.360–0.672	
Utility at Hb 9.0–10.0 g/dL	0.408–0.700	
Utility at Hb 10.0–10.5 g/dL	0.446–0.704	
Utility at Hb 10.5–11.0 g/dL	0.454–0.722	
Utility at Hb 11.0–12.0 g/dL	0.545–0.759	
Utility at Hb 12.0 g/dL +	0.611–0.765	

Notes: ACAS = Australian Cancer Anaemia Survey; CI = confidence interval; EPO = erythropoietin; ECAS = European Cancer Anaemia Survey; ITT = intention to treat; SA = sensitivity analysis; TTO = time trade-off.



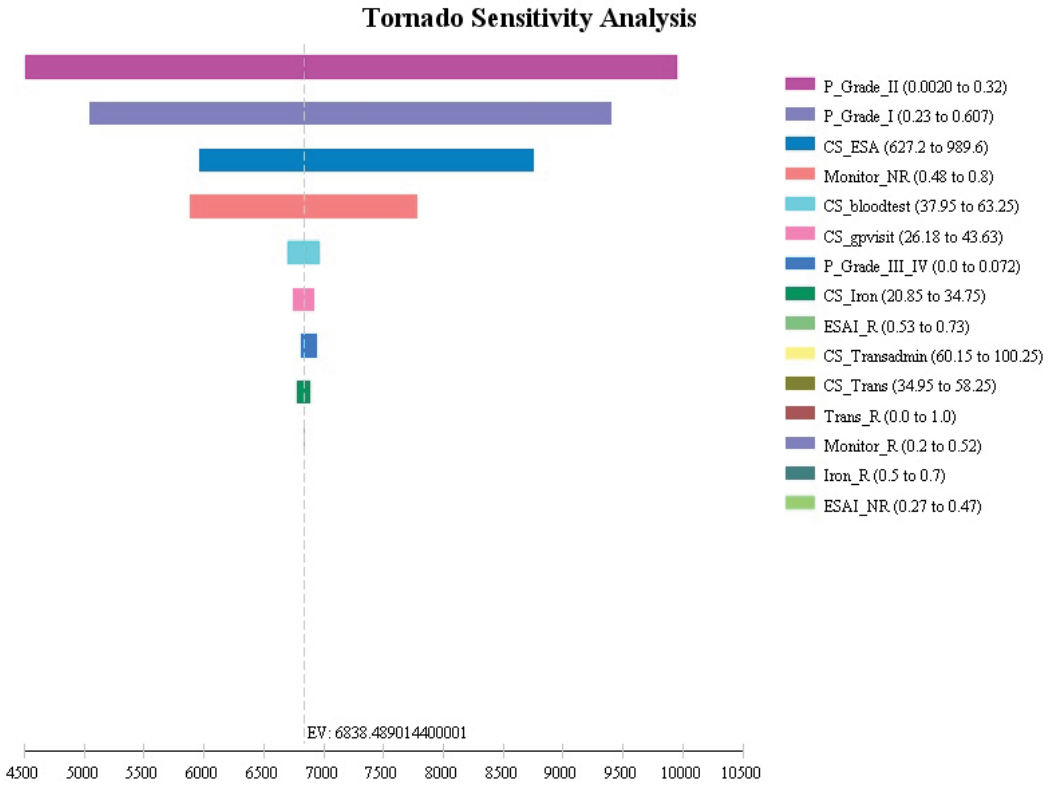
Note: x-axis represents cost; CS = cost (to the healthcare system); EV = expected value; Eval = anaemia evaluation; G2 = grade II; G3 = grade III; G4 = grade IV; P = probability; RBC = red blood cell; Trans = transfusion

Figure 3.7: One-way sensitivity analysis of curative anaemia model—all parameters



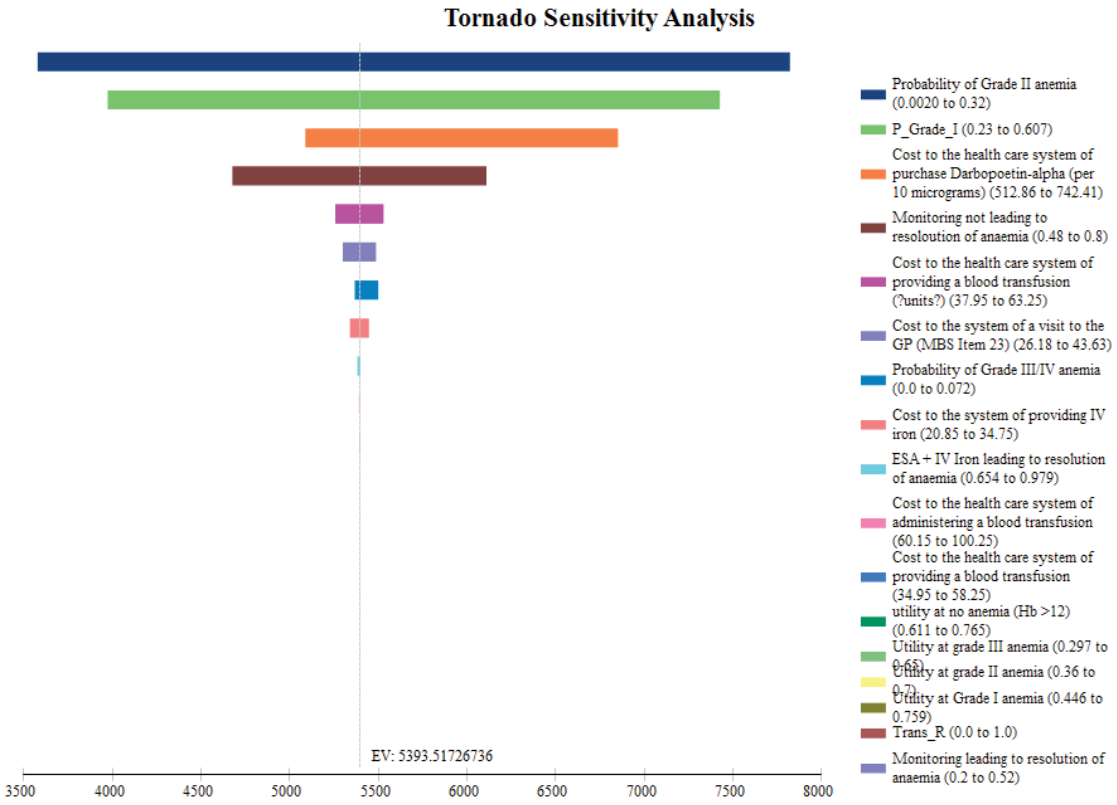
Note: x-axis represents cost; admin = administration; CS = cost (to the healthcare system); ESA = erythroietic stimulating agent; EV = expected value; Eval = anaemia evaluation; G2 = grade II; G3 = grade III; G4 = grade IV; GP = general practitioner; NR = not responsive (to treatment); P = probability; RBC = red blood cell; R = responsive (to treatment); Trans = transfusion

Figure 3.8: One-way sensitivity analysis of anaemia model—EPO three times weekly



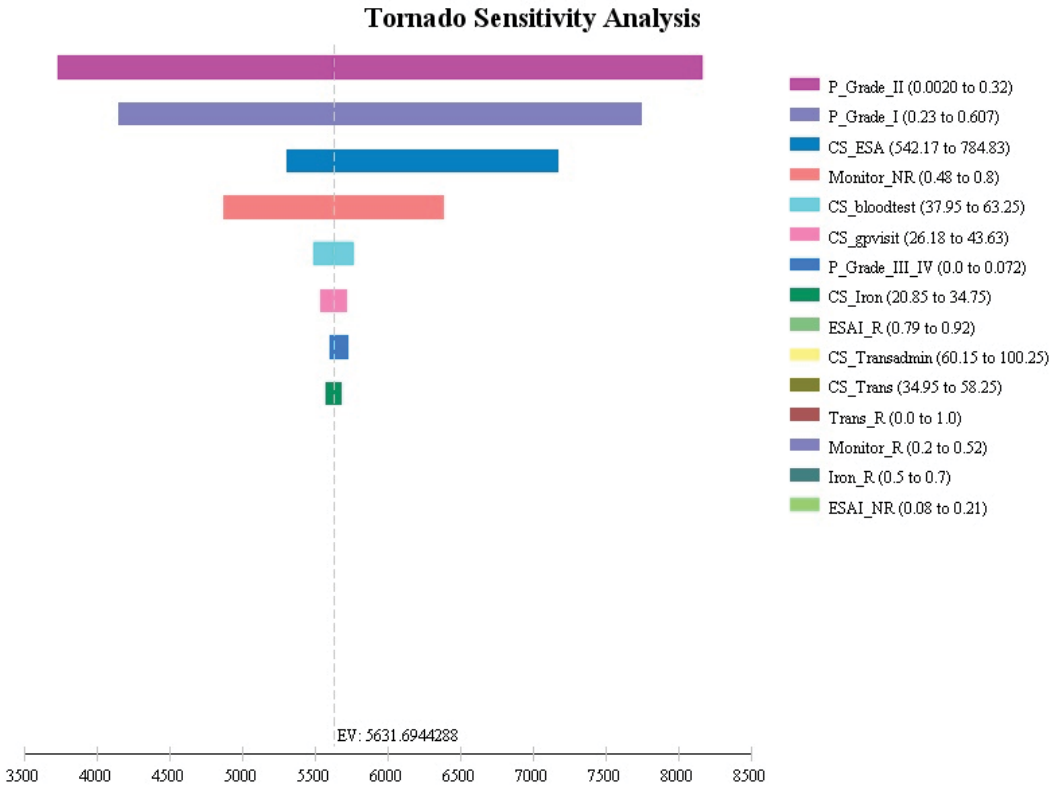
Note: x-axis represents cost; admin = administration; CS = cost (to the healthcare system); ESA = erythroietic stimulating agent; EV = expected value; Eval = anaemia evaluation; G2 = grade II; G3 = grade III; G4 = grade IV; GP = general practitioner; NR = not responsive (to treatment); P = probability; RBC = red blood cell; R = responsive (to treatment); Trans = transfusion

Figure 3.9: One-way sensitivity analysis of anaemia model—EPO weekly



Note: x-axis represents cost; admin = administration; CS = cost (to the healthcare system); ESA = erythroietic stimulating agent; EV = expected value; Eval = anaemia evaluation; G2 = grade II; G3 = grade III; G4 = grade IV; GP = general practitioner; NR = not responsive (to treatment); P = probability; RBC = red blood cell; R = responsive (to treatment); Trans = transfusion

Figure 3.10: One-way sensitivity analysis of anaemia model—darbepoetin weekly



Note: x-axis represents cost; admin = administration; CS = cost (to the healthcare system); ESA = erythroietic stimulating agent; EV = expected value; Eval = anaemia evaluation; G2 = grade II; G3 = grade III; G4 = grade IV; GP = general practitioner; NR = not responsive (to treatment); P = probability; RBC = red blood cell; R = responsive (to treatment); Trans = transfusion

Figure 3.11: One-way sensitivity analysis of anaemia model—darbepoetin three-weekly

For model-builders or decision-makers using this model within an economic evaluation of chemotherapy, these results indicate that an accurate profile of anaemia in patients undergoing the chemotherapy treatment of interest is important. This is because uncertainty about the probability of experiencing anaemia consistently affected the results across all models. In addition, the cost of ESAs also influences the cost of managing chemotherapy-induced anaemia, presumably because it is a high-cost item.

3.5.6 Discussion

It is difficult to compare the results of this model with previous studies of chemotherapy-related anaemia, because the definition of anaemia is inconsistent. Although some studies use standard definitions, such as the NCI CTCAE version

4.0 used in this model, many others use various cut-offs based on Hb levels. The NCI CTCAE version 4.0 is the current standard definition of anaemia used in clinical trials and clinical practice in oncology, and was therefore selected as the basis for this model.

Numerous studies have investigated the management of anaemia, primarily examining the introduction of erythropoietic stimulating agents to the management of anaemia. These studies compare ESAs to transfusions, as well as examining different ESA implementation strategies, for example, comparing different regimens, comparing ESAs with and without iron supplementation, comparing different Hb 'triggers' for ESA therapy, and so on. This model utilises evidence-based best-practice guidelines for the management of chemotherapy-induced anaemia.

The costs included in the model were all those applicable from the perspective of the healthcare system: GP visits, blood tests, RBCs and their administration, ESA drugs and their administration, and iron and its administration. This collection of costs is more comprehensive than many previously published studies that included costs associated with chemotherapy-induced anaemia. Most studies included resource-use focused on hospitalisation costs, transfusions and laboratory tests. Those with a focus on ESA treatments included medication costs—sometimes as the only resource under consideration.

This model does not include resource-use associated with hospitalisation or laboratory tests. The decision to exclude hospitalisation was taken on the basis that the model structure is based on best-practice guidelines, and none of these guidelines recommended hospitalisation for the treatment of chemotherapy-induced anaemia. Laboratory tests were also excluded. The laboratory test to diagnose anaemia would come before the diagnosis, and would therefore be outside the scope of the model. Ongoing blood tests for resolution of anaemia would primarily occur as part of a panel of standard pre-chemotherapy blood tests.

Previous models that included a cost of anaemia primarily included only the cost of Grade III/IV (serious) events. Although this analysis found that less-serious

anaemia has lower costs than more-serious events, the high probability of anaemia in this scenario indicates that low-grade anaemia is still a significant event of interest.

It is uncertain to what extent treatment patterns have changed since the Australian Cancer Anaemia Survey was conducted in 2001. If practice patterns remain the same, then the majority of patients in Australia would be treated according to the model of curative chemotherapy-induced anaemia, as the use of erythropoietic agents was uncommon. The rates of chemotherapy-induced anaemia appear to be generally similar between the Australian Cancer Anaemia Survey and the ECAS study used as the basis for the model presented here, although it is difficult to compare with any accuracy given the differing populations and definitions of anaemia.

It is difficult to compare the cost of chemotherapy induced anaemia obtained from these models with the costs from previous studies of anaemia due to differences in the structure, inputs and assumptions of the different models. Previous studies have estimated the cost of anaemia to range from Int$269 (102) to Int$3973 (157). The least expensive branch in this model was Grade I anaemia caused by curative chemotherapy, with a cost of AUD$51 (Int$40). The most expensive was AUD$17,100 (Int$13,571) for grade II anaemia treated with Epoetin weekly. While it is clearly the cost of ESAs which is driving this particularly high cost, there are many distinctions between the models developed here and those in the previous literature which make it difficult to see the cause of this particularly high result given that many of the previous studies were of the use of ESAs.

Of particular note is that the highest estimate here is for grade II anaemia with palliative chemotherapy. Many of the previous studies were limited to grade III or IV anaemia, which would account for the underestimation of costs in comparison to this model (where only a simple blood transfusion is used for grade III/IV anaemia). However this cannot explain the full difference in estimates, as a number of studies included the use of ESAs at all grades.

The distinction between the cause of anaemia as curative or palliative chemotherapy is unique in comparison to the previous studies, which may have

been limited to metastatic or advanced disease, but were not specifically limited to palliative chemotherapy.

Selection of adverse events for inclusion

When taken as a cost-of-illness estimate, the results of this model show that anaemia is an adverse event that can be associated with a significant cost. This cost is particularly high for individuals undergoing palliative chemotherapy who may therefore be treated with erythropoietic agents. However, the high proportion of people identified as having anaemia over the course of chemotherapy means that even less-serious, less-expensive anaemia events can influence overall costs. This implies that the costs and outcomes of chemotherapy-induced anaemia should be included in all chemotherapy cost-effectiveness analyses where anaemia is a potential adverse event.

Impact of adverse events on quality of life

The impact of the adverse event anaemia on quality of life appears to be poorly understood, and there is limited rigorous evidence for use as inputs to this component of the model. In this model, values for utility are given for each of the three levels of anaemia. In the future, this model could be improved by populating the utility components of the model with utility decrements that are specifically associated with the experience of anaemia associated with chemotherapy, and that exclude the utility values associated with cancer and chemotherapy. This is because it is assumed that if a modeller is using this model as an input to a larger model of chemotherapy cost-effectiveness, there will be utility values associated with the experience of having cancer and undergoing chemotherapy already included, and therefore they should be separate from the experience of having an adverse event in order to avoid double counting.

Influence of adverse events on dose of chemotherapy

There was no rigorous evidence identified for the proportion of individuals who have dose modifications because of chemotherapy-induced anaemia. As a result, models of chemotherapy cost-effectiveness that incorporate this model of anaemia will not be able address the consequences of anaemia for the overall quantity of

chemotherapy received and for the efficacy of chemotherapy. This reduces the model's ability to capture all of the costs and consequences of chemotherapy-induced anaemia, and provides a high-priority opportunity for future research.

Consideration of multiple adverse events

The decision-tree structure allows recurrent episodes of anaemia to be included in a model of chemotherapy cost-effectiveness. In reviewing the literature, there was little to indicate that the management of anaemia is changed significantly when multiple episodes of anaemia are experienced over time, and therefore to use the same model for each episode would appear to be appropriate.

By modelling chemotherapy-induced anaemia as a stand-alone event, it is not possible to explore whether the management and resources associated with chemotherapy-induced anaemia is altered when it occurs in combination with another adverse event. Little literature was identified about this, neither for anaemia specifically, nor for adverse events in general. This will be explored further in Chapters 4 and 5.

Influence of the severity of adverse events on cost

The results of the model of anaemia related to palliative chemotherapy are not consistent with the general prediction that an increasing severity of an adverse event will be associated with increased costs. In this case, the cost of Grade I anaemia was $9,568 per event; the cost of Grade II anaemia was $13,988 per event, and the cost of serious anaemia (Grade III/IV) was $1,837 per event. These results are due to the use of the high-cost erythropoietic agents to manage less-severe cases of anaemia, while relatively inexpensive blood transfusions are used for individuals with very low Hb levels. These results provide a strong justification for the inclusion of all levels of severity of adverse events, particularly of anaemia, in models of chemotherapy cost-effectiveness.

3.5.7 **Conclusion**

The objective was to answer the question, 'What is the cost of treating chemotherapy-induced anaemia in Australian adults, based on best clinical practice?' Two decision-tree models were developed to represent best practice in

the management of chemotherapy-induced anaemia. Inputs included costs, effectiveness and health utilities obtained from reviews of the literature. Based on a number of estimates and assumptions:

- The average cost of managing curative chemotherapy-induced anaemia according to best-practice guidelines in Australia is $37 per adverse event.
- The average cost of managing palliative chemotherapy-induced anaemia according to best-practice guidelines in Australia is between $5393 and $6,838 per adverse event.
- There is a utility decrement associated with anaemia of up to 0.125.
- The curative model is most sensitive to changes in the probability of anaemia and the cost of evaluation.
- The palliative model is most sensitive to changes in the probability of anaemia and the cost of ESA treatment.

The cost of managing chemotherapy-induced anaemia can be significant, particularly for anaemia that is managed with ESAs. This cost can be incurred at all grades of anaemia. Given this, and the potential impact on the quality of life for patients, the costs and consequences of chemotherapy-induced anaemia should be included in economic evaluations of chemotherapy cost-effectiveness.

3.6 Nausea and vomiting

3.6.1 Background

According to the CTCAE (31), nausea is defined as '[a] disorder characterized by a queasy sensation and/or the urge to vomit' (p46) and vomiting as 'a disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth' (p54). Nausea and vomiting are different conditions that can be experienced individually or simultaneously. In the context of this thesis, the treatments for the two conditions are generally the same and therefore they are referred to as one condition.

Nausea and vomiting is ranked by patients as the most distressing of all chemotherapy adverse events (32). It affects patients' quality of life and can result in dehydration, electrolyte imbalances, malnutrition and aspiration pneumonia (175, 176). If nausea and vomiting are not controlled, up to 50 per cent of patients may delay or refuse ongoing chemotherapy treatment (177).

Rates of nausea and vomiting of more than 90 per cent are associated with some high-emetogenic-risk IVT chemotherapeutic agents, such as cisplatin (178), and in general it has been estimated that up to 60 per cent of all patients receiving chemotherapy do experience some level of nausea or vomiting (179). Nausea and vomiting can be classified as one of three types: acute (occurring within 24 hours of chemotherapy), delayed (occurring more than 24 hours after chemotherapy and lasting up to seven days) or anticipatory (occurring prior to chemotherapy, or prior to when symptoms would be expected to occur). Symptoms that occur despite prophylactic treatment are referred to as *breakthrough nausea and vomiting*, and *refractory nausea and vomiting* is that which does not respond to treatment during several doses of chemotherapy (175).

The biological mechanisms of nausea and vomiting are only partially understood (178, 180). Greater knowledge of pathophysiology and recognition of the different treatment requirements for acute and delayed nausea and vomiting have allowed for progress in developing better prevention strategies (178). One of the major advances in the prevention and management of nausea and vomiting was the

development of serotonin-receptor antagonists (176, 178, 181) and neurokinin-1 receptor antagonists (181), which are now considered the gold standard of treatment (176).

Chemotherapy-related vomiting can be graded according to the number of episodes per day, whereas nausea has a more descriptive definition (see Table 3.18) (31). Grade I and Grade II are commonly considered mild, while Grades III and IV are considered serious. This is the grading criteria referred to throughout this thesis, unless otherwise specified.

Table 3.18: NCI CTCAE version 4.03 nausea and vomiting grading (31)

Grading of gastrointestinal disorders					
	I	**II**	**III**	**IV**	**V**
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalisation indicated	–	–
Vomiting	1–2 episodes (separated by 5 minutes) in 24 hrs	3–5 episodes (separated by 5 minutes) in 24 hrs	≥ 6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalisation indicated	Life-threatening consequences; urgent intervention indicated	Death

Note: hrs = hours; TPN = total parenteral nutrition

In general, it is recognised that the most effective way to manage nausea and vomiting is through prevention, because breakthrough nausea and vomiting is difficult to treat, and there is little evidence of the effectiveness of various drugs (182). Typical management of both prevention and treatment of chemotherapy-related nausea and vomiting is based around the use of antiemetic pharmacological agents, such as benzodiazepines, corticosteroids, 5-HT3 receptor antagonists (5-HT3RAs) and NK1 receptor antagonists (176). The various classes

of antiemetic drugs available act on various neurotransmitter systems, which appear to mediate the emetic response (176).

Benzodiazepines such as metoclopramide and lorazepam, and corticosteroids such as dexamethasone and methylprednisolone are the traditional treatments for nausea and vomiting. However, it is now recognised that 5-HT3RAs, such as ondansetron, granisetron, tropisetron, dolasetron and palonosetron, are the new gold-standard treatments for nausea and vomiting (176). While the use of benzodiazepines and corticosteroids has reduced, these agents are still used in combination with, or as alternatives to, 5-HT3RAs (176). More recently, the role of neurokinin-1 receptor antagonists has been investigated for the prevention of nausea and vomiting in high-emetogenic-risk chemotherapies (183).

A significant body of research has been conducted into treatments for nausea and vomiting, generally and specifically in relation to chemotherapy. These studies have demonstrated that self-reported or observed number of vomiting episodes, and self-reported frequency, intensity and duration of nausea are reliable and valid outcome measures (184). The use of *complete response*, usually defined as 'no nausea or vomiting during the follow-up period following chemotherapy' has been accepted as the gold-standard outcome measure for antiemetic drugs (184).

Previous studies of nausea and vomiting cost

Nineteen studies that included a cost of nausea and vomiting were identified, see Appendix L for details. Fifteen of these were analyses of the cost-effectiveness of specific chemotherapy treatments, with the remaining four specifically examining the costs of managing chemotherapy-induced nausea and vomiting.

Most studies included only Grade III/IV events, although some (98, 99) included multiple grades of each event. In most cases, the costs of outpatient visits and medications were included as the resources to determine costs; however, the management of nausea and vomiting varied significantly across trials.

One of the striking features of these results is the variation in estimates of the costs of chemotherapy-induced nausea and vomiting. This variation could be a result of the differing methodologies used by the various studies. The model

structure, resources included and local practice variations may all contribute to variation in the results. Although this is understandable, it highlights one of the key issues in the modelling of chemotherapy. Even when adverse events are included, the variation in the way adverse events are considered can have an important effect on the overall results of the model.

Best-practice treatment pathway

The search strategy identified five guidelines for the management of chemotherapy-induced nausea and vomiting: the American Society of Clinical Oncology (185), the Oncology Nursing Society (186), the Multinational Association of Supportive Care in Cancer (MASCC) and European Society of Medical Oncology (ESMO) (187), Cancer Care Ontario (183) and the NCCN (188). None of these guidelines was Australian. In addition, a section titled 'Antiemetic regimens' was identified on the eviQ website, which provides recommendations based on the MASCC and NCCN guidelines, not original reviews of the literature (182).

Overall, there was a high level of agreement between the guidelines regarding management recommendations, although some minor discrepancies were noted. A paper by Jordan summarises and compares the management recommendations of three of the guidelines: MASCC, ASCO and NCCN (181). Nausea and vomiting is generally managed according to four categories or levels of the emetogenic risk of the chemotherapeutic agents (high, moderate, low or minimal). A comparison of the recommendations according to these three guidelines for antiemetic prevention, based on nausea and vomiting risk category, is presented in Table 3.19.

In general, patients on high-risk chemotherapies are treated with a triplet of 5-HT3RA, dexamethasone and aprepitant to prevent acute nausea and vomiting, followed by the doublet of dexamethasone and aprepitant for delayed chemotherapy-induced nausea and vomiting. For moderate risk patients, the same triplet for acute prevention can be used, although the NCCN guidelines suggest that for some patients the aprepitant can be excluded (188), while the ASCO guidelines include aprepitant only for those patients receiving a combination of

anthracyclines and cyclophosphamide (AC) (185). Prevention of delayed chemotherapy-induced nausea and vomiting in these patients is with dexamethasone (unless aprepitant is used for acute prevention, in which case dexamethasone should be used as monotherapy for prophylaxis of delayed chemotherapy-induced nausea and vomiting (185, 187)).

Low-risk patients should be treated with a steroid or dexamethasone for acute chemotherapy-induced nausea and vomiting, with no prophylaxis after 24 hours. The NCCN also suggests the use of prochlorperazine or metoclopramide as alternatives to dexamethasone (188). No antiemetic drug should be routinely administered before chemotherapy treatment that has a minimal emetogenic risk.

If optimal treatment has been given as prophylaxis, repeated dosing of the same agents is unlikely to be successful. The addition of dopamine-receptor antagonists (metoclopramide) might be useful, or adding other agents such as benzodiazepines or neuroleptics. Olanzapine, an atypical neuroleptic, could also be considered (185, 187).

Table 3.19: Comparison of recommendations for nausea and vomiting prophylaxis (adapted from Jordan 2007 (181))

Emetogenic risk of chemotherapy	CINV type	Group recommendation		
		MASCC	ASCO	NCCN
High	Acute CINV	5-HT3RA + dexamethasone + aprepitant	5-HT3RA + dexamethasone + aprepitant	5-HT3RA + dexamethasone + aprepitant +/– lorazepam
	Delayed CINV	Dexamethasone + aprepitant	Dexamethasone + aprepitant	Dexamethasone + aprepitant +/– lorazepam
Moderate	Acute CINV – anthracycline/ cyclophosphamide	5-HT3RA + dexamethasone + aprepitant	Anthracycline/ cyclophosphamide: 5-HT3RA + dexamethasone + aprepitant	Anthracycline and/or cyclophosphamide: 5-HT3RA + dexamethasone + aprepitant +/– lorazepam
	Acute CINV – other chemotherapies	5-HT3RA + dexamethasone	Other chemotherapies: 5-HT3RA + dexamethasone	Other chemotherapies: 5-HT3RA + dexamethasone +/– lorazepam
	Delayed CINV – anthracycline/ cyclophosphamide	Aprepitant or dexamethasone	Aprepitant	Aprepitant +/– dexamethasone +/– lorazepam
	Delayed CINV – other chemotherapies	Dexamethasone; 5-HT3RA may be used as an alternative	Dexamethasone or a 5-HT3RA	Dexamethasone or 5-HT3RA; both +/– lorazepam
Low	Acute CINV	Dexamethasone	Dexamethasone	Dexamethasone +/– lorazepam, or prochlorperazine +/– lorazepam, or metoclopramide +/– lorazepam
	Delayed CINV	No ongoing prophylaxis	No ongoing prophylaxis	No ongoing prophylaxis
Minimal	Acute CINV	No routine prophylaxis	No routine prophylaxis	No routine prophylaxis
	Delayed CINV	No ongoing prophylaxis	No ongoing prophylaxis	No ongoing prophylaxis

Note: ASCO = American Society of Clinical Oncology; CINV = chemotherapy-induced nausea and vomiting; 5-HT3RA = 5-HT3 receptor antagonists; MASCC = Multinational Association of Supportive Care in Cancer; NCCN = National Comprehensive Cancer Network.

The **ASCO guidelines** were originally developed in 1999, and updated in 2006, based on a systematic review of high-quality literature and with reference to the MASCC guidelines (185). For breakthrough nausea and vomiting, lorazepam or alprazolam should be considered, along with consideration to substituting a high-dose metoclopramide for the 5-HT3RA or adding a dopamine-receptor antagonist to the prophylactic regimen (185).

The **MASCC–ESMO guidelines** were originally developed in 2004 with the intention of clarifying the best evidence for clinical practice regarding antiemetics, because a number of clinical guidelines were available but conflicting (187). These were then updated in April 2010, based on the Perugia Consensus Conference on Antiemetic Therapy, held in June 2009 (187). These guidelines are now continually monitored and updated by a series of committees specialising in specific areas of the guidelines. The committees review relevant evidence every six months for new and emerging research and evidence in their area; if any such evidence is available, discussion among the whole committee is undertaken until a consensus opinion is reached on whether the guidelines should be changed (187). An additional recommendation for patients receiving multiple-day cisplatin is provided: they should receive a 5-HT3RA plus dexamethasone for acute nausea and vomiting and dexamethasone for delayed nausea and vomiting (187). There are no recommendations for the treatment of breakthrough or refractory nausea and or vomiting.

The **NCCN guidelines** were originally developed in 2009 and have been regularly updated since then, the most recent version being 2.2010 (188). Additional recommendations are provided for those on multi-day chemotherapy regimens and for the management of breakthrough nausea and vomiting. The guidelines stress that it is generally far easier to prevent nausea and vomiting than it is to treat it. However, the general principle is to treat nausea and vomiting with an additional agent from an alternative drug class and to consider providing around-the-clock administration through IVT or rectal therapy (188).

Cancer Care Ontario has produced two guidelines in relation to chemotherapy-induced nausea and vomiting: the first is specifically in relation to the use of 5-

HT3RAs in patients receiving moderate- or high-emetogenic-risk chemotherapy (189) and the second is on the role of neurokinin-1 receptor antagonists in the prevention of nausea and vomiting due to high-dose cisplatin (183). Each of these is based on a systematic review of the literature to answer specific clinical questions and to provide practice guidelines based on the evidence. Each guideline includes a report on the results of an external review of the review and guidelines. These guidelines provide similar recommendations to those reviewed above, with IVT 5-HT3RAs considered equally efficacious and well tolerated, and recommended for use with dexamethasone for the first 24 hours in patients receiving moderate- or high-emetogenic-risk chemotherapy (189). The use of neurokinin-1 receptor antagonists is recommended for patients receiving high-dose cisplatin, in combination with 5-HT3RA and dexamethasone (183).

The **Oncology Nursing Society Guidelines** were developed by a group including researchers, advanced practice nurses and staff nurses, with the intention of developing resources that would provide evidence-based guidelines for chemotherapy-induced nausea and vomiting interventions (186). The guidelines are based on a systematic database search covering 1988 to 2005 that identified studies of adults receiving chemotherapy for cancer who experienced objectively measured nausea and/or vomiting (186). The only interventions with sufficiently strong evidence to support recommendations for practice were pharmacologically based, with the NCCN and the MASCC–ESMO guidelines for management of nausea and vomiting recommended (186). A number of non-pharmacological interventions were found to be likely to be effective based on the limited evidence available. These included dietary management, acupuncture, acupressure, guided imagery, music therapy, progressive muscle relaxation and psycho-educational support and information (186).

The **eviQ guidelines** for prophylaxis are based on the NCCN and MASCC guidelines and include recommendations for the combination and doses of drugs for prevention of nausea and vomiting (182). Recommendations are given for acute, delayed and breakthrough nausea and vomiting, with an emphasis on the importance of prevention (182).

3.6.2 Structure of the decision models

Decision-tree models were developed to estimate the costs and benefits of best-practice management for chemotherapy-induced nausea and vomiting, based on the emetogenic risk of the chemotherapy treatment. Four models were developed in total: one for low-emetic-risk chemotherapy, one for moderate-emetic-risk chemotherapy, one for cyclophosphamide chemotherapy (moderate-emetic-risk) and one for high-emetic-risk chemotherapy. The principle that prevention is the best form of management was consistent throughout all guidelines and was therefore incorporated in all four of the models. The overall structure of the four models was the same, and was based on the similar clinical pathways described in the guidelines prepared by the MASCC, ASCO and the NCCN. This structure is shown in Figure 3.12. The four full TreeAge models are in Appendix M.

The model was designed to be adaptable to any type of chemotherapy. It is a model based on principles of prevention, and therefore the efficacy of the preventative methods forms the initial branches of the decision tree. Unlike the previously presented models of diarrhoea and anaemia, a case study is not required to demonstrate the model, which is chemotherapy-independent.

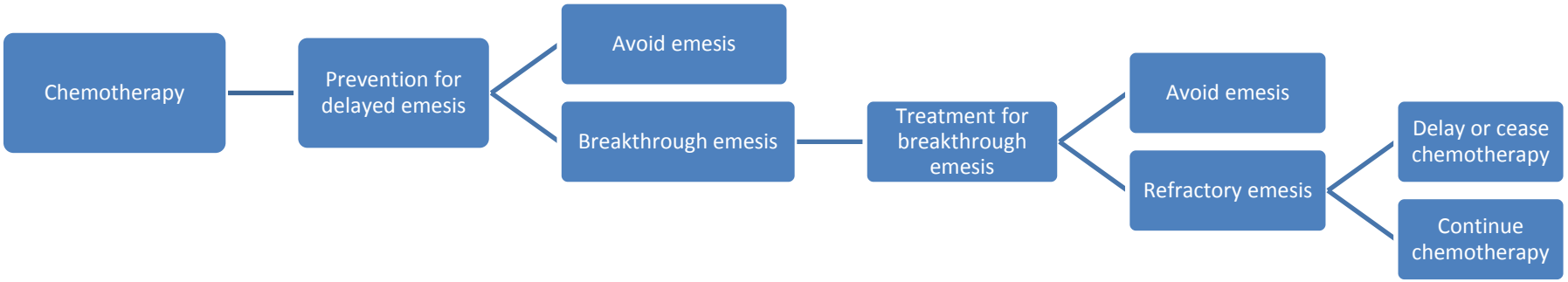


Figure 3.12: Decision-tree model of nausea and vomiting

The assumptions underlying the structure of the models are listed below.

General assumptions for all four models:

- Nausea and vomiting is limited to chemotherapy-induced nausea and vomiting. All other causes of nausea and/or vomiting have been excluded or treated appropriately.
- Chemotherapy-induced nausea and vomiting is managed in the same way based on the emetogenic risk of the chemotherapy, regardless of the specific causative chemotherapy.
- Prevention is the primary strategy for management of chemotherapy-induced nausea and vomiting.
- Where more than one brand is available at different prices for a PBS product, the average price is used for the base-case cost, with the highest and lowest cost tested in the sensitivity analysis.

General assumptions for minimal-emetogenic-risk chemotherapy:

- No routine prevention is recommended for minimal-emetogenic-risk chemotherapy treatments.

General assumptions for low-emetogenic-risk chemotherapy:

- 8-mg oral dexamethasone is used prior to chemotherapy for the prevention of acute nausea and vomiting.
- No routine prevention is recommended for delayed nausea and vomiting with chemotherapy treatments.
- Where prevention is not successful, metoclopramide can be used for breakthrough nausea and vomiting for up to 24 hours.

General assumptions for moderate-emetogenic-risk chemotherapy (excluding anthracycline and/or cyclophosphamide regimens):

- A combination of dexamethasone and 5-HT3RA is recommended prior to chemotherapy for the prevention of acute nausea and vomiting.

- Dexamethasone for 24 hours after chemotherapy is used for the prevention of delayed nausea and vomiting.
- The 5HT3RA are interchangeable in terms of efficacy. The median-priced product is used as the base-case cost, with the most-expensive and least-expensive prices tested in the sensitivity analysis.
- Dolasetron is recommended (along with the other 5HT3RAs) in all of the guidelines reviewed; however, because this is not available on the PBS in Australia it was excluded from the costing.

General assumptions for anthracycline and/or cyclophosphamide regimens (moderate emetogenic risk):

- A combination of dexamethasone, 5-HT3RA and aprepitant is recommended prior to chemotherapy for the prevention of acute nausea and vomiting.
- Aprepitant on days 2 and 3 after chemotherapy is used for the prevention of delayed nausea and vomiting.
- The 5-HT3RAs are interchangeable in terms of efficacy. The median-priced product is used as the base-case cost, with the most-expensive and least-expensive prices tested in the sensitivity analysis.
- Dolasetron is recommended (along with the other 5-HT3RAs) in all of the guidelines reviewed; however, because this is not available on the PBS in Australia it was excluded from the costing.

General assumptions for high-emetogenic-risk chemotherapy:

- A combination of dexamethasone, 5-HT3RAs and aprepitant is recommended prior to chemotherapy for the prevention of acute nausea and vomiting.
- Dexamethasone and aprepitant on days 2 and 3 after chemotherapy is used for the prevention of delayed nausea and vomiting.
- The 5-HT3RAs are interchangeable in terms of efficacy. The median-priced product is used as the base-case cost, with the most-expensive and least-expensive prices tested in the sensitivity analysis.

- Dolasetron is recommended (along with the other 5-HT3RAs) in all of the guidelines reviewed; however, because this is not available on the PBS in Australia it was excluded from the costing.

3.6.3 Synthesising the evidence

The probabilities for managing nausea and vomiting were estimated from a variety of sources as shown in Table 3.20. Although the best available Australian evidence was sought, in many instances Australia-based data were not available. In this case, the best available international evidence was used.

Utility values were based on the highest-quality Australian data where available, and international data in other cases. Both utility decrements and overall utility values were considered for inclusion in the model; however, for consistency in model calculations, only one type was selected for inclusion. In the case of nausea and vomiting, the highest-quality available evidence was sourced from a cross-sectional study conducted in Australia and the UK to obtain health states for advanced melanoma, including treatment toxicity states, using standard gamble questionnaires with the general public (116). In the study design, toxicities were described in association with partial response, with the intention that a decrement for each toxicity could be calculated (116). A decrement was identified for Grade I/II nausea and vomiting and for one day of treatment for a severe toxicity, as either as an inpatient or an outpatient (116). As no hospitalisation for nausea and vomiting is included in the model, only the value for low-grade nausea and vomiting is included in the models. The values identified by Australian patients are used in the models.

Given the short-term nature of nausea and vomiting, and therefore the model, no discounting was applied.

Table 3.20: Assumptions used in the economic model of nausea and vomiting

Assumptions	Value	Source	Justification for source
Transitions (probabilities)			
Low-emetogenic-risk chemotherapy			
Probability of no vomiting when treated with dexamethasone	48%	Ioannidis et al. 2000, meta-analysis (190)	Meta-analysis of dexamethasone effectiveness in prevention of acute and delayed CINV
Moderate-emetogenic-risk chemotherapy			
Probability of no vomiting when treated with dexamethasone, and 5-HT3RA ondansetron. Dexamethasone for delayed nausea and vomiting.	46–79%	Review and meta-analysis Peterson et al. 2009 (191)	As the efficacy of the three products is found to be no different, the median rate of complete response (60%) is used, with the highest and lowest rates tested in the sensitivity analysis
Probability of no vomiting when treated with dexamethasone and 5-HT3RA granisetron. Dexamethasone for delayed nausea and vomiting.	48–53%		
Probability of no vomiting when treated with dexamethasone and 5-HT3RA dolasetron. Dexamethasone for delayed nausea and vomiting.	40–76%		
Anthracycline and cyclophosphamide chemotherapy			
Probability of no vomiting when treated with dexamethasone, 5-HT3RA and aprepitant. Aprepitant for delayed nausea and vomiting.	46%	Warr 2005, systematic review & meta-analysis (183)	Total control rates of acute and delayed CINV ranged from 44% to 47% (not significantly different). Median (46%) used as base case
High-emetogenic-risk chemotherapy			
Probability of no nausea and vomiting when treated with dexamethasone, 5-HT3RA and aprepitant. Dexamethasone and aprepitant for delayed nausea and vomiting	46%	Warr 2005, systematic review and meta-analysis (183)	Rates of total control of acute and delayed CINV ranged from 44% to 47% (not significantly different). Median (46%) used as base case
Across all models			
Probability of control of refractory nausea and vomiting when treated with metoclopramide	28%	Ibrahim et al. 1986 (192)	Randomised, double-blind crossover study of metoclopramide vs. dexamethasone

Assumptions	Value	Source	Justification for source
Dose changes (probabilities)			
In patients where nausea and vomiting are not controlled, percentage of patients who delay or refuse ongoing chemotherapy treatment	50%	Laszlo 1983 (177)	A paper by Ritter is cited by a number of articles; however, on review, Ritter cites a review by Hesketh, which cites a paper by Laszlo, which has an unreferenced statement that from 25% to 50% of patients with nausea and vomiting may be non-compliant
Health utility decrements (utility decrements)			
Grade I/II nausea and vomiting	–0.12	Beursterien et al. 2009 (116)	Utility decrement associated with treatment toxicity elicited, using standard gamble in Australian general public
Pharmaceutical product doses and duration (dosage)			
Dexamethasone for prevention of acute nausea and vomiting with low- or moderate-emetogenic-risk chemotherapy	8 mg orally, 60 minutes pre-chemotherapy	eviQ 2010 (182)	As per eviQ and other guidelines
Dexamethasone for prevention of acute nausea and vomiting with high-emetogenic-risk chemotherapy	12 mg orally 60 minutes pre-chemotherapy	eviQ 2010 (182)	As per eviQ and other guidelines
Dexamethasone for prevention of delayed nausea and vomiting with moderate- or high-emetogenic-risk chemotherapy	8 mg orally, one daily for up to 4 days	eviQ 2010 (182)	As per eviQ and other guidelines
Granisetron for acute nausea and vomiting with moderate-emetogenic-risk chemotherapy	3 mg IVT 60 minutes pre-chemotherapy	eviQ 2010 (182)	As per eviQ and other guidelines
Ondansetron for acute nausea and vomiting with moderate- or high-emetogenic-risk chemotherapy	12 mg IVT 60 minutes pre-chemotherapy	eviQ 2010 (182), Jordan et al. 2007 (181)	eviQ guidelines state 8–12 mg; however, Jordan et al.'s summary paper states high-dose ondansetron appeared to be more effective in a sub-analysis of a trial, and therefore the higher dose was chosen

Assumptions	Value	Source	Justification for source
Tropisetron for acute nausea and vomiting with moderate- or high-emetogenic- risk chemotherapy	5 mg IVT 60 minutes pre-chemotherapy	eviQ 2010 (182)	As per eviQ and other guidelines
Aprepitant for prevention of acute nausea and vomiting with anthracycline and cyclophosphamide or high-emetogenic-risk chemotherapies	125 mg orally 60 minutes pre-chemotherapy	eviQ 2010 (182)	As per eviQ and other guidelines
Aprepitant for prevention of delayed nausea and vomiting with anthracycline and cyclophosphamide or high-emetogenic-risk chemotherapies	80 mg orally on days 2 and 3	eviQ 2010 (182)	As per eviQ and other guidelines
Metoclopramide for breakthrough nausea and vomiting	20 mg orally, followed by 10 mg orally every 4 hrs for 24 hrs	eviQ 2010 (182)	As per eviQ and other guidelines

Note: CINV chemotherapy-induced nausea and vomiting; IVT = intravenous therapy; mg = milligrams

Costs are based on Australian sources and are estimated based on the best available evidence from reliable sources in 2012 Australian dollars. High-quality evidence traditionally includes well-designed randomised controlled trials or meta-analyses published in peer-reviewed literature. However, where this is not available, or not appropriate, data from well-conducted observational studies, national policy documents or guidelines for clinical best practice may also provide high-quality evidence. The costs associated with managing nausea and vomiting were limited to the cost of pharmaceutical products, because it was assumed that prescriptions for oral tablets were obtained during routine oncology visits and that administration of IVT antiemetics was completed using IVT equipment already in use for chemotherapy administration. Treatments for delayed nausea and vomiting are oral, and therefore no administration costs apply. Hospitalisation for nausea and vomiting is rare and was not included in the guidelines examined, and it was therefore not included in the model. Costs and their sources are described in Table 3.21.

Pharmaceutical costs are derived from the PBS price for the maximum quantity prescribed. The average price of the drug for the maximum quantity was calculated using all available brands. The impact of using the highest- and lowest-priced brands is tested in the sensitivity analysis. To calculate costs associated with different doses, the cost of the drug was divided to find the cost per drug-specific unit (e.g. per capsule or per 50 μg), and used to calculate the cost per dose of the drug. This calculated cost does not account for bulk purchasing (resulting in savings) or wastage by the dispenser (resulting in additional cost).

Table 3.21: Costs used in the economic model of nausea and vomiting

Resource	Cost (A$)	Source	Notes
Dexamethasone	$0.42 per 4-mg tablet	PBS	Dispensed price for max. quantity (30 x 4-mg tablets) $12.50
Metoclopramide	$0.54 per 10-mg tablet	PBS	Dispensed price for max. quantity (25 x 10-mg tablets) $13.52
Aprepitant	$125.50 per 1 x 125-mg tablet and 2 x 80-mg tablets	PBS	Dispensed price for max. quantity (1 x 125-mg tablet and 2 x 80-mg tablets (for delayed nausea and vomiting) $112.01 or $138.99
Granisetron	$33.77 per 3-mg IVT dose	PBS	Average dispensed price for max. quantity (1 x 3-mg IVT ampoule) $33.77 per 3-mg IVT dose
Ondansetron	$5.26 per 4-mg IVT dose	PBS	Average price of 6 products for max. quantity (1 x 4-mg/2-mL injection or 1 x 8-mg/4-mL injection) is $5.26 per 4 mg. Max. price is $8.91; minimum price is $1.93
Tropisetron	$23.95 per 5-mg IVT dose	PBS	Average price of the 2 products for max. quantity (1 x 5-mL ampoule) $18.50 or $29.95

Note: IVT = intravenous therapy; max. = maximum; mg = milligram; mL = millilitre; PBS = Pharmaceutical Benefits Scheme.

3.6.4 Modelling the results

The decision-tree model provides a cost for each branch of the tree, based on the inputs. As nausea and vomiting have been modelled for prevention, the efficacy of the treatment forms the initial branches of the tree.

The average cost of managing nausea and vomiting with low-emetogenic-risk chemotherapy according to best-practice guidelines in Australia was three dollars per event. When nausea and vomiting was completely avoided, the cost was 84 cents; however, when breakthrough nausea and vomiting occurred, costs rose to five dollars. The average cost of managing nausea and vomiting with moderate-emetogenic-risk chemotherapy was $29. The average cost of managing nausea and vomiting with anthracycline and cyclophosphamide is $153. The average cost of managing nausea and vomiting with high-emetogenic-risk chemotherapies is $156. The details of the results of each decision analysis are shown in Table 3.22, Table 3.23, Table 3.24 and Table 3.25.

For all models the utility decrement associated with experiencing nausea and vomiting was 0.12.

Table 3.22: Base-case results—low-emetogenic-risk chemotherapy

Tree branch	Probability	Cost (A$)
No nausea and vomiting	0.48	$0.84
Breakthrough nausea and vomiting treated successfully	0.15	$5.16
Breakthrough and refractory nausea and vomiting—continue chemotherapy	0.19	$5.16
Breakthrough and refractory nausea and vomiting—chemotherapy dose changes	0.19	$5.16

Table 3.23: Base-case results--moderate-emetogenic-risk chemotherapy

Tree branch	Probability	Cost (A$)
No nausea and vomiting	0.6	$27.31
Breakthrough nausea and vomiting treated successfully	0.11	$31.63
Breakthrough and refractory nausea and vomiting—continue chemotherapy	0.14	$31.63
Breakthrough and refractory nausea and vomiting—chemotherapy dose changes	0.14	$31.63

Table 3.24: Base-case results—anthracycline and cyclophosphamide chemotherapy

Tree Branch	Probability	Cost (A$)
No nausea and vomiting	0.46	$150
Breakthrough nausea and vomiting treated successfully	0.15	$155
Breakthrough and refractory nausea and vomiting—continue chemotherapy	0.19	$155
Breakthrough and refractory nausea and vomiting—chemotherapy dose changes	0.19	$155

Table 3.25: Base-case results—high-emetogenic-risk chemotherapy

Tree Branch	Probability	Cost (A$)
No nausea and vomiting	0.46	$153
Breakthrough nausea and vomiting treated successfully	0.15	$158
Breakthrough and refractory nausea and vomiting—continue chemotherapy	0.19	$158
Breakthrough and refractory nausea and vomiting—chemotherapy dose changes	0.19	$158

3.6.5 Assessing uncertainty

To explore the source and impact of any uncertainty in the model, one-way sensitivity analyses were undertaken to establish which estimates have the greatest effect on the average cost of managing chemotherapy-induced nausea and vomiting. All parameters were tested in the sensitivity analysis and the values used are shown in Table 3.26. The full results of the sensitivity analysis, along with tornado diagrams are shown in Figure 3.13, Figure 3.14, Figure 3.15, and Figure 3.16.

Table 3.26: Parameters and values tested in the sensitivity analysis for nausea and vomiting model

Transition/utility/cost item	Values used in sensitivity analysis	Source
Low-emetogenic-risk chemotherapy transitions		
Probability that dexamethasone is effective in preventing nausea and vomiting	40% to 57%	Confidence intervals for estimates based on meta-analysis of clinical trials (Ioannidis 2000)(190)
Moderate-emetogenic-risk chemotherapy transitions		
Probability of no vomiting when treated with dexamethasone, and 5-HT3RA ondansetron. Dexamethasone for delayed nausea and vomiting	40% to 79%	Review and analysis by Peterson et al. 2009 (195) found that the efficacy of all three products did not differ. Test lowest rate (40%) and highest rate (79%) found in trials
Probability of no vomiting when treated with dexamethasone, and 5-HT3RA granisetron. Dexamethasone for delayed nausea and vomiting		
Probability of no vomiting when treated with dexamethasone, and 5-HT3RA dolasetron. Dexamethasone for delayed nausea and vomiting		
Anthracycline and cyclophosphamide chemotherapy		
Probability of no vomiting when treated with dexamethasone, 5-HT3RA and aprepitant. Aprepitant for delayed nausea and vomiting	33% to 58.75%	Rates of total control ranged from 44% to 47% with no statistically significant difference between them. Used low and high values +/– 25% (Warr et al. 2005) (183)
High-emetogenic-risk chemotherapy		
Probability of no nausea and vomiting when treated with dexamethasone, 5-HT3RA and aprepitant Dexamethasone and aprepitant for delayed nausea and vomiting	33% to 58.75%	Rates of total control ranged from 44% to 47% with no statistically significant difference between them. Used low and high values +/– 25% (Warr et al.

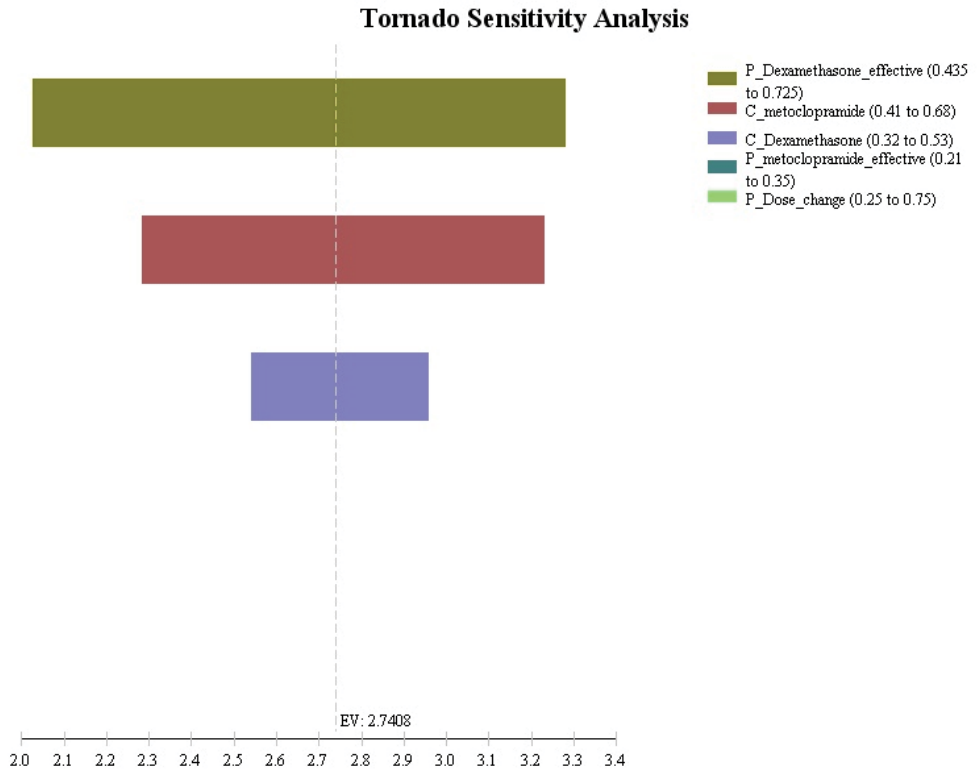
Transition/utility/cost item	Values used in sensitivity analysis	Source
		2005) (183)
Across all models		
Probability of control of refractory nausea and vomiting when treated with metoclopramide	21% to 35%	Original source +/– 25%
Dose changes		
In patients where nausea and vomiting are not controlled, percentage of patients who delay or refuse ongoing chemotherapy treatment	25% to 75%	Original source +/– 50% (increased range due to relatively low level of evidence available for original source)
Costs		
Cost of dexamethasone (per 4-mg tablet)	$0.32 to $0.53	25% +/– high and low prices in cost range
Cost of metoclopramide (per 10-mg tablet)	$0.41 to $0.68	25% +/– high and low prices in cost range
Cost of aprepitant (per 125-mg tablet and 2 x 80-mg tablet)	$94.13 to $156.88	25% +/– high and low prices in cost range
Cost of 5-HT3RA per dose	$4.34 to $42.21	25% +/– high and low prices in cost range

Note: mg = milligram

The parameters to which each of the models was most sensitive were as follows:

1) Low-emetogenic-risk chemotherapy:

- probability that dexamethasone is effective
- the cost of metoclopramide
- the cost of dexamethasone.

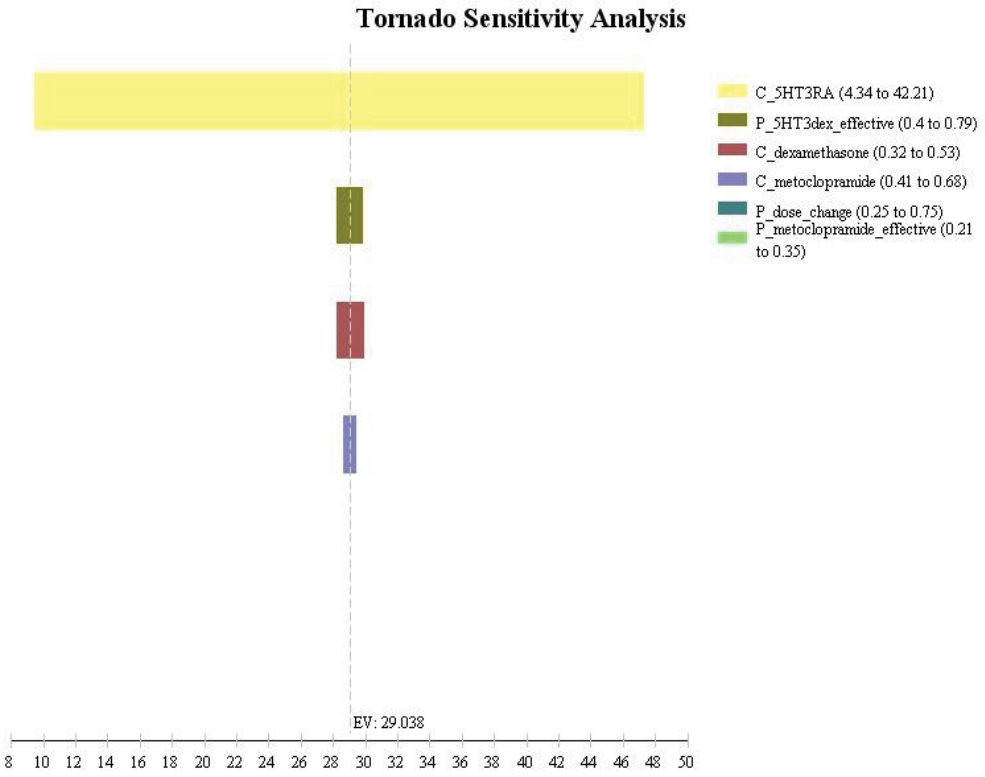


Note: x-axis represents cost; C = cost (to the healthcare system); EV = expected value; P = probability

Figure 3.13: Sensitivity analysis—low-emetogenic-risk chemotherapy

2) Moderate-emetogenic-risk chemotherapy:

- the cost of 5-HT3RAs
- the probability that nausea and vomiting can be prevented with a combination of 5-HT3RAs and dexamethasone
- the cost of dexamethasone
- the cost of metoclopramide.

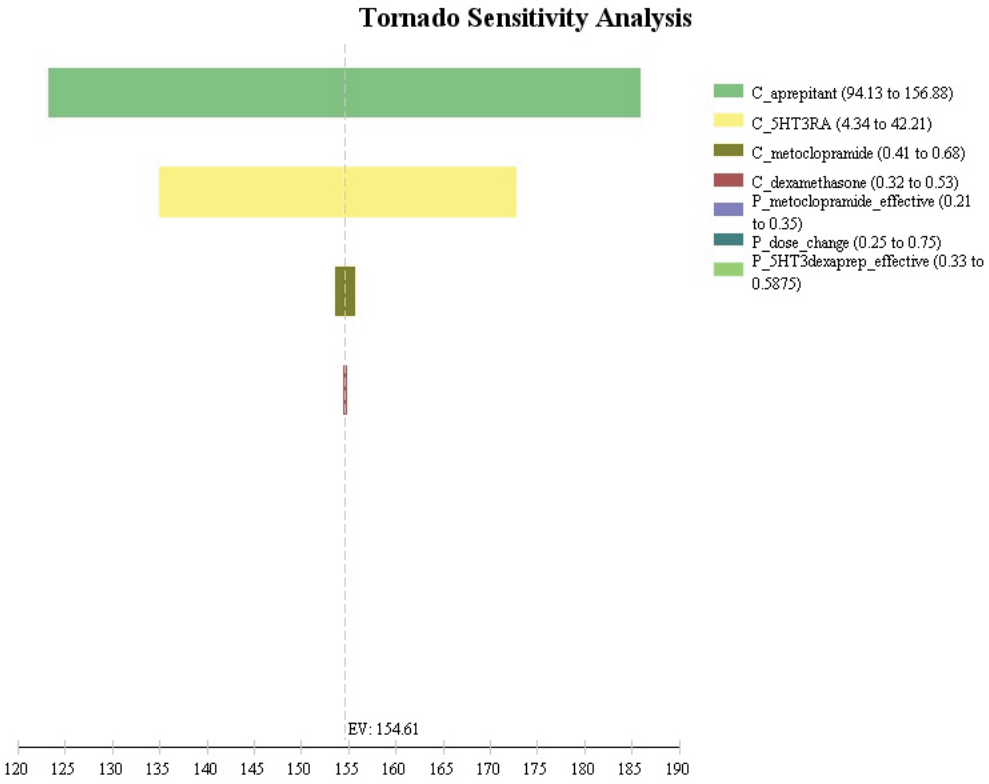


Note: x-axis represents cost; C = cost (to the healthcare system); EV = expected value; P = probability

Figure 3.14: Sensitivity analysis—moderate-emetogenic-risk chemotherapy

3) Anthracycline/cyclophosphamide chemotherapy:

- cost of aprepitant
- cost of 5-HT3RAs
- cost of metoclopramide
- cost of dexamethasone.

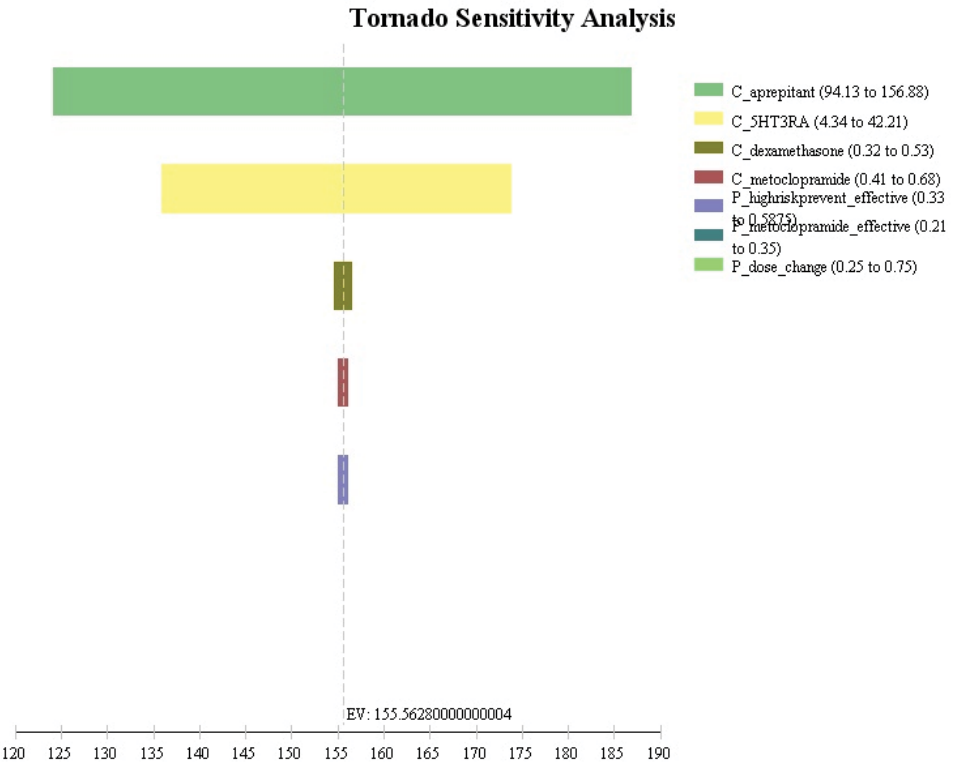


Note: x-axis represents cost; Aprep = aprepitant; C = cost (to the healthcare system); EV = expected value; P = probability

Figure 3.15: Sensitivity analysis—anthracycline/cyclophosphamide chemotherapy

4) High-emetogenic-risk chemotherapy

- cost of aprepitant
- cost of 5HT3RA
- cost of dexamethasone
- cost of metoclopramide
- probability that the triplet will prevent chemotherapy-induced nausea and vomiting.



Note: x-axis represents cost; C = cost (to the healthcare system); EV = expected value; P = probability

Figure 3.16: Sensitivity analysis—high-emetogenic-risk chemotherapy

For model-builders or decision-makers using this model within an economic evaluation of chemotherapy, these results indicate that the model is relatively robust to variations in the efficacy of treatments for nausea and vomiting. However, in all models, uncertainty about the cost of treatments for nausea and vomiting had an impact on the costs.

3.6.6 Discussion

It is difficult to compare the costs obtained through these models with those from previous studies of the cost of nausea and vomiting, given the variation in methodologies used. While the models presented here had results ranging from $5 to $158, estimates of the cost per nausea and vomiting event range from Int$0.02 to Int$5,563.

Many previous models or studies of the costs of chemotherapy-induced nausea and vomiting have not specified the management of nausea and vomiting. This model utilises evidence-based best-practice guidelines for the management of chemotherapy-induced nausea and vomiting. These guidelines, which have been developed to cover nausea and vomiting caused by any chemotherapy regimen, were a highly suitable source of information for generating the structure of the decision analytic models used here.

The costs included in the model were limited to pharmaceuticals, because these are the primary costs applicable to the perspective of the healthcare provider. This is consistent with the collection of costs in many previously published studies and models of the costs associated with chemotherapy-induced nausea and vomiting.

Previous models that included a cost of nausea and vomiting primarily included only the cost of Grade III/IV (serious) events. This analysis, structured around the prevention of chemotherapy-induced nausea and vomiting, is applicable to all individuals receiving chemotherapy. Additional costs for those experiencing breakthrough nausea and vomiting or refractory nausea and vomiting are also included in the model. These models demonstrate that there are costs associated with both the prevention of nausea and vomiting and the management of low-grade events. This indicates that nausea and vomiting should be included in models of chemotherapy, with provision made for costs of prevention as well as of managing low-grade and high-grade events.

One of the primary differences between the models presented here and those seen previously in the literature is that these models are stratified based on chemotherapy emetogenicity. The previous studies often included nausea and vomiting as a side effect in a cost effectiveness of specific chemotherapy

regimens, or specific treatments for nausea and vomiting, thus potentially losing some of the finer differentiation between the management of chemotherapy products with different emetogenic profiles.

In addition, the models presented here could result in lower estimates than those seen previously due to hospitalisation not being included in the costing. Hospitalisation was not considered for the models based on best practice guidelines, although this may not reflect clinical practice.

Selection of adverse events for inclusion

When taken as a cost-of-illness estimate, the results of this model show that nausea and vomiting is a relatively inexpensive adverse event to manage. However, because this model provides the cost of prophylactic (preventative) treatment for nausea and vomiting—a cost incurred for every patient who receives the chemotherapy under consideration—this means that even as a low-cost item, the cost of preventing nausea and vomiting could influence overall costs of chemotherapy treatments. The implication is that the cost of preventing nausea and vomiting should be included in all chemotherapy cost-effectiveness analyses where nausea and vomiting are potential adverse events.

Impact of adverse events on quality of life

There is relatively robust evidence available for the impact of nausea and vomiting on patient quality of life, with this model using a utility decrement associated with treatment toxicity elicited using the standard gamble technique in an Australian general public sample. Using a utility decrement enables this model to be used as an input to a larger model of chemotherapy cost-effectiveness, together with the utility values presumably already associated with the experience of having cancer and undergoing chemotherapy. This prevents double counting.

Influence of adverse events on dose of chemotherapy

There was a poor level of evidence regarding the proportion of individuals who have a dose modification due to nausea and vomiting. The only evidence identified for this input was a study by Ritter (193), which was cited by a number of papers as the source for an estimate that 25 to 50 per cent of individuals with

uncontrolled nausea and vomiting will delay or cease chemotherapy as a result. However, the Ritter paper, which is a study of the efficacy of granisetron to control nausea and vomiting associated with cisplatin-based chemotherapy, references this statement to a review by Hesketh (194). In his literature review of serotonin antagonists and prevention of nausea and vomiting in general, Hesketh states in his introduction that suboptimal control of nausea and vomiting may increase the likelihood of treatment non-compliance (194). Hesketh references this statement to an overview of nausea and vomiting relating to chemotherapy by Laszlo in 1983 (177). It is here that Laszlo makes an unreferenced statement, that 'inadequate compliance because of severe nausea and vomiting may be as high as 25 per cent to 50 per cent' (177).

The difficulty in identifying an accurate estimate of the proportion of individuals who have chemotherapy dose modifications due to nausea and vomiting highlights one of the main challenges in populating models of chemotherapy adverse events (and models in general). Where evidence is lacking, or of poor quality, there is a trade-off between benefits to the model structure that can be obtained by including the variable in the model and the added uncertainty related to the inclusion of an estimate which, as in this case, appears to be an 'educated guess'. To address these competing concerns, this model included a probability node associated with dose modifications as a result of nausea and vomiting, but also included a wide range of values for the sensitivity analysis of this input.

Consideration of multiple adverse events

The decision-tree structure allows recurrent episodes of nausea and vomiting to be included in a model of chemotherapy cost-effectiveness. As the model primarily focuses on prevention of chemotherapy-induced nausea and vomiting, it is assumed that the model (or model outcome) will be included with every dose of chemotherapy.

By modelling nausea and vomiting as a stand-alone event, it is not possible to explore whether the management and resources associated with chemotherapy-induced nausea and vomiting are altered when it occurs in combination with another adverse event. Little literature was identified about this, neither in the case

of nausea and vomiting specifically nor for adverse events in general. This will be explored further in Chapters 4 and 5.

Influence of the severity of adverse events on cost

As the model for chemotherapy-related nausea and vomiting is based on the principle of prevention, it is not possible to assess if more-serious cases of nausea and vomiting are related to higher costs.

3.6.7 **Conclusion**

The objective was to answer the question, 'What is the cost of managing chemotherapy-induced nausea and vomiting in Australian adults, based on best clinical practice?' Four decision-tree models were developed to represent best practice in management of chemotherapy-induced nausea and vomiting, based on the level of emetogenic risk of the chemotherapy treatment. Each model had inputs, including costs, effectiveness, health utilities and dose modifications obtained from reviews of the literature. Based on a number of estimates and assumptions:

- The average cost of managing chemotherapy-induced nausea and vomiting according to best-practice guidelines in Australia is less than three dollars per event for chemotherapies with low emetogenic risk, up to $156 for chemotherapies with high emetogenic risk.
- The models are most sensitive to changes in the costs of dexamethasone, 5-HT3RAs and aprepitant.

The cost of managing chemotherapy-induced nausea and vomiting can be significant, particularly when prevention is ineffective. The management of nausea and vomiting—both prevention and treatment—should be included in economic evaluations of chemotherapy cost-effectiveness.

3.7 Febrile Neutropoenia model

3.7.1 Background

Neutropoenia is defined as an absolute neutrophil count < 1000/mm3. This lowered number of neutrophils circulating through the body reduces the body's ability to fight infection (195). Neutropoenia rarely presents with symptoms; however, if an infection occurs in an individual with neutropoenia, it will often present as a fever. If an individual has neutropoenia and a temperature of > 38.3 °C is recorded, or a temperature over 38 °C is sustained for more than an hour, this is then classified as *febrile neutropoenia* (31).

As the neutrophil count decreases, the risk of infection increases (196). The infections resulting from neutropoenia can be serious and may lead to significant morbidity and mortality (197), as well as to chemotherapy dose modifications, higher rates of other chemotherapy adverse events and reductions in quality of life (196).

Neutropoenia is a relatively common adverse event of chemotherapy, occurring in 10 to 50 per cent of patients with solid tumours or lymphomas (198) and is more likely to occur earlier rather than later in chemotherapy treatment (199). However, neutropoenia is one of the most serious adverse events. The mortality rate associated with febrile neutropoenia in cancer patients is between two per cent and 21 per cent (200). Recent progress has been made in identifying individual patient factors that may increase the risk of neutropoenia. Factors such as cancer type, comorbidities, dehydration and older age have all been implicated, and there are now risk indices such as that developed by the MASCC to identify high-risk individuals (199).

Neutropoenia has no specific grading under the NCIC CTCAE v4.03 system; however, febrile neutropoenia is graded into three levels of severity (see Table 3.27) (31). Unlike many other adverse events, lower gradings are not included (i.e. Grades I and II), because any incidence of febrile neutropoenia is considered to be a serious adverse event.

Table 3.27: NCI CTCAE v4.03 neutropoenia grading (31)

Grading of neutropoenia					
Grade	**I**	**II**	**III**	**IV**	**V**
Febrile neutropoenia	–	–	ANC < 1000/mm3 with a single temp. of > 38.3 °C (101 °F) or a sustained temp. of ≥ 38 °C (100.4 °F) for more than 1 hour	Life-threatening consequences; urgent intervention indicated	Death

Note: ANC = absolute neutrophil count; temp. = temperature

Management

Neutropoenia is primarily treated through the modification of chemotherapy dose. Although prophylactic management can be implemented, most patients with solid tumours who are receiving chemotherapy are considered to be at low risk of developing neutropoenia, and therefore prophylactic management to prevent infection is not generally recommended (201, 202). Any fever or suspicion of infection should be investigated immediately and managed aggressively (195). If febrile neutropoenia does develop, antibiotics are the primary form of treatment. Recent developments in the risk stratification of patients for complications of febrile neutropoenia have allowed some low-risk patients to be treated in the outpatient setting (202, 203).

There has been recent debate about the role of antibacterial prophylaxis (201) and the use of granulocyte stimulating factors (GSF) as either prophylaxis or treatment for cancer patients with febrile neutropoenia (195, 198, 202, 204).

Previous studies of neutropoenia cost

Thirty-one studies that included a cost of neutropoenia were identified, see Appendix N for details. Eighteen of these were analyses of the cost-effectiveness of specific chemotherapy treatments, with the remaining 13 specifically examining various costs associated with managing chemotherapy-induced neutropoenia.

All studies included Grade III/IV events because this is the definition of neutropoenia. In most cases, the costs of hospitalisations, outpatient visits and

medications were included; however, the management of neutropoenia varied across trials. It was not possible to compare across studies the costs of managing chemotherapy-induced neutropoenia due to the variation in methodologies and outcome measures used.

One of the striking features of these results is the variation in estimates of the costs of chemotherapy-induced neutropoenia. This variation could be a result of the differing methodologies used by different studies. The model structure, resources included and local practice variations may all contribute to variation in the results. Although this is understandable, it highlights one of the key issues in the modelling of chemotherapy. Even when adverse events are included, the variation in the way in which adverse events are considered can have an important effect on the overall results of the model.

Best-practice treatment pathway

The search strategy identified five guidelines for the management of chemotherapy-induced neutropoenia: the BCCA (205), the NCCN (202), the EORTC (199) and the Australian consensus guidelines (206-209). The eviQ website provides guidelines for the immediate management of febrile neutropoenia (195); however, the source of these is not clear. A number of additional guidelines were excluded because they interpreted the above guidelines for nursing practice or they were focused on either non-solid tumours or cancer in children.

Overall, guidelines tended to focus on the prevention of neutropoenia or its treatment once diagnosed, rather than on the full pathway of care. Generally, there was a high level of agreement between the guidelines regarding management recommendations, although some minor discrepancies were noted, particularly with regard to the choice of medications, such as antibiotics. In general, patients receiving standard chemotherapy for solid tumours are considered at low risk of developing febrile neutropoenia, and therefore prophylactic treatment is not recommended (199, 202, 207). If febrile neutropoenia is diagnosed, a septic workup should be undertaken to identify the cause of infection (195). However, treatment should be commenced without waiting for results (195).

The BCCA (205) provides concise guidelines in the form of a flow chart for the empiric treatment of febrile neutropoenia. These guidelines are a compilation of other published guidelines, including the EORTC guidelines (199) as well as some research evidence. For low-risk patients who are diagnosed with febrile neutropoenia, outpatient treatment with oral ciprofloxacin and oral amoxicillin-clavulanate is recommended. Evaluation of treatment progress should be undertaken after two to three days; once the patient has been afebrile for at least 48 hours and had two days of neutrophils greater than 0.5, antibiotics may be discontinued. If this is not the case after three days, admission to hospital is indicated. Once admitted, and for patients who are at high risk and are admitted immediately, a range of antibiotics is recommended.

The EORTC published a 2010 update to their guidelines for the use of G-CSF to reduce the incidence of chemotherapy-induced febrile neutropoenia, which include a focus on adults with solid tumours (199). The guidelines are based on a systematic review of the literature considered by a multidisciplinary working party. The recommendations include:

- Patient related risk factors that may increase risk of febrile neutropoenia and the type of chemotherapy should be considered prior to each cycle of chemotherapy to determine the appropriate risk-level-based management strategy.
- For patients at low risk of febrile neutropoenia, no prophylactic management is recommended; however, those with higher risk levels may benefit from prevention.
- G-CSFs are not generally recommended as treatment for diagnosed febrile neutropoenia except in life-threatening cases. As these guidelines are specifically for the use of G-CSFs, no additional recommendations on alternative treatment for neutropoenia are provided.
- When a G-CSF is indicated, filgrastim, lengrastim and pegfilgrastim are recommended based on the evidence of clinical efficacy.

The EORTC published an earlier set of guidelines in 2003 for the use of colony-stimulating factors in elderly patients with cancer (210). Based on a systematic review of the literature, these guidelines highlighted a general lack of evidence at that time about the use of colony-stimulating factors in elderly patients. The guidelines recommend that the use of colony-stimulating factors is supported as prophylaxis for elderly patients with non-Hodgkin's lymphoma, small-cell lung cancer or urothelial tumours. Specific recommendations regarding products, doses and schedules are not provided.

The NCCN in 2009 produced guidelines for the prevention and treatment of cancer-related infections (202). They recommend that individuals with febrile neutropoenia be thoroughly evaluated to determine the cause of the infection and to assess their risk of developing additional complications because of the infection. This assessment should include the collection of culture specimens for analysis. The primary strategy for management of febrile neutropoenia is the treatment of the infection with broad-spectrum antibiotics. Patients should be followed up daily, and most patients take two to seven days (median five days) to recover from fever. Antibiotics should be continued until the absolute neutrophil count (ANC) is 500 or more cells per microlitre. For patients who do not respond to initial treatment, consultation with an infectious disease expert should be considered. Although there is not strong supporting evidence, the use of G-CSFs in this population should be considered. There is significant discussion in the guidelines of various infection prevention strategies; however, as prevention is not covered in this model, these will not be described in this thesis..

The *Internal Medicine Journal* published a series of papers in a special edition, which described the Australian consensus guidelines for the management of neutropenic fever in adult cancer patients (206-209). The guidelines focus on five key areas: risk stratification to guide empiric therapy, hospital-based empirical therapy, outpatient empirical therapy, antibacterial prophylaxis and the choice of antibacterial agent. A panel of representatives from key stakeholder groups formed a steering committee to consider the evidence presented through literature reviews and to generate best-practice recommendations.

The MASCC criteria are recommended for the risk stratification of patients who present with neutropenic fever (207). These criteria allow for individual patients to be classified as either low or high risk of complications and for treatment to be tailored accordingly (207). For patients who are considered low risk, and where the institution has the capacity, an early discharge clinical pathway utilising oral antibiotics and outpatient-based follow-up care is recommended (207). In general, most patients with solid tumours are considered to be low risk, unless a high-intensity chemotherapy regimen is being used or there is a significant cumulative immune-suppressive effect of prior treatments (207). For all other patients, or in situations where the hospital is unable to provide adequate ambulatory care, inpatient antibiotic therapy is recommended (207).

The standard of care for low-risk patients is described as early discharge after at least 24 hours of inpatient observation, followed by structured follow-up in the community (207). During inpatient observation, antibiotics may be administered orally, or with an initial dose delivered parenterally (207). The recommended antibiotic therapy is a combination of amoxicillin-clavulanate and ciprofloxacin (207). However, the guidelines note that, at the time of publication, ciprofloxacin is neither TGA-approved nor listed on the PBS for this indication, and therefore requires formulary approval by the hospital pharmacy for inpatient administration, and a non-PBS script for community pharmacy (207). This means that patients would be required to pay the full price of this product in the community (207). Antibiotic treatment should be continued for a minimum of seven days (207).

If outpatient-based therapy is not successful, or fever re-occurs, inpatient parenteral beta-lactam monotherapy is the recommended treatment (207). The suggested first choice of agent is piperacillin-tazobactam 4.5 mg IVT six to eight hourly, or cefepime 2 g IVT eight hourly; however, institutional circumstances may dictate alternative regimens be used (208). For patients who are considered to be systemically compromised, the addition of gentamicin is recommended (208).

Antibacterial prophylaxis is not recommended for patients at low risk of developing neutropenic fever, nor for routine use in those at risk (209).

Finally, **eviQ** provides some brief guidance for the immediate management of febrile neutropoenia, although the basis of these recommendations is unclear (195). These guidelines recommend a septic workup be completed, although this should not delay the commencement of antibiotics (195). Intravenous antibiotic therapy should be commenced with gentamicin plus either Timentin® or Tazocin® (195). Subsequent treatment beyond this initial therapy is then left to the discretion of the treating clinician (195).

Given the availability of comprehensive and high-quality guidelines specific to the Australian setting, these have been used as the basis of model development with additional recommendations from the other guidelines considered where necessary.

3.7.2 Structure of the decision model

A decision-tree model was developed to estimate the costs and benefits of best-practice management for chemotherapy-induced neutropoenia in low-risk patients. The decision to select only the low-risk patient group for modelling was because most solid tumour chemotherapies, which are the focus of this thesis, fall into this category.

Given that the use of prophylaxis in this group is not recommended, this has not been incorporated into the model. The structure of the model is based on the Australian consensus guidelines for the management of neutropenic fever in adult cancer patients, and is shown in Figure 3.17. The full TreeAge model is in Appendix O.

The model was designed to be adaptable to any type of chemotherapy. Unlike the models of diarrhoea and anaemia previously presented, febrile neutropoenia is defined at grade III/IV. It is therefore not necessary to use a case study to demonstrate the model, as all who enter the model have diagnosed febrile neutropoenia.

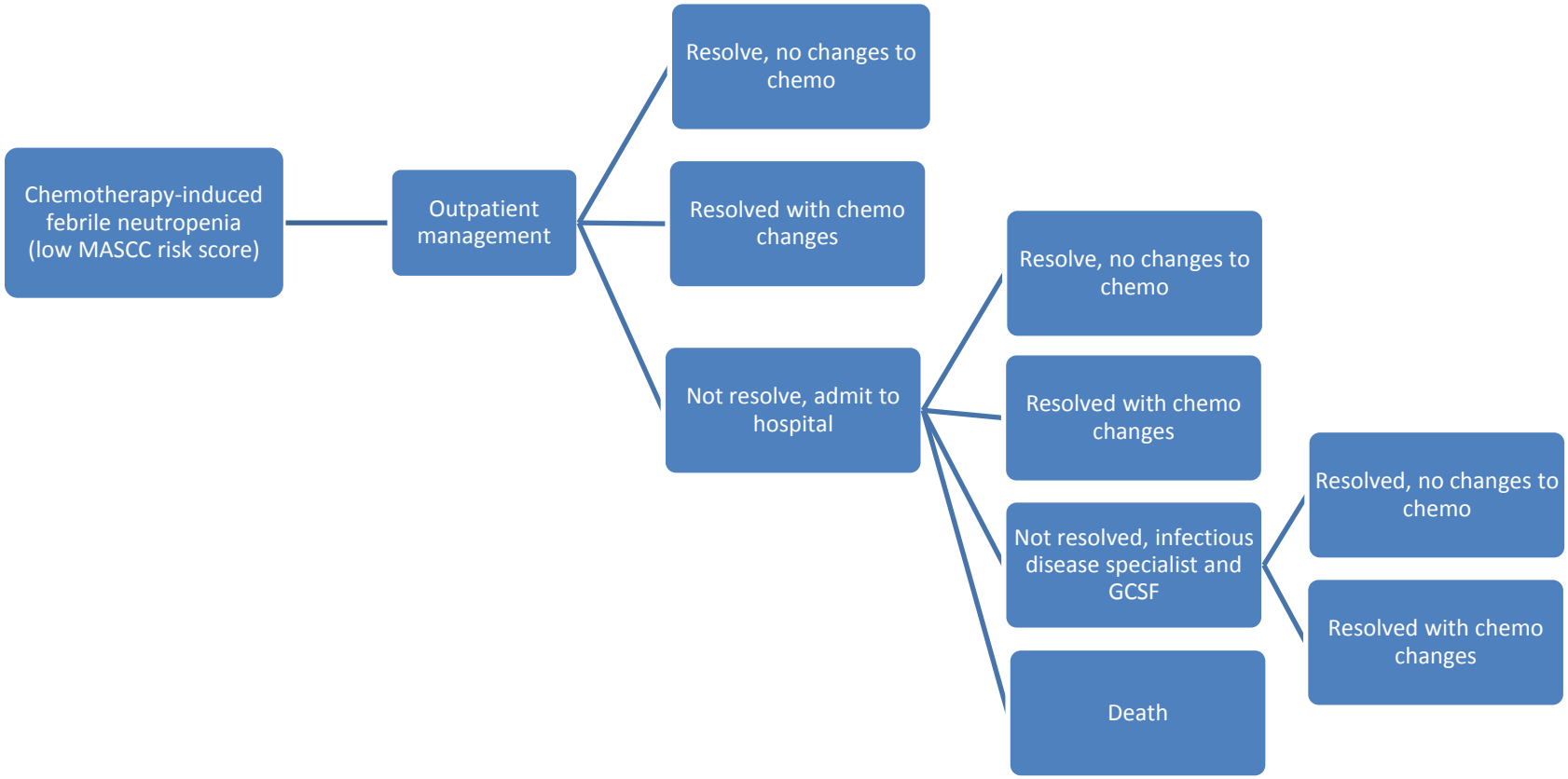


Figure 3.17: Decision-tree model for chemotherapy-induced neutropoenia

The assumptions related to the structure of the model are as follows:

- Neutropoenia is limited to chemotherapy-induced neutropoenia. All other causes of neutropoenia have been excluded and/or treated appropriately.
- The cancer and chemotherapy under assessment are considered low risk for neutropoenia and neutropenic complications. For high-dose chemotherapy or chemotherapy regimens specifically for individuals at high risk of neutropoenia, the costs associated with neutropoenia should be modelled differently, because prophylactic management and inpatient treatment would need to be costed.
- Chemotherapy-induced neutropoenia caused by low-risk regimens is managed in the same way, regardless of the specific causative chemotherapy.
- Where more than one brand is available at different prices for a PBS product, the average price is used for the base-case cost, with the highest and lowest cost tested in the sensitivity analysis.
- The management of neutropoenia in patients at low risk of complications is based on the Australian guidelines for best practice (207-209), including:
    - a blood test for assessment of infection
    - 24 hours of inpatient care to commence antibiotics. The cost of the IVT antibiotics administered as an inpatient is incorporated into the AR-DRG cost
    - discharge for outpatient monitoring, with seven days of doublet oral antibiotics (amoxicillin and ciprofloxacin)
    - a further blood test and one outpatient visit for follow-up of neutropoenia and fever resolution
    - if neutropoenia or fever has not resolved after seven days, admission to hospital is indicated. From here, individuals may recover, be admitted to an intensive care unit (ICU) or die
    - all individuals who recover may do so either with no changes to their chemotherapy regimen or with changes that result in them receiving less than 85 per cent of their chemotherapy RDI.

- The cost of ciprofloxacin has been included in the model, despite the cost to the community currently being borne by patients because it is not approved by the TGA or PBS for this indication (207). The cost used is the current cost for approved indications.
- The rate of dose modifications associated with neutropoenia is an overall rate of 20 per cent from a study of more than 20,000 women with early breast cancer (76). Although this rate is probably higher in individuals who require hospitalisation or ICU, this rate is used for all branches of the model. The study also reports subgroup analyses with rates of dose modifications up to 56 per cent, and these rates will be tested in the sensitivity analysis (76).
- The rates of ICU admissions and mortality are modelled as separate outcomes, because this is the data available (211); however, in reality, a proportion of the individuals who have not survived will have been to ICU. This means that the model underestimates costs, because currently individuals who die do not consume ICU resources.

3.7.3 Synthesising the evidence

The probabilities for managing neutropoenia were estimated from a variety of sources, as shown in Table 3.28. Although the best available Australian evidence was sought, in some instances Australia-based data were not available. In this case, the best available international evidence was used.

Utility values were based on the highest-quality Australian data available, and international data in other cases. Both utility decrements and overall utility values were considered for inclusion in the model; however, for consistency in model calculations, only one type was selected for inclusion. In the case of neutropoenia, the highest-quality available evidence came from a combination of studies. The first was a cross-sectional study, which was conducted in Australia and the UK, to obtain health states for advanced melanoma, including treatment toxicity states. This study used standard gamble questionnaires with the general public, and although neutropoenia was not specifically addressed, utility decrements were elicited for hospital stays of one day and of two to five days (116). The values

identified by Australian patients were used in the models. The second study used standard gamble with 100 members of the general public to generate health utilities for non-small-cell lung cancer, including disease states and utilities (212). Specific utilities for neutropoenia and febrile neutropoenia were obtained separately (212). Given the short-term nature of neutropoenia, and therefore the model, no discounting was applied.

Table 3.28: Assumptions used in the economic model of chemotherapy-induced febrile neutropoenia

Assumptions	Value	Source	Justification for source
Transitions	***Probabilities***		
Probability of treatment failure	28%	Vidal 2004 (213)	Cochrane review and meta-analysis of treatment failure rates in combined initial oral and sequential oral treatment studies
Probability of an admitted patient being admitted to ICU	5.9%	Lingaratnam 2011 (211)	Hospital outcome measure of ICU admission rate for neutropenic fever for patients with solid tumour cancer
In-hospital mortality rate	7.6%	Lingaratnam 2011 (211)	Hospital outcome measure of mortality rate for neutropenic fever for patients with solid tumour cancer
Dose changes	***Proportion***		
Proportion of patients who have dose modifications resulting in delivery of less than 85% of recommended dose intensity due to febrile neutropoenia	20%	Lyman 2003 (76)	-
Health utility decrements	***Utility decrement***		
Febrile neutropoenia	–0.09	Nafees 2008 (212)	Utility decrement associated with treatment toxicity elicited using standard gamble in UK general public
Pharmaceutical product - dosage and duration			
Amoxicillin-clavulanate as part of dual therapy for outpt care of patients with febrile neutropoenia	500 mg tid for 7 days	Worth 2011 (207); Vidal et al. 2004 (222); BCCA guidelines (205)	Product recommended in Worth 2011 (216), based on Cochrane review Vidal et al. 2004 (222). Dose from BCCA guidelines (214)

Assumptions	Value	Source	Justification for source
Ciprofloxacin as part of dual therapy for outpt care of patients with febrile neutropoenia	750 mg every 12 hrs for 7 days	Worth 2011 (207); Vidal 2004 (213); BCCA guidelines (205)	Product recommended in Worth 2011 (216), based on Cochrane review, Vidal et al. 2004 (222). Dose from BCCA guidelines (214)
Length of hospital stay	9.5 days	Lingaratnam 2011 (211)	Mean length of hospital stay as a hospital outcome measure for neutropenic fever in patients with solid tumour cancer

Note: BCCA = British Columbia Cancer Agency; ICU = intensive care unit; outpt = outpatient; tid = three times per day

Costs are based on Australian sources and are estimated based on the best available evidence from reliable sources in 2012 Australian dollars. High-quality evidence traditionally includes well-designed randomised controlled trials or meta-analyses published in peer-reviewed literature. However, where this is not available, or not appropriate, data from well-conducted observational studies, national policy documents or guidelines for clinical best practice may also provide high-quality evidence. The costs associated with managing neutropoenia were limited to medications such as antibiotics, blood tests, outpatient follow-up visits and hospital admissions. Quality of life was also assessed as a model output.

Costs and their sources are described in Table 3.29. Pharmaceutical costs are derived from the PBS price for the maximum quantity prescribed. The average price of the drug for the maximum quantity was calculated using all available brands. The impact of using the highest- and lowest-priced brands is tested in the sensitivity analysis. To calculate costs associated with different doses, the cost of the drug was divided to find the cost per drug-specific unit (e.g. per capsule or per 50 µg), and used to calculate the cost per dose of the drug. This calculated cost does not account for bulk purchasing (resulting in savings) or wastage by the dispenser (resulting in additional cost).

Table 3.29: Costs used in the economic model of chemotherapy-induced febrile neutropoenia

Resource	Cost (A$)	Source	Notes
Ciprofloxacin	$2.80 per 750-mg tablet	PBS	Dispensed price for max. quantity (14 x 750-mg tablets) $39.17 (including brand premium)
Amoxicillin and clavulanate	$1.18 per tablet	PBS	Dispensed price for max. quantity (10 x 500-mg amoxicillin and 125-mg clavulanate tablets) $11.75 (including brand premium)
Admission of low-risk patients for commencement of antibiotic treatment	$2,035	NHCDC 2006/2007	T62B—Fever of unknown origin, without catastrophic consequences. Average length of stay 1.98 days
Admission to hospital for non-resolution of febrile neutropoenia in the outpt setting	$9,547	NHCDC 2006/2007	Q60A—Reticuloendothelial and immunity disorders with catastrophic or severe complications or comorbidity, not including ICU costs ($272). Average length of stay 6.95 days. This AR-DRG was selected on the basis of Lingaratnam et al. (220) (burden) as it is the most frequent AR-DRG associated with admitted episodes for neutropenic fever in their study
Admission to ICU for non-resolution of febrile neutropoenia in the outpt setting	$272	NHCDC 2006/2007	The critical-care cost component of AR-DRG Q60A
GP or specialist visit for neutropoenia and/or fever assessment or review	$34.90	MBS	MBS Item 23 (Level B GP consultation in rooms)
Blood test	$50.60	MBS	Items 65070 and 66596, cost of CRC with indices and blood smear morphology

Note: AR-DRG = Australian Refined Diagnosis Related Group; CRC = colorectal cancer; GP = general practitioner; ICU = intensive care unit; max. = maximum; MBS = Medicare Benefits Schedule; NHCDC = National Hospital Cost Data Collection; outpt = outpatient; PBS = Pharmaceutical Benefits Scheme

3.7.4 Modelling the results

The decision-tree model provides a cost for each branch of the tree, based on the inputs. The average cost of managing neutropoenia in low-risk patients according to best-practice guidelines in Australia is $4,913 per event. When neutropoenia is

resolved with outpatient-based treatment, the cost is $2,235 per event; however, when neutropoenia does not resolve and prolonged hospitalisation is required, the average cost is $11,798 per event. The details of the results of each arm of the tree are shown in Table 3.30. The quality of life decrement associated with any experience of neutropoenia was 0.09.

Table 3.30: Results of low-risk neutropoenia management model

Tree branch	Probability	Cost (A$)
Resolve with outpt management—no change to chemotherapy dose	0.520	$2,235
Resolve with outpt management—dose modifications result in less than 85% RDI	0.200	$2,235
Requires admission to hospital, and then resolves with no change to chemotherapy dose	0.186	$11,782
Requires admission to hospital, and then resolves with dose modifications resulting in less than 85% RDI	0.056	$11,782
Does not resolve with admission to hospital and requires admission to ICU, but resolves with no changes to chemotherapy dose	0.013	$12,054
Does not resolve with admission to hospital and requires admission to ICU, and then resolves with dose modifications resulting in less than 85% RDI	0.003	$12,054
Does not resolve with admission to hospital and results in patient death	0.021	$11,782

Note: ICU = intensive care unit; RDI = relative dose intensity

3.7.5 Assessing uncertainty

To explore the source and impact of any uncertainty in the model, one-way sensitivity analyses were undertaken to establish which estimates have the greatest effect on the average cost of managing chemotherapy-induced neutropoenia. All parameters were tested in the sensitivity analysis and the values used are shown in Table 3.31. The full results of the sensitivity analysis displayed as tornado diagrams are shown in Figure 3.18.

Table 3.31: Parameters and values tested in sensitivity analysis for chemotherapy-induced neutropoenia model

Transition/utility/cost item	Values used in sensitivity analysis	Source
Transitions		
Probability of treatment failure	1% to 60%	Range of estimates in Vidal (213) systematic review, used for meta-analysis
Probability of an admitted patient being admitted to ICU	4.4% to 7.4%	Original source +/– 25%
In-hospital mortality rate	5.7% to 9.5%	Original source +/– 25%
Dose changes		
Proportion of patients who have dose modifications resulting in delivery of less than 85%of recommended dose intensity due to febrile neutropoenia	10% to 56%	Upper limit is highest value from original source; lower limit is original source: 50%
Utilities		
Utility decrement associated with febrile neutropoenia	–0.05736 to –0.17	Lower limit is 2 times the SE of the original estimate (212); the upper limit is the utility of a 2–5 day hospitalisation for severe toxicity (116)
Costs		
Ciprofloxacin	$2.10 to $3.50 per 750-mg tablet	25% +/– high and low prices in cost range
Amoxicillin and clavulanate	$0.89 to $1.50 per tablet	25% +/– high and low prices in cost range
Admission of low-risk patients for commencements of antibiotic treatment	$1,526 to $2,544	25% +/– high and low prices in cost range
Admission to hospital for non-resolution of febrile neutropoenia in the outpt setting	$7,160 to $11,934	25% +/– high and low prices in cost range
Admission to ICU for non-resolution of febrile neutropoenia in the outpt setting	$204 to $340	25% +/– high and low prices in cost range
GP or specialist visit for neutropoenia and/or fever assessment or review	$26.12 to $43.63	25% +/– high and low prices in cost range
Blood test	$37.95 to $63.25	25% +/- high and low prices in cost range

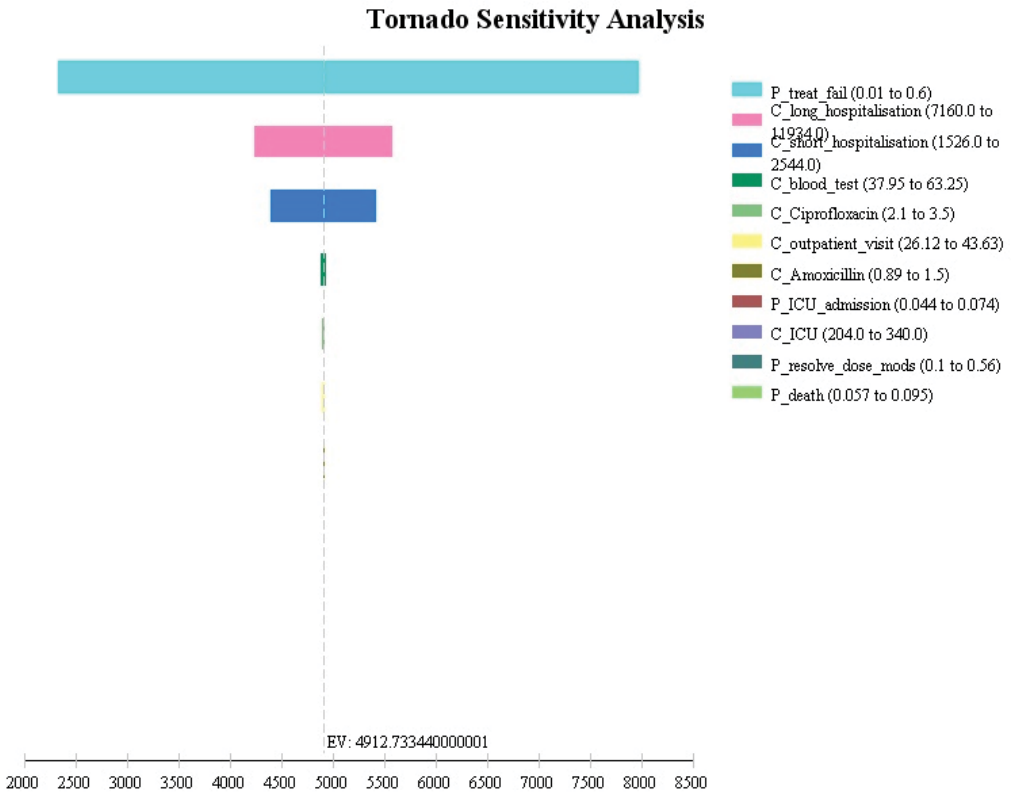
Note: GP = general practitioner; ICU = intensive care unit; outpt = outpatient; SE =standard error

The model was most sensitive to:

- probability of treatment failure
- the cost of a long hospitalisation
- the cost of a short hospitalisation.

The model was moderately sensitive to:

- cost of blood tests
- costs of the various antibiotics
- cost of outpatient visits.



Note: x-axis represents cost; C = cost (to the healthcare system); EV = expected value; ICU = intensive care unit; mods = modifications; P = probability; Treat = treatment;

Figure 3.18: One-way sensitivity analysis of neutropoenia model

For model-builders or decision-makers using this model within an economic evaluation of chemotherapy, these results indicate the importance of having accurate estimates for the key variable relating to the probability of treatment failure, because uncertainty about this parameter has a significant impact on costs.

However, it is also noted that uncertainty about the cost of treatments for neutropoenia had an impact on the costs.

3.7.6 **Discussion**

Many previous models or studies of the costs of chemotherapy-induced neutropoenia have not specified the management of neutropoenia, nor provided highly varied definitions. This model utilises evidence-based best-practice guidelines for the management of chemotherapy-induced neutropoenia. These guidelines were developed to cover neutropoenia caused by any chemotherapy regimen with low neutropenic risk, and were therefore a highly suitable source of information for generating the structure of the decision analytic model used here.

The costs included in the model were limited to pharmaceuticals, hospitalisations, outpatient visits and blood tests, because these are the primary costs applicable to the perspective of the healthcare provider. This is consistent with, or more thorough than, the collection of costs in many previously published studies and models of the costs associated with chemotherapy-induced neutropoenia.

This model demonstrates that there are costs associated with neutropoenia, even with those chemotherapy regimens and patients considered low risk. This indicates that neutropoenia, and in particular febrile neutropoenia, should be included in models of chemotherapy with provision made for costs of prevention, low-grade and high-grade events.

The models presented here result in estimated costs of febrile neutropoenia which are similar to those in previous studies of the cost of neutropoenia. Previous studies have estimated a range of I$171 (88) and I$11,339 per event (214), while the range from the models here is AUD$2235 to AUD$11782. However differences in the methodologies and approaches of previous studies compared to the current models makes comparisons difficult.

Different to the models of other adverse events earlier in this chapter, the definition of febrile neutropoenia means that all events were modelled at grade III/IV. However the management of febrile neutropoenia still varied between studies, making costing inputs different. One of the primary differences was the

consideration of inpatient and outpatient management. A number of previous studies were focussed on comparing inpatient and outpatient management approaches, whereas the treatment modelled here included a mixed model.

Selection of adverse events for inclusion

When taken as a cost-of-illness estimate, the results of this model demonstrate that neutropoenia is associated with significant costs to the healthcare system. Even neutropoenia events that resolve without requiring inpatient treatment are relatively expensive. Therefore, even as a somewhat infrequent event, the cost of neutropoenia could have a major impact on the overall cost of chemotherapy. This demonstrates that the costs and consequences of neutropoenia should be included in all chemotherapy cost-effectiveness analyses where neutropoenia is a potential side effect.

Impact of adverse events on quality of life

There is relatively robust evidence available for the impact of febrile neutropoenia on patient quality of life with this model using a utility decrement associated with treatment toxicity elicited using the standard gamble technique in a UK general public sample. The use of a utility decrement enables this model to be used as an input to a larger model of chemotherapy cost-effectiveness, which can also include the utility values presumably already associated with the experience of having cancer and undergoing chemotherapy. This prevents double counting.

Influence of adverse events on dose of chemotherapy

There is moderately rigorous evidence regarding the proportion of individuals who have dose modifications due to neutropoenia or febrile neutropoenia. Given that this proportion is estimated at 20 per cent of patients, it is important to include the influence of adverse events on the dose of chemotherapy. These dose modifications affect both the total quantity of chemotherapy product(s) received and the efficacy of the treatment. However, this model of adverse events is designed to fit into larger models of chemotherapy cost-effectiveness, and therefore the quantity of chemotherapy drug and chemotherapy efficacy are not included in the model of adverse events. If this model of neutropoenia is

incorporated into a larger chemotherapy cost-effectiveness model, dose and efficacy of chemotherapy should be adjusted based on these results.

A model-builder wishing to incorporate this model of neutropoenia into a model of chemotherapy cost-effectiveness could use these rates of dose modifications to calculate their impact on chemotherapy quantity and chemotherapy efficacy. By adjusting the total quantity of chemotherapy drug(s) received, the influence on the total cost of treatments, through reduced product and fewer clinic visits, et cetera, could be accounted for. The proportion of individuals who have dose modifications should also be included in the estimates of survival for each treatment, to account for the evidence that receiving a lower than planned dose of chemotherapy reduces rates of chemotherapy response and overall survival. It is unclear whether this type of information will be available from all clinical trials for all chemotherapy treatments; however, the results of this model demonstrate the importance of considering this as a consequence of the chemotherapy adverse event neutropoenia.

Consideration of multiple adverse events

The decision-tree structure allows recurrent episodes of neutropoenia to be included in a model of chemotherapy cost-effectiveness. Previous models have been developed that include a cost within the first episode of neutropoenia for managing future episodes of neutropoenia; this is in recognition of the increased probability of having repeated episodes of neutropoenia.. This has not been included in this model, because it was not indicated in any of the clinical practice guidelines that this should be the case.

By modelling neutropoenia as a stand-alone event, it is not possible to explore whether the management and resources associated with chemotherapy-induced neutropoenia are altered when it occurs in combination with another adverse event. Little literature was identified about this, neither for neutropoenia specifically, nor for adverse events in general. This will be explored further in Chapters 4 and 5.

Influence of the severity of adverse events on cost

This model is consistent with the assumption that an increasing severity of an adverse event is likely to result in increased cost. In this case, death from unresolved neutropoenia is slightly less expensive than neutropoenia that resolves after inpatient treatment and intensive care, presumably because it is assumed that the patient who dies does not receive treatment in intensive care. Although this assumption is probably false, based on the data available it is a necessary assumption and, if true, would result in a more conservative estimate of cost.

3.7.7 **Conclusion**

The objective was to answer the question, 'What is the cost of managing chemotherapy-induced neutropoenia in Australian adults, based on best clinical practice?' A decision-tree model was developed to represent best practice in management of chemotherapy-induced neutropoenia for chemotherapy regimens with low risk of neutropoenia in populations with low risk of neutropenic complications. The model has inputs, including costs, effectiveness, health utilities and dose modifications obtained from reviews of the literature. Based on a number of estimates and assumptions:

- The average cost of managing chemotherapy-induced neutropoenia according to best-practice guidelines in Australia is $4,913 per event for chemotherapies with low risk of neutropoenia.
- The model is most sensitive to changes in probability of treatment failure, and to the costs of hospitalisation, outpatient visits, medications and blood tests.

Not only is neutropoenia a serious adverse event for individuals, the cost of managing chemotherapy-induced neutropoenia can be significant. The management of neutropoenia, even in those chemotherapy regimens with low neutropenic risk, should be included in economic evaluations of chemotherapy cost-effectiveness.

3.8 Overall discussion of findings from modelling

To demonstrate that it is possible to develop robust models of chemotherapy adverse events, this thesis has presented models of four chemotherapy adverse events. The structure of each model was based on best-practice guidelines for the management of adverse events and included a range of prevention, treatment and acute and chronic management strategies. For some adverse events more than one model was required to enable specific aspects of the event to be incorporated, and to allow the models to be used across any chemotherapy drugs. The model structure and approach was tailored to the specific needs of each adverse event. This allowed the models to take account of clinical factors such as a preference for prevention over treatment of nausea and vomiting, or the inclusion of febrile neutropoenia only at grades III and IV. In addition, for each adverse event where 'case study' inputs were required to demonstrate model function, the most appropriate source was selected. Inputs were based on the best available evidence, Australia-based where possible. Resources and costs were based on Australian data.

The use of decision tree analysis methods was appropriate for the clinical characteristics of the decision problem under consideration. However, the need to account for multiple events over time, and the potential role of adverse event treatment history in determining future treatments and outcomes means that microsimulation models would also be appropriate. If high quality data was available to populate a microsimulation model, these methods would improve validity of the models and their results. However this comes at the expense of increased complexity and decreased transparency, efficiency and ease of use. An area for future research would be the identification of appropriate high quality evidence to warrant the development of microsimulation methods for the modelling of chemotherapy adverse events.

The literature review presented in Chapter 1 indicated that to date there has been no rigorous or systematic way of including adverse events in models of chemotherapy cost-effectiveness. Examination of previous models that included a cost of each of the adverse events modelled here indicated wide variation among

estimates of the costs associated with specific adverse events. Although much of this can be attributed to differences between model structures, assumptions, local practices and sources of resource-use and cost information, the wide range of estimates was striking. This highlighted the need for rigorous modelling methods that could be applied to any model of chemotherapy cost-effectiveness and that would provide transparent, reliable Australia-specific estimates including all relevant aspects of chemotherapy adverse events.

The four models presented in this thesis represent best-practice modelling techniques for chemotherapy adverse events. Each has been designed to enable either the results or the model structure itself to be incorporated into larger models of chemotherapy cost-effectiveness. This will allow model-builders to incorporate rigorous Australia-specific estimates of the costs and consequences of chemotherapy adverse events into models of chemotherapy cost-effectiveness. Again, the inclusion, where possible, of not only the resource-use and costs associated with adverse events but also the consequences for quality of life, chemotherapy dose and chemotherapy efficacy make these four models broader and more reflective of the true impact of chemotherapy adverse events on the total costs and consequences of chemotherapy treatments.

The models presented provide Australia-based estimates of the costs associated with four common chemotherapy adverse events. While methodological differences make comparisons to previous studies of adverse event costs, in general the estimates are consistent with other research in the area. For decision-makers, these estimates represent the first opportunity to assess the true impact of chemotherapy adverse events on the costs of chemotherapy treatment. Including, where possible, not only the costs of adverse events in terms of resource-use but also the consequences of adverse events in terms of quality of life, dose reductions and possible effect on survival, results in a more-complete picture of the wide-ranging impact of adverse events on the experience of chemotherapy.

Five key aspects of chemotherapy adverse events were identified in the literature review described in Chapter 2 as important, but often poorly modelled:

- the process for selecting adverse events for inclusion of adverse events in models
- the impact of adverse events on quality of life
- the influence that adverse events have on dose of chemotherapy, and the potential flow-on effect this has on survival
- the consideration of multiple events, either recurrent or simultaneous
- the assumption that more-serious adverse events result in higher costs.

All of the models presented in this chapter demonstrate that adverse events at all grades should be included in models of chemotherapy cost-effectiveness. Low-cost events, such as prophylactic management of nausea and vomiting, can affect overall costs due to the high proportion (in this case, all) of patients who require this treatment. Similarly, relatively uncommon events, such as febrile neutropoenia, can have extremely high costs with the potential to have a major impact on the cost of chemotherapy.

Although there is substantial evidence to suggest that adverse events can have a significant effect on the quality of life of individuals undergoing chemotherapy, there was limited evidence in the form of utility values for these conditions. Ideally, these models would incorporate a utility decrement associated solely with the additional loss of quality of life associated with having an adverse event exclusive of the effects of having cancer and undergoing chemotherapy. However, separating out the decrements associated with having cancer, being treated with chemotherapy and having one or more adverse events is difficult, and few studies have done so. In the absence of this type of evidence, careful consideration of how adverse events affect quality of life should be included in larger models of chemotherapy cost-effectiveness.

Poor to moderate evidence was available about the impact of adverse events on dose modifications for the four models. There is the possibility that dose delays and reductions could reduce the total amount of chemotherapy an individual receives, thus reducing the drug costs associated with a specific treatment. In addition, patients who receive less than the planned dose of chemotherapy may have reduced survival, and this component, which could have a significant effect

on chemotherapy efficacy, is often ignored in models of chemotherapy cost-effectiveness. The inclusion of this parameter where possible represents a significant improvement in the ability of models to reflect the experience of chemotherapy in standard-practice settings. This area requires more research, and additional data could be obtained from either randomised controlled trials or observational research; each would bring its own benefits and disadvantages. The decision-tree model structure allows recurrent events to be accounted for by repeated running of the model. However, each adverse event is modelled independently. It is clinically plausible that once a particular type of adverse event has occurred, other related adverse events may be more likely to occur. In addition, it is logical to assume that if two events occur concurrently, each will be treated differently than if they were to occur independently. This may result in cost savings, for example, in the case of one hospitalisation to treat simultaneous events, or in cost increases, for example, in the case of simultaneous events resulting in more difficult and therefore most costly treatment. It is beyond the scope of this thesis to develop a model of simultaneous adverse events; however, there will be some exploration of this in the analysis of observational data in Chapters 4 and 5.

Although each of the models presented in this thesis generally supports the assumption that more-severe events are more costly to manage, there is evidence that this is not always so. In the case of anaemia, significant cost savings were associated with having anaemia severe enough to warrant an immediate blood transfusion because erythropoietic agents are an expensive treatment. This work therefore contradicts the common assumption that only severe events should be included in models of chemotherapy cost-effectiveness.

Limitations of the models

In accordance with the Principles for Good Research Practice, these models should not be considered ‘complete’. While the management of adverse events is evolving, it is relatively well developed, meaning minimal structural changes should be required to the models in the near future. However, while Australian specific guidelines were preferred as the basis of model structure, these were not

available for three of the four models. This may have resulted in models which, although populated with Australian-specific inputs, do not reflect the current best-practice in Australia. Should Australian specific guidelines become available in the future, the model structure will need to be assessed and potentially refined to match these guidelines. In the meantime, those using the models should be aware of the potential differences between Australian practice and that internationally, as are clinicians.

The models will also require an ongoing process of considering and incorporating new evidence regarding model structure and parameter estimates. This is particularly important if the models are to be used within chemotherapy cost effectiveness analyses in the future, as accurate and up to date estimates of the impacts of adverse events will be required for newly developed models.

The models presented here are also subject to uncertainty. Best practice modelling suggests that probabilistic sensitivity analysis should be conducted wherever possible. The models presented here are not standard decision tree models, in that they do not have a decision node as their base node. This is because they are designed to fit within larger models of chemotherapy cost effectiveness. This structural element means that it is not possible to conduct probabilistic sensitivity analysis. This has the potential to results in an under-representation of decision uncertainty, and does not account for correlation of variables (46). Whilst the one-way sensitivity analysis that was conducted could be extended to a multi-way sensitivity analysis, this is unlikely to contribute information useful to decision makers about combinations of outcomes, and are cumbersome to execute. It is hoped that future modellers incorporating these models of chemotherapy adverse events into larger models of chemotherapy cost effectiveness will subject the full model to probabilistic sensitivity analysis, providing additional information on the uncertainty related to adverse event model parameters.

Similarly, while the use of one-way sensitivity analysis addresses parameter uncertainty, probabilistic sensitivity analysis would have added to this analysis. Structural uncertainty is associated with the use of best practice guidelines to select the model structure. While the qualitative description of assumptions within

the model goes some way to addressing this, it is likely that different assumptions would lead to different model outcomes. Similarly, the economic theories and approaches to decision analytic models in health are continuously evolving, and methodological uncertainty will remain an issue. As noted in the examinations of previous studies of each adverse event cost, one of the striking features is the variation in estimates of the costs. Whilst this is partially an issue of structural uncertainty, methodological uncertainty is also a significant factor.

It is proposed that the models and their outcomes will be made available to future modelers in two ways. The first will be the publication of Australian average costs of the selected adverse events, which would allow modelers to include a cost for each adverse event in their model without having to incorporate the model structure. This publication will reflect the current model outputs, based on literature searches covering 2000 – 2011. Secondly, the models themselves will be available as interactive forms online. This will allow users to modify some components to establish a locally applicable cost of each adverse event. By facilitating model access online, an ongoing method of version control can be implemented. This will allow ongoing updating of both the model structure and inputs as required.

Another avenue to take the models presented here forward would be to demonstrate incorporating these adverse event models into a larger model of chemotherapy cost effectiveness. Using an existing model of chemotherapy cost effectiveness would display the difference including these adverse events made to the cost effectiveness results. Whilst this would be a valuable extension of the work conducted to date, it is beyond the scope of this thesis. Part of the difficulty in undertaking this exercise is the availability of models which provide enough information not only to replicate the model structure, but also to extend the consideration of adverse events. The source of information about the incidence of adverse events at all grades, dose modifications and quality of life are all required to extend the model, and these are often not available in peer-reviewed publications. However, the development of a case study demonstrating impact of the adverse event models is a natural and valuable next-step for this work.

Box A: Priorities for research to improve model parameter estimates

For each model there was variation in the availability and quality of data to populate the parameter estimates. While the Principles of Good Practice (215) note that a model should not be faulted because the available data is not scientifically rigorous, there is an opportunity to recommend priorities for research in order to improve model parameter estimates for the future. While some methodologies are suggested, in many cases these research areas will require consideration as part of larger studies or using existing data. These priority areas include:

- Utility decrements specific to the experience of having an adverse event, independent of the experience of having cancer and chemotherapy
- Research into the assumptions of utility values associated with cancer and chemotherapy, and whether they include decrements for adverse events or not
- Observational studies into the proportion of planned dose received by patients in clinical practice
- Additional randomised clinical trial evidence of the impact of receiving reduced dose intensity chemotherapy on overall survival outcomes
- Research into the types of adverse events that occur simultaneously and in clusters, and how these clustered events impact on adverse event management, and in turn resource utilisation.

3.8.1 Conclusion

By developing models of the costs and consequences of four common chemotherapy adverse events—diarrhoea, anaemia, nausea and vomiting, and neutropoenia—it has been demonstrated that in many cases it is possible to address these important components of adverse events in models of chemotherapy cost-effectiveness. The inclusion of these common adverse events may increase the overall cost of chemotherapy treatments, particularly as additional consequences such as the impacts on quality of life and survival are taken into

account along with the extra costs associated with including additional adverse events in the model.

There is potential for these models of adverse events to be included in larger models that others may develop to assess the cost-effectiveness of chemotherapy. In particular, policymakers who consider multiple chemotherapy cost-effectiveness analyses, such as the PBAC, may be interested in introducing these as standardised Australia-based costs of adverse events to ensure modelling transparency and consistency. By ensuring that determination of chemotherapy cost-effectiveness is based on high-quality rigorous models that include all relevant components of treatment, including the management of adverse events, Australia can continue to be a world leader in decision-making about new cancer treatments.

The structure of these models was based on best-practice guidelines, and clinical trial data was often used for model inputs. For a variety of reasons, clinical practice may not always reflect best practice. In addition, the results of clinical trials may not reflect clinical practice. Therefore, it is important to identify the incidence, costs and consequences of chemotherapy adverse events in a clinical practice setting, and these issues are explored in Chapter 4 and Chapter 5.

Chapter 4: The incidence and costs of chemotherapy adverse events in a large administrative dataset

This chapter explores the incidence and costs of chemotherapy adverse events in a clinical practice cohort. The literature review (see Chapter 2) revealed that clinical trials constitute the primary source of data on the incidence of chemotherapy adverse events for use in economic evaluations of chemotherapy treatments. For information about the resources associated with these adverse events, expert opinion and estimates are often used. Each of these data sources has the potential to produce biased results and may not reflect the adverse-event incidence and resources experienced in clinical practice.

This chapter focuses on an analysis of a large administrative dataset of NSW-based clients of DVA. The questions explored are:

- What is the incidence of chemotherapy adverse events in older people in clinical practice?
- What factors influence the incidence of chemotherapy adverse events in older people in clinical practice?
- What is the additional cost of chemotherapy adverse events in older people in clinical practice?

The analysis focuses in particular on the four common and important adverse events addressed in the models in Chapter 3: diarrhoea, nausea and vomiting, anaemia and neutropoenia. The data available do not directly identify whether an individual experiences an adverse event; therefore, a proxy measure based on pharmaceutical prescriptions, medical services and hospitalisations is developed for each adverse event.

The analysis of incidence is conducted both by chemotherapy dose and by individual. In assessing the factors associated with the incidence of chemotherapy adverse events, methods to address correlation of the data, including use of a

summary measure and generalised estimating equations (GEE) are explored. As with much cost data, the cost variable in the analysis of the resources associated with adverse events is skewed, and a number of alternative methods of managing this are presented.

The incidence of chemotherapy adverse events in this cohort is found to be low. This chapter suggests that the proxy measure may not identify all individuals experiencing an adverse event, and therefore this analysis may underestimate the incidence of chemotherapy adverse events in clinical practice. However, it appears that those with multiple comorbidities are more likely to have treatment for a likely adverse event, whereas the relationship between age and adverse events is less clear and may not be linear. The additional costs associated with chemotherapy adverse events during the first six months of commencing a chemotherapy treatment are significant.

The results presented in this chapter provide decision-makers with more information about the additional costs associated with four common chemotherapy adverse events. In addition, a strong case is made for prospectively collecting data on chemotherapy adverse events in a clinical practice setting to estimate more accurately the incidence of the adverse events of chemotherapy. This forms the background to the prospective cohort study described and analysed in Chapter 5.

4.1 Background

It is well established that randomised clinical trials provide the optimal method for determining the clinical effectiveness of interventions. However, the high internal validity of these trial designs may not compensate for its low generalisability (external validity). Protocol-defined events may drive resource-use in clinical trials, and the use of endpoints unsuitable for economic evaluations (e.g. cost per percentage reduction in cholesterol) is common (48). Although many cancer trials follow people until death, there are many studies that require extrapolation beyond trial endpoints, such as progression-free survival (48).

There are other data used in economic evaluations, such as the quantities of resources used, that may be influenced as a result of being collected in the clinical trial setting. In addition, issues such as the additional monitoring of patients during trials (48), the fact that most trials are run in larger specialist centres (48), and that older patients and those with comorbidities are often excluded from clinical trials (216), contribute to a setting quite different from that typically faced by clinicians in clinical practice. The use of observational data of clinical practice has the potential to overcome these issues and may provide a better basis for developing policy about the funding or provision of new treatments (48). Additionally, administrative data are often highly cost-effective to obtain, can provide a wide scope of data, often large in size and/or collected over an extended period (48). However, it is also important to recognise that the biases controlled for by randomisation are not controlled for in observational studies (48).

The literature review (see Chapter 2) identified that the costs and outcomes of chemotherapy adverse events are not included in any systematic way in economic evaluations of chemotherapy treatments. The literature review revealed that the primary source of data for estimating probabilities of adverse events are clinical trials, while resource-use is often estimated based on expert opinion or other sources of low-level evidence. The use of these types of data sources as the basis for economic evaluations may result in biased estimates of the cost of chemotherapy, because they do not necessarily reflect clinical practice.

The incidence of adverse events is an important input in many chemotherapy economic evaluations, and it is essential to use estimates that are as accurate as possible. The use of clinical trial data to populate models of chemotherapy cost-effectiveness in terms of the incidence of adverse events has the advantages of high internal validity owing to the randomisation of individuals within clinical trials. This randomisation removes any potential differences between groups; therefore, any differences in the rates of adverse events are likely to be due to the differences in treatments received. However, the low external validity of clinical trials may influence the rates of adverse events, resulting in biased inputs to cost-effectiveness analyses. A number of population-based studies have identified that

adverse-event rates in clinical practice are higher than rates reported in clinical trials (52, 55, 217).

Rothwell (52) suggests that the following aspects of clinical trials may influence the external validity of results related to adverse events:

- Completeness of reporting of relevant adverse effects
- Rate of discontinuation of treatment
- Selection of trial centres and/or clinicians on the basis of skill or experience
- Exclusion of patients at risk of complications
- Exclusion of patients who experienced adverse effects during a run in period
- Intensity of trial safety procedures. (p 83)

In addition, the reporting of safety information, including information about toxicities related to treatment, is generally poor in clinical trial publications (53, 54, 218, 219), and even in tightly controlled clinical trials, clinician reporting of patient symptoms is neither sensitive nor specific (220).

Aside from the specific chemotherapy drug, a number of factors influence the probability of an individual experiencing an adverse event; these include gender, age, tumour stage, comorbidities, previous adverse events, and geographic location (217, 219). Given that clinical trials often base the selection of participants on all of these factors, it is reasonable to assume that the rates of adverse events reported in clinical trials may be biased and not reflect the experience of patients receiving chemotherapy outside a clinical trial setting.

This higher incidence of chemotherapy adverse events in clinical practice than in clinical trials has implications for economic evaluation, because the resources associated with adverse events will be incorrectly estimated. Although some research uses cost-of-illness methods to estimate the resources and costs associated with chemotherapy adverse events, many economic evaluations use inputs based on expert opinion or estimation, which introduces an additional bias to the results.

Studies using observational data allow examination of health issues such as adverse events in clinical practice. Observational designs, such as cohort studies, do not include an intervention by the researchers, but rather observe changes as

they occur (221). Administrative data can be used to conduct observational research, particularly when linked to health data. Linked datasets allow for research into disease profiles within the community, including prevention, detection and management (222). This type of research is particularly policy relevant, because it can include examination of long-term trends or outcomes and is generalisable to the real-world setting (222). There are additional advantages: it is often a very cost efficient way to investigate issues in large numbers of individuals, and data and outcomes from various sectors can be integrated in the investigation of complex health outcomes (222).

Although observational data can provide information about health issues in clinical practice, suitable data can be difficult to find. Issues such as confidentiality, access to data, and the collection of research appropriate data can make the use of administrative data for assessing health issues difficult (222).

4.1.1 Australian Government Department of Veterans' Affairs

The DVA provides services to over a quarter of a million veterans, spouses, widows, widowers and dependants in Australia (223). These services include a broad range of healthcare and supports, and holders of a DVA gold card are entitled to the full range of healthcare services at DVA's expense, including medical, dental and optical care, where they are provided through DVA arrangements (61). In addition, the RPBS provides access at a concessional rate to all items on the Schedule of Pharmaceutical Benefits available to the general community under the PBS, as well as an additional list contained in the RPBS, which is available at subsidised cost only to veterans (62).

The DVA pharmaceutical claims database is a unique resource enabling examination of prescription medicine use at the individual level. The population served by the DVA is an older one, and therefore this particular dataset is particularly useful for investigating medicine use in older individuals. The primary advantage of the DVA data is that there is close to complete capture of prescribed medicines, whereas most administrative datasets do not capture information about low-cost prescription medicines.

The use of DVA data enables pharmacoepidemiological research to be undertaken, such as that undertaken by the Veterans' Medicines Advice and Therapeutics Education Services (Veterans' MATES) program (224). The DVA population is older than the general Australian population, and this needs to be considered when determining appropriate research questions to address with this cohort. However, these high-quality data, which include data on pharmaceutical usage at an individual unit record level and have close to complete coverage of pharmaceutical products, are an excellent resource for examining the use of pharmaceuticals, such as chemotherapy, in a clinical practice setting in older Australians. For the purpose of this research an extract of NSW DVA residents will be used.

The NSW CHeReL links multiple sources of administrative data using best-practice privacy protocols for the purposes of research (225). The centre maintains a master linkage key, which consists of records from a number of NSW and ACT administrative datasets, including records of hospitalisation, emergency department presentations, births, cancer registrations and deaths (225). This enables the CHeReL to facilitate linkage of other datasets, such as the MBS, the PBS and the DVA client database, to the master linkage key (225).

High-quality client data from the DVA, linked with extensive administrative data on healthcare products and services, provide an ideal opportunity to explore the adverse events of chemotherapy in older individuals in a clinical practice setting.

4.1.2 Aims and objectives

The aim of this research was to examine the incidence and resource use associated with chemotherapy adverse events in older people in clinical practice.

More-accurate estimates of the incidence of chemotherapy adverse events and the resources associated with chemotherapy use are essential if the results of economic evaluations of chemotherapy are to be useful to decision-makers. Examining the incidence of chemotherapy adverse events in clinical practice the factors influencing the incidence, and the resources associated with the events will

better inform models of chemotherapy cost-effectiveness and economic evaluations of new chemotherapy treatments.

The three objectives of this analysis were to explore:

1. the incidence of chemotherapy adverse events in older people in clinical practice
2. the factors that influence the incidence of chemotherapy adverse events in older people in clinical practice
3. the resource-use associated with chemotherapy adverse events in older people in clinical practice.

These objectives were addressed using regression analyses in a large, linked cohort from the DVA.

4.1.3 Data

The CHeReL provided a linked dataset using the DVA client file, pharmaceutical claims database and other key NSW population-level data collections, including Medicare Australia, the NSW Registry of Births, Deaths & Marriages and the NSW CCR. The CHeReL maintains a Master Linkage Key which is a series of health-related NSW datasets which are linked at the individual level on the basis of demographics and updated regularly. The extract contains data for approximately 195,000 DVA clients residing in NSW for all or part of 1994 to 2007.

Table 4.1 shows the dates and contents for each dataset, and the overall data utilisation period used. The DVA client database was used as the base database, with resource utilisation databases continuing beyond 2007 to track resource utilisation beyond the period of initial DVA registration.

The NSW CCR is a population-based registry that records all new cancer diagnoses and all cancer deaths in NSW. The database captures basic demographic information and cancer details. Although degree of spread is collected at diagnosis, no ongoing collection of information about disease progression is undertaken. This field is therefore not necessarily reflective of

current cancer stage. Each unique cancer diagnosis in an individual is recorded as a separate record in the database.

The RPBS dataset includes all pharmaceutical transactions paid for by the DVA. This includes items listed on the PBS for which all Australians are eligible, RPBS items which are only available to veterans, and items requiring pre-approval for veteran access. Similarly, the DVA medical services data include all medical and allied health services paid for by DVA. Although pharmacy data are also available through this database, they were excluded from this request given they had been captured in the RPBS data.

The NSW APDC covers all inpatient separations from all public and private hospitals, including those provided under DVA arrangements, in NSW. The inclusion of these data allows for the addition of data from hospital admissions where a DVA client has not declared their DVA status or that may not be billed to the DVA. The NSW EDDC covers all emergency department visits in NSW.

Table 4.1: Datasets linked for the analysis of adverse events in DVA clients

Database	Start date	End date	Data items
Base database			
DVA client database	01 Jan 1994	31 Dec 2007	Gender, date of birth, date of death, DVA card details (type, issue number, start and stop dates, veteran status)
Resource utilisation databases			
NSW CCR	Jan 1994	Dec 2009	Age at diagnosis, date of diagnosis, date of birth, gender, morphology, site, cancer death flag, cause of death (cancer cases), date of death, degree of spread
RPBS	01 July 2004	31 Jan 2010	Gender, age at supply, safety-net flag, scheme, item identification code, date of supply, date of processing, number/quantity supplied
DVA medical services data	01 Jan 2000	31 Jan 2010	Service item, service item code, category and category code, date of service and paid amount
NSW APDC	01 July 2000	30 June 2009	Date of admission, date of separation, principal diagnosis, additional diagnosis, stay diagnosis, DRG, principal procedure, additional procedure, LOS, source of referral, separation mode
NSW EDDC	01 Jan 2005	31 Dec 2009	Date and mode of arrival, date of

			separation, separation mode, primary ED diagnosis and additional ED diagnosis
Resource-utilisation period	**01 Jan 2005**	**30 June 2009**	**This is the period of overlap for all resource utilisation databases**

Note: APDC = Admitted Patient Data Collection; DRG = diagnosis related group; DVA = Australian Department of Veterans' Affairs; LOS = length of stay; ED = emergency department

The sample was restricted to those individuals holding a gold card, because the DVA pays for all pharmaceuticals and medical services for these individuals. There were 129,307 individual gold card holders in the dataset. Of these, 29,480 (23 per cent) had a diagnosis of cancer during this time, and 12,030 (9 per cent) had received chemotherapy. A total of 111,059 doses of chemotherapy had been administered.

4.1.4 Demographic variables in the dataset

Age: The date of birth of each individual was taken from the DVA client database. For descriptive statistics, age was calculated as the number of months between date of birth and the DVA client extract end date (31-DEC-2007) and divided by 12. For analysis of specific events, such as cancer diagnosis or chemotherapy doses, age was calculated as age at the time of the event in question.

Age is a highly significant factor in analysis of cancer patients and their patterns of care. Age is highly related to cancer incidence, with incidence rising with increasing age. Many cancers have different disease profiles depending on age at diagnosis; for example, breast cancers are more aggressive in younger women. However, older age is often used in clinical trials as an exclusion criterion. It has been suggested that this is due to the frailty and comorbid conditions of elderly people, which may put them at increased risk from participation in a clinical trial (216, 226). A large literature review found that rates of participation of elderly individuals in clinical trials is slowly increasing, although often these represented the very fit elderly (226). However, oncologists have continued to appear reluctant to involve those in older age groups in clinical trials (226). The older median age of the DVA cohort provides an excellent opportunity to examine chemotherapy adverse events in an older cohort in clinical practice.

Gender: The gender of each individual was taken from the DVA client database. Given the higher proportion of males to females in the database, males were coded as the base case '0' and females were coded '1'. There are some cancers for which gender is an obvious risk factor (such as prostate and breast cancers) and many other cancers with an uneven distribution of incidence by gender, such as colorectal cancer (227). There is also some evidence that in a variety of cancers females may have different rates of survival (227-229) and response to chemotherapy (229-231) than males; however, the direction of these gender differences are inconsistent.

RxRisk score: The presence of comorbidities influences the prognosis, therapy and outcomes of patients, and should therefore be controlled for in health research to maximise internal validity (232). A number of methods of estimating and adjusting for comorbidities in observational research have been developed using algorithms such as the number of conditions based on medical-record review, Diagnosis Related Groups (DRGs—the system used to classify hospital cases into diagnosis groups for payment), ambulatory clinical groups, laboratory tests (233) and pharmaceutical dispensing (233, 234).

The RxRisk score is a pharmacy-based measure of comorbidity (234). Pharmacy-based instruments such as the RxRisk have some advantages over diagnosis-based strategies, including improved availability and accuracy of pharmacy dispensing data (234). In Australia, this means that adjustments for comorbidities can be made to data from the outpatient as well as inpatient settings, as outpatients often only have pharmaceutical data available. A comparison of the Charlson (diagnoses based) and the RxRisk score in the DVA population in Australia found that either would be suitable for use (232). The RxRisk score was less likely to identify cancer and dementia, but better at identifying gastric, respiratory and cardiovascular conditions (232). The RxRisk score was selected as the comorbidity measure for this analysis because an individual's cancer status is already known, and the primary interest is in events that occur to individuals treated in the ambulatory setting. The RxRisk score involves the creation of 43 indicators for general drug categories (e.g. antihypertensive agents, anti-diabetic

drugs). These indicator variables are then summed to create a total RxRisk score, which can be used as weighted or unweighted. For this analysis, the original unweighted scores were used, because the weighted scores were developed to better predict mortality in outpatient populations (235), which was not the purpose of this study.

RxRisk score was calculated using a SAS-macro based on the algorithm created by Christine Lu (232). The macro utilised data from the PBS dataset to create the 43 indicator variables, and one total unweighted RxRisk score variable. This total RxRisk score was applied in all analyses.

Cancer site: The site of cancer in each individual was taken from the NSW CCR dataset and was used to identify the type of cancer diagnosed for each individual. To account for individuals who may have more than one record (due to more than one cancer diagnosis), when analysing data for specific events, the most recent cancer diagnosis prior to the date of the event was used to ensure that the correct diagnosis was allocated to each event. For regression analyses, urinary cancer was selected as the baseline category.

Chemotherapy: Doses of chemotherapy were identified for each individual through the PBS dataset. The Anatomical Therapeutic Chemical (ATC) Classification System is a pharmaceutical coding system that classifies drugs into different groups based on the body system on which they act and their chemical characteristics.The ATC category code for antineoplastic agents is 'LO'. Items with ATC codes commencing with 'LO' were flagged as being chemotherapy. To remove the (small) number of people who potentially received chemotherapy drugs for diseases other than cancer, each analysis was limited to those who had also received a cancer notification in the NSW CCR. For regression analyses, immunosuppressants were selected as the baseline category.

4.1.5 Adverse-event variables

The adverse events considered for examination were the same as those selected for modelling in Chapter 3: diarrhoea, anaemia, nausea and vomiting, and neutropoenia. As discussed in Chapter 1, these are all common adverse events that

are often omitted from economic evaluations of chemotherapy. They are also adverse events commonly reported by patients as being highly distressing.

The best-practice guidelines (see Chapter 3) for the development of models were used to identify the drugs, medical resources and hospitalisations that would potentially be associated with treating each of the selected adverse events. It is recognised that clinical practice does not always follow best-practice guidelines; therefore, common alternative treatments for each adverse event were also included in the analysis. A drug, medical resource or hospitalisation was considered related to chemotherapy when it was prescribed or delivered either on the day of chemotherapy or up to three days later. For each adverse event, indicator variables were created for the major treatment types and hospitalisation. For anaemia, an indicator for blood transfusions was also created. Table 4.2 describes those resources identified as being related to treatment for each adverse event.

Table 4.2: Resources identified as treatments for each adverse event

Treatment	Description	Codes
Diarrhoea		
Best-practice anti-diarrhoeal drugs	Loperamide and octreotide are best-practice pharmaceutical management of CID	ATC codes for loperamide: A07DA03, A07DA05, A07DA53; ATC code for octreotide: H01CB02
Other anti-diarrhoeal drugs	Additional anti-diarrhoeal products that may be used but are not considered best practice	All other anti-diarrhoeal ATC code are those starting with A07
Hospitalisation	Hospitalisation where diarrhoea was the primary diagnosis, or in the top 10 accompanying diagnoses	ICD codes: K59.1, R19.8, A09.0 or A09.9
Anaemia		
Anti-anaemia drugs	Iron sucrose, epoetin and darbepoetin are best-practice pharmaceutical management of chemotherapy-induced anaemia	ATC codes: B03Axx or B03XA01 or B03XA03
Blood transfusions	Blood transfusions are commonly used to treat anaemia and are considered	MBS service item code: 13709 (collection of blood) or 13706

	best practice for many patients. The cost of blood products is not publically available, in lieu of actual costs, collection of blood (MBS item 13709) was used. Item 13706 is the cost of administering a blood transfusion.	(administration of blood transfusion)
Hospitalisation	Hospitalisation where anaemia was the primary diagnosis, or in the top 10 accompanying diagnoses	ICD codes: D50.1 or D50.8 or D50.9
Nausea and Vomiting		
Best-practice antiemetic drugs	NK1 receptor antagonists, 5-HT3RAs and corticosteroids are best-practice pharmaceutical management of chemotherapy-induced nausea and vomiting	ATC codes that start with A04AA or A04AD, or ATC codes R06AE03 or A03FA03 or N05AD01 or N05AA02 or N05AB04 or H02AB02 or R06AD02 or N06AX11
Hospitalisation	Hospitalisation where nausea or vomiting was the primary diagnosis, or in the top 10 accompanying diagnoses	ICD codes: R11 or R11.0 or R11.1 or R11.10 or R11.12 or R11.13 or R11.14 or R11.2
Neutropoenia		
G-CSFs	The use of the G-CSFs filgrastim, pegfilgrastim and sargramostim are best-practice pharmaceutical management of chemotherapy-induced neutropoenia	ATC codes: filgrastim L03AA02; pegfilgrastim L03AA13; sargramostim L03AA09
Fluoroquinolones	Fluoroquinolones are oral antibiotics often used in combination with G-CSFs for the treatment of chemotherapy-induced neutropoenia	J01MA01–J01MA21
Hospitalisation	Hospitalisation where neutropoenia was the primary diagnosis, or in the top 10 accompanying diagnoses	ICD code: D70.0

Note: ATC = Anatomical Therapeutic Chemical; CID = chemotherapy-induced diarrhoea; G-CSF = granulocyte colony-stimulating factor; ICD = International Classification of Diseases; MBS = Medicare Benefits Schedule

4.1.6 Summary statistics

Table 4.3 presents the demographic and clinical characteristics of the sample who had a diagnosis of cancer and received chemotherapy. The sample is predominantly older males, with high rates of comorbidities as measured using the

RxRisk score. Although this sample may not be representative of the NSW population in general, it could be considered to represent individuals traditionally excluded from clinical trials. Many cancer clinical trials specifically exclude older people and those with comorbidities (216).

Table 4.3: Demographic and clinical characteristics of the DVA cohort

Demographic & clinical characteristic		DVA chemotherapy cohort	DVA gold card cohort	NSW population	NSW population reference
Proportion of males		72%	55%	50%	(236)
Mean age (median) in years		81 (83)	79 (82)	38 (37)	(236)
Age range (years)		46–106	0–106	0–100+	(236)
Age group	< 70 years	14%	19%	90%	(236)
	70–80 years	23%	21%	6%	(236)
	> 80 years	63%	60%	4%	(236)
Mean RxRisk score*		8.83	7.83	1.98	(237)**
RxRisk score range*		0–26	0–26	Unknown	N/A

* RxRisk score is a measure of comorbidities based on pharmaceutical prescriptions
** A study of the general adult population in the US
Note: DVA = Australian Department of Veterans' Affairs

The types of cancers seen in the sample are presented in Table 4.4, and are similar to those seen in the general NSW population. In NSW, prostate cancer is the most common cancer (19 per cent), followed by bowel cancer (13 per cent), breast cancer (12 per cent), melanoma (10 per cent) and lung cancer (9 per cent) (238). The higher incidence of prostate cancer in the DVA cohort may be due to the older age of the sample, because age is an established risk factor associated with prostate cancer (239), and the higher proportion of males in the sample relative to the NSW general population.

Table 4.4: Types of cancers—DVA cohort

Cancer site	Total number of cases	Percentage of total cancers in DVA cohort	Percentage of total cancers in the NSW population (238)
Prostate	3,124	39	19
Breast	1,059	13	12
Melanoma of skin	881	11	10
Colon	491	6	13 (bowel cancer)
Lung	354	4	9
Non-Hodgkin's lymphoma	349	4	4
Rectum, rectosigmoid, anus	279	4	- (inc. in bowel cancer)
Bladder	186	2	2
Ill-defined or unspecified	136	2	3
Head and neck	591	< 1	N/A

Note: Note: DVA = Australian Department of Veterans' Affairs; inc. = include; N/A = not applicable

The most commonly used anti-neoplastic drugs in the cohort (reported in Table 4.5) were reviewed using the eviQ website (39) to identify for which types of cancer they are recommended. The anti-neoplastic treatments seen in the corhort are consistent with the most common cancers seen in the cohort (see Table 4.4).

Table 4.5: Ten most administered anti-neoplastic drugs—DVA cohort

Drug	Number of patients receiving each drug	Percentage of total chemotherapy treatment	Recommended for treating (39)
Fluorouracil	2,198	18.20	Breast, colorectal
Goserelin acetate	1,909	15.80	Prostate, breast
Leuprorelin acetate	1,307	10.82	Prostate
Bicalutamide	1,005	8.32	Prostate, breast
Tamoxifen citrate	776	6.42	Breast
Capecitabine	327	2.71	Breast, colorectal
Rituximab	321	2.66	Lymphoma
Cyclophosphamide	305	2.53	Breast, leukaemia
Anastrozole	280	2.32	Breast
Gemcitabine	276	2.28	Breast, lung, bladder, pancreas

4.1.7 Data issues

Three issues were identified with the available data, which influenced the design and conduct of the analysis: 1) the size of the dataset (see Appendix P), 2) the use of a proxy for adverse events and 3) the existence of correlation between observations.

Use of a proxy

The dataset does not include specific information about the diagnosis of an adverse event. A proxy measure is appropriate when the data do not enable the direct measurement of the event of interest. However, given certain treatments are likely to be used when an individual experiences an adverse event, and it is possible to relate these treatments to chemotherapy administration by time, receipt of these treatments for the adverse events is used as a proxy for having experienced an adverse event. Caution is needed when interpreting the results, because a proxy is not a replacement for the outcome of interest but an approximation. In this analysis, the results of analyses that use the proxy of treatment for an adverse event can be interpreted as 'the individual has been treated for a likely adverse event'. The appropriateness and accuracy of the use of this proxy will be examined using comparative self-reported data in Chapter 5.

Correlation of observations

The existence of correlated data is common in epidemiological and clinical science research, often because of the use of longitudinal analysis (240, 241). Most standard statistical analysis techniques, including regression, assume that each of the primary observations within a dataset is independent of the others (240, 242). This assumption is inappropriate when multiple observations of the same individual are included in the data, because the responses from individuals tend to be correlated with each other (240, 243). This correlation means that if two observations are chosen at random from one individual, they are likely to be more similar than two observations chosen at random from different individuals (240, 242). This results in less additional information provided from a new observation in an individual than from a new observation in a new individual (240). The intra-class correlation coefficient can be used to measure correlation, with a value of

1.0 indicating that each repeated observation for an individual provides no additional information (244).

This dataset contains multiple observations of each individual at different points in time. There is clinical reasoning to suggest that certain individuals may be more or less susceptible to particular adverse events compared with the rest of the cohort. This means that observations of an individual are likely to be correlated.

The effect of correlation on data analysis, if undertaken using standard statistical techniques, is that the resultant standard errors and p-values are misleading. Depending on the type of analysis, the results may either overestimate or underestimate the effect (240, 242). For within-subject comparisons such as in this cohort, analysis that ignores correlations will overestimate the variability, which has the effect of increasing p-values and decreasing the chances of observing a significant effect due to decreased statistical power (242).

Correlated data can be analysed in a number of ways. One approach is to develop a summary statistic, which resolves the repeated measurements in each individual. Examples might be the mean, difference or slope of measurements over time (240). This approach is inefficient in that only part of the available information is used (240), although it is possible to simply remove correlated observations from the dataset, this results in a loss of information and therefore a loss of statistical power (242). In addition, it may be difficult to select an appropriate summary measure that captures the desired changes.

To analyse correlated observations appropriately, specialised statistical methods are required. A number of approaches have been developed for regression analysis of correlated data, including multi-level modelling—a form of linear mixed modelling—and GEE. These methods will be considered in more detail in Section 4.3.2.

4.2 Incidence of chemotherapy adverse events in clinical practice

Data about the incidence of chemotherapy adverse events for economic evaluations are often taken from clinical trials. However, these may not reflect what happens in clinical practice settings. This analysis explores the use of an administrative dataset to identify the incidence of chemotherapy adverse events in a clinical practice cohort.

4.2.1 Methods

Data

A separate dataset was generated for each adverse event from three merged datasets. The datasets and variables used are shown in Table 4.6.

Table 4.6: Variables used to create the analysis dataset of the DVA cohort

Dataset	Contribution	Variables
DVA client file	Demographic details	PPN, card type, RxRisk, gender, age (at date of chemotherapy)
PBS	All chemotherapy doses (ATC codes 'LO')	PPN, pharmaceutical item code, pharmaceutical claim supply date, service paid amount, ATC, cancer site, cancer topography, and cancer histology
	Pharmaceutical items for treatment of the adverse event in the period 01 July 2004–30 June 2009	PPN, pharmaceutical claim supply date, ATC
APDC	Hospital admissions where the diagnosis 1–10 was for treatment of the adverse event in the period 01 July 2004–30 June 2009	PPN, ICD codes 1–25 (the codes for 26+ were all blank, and so not included), date of admission, and length of stay

Note: APDC = Admitted Patient Data Collection; ATC = Anatomical Therapeutic Chemical; DVA = Australian Department of Veterans' Affairs; PBS = Pharmaceutical Benefits Scheme; ICD = International Classification of Disease; PPN = unique person identifier

The three datasets were merged; thus the demographic, cancer type and chemotherapy information were known for each chemotherapy dose and were located in the same dataset. A visual representation of this merge is provided in Figure 4.1. Each observation (row) within the dataset represents one dose of chemotherapy given to a unique individual on a unique day. Binary variables were generated for each type of adverse-event pharmaceutical treatment or hospitalisation and populated by searching the PBS and APDC datasets to identify

observations of an individual receiving an adverse-event treatment on the day, or within three days, of each chemotherapy dose. Any records from the PBS or APDC with no dispensing date or service date were dropped, because it was not possible to relate them to a dose of chemotherapy. Finally, a combined indicator for 'any treatment' was created for each adverse event.

Where two different pharmaceutical products were received by the same individual on the same day for the same adverse event, these were recorded within the single chemotherapy dose observation. In cases where two (or more) chemotherapy treatments were received within three days, only the first of these was retained in the analysis dataset, with all related adverse-event treatments recorded within that observation.

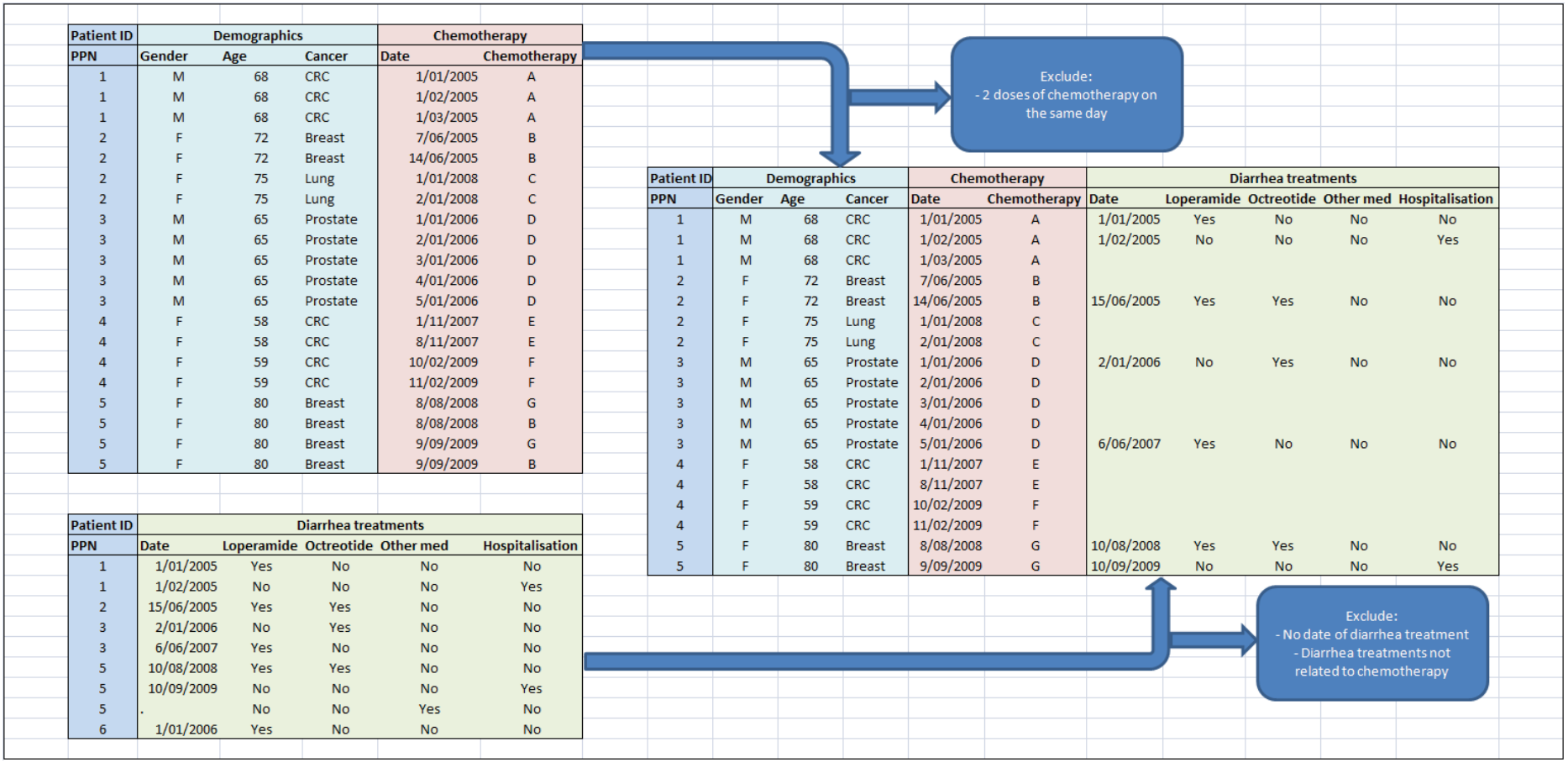


Figure 4.1: Visual representation of dataset merge (using mock data)

The predominantly binary variables used for the analysis of incidence for each adverse event are listed in Table 4.7.

Table 4.7: Variables in DVA adverse-event dataset for calculating incidence

Variable	Variable name	Description	Format	Options
Chemotherapy doses	Doses	Total number of doses of chemotherapy that individual received over 4.5-year observation period	Continuous	
Loperamide treatment	Lop	Whether loperamide was dispensed on the day of or up to 3 days after a chemotherapy dose	0	No
			1	Yes
Octreotide treatment	Oct	Whether octreotide was dispensed on the day of or up to 3 days after a chemotherapy dose	0	No
			1	Yes
Other diarrhoea treatment	Other	Whether other diarrhoea pharmaceuticals were dispensed on the day of or up to 3 days after a chemotherapy dose	0	No
			1	Yes
Diarrhoea hospitalisation	Diahosp	Whether there was a diarrhoea-related hospitalisation on or up to three days after a chemotherapy dose	0	No
			1	Yes
Any diarrhoea	Anydia	Whether that individual experienced any diarrhoea treatments within three days of a chemotherapy dose	0	No
			1	Yes
HT3 treatment	HT3	Whether HT3 was dispensed on the day of or up to 3 days after a chemotherapy dose	0	No
			1	Yes
A04AD treatment	A04AD	Whether A04AD was dispensed on the day of or up to 3 days after a chemotherapy dose	0	No
			1	Yes
Other nausea and vomiting treatments	Other	Whether other nausea or vomiting pharmaceuticals were dispensed on the day of or up to 3 days after a chemotherapy dose	0	No
			1	Yes
Nausea and vomiting hospitalisation	Nauseahosp	Whether there was a nausea-and-vomiting-related hospitalisation on the day of or up to three days after a chemotherapy dose	0	No
			1	Yes
Any nausea or vomiting	Anynausea	Whether that individual received treatment for nausea or vomiting within 3 days of a chemotherapy dose	0	No
			1	Yes
Iron treatment	Iron	Whether iron was dispensed on the day of or up to 3 days after a chemotherapy dose	0	No
			1	Yes
ESA treatment	ESA	Whether an ESA was dispensed on the day of or	0	No

Variable	Variable name	Description	Format	Options
		up to 3 days after a chemotherapy dose	1	Yes
Blood transfusion	Trans.	Whether a blood transfusion was given on the day of or up to 3 days after a chemotherapy dose	0	No
			1	Yes
Anaemia hospitalisation	Anaemiahosp	Whether there was an anaemia-related hospitalisation on the day of or up to three days after a chemotherapy dose	0	No
			1	Yes
Any anaemia	Anyanaemia	Whether that individual was recorded as receiving treatment for anaemia within 3 days of a chemotherapy dose	0	No
			1	Yes
Antibiotic treatment	AB	Whether antibiotics were dispensed on the day of or up to 3 days after a chemotherapy dose	0	No
			1	Yes
G-CSF treatment	G-CSF	Whether a G-CSF was dispensed on the day of or up to 3 days after a chemotherapy dose	0	No
			1	Yes
Neutropoenia hospitalisation	Neuthosp	Whether there was a neutropoenia-related hospitalisation on the day of or up to three days after a chemotherapy dose	0	No
			1	Yes
Any neutropoenia	Anyneut	Whether that individual was recorded as receiving treatment for neutropoenia within 3 days of a chemotherapy dose	0	No
			1	Yes
Any adverse event	Anyae	Whether that individual was recorded as receiving treatment for diarrhoea or nausea or vomiting or anaemia or neutropoenia within 3 days of a chemotherapy dose	0	No
			1	Yes

Note: G-CSF = granulocyte colony-stimulating factor

Analysis

The incidence (newly diagnosed cases over a period of time) of treatment for each adverse event in individuals who had a diagnosis of cancer and received chemotherapy was calculated. The total number of chemotherapy doses was calculated, and the number of these doses that had a related treatment for an adverse event was identified. This incidence was then calculated as a percentage of total doses of chemotherapy. This calculation was repeated for individuals. This was achieved by converting the dataset so that one row represented one person, with a summary variable indicating whether they had ever received a treatment for the chemotherapy adverse event under analysis. The total number of each adverse event was then divided by the total number of people.

Additional analyses were conducted to determine the sensitivity of using a three-day 'window' for assessing whether an adverse-event treatment was related to a dose of chemotherapy. To assist in interpretation of the results, the 'baseline' rate of these same treatments were observed in individuals from the DVA client database without a diagnosis of cancer.

4.2.2 Results

Incidence of adverse events

The incidence of each of the four adverse events is presented by drug dose and by person in Table 4.8. The incidence of nausea and vomiting was the highest in both measures, with neutropoenia the least common.

Table 4.8: Incidence of adverse events by dose and by person in the DVA cohort

	Adverse events	No. with chemotherapy	No. with adverse event	Percentage with adverse event
By doses	Diarrhoea	89,594	879	0.98
	Anaemia	84,872	638	0.75
	Nausea and vomiting	84,378	5,415	6.42
	Neutropoenia	84,495	601	0.71
By person	Diarrhoea	7,978	396	4.96
	Anaemia	8,158	330	4.05
	Nausea and vomiting	9,173	1,535	16.73
	Neutropoenia	8,069	242	3.00

Note: no. = number

Additional analyses

A period of three days was selected as a clinically appropriate period for chemotherapy-related adverse events to occur and to be detected and treated. However, an additional analysis using a 10-day period was also conducted, because it is possible that data-collection procedures will result in delayed entries. The longer period resulted in an increased number of adverse-event treatments identified for all events.

To assess whether the 10-day data were capturing additional relevant adverse-event treatments or were identifying non-related treatments, the baseline rate of the same treatments in non-cancer patients was calculated. These rates were compared with the rates at 3 days and at 10 days for people receiving chemotherapy for cancer (see Table 4.9). The relatively high rates of these treatments being used in those without a cancer diagnosis suggests that extending the window for considering a treatment as relating to an adverse event of chemotherapy may result in additional unrelated treatments being included. It was therefore considered that the three-day window was the most appropriate, although it was also acknowledged that there was the risk of a small number of adverse-event-related treatments with a delayed entry to the database being missed.

Table 4.9: Rates of treatments in DVA non-cancer cohort, and at 3 and 10 days post-chemotherapy

Variable	3 day %	10 day %	Non-cancer* %
Diarrhoea			
Per dose	0.98	1.49	N/A
Per person	5.00	6.42	13.19
Anaemia			
Per dose	0.75	1.43	N/A
Per person	4.00	5.84	6.15
Nausea and vomiting			
Per dose	6.42	9.70	N/A
Per person	16.73	20.14	30.30
Neutropoenia			
Per dose	0.71	1.10	N/A
Per person	3.00	4.72	12.28

* Not including hospital or MBS.
Note: N/A = not applicable

4.2.3 Discussion

The incidence rates of adverse events in this database are markedly lower than those that are reported in the literature. Most reports of adverse-event incidence are in individuals receiving a specific chemotherapy, and the estimates vary

widely. There are some estimates of incidence in heterogeneous samples of patients with cancer receiving chemotherapy. One study of diarrhoea found an incidence of 14 per cent (245), while anaemia has been estimated at 67 per cent (168) and nausea and vomiting at 68 per cent (246).

The higher rates of adverse events when calculated per person rather than by dose indicates that many people are having a small number of adverse events. This is consistent with the clinical expectation that although many people have adverse events, only a few have the same adverse event multiple times, because it is usually treated or managed.

The low incidence rates of adverse events in the DVA cohort could be reflective of the older and sicker veteran population. Given the types of chemotherapy they are receiving are less toxic, it is possible that they would experience fewer adverse events than the general population who are receiving more-toxic chemotherapy. It may also be that given the older age and high level of comorbidities in these patients, doctors are more likely to cease chemotherapy altogether to prevent adverse events, or to reduce the dose at an earlier sign of an adverse event.

However, it is also likely that the rates are an underestimate of the true rates, because this analysis is able to identify only those individuals who receive treatments for an adverse event. It is likely that some patients experiencing less-severe events (such as Grade I diarrhoea or Grade I nausea and vomiting) may not require treatment beyond dietary and lifestyle changes to manage their symptoms. Although such cases may be reported in studies of patient-reported symptoms, they would be excluded from this analysis, which would result in under-counting. For similar reasons, clinical trials also would be likely to exclude less-severe events from reporting.

These rates of adverse events in individuals are either approaching or are over the five per cent threshold level of importance seen in the literature review (see Chapter 2) as often used in economic evaluation of chemotherapies. Although this thesis argues that the five per cent threshold is not always appropriate, this analysis provides an indicator that despite possible underestimation of incidence,

these chemotherapy adverse events are important to include in economic evaluations of chemotherapies.

If the assumption is that the incidence rates described in this analysis are underestimates of the true incidence of adverse events, it is also reasonable to assume that they provide a conservative estimate of incidence for use in economic modelling. This would result in models that may underestimate the total costs, and therefore the impact of adverse events on the cost-effectiveness of chemotherapy.

4.3 Factors that influence the incidence of adverse events in clinical practice

Most clinical trials of new chemotherapy treatments restrict or exclude the participation of individuals who are older or who have comorbidities. This analysis uses regression techniques to explore the factors that influence the incidence of chemotherapy adverse events in clinical practice to identify whether the profile of adverse events in those individuals excluded from clinical trials is different from those who are included.

4.3.1 Background to regression analysis with correlated data

Regression analysis

Regression analysis is widely used to estimate the relationship between a variable of interest and a set of related predictor variables (244, 247). It develops a model (an equation) that describes a statistical relationship that may or may not be causal (244). This model can be described with the equation below, which describes the straight line relating two variables.

Equation 1

$$Y = \beta_0 + \beta_{1x} + e$$

Where Y is the variable of interest, B_0 is the intercept and B_1 is the slope of the line. e is the error term, which is a random variable that accounts for the failure of the model to fit the data exactly. Often, more than one variable might help predict the value of Y, and so multiple regression is used.

Univariate analysis was conducted to examine each of the variables in the dataset for distribution, skew, missing data and other indicators that it may not be suitable for use in regression analysis.

Multiple regression was used to identify factors that influence the incidence of each adverse event. The model for the regression was specified as below, where *a* is a constant and *e* an error term:

Equation 2

$$adverse\ event = a + gender + age + RxRisk + chemo + cancer + e$$

The outcome variable is binary (*yes/no*: there was treatment for an adverse event); therefore, a logistic regression model was required. A logistic regression model differs from a linear regression model, because the outcome variable is binary or dichotomous, rather than continuous. The methods for logistic regression follow the same general principles of linear regression, with some different assumptions around the distribution of the relationship (logistic) and the error term (binomial) (248).

Correlated data

In specifying the model, the presence of correlation in the data was noted. Clinically, it is likely that some individuals may be more or less susceptible to specific adverse events than others in the sample. For example, regardless of their cancer or chemotherapy, some individuals may be more prone, in general, to stomach upsets, such as diarrhoea or nausea and vomiting than may others. This means that observations within this individual are correlated, because two observations taken at random from that individual are more likely to be similar than two observations taken at random from two individuals.

One way to address this issue is to remove the correlation from the data by restructuring it to have a single observation per individual (240, 242). In this data structure, a summary variable of 'ever adverse event' was used, and the details of the chemotherapy drugs were replaced with the number of doses of any chemotherapy that individual had. With this data structure, a simple logistic

regression is appropriate because the potential within patient correlation is removed. This analysis is similar to that often used in clinical trials to analyse the difference between groups in incidence rates of adverse-event rates.

However, although this method addresses the issue of correlation within the data, it has limitations. The use of a summary statistic limits the questions that can be answered with the analysis, and to use only some of the available data is inefficient (240, 242). GEE can be used when a simple logistic regression would be suitable except where there is correlation in the data (240, 249, 250). GEEs are typically used in epidemiology and health, and most commonly with responses that are binomial or that count data (243, 250). GEE allows the correlation of outcomes within an individual to be estimated and taken into account in the regression coefficients and their standard errors (249, 250). This is an extension of generalised linear models. Similarly, GEE permits the calculation of robust estimates for the standard errors of the regression coefficients, ensuring consistent inferences, even if the correlation structure is incorrect (249, 250).

The selection of logistic regression models for analysis of correlated data should be based on the data available and on the desired interpretation of parameters (population average vs. subject specific) (251). In this case, population average parameters were thought to be appropriate.

Compared with a random-effects model, where regression coefficients are permitted to vary between individuals, in GEE the correlation structure is specified (240, 252). An advantage of GEE analysis is that it can deal with different numbers of observations per person (240). Another advantage is that even with an incorrect working correlation structure, the resulting regression coefficient estimate is still consistent and asymptotically normal (although the detriment in choosing an incorrect correlation structure can be loss of efficiency) (240, 243).

There are a number of correlation structures available for use in GEE. An independent structure is the simplest assumption, but is usually incorrect (240, 241, 253). This assumes that each observation for an individual is uncorrelated

with every other observation from that individual (240, 241, 253). This, in effect, reduces the GEE to the generalised linear model estimating equation. Exchangeable correlation structure (also called 'compound symmetry') assumes that every observation within an individual is equally correlated with every other observation from that individual (240, 241, 253). This structure is fully characterised by the intra-cluster (or intra-class) correlation coefficient (240, 241, 253). The autoregressive structure is derived from time series analysis and assumes that two observations of the same individual taken close in time will be more highly correlated than two observations of the same individual taken further apart in time (240, 241, 253). These are the most commonly used correlation structures in observational data such as this (240, 241, 253), although there are other structures available for use in specific situations, such as unstructured or user-defined structures. The selection of the most appropriate correlation structure should be undertaken prior to commencing analysis and, where possible, should be based on clinical reasoning (240, 253).

First, GEE analysis fits a standard regression model, which assumes that all observations are independent. The residuals from this regression are then used to estimate the parameters that quantify the correlation between observations in the same individual (254). The regression model is then refitted, using a modified algorithm incorporating a matrix that reflects the magnitude of the estimated correlation (254). These last two steps continue to iterate until all the estimates stabilise, which is where the model converges (254).

Checking adequacy of model fit with GEE is done in a number of ways. The results of the likelihood ratio, score test and Wald chi-square test can all be used to detect whether the model as a whole fits better than an 'empty' model (that is, one with no regressors) (254). In order to determine which variables improve model fit through significant prediction of *y*, the type-3 effects can be assessed (254). However, it is important to note that although many methods are available to assess and improve the fit and performance of regression models, careful consideration of the clinical reasoning and interpretation of model structure, fit

and results should guide decisions about the statistical results in isolation (244, 248, 255).

The interpretation of the regression coefficients obtained from GEE is in a 'population-averaged' manner (240, 243, 250). For example, using GEE methods would allow the researcher to estimate the odds of the average male being treated for diarrhoea compared with the odds of the average female being treated for diarrhoea. This is similar to the interpretation of a simple logistic regression that has been specified for cluster but is different from a random-effects logit, which calculates the individual effect, such as the odds of a person having diarrhoea if male compared with the odds of the same person having diarrhoea if female (240, 243, 250). It has been found that in many cases the population-averaged and subject-specific estimates are close, but not always (240, 243, 250). It has been noted that the marginal odds ratio obtained through GEE (and other similar) methods will result in smaller estimates of treatment effect than those generated through random-effects models (240, 243, 250).

4.3.2 Methods: logistic regression with summary statistic

Initially, a binary logistic regression using a summary measure for ever having had each adverse event was run to avoid the issues of correlated data. The independent variables were gender, age, RxRisk, cancer site (condensed), chemotherapy (all categorical variables), and number of chemotherapy doses and dose number when the adverse event occurred (continuous variables). The summary measure of ever having had each adverse event was the dependent variable.

Each model was specified to model events such that a positive coefficient would correspond to a positive relationship for having an adverse event, and a negative coefficient would indicate a negative relationship with having an adverse event.

The model fit statistics used to assess model fit were the Akaike's Information Criteria (AIC) and Schwarz Criterion (SC). For both measures, the smallest value when comparing models is considered to be best; however, the value itself is not considered meaningful (254). The likelihood ratio chi-square statistic, score test

and Wald test are asymptotically equivalent tests of the hypothesis that at least one of the regression coefficients in the model is not equal to zero (254). These scores and their associated p-values were used to assess whether the model as a whole fitted significantly better than an empty model (254).

The interpretation of type-3 analysis of effects can be useful when analysing a model with categorical/class variables, because this provides the multiple degree-of-freedom test for the overall effect of the variable (256). However, given the size of the dataset, the additional degrees of freedom associated with the inclusion of non-significant variables was not an issue of concern. Given the clinical relevance of each of the included variables, even those that were found not to be significant were kept in the model.

Conventionally, the results of logistic regression include presentation of the coefficients, their standard errors, the Wald chi-square statistic and associated p-value result (256). The coefficients indicate the change in the log-odds of the outcome for a one-unit increase in the predictor values (256). The chi-square tests the null hypothesis that an individual predictor's regression coefficient is zero, given the other predictor variables that are included in the model (256). The p-value indicates the probability that a particular chi-square test statistic is as extreme as, or more so, than what has been observed under the null hypothesis (256). However, as the log-odds can be difficult to interpret, the coefficients are also presented as point estimates of the odds ratio, obtained by exponentiating the coefficient estimates and interpreted as the multiplicative change in the odds for a one-unit change in the predictor variable (256). The Wald Confidence Interval of an individual odds ratio can also be interpreted as being 95 per cent confident that upon repeated trials, 95 per cent of the Wald Confidence Intervals would include the true population odds ratio (256). If the CI includes one, we would fail to reject the null hypothesis that a particular regression coefficient equals zero and the odds ratio equals one, given the other predictors that are included in the model (256).

4.3.3 **Methods: GEE**

To analyse the data appropriately, taking account of the correlation between observations but without losing data unnecessarily, GEEs were used.

For the GEE analysis, the repeated subject variable was the unique patient identifier, labelled PPN. A binomial distribution and logit link function were used, given the binary nature of the outcome variable. A comparison of four alternative correlation structures—exchangeable, independent, autoregressive and unstructured—was undertaken to select the most appropriate model structure.

The dependent variable in the analysis was any treatment for the specific adverse event under consideration. The independent variables were gender (categorical), age (continuous), RxRisk (categorical), cancer site (categorical) and chemotherapy type (categorical). The inclusion of age as a categorical variable and of an alternative categorisation of chemotherapy drugs were investigated to identify the best option for model fit.

In generalised linear modelling (GLM), AIC is used to assess model fit (253). AIC provides a trade-off between the goodness of fit and the simplicity of the model as measured by the number of variables included (255). However, because GEE analysis is based on quasi-likelihood theory rather than maximum likelihood theory, AIC is not appropriate (257). In order to compare GEE model fit, the QIC (quasi-likelihood under the independence model criterion) and QICu (simplified quasi-likelihood under the independence model criterion) for each model are examined (253, 257). QIC can be used to select an optimal subset of covariates in the regression model, as well as to select the best working-correlation structure for more efficient parameter estimation in GEE analysis (253, 257). QICu is based on the assumption that the selected correlation structure is correct; therefore, it is not suitable for selecting correlation structure but can be used to guide parameter selection (253). When using QIC or QICu to compare model structures or two models, the model with the smaller statistic is preferred, but the number itself has no meaning (254).

The model was run with all variables at the least aggregated level of categorisation possible to test for the best correlation structure to maximise model fit. The unstructured model was not able to run for any adverse event, because the number of response pairs for estimating correlation was less than (or equal to) the

number of regression parameters. This indicates that the unstructured covariance structure was too complex for the data available in the model.

For models estimated with an exchangeable correlation structure, an exchangeable working correlation output is also derived. This can be interpreted as the intra-cluster correlation, which is a measure of the correlation between two variables (258). A correlation value of '1'indicates complete agreement within the cluster, and a value of '0' indicates that there is no correlation between observations of an individual (258). Values less than 0.2 are often considered to demonstrate low correlation, while values of 0.3–0.4 indicate fair correlation, 0.5–0.6 moderate correlation, 0.7–0.8 strong correlation and above 0.8 near-perfect correlation.

Once a correlation structure was selected, the QIC and QICu were further calculated for valid variations of the full model. The first model was the original model with continuous age and categorical gender, RxRisk, cancer site and chemotherapy type. Model 2 was run with age as a categorical (< 70 years, 70–79 years, and 80+ years) rather than as a continuous variable. The third model was the same as the first model but with a condensed categorisation of cancer site, using eight levels rather than 16. The final model was the same as the first model but with an adjusted categorisation of chemotherapy categories.

The SAS output of GEE analysis reports the GEE parameter estimates as log-odds; therefore, the exponential value of these estimates was calculated and is reported.

4.3.4 Data

The datasets that were developed for the analysis of the incidence of adverse events were also used to identify the factors influencing the incidence.

The variables for RxRisk and age were replicated as categorical variables to test the most appropriate format for optimal logit model performance. A four-level categorical variable was created for RxRisk based on quantiles of RxRisk in the regression dataset: 0–7, 8–9, 10–12, 13–26. The average (mean) RxRisk score in the gold card cohort is 7.83, and 8.82 in the cancer chemotherapy cohort. Three categories were defined for the categorical age variable based on the distribution

of ages in the data < 70 years, 70–80, and 80+ (gold card cohort has approximately 19 per cent < 70 years, 21 per cent 71–80, and 56 per cent 80+; in the cancer cohort this increases to 70 per cent 80+). An additional variable of age binary was also developed, which has age as two categories: < 80 or 80+.

In addition, two categorical variables that each had a large number of categories were condensed to fewer levels. For cancer site the levels were changed to the following: breast (21 per cent), colorectal (upper digestive tract or colorectal, 6 per cent), lung (respiratory, 3 per cent), male genital (44 per cent), urinary (2 per cent) and other (all others, 17 per cent).

For chemotherapy, the second level ATC code was used to identify classes of chemotherapy drugs. The use of a binary variable for chemotherapy drugs likely to be associated with an adverse event was tested in the analysis of diarrhoea, based on a paper summarising those chemotherapy treatments most likely to be associated with diarrhoea (139). Finally, the additional variable 'chemobinary' was generated, which divided chemotherapy agents into those most likely to be associated with diarrhoea (value = 1) versus those not commonly associated with diarrhoea (value = 0). However, because this was of limited value, it was not created for the analysis of the other adverse events.

Two additional variables were created in relation to the doses of chemotherapy received. The first of these was the total number of doses of chemotherapy that an individual received; this allowed for a dose response to be assessed between those who experience any adverse event during their treatment and the number of chemotherapy doses received in total. The second variable was the dose number when the adverse event occurred. This variable was constructed by counting the doses of chemotherapy preceding the identification of an adverse event. Again, this aimed to assess the potential dose-response relationship between chemotherapy and adverse events. The variables in the dataset and their categories are listed in Table 4.10.

Table 4.10: Variables in the DVA adverse-event regression dataset

Variable	Levels
Adverse event	0/1
Gender	M/F
Age	< 70 70–79 > 79
RxRisk (comorbidities)	Quartiles (0–7, 8–9, 10–12, 13–26)
Chemotherapy	Consolidated to 8 levels based on ATC codes: alkylating agents, antimetabolites, plant alkaloids and other natural products, cytotoxic antibiotics, other antineoplastic, endocrine, immunostimulants, immunosuppressants
Cancer	Consolidated to 7 levels based on ICD classification: breast, colorectal (CRC), genital, lung, non-solid, urinary, other

Note: ATC = Anatomical Therapeutic Chemical; ICD = International Classification of Disease ; M/F = male or female

4.3.5 Results: logistic regression with summary statistic

Univariate analysis of each variable was conducted. After assessing distribution, skew and number of missing values it was determined that all variables were suitable for inclusion in the regression models.

Diarrhoea

There were 7,822 observations used for the analysis, with 20 being deleted (using listwise deletion method) due to a missing value for the dependent or an independent variable. Of the included observations, 384 had a '1' for 'any diarrhoea treatment'. Table 4.11 presents the logistic regression model fit statistics. The likelihood ratio, score test and Wald chi-squared statistics all had probabilities < 0.0001, indicating that the model as a whole fits significantly better than an empty model. When examining the type-3 analysis of effects, it can be seen that all variables other than gender significantly improve model fit.

Table 4.11: Model fit statistics—diarrhoea

Model fit statistics		
Criterion	**Intercept only**	**Intercept and covariates**
AIC	3,065.625	2,411.911
SC	3,072.590	2,516.382
–2 Log L	3,063.625	2,381.911

Testing global null hypothesis: beta = 0			
Test	**Chi-square**	**DF**	**Pr > ChiSq**
Likelihood ratio	681.7135	14	< .0001
Score	1,433.4296	14	< .0001
Wald	514.3042	14	< .0001

Type-3 analysis of effects			
Effect	**DF**	**Wald chi-square**	**Pr > ChiSq**
Gender	1	0.4884	0.4847
Age category	2	24.4101	< .0001
RxRisk category	3	17.4282	0.0006
Cancer category (condensed)	6	155.0203	< .0001
Total number of doses	1	6.9925	0.0082
Dose number when adverse event occurred	1	251.0882	< .0001

Note: AIC = Akaike Information Criteria; DF = degrees of freedom; SC = Schwarz Criterion

Table 4.12 presents the results of the logistic regression displayed as both an analysis of maximum likelihood and an odds ratio. The results of the logistic regression show that gender does not affect the odds of receiving diarrhoea treatment. Although both the younger and middle-age categories are significantly different from the oldest age group, this relationship is not ordered, with the youngest age group being almost half as likely to experience treatment for diarrhoea as the oldest group, while those in the middle-age group are 43 per cent more likely to experience treatment for diarrhoea than the oldest age group.

The lowest RxRisk category is half as likely to have treatment for an adverse event. As expected, this trend of lower odds continues with the other RxRisk categories compared with the highest group; however, it is not significant. Only individuals with a diagnosis of colorectal cancer have significantly different odds of being treated for a diarrhoea adverse event compared with individuals with a diagnosis of urinary cancer, with the former having a threefold increase in odds. Given that those with colorectal cancer have an already compromised digestive system, this is consistent with clinical expectations. The doses of chemotherapy are significantly related to the odds of treatment for diarrhoea. There is a one per cent increase in odds associated with each additional dose of chemotherapy added to the total doses of chemotherapy an individual has. When considering the dose at which the adverse event occurs, each additional dose of chemotherapy increases the odds of treatment for diarrhoea by 12.1 per cent.

Table 4.12: Analysis of maximum likelihood estimates—diarrhoea

Analysis of maximum likelihood estimates						
Parameter	**Categories**	**DF**	**Estimate**	**Standard error**	**Wald chi-square**	**Pr > ChiSq**
Intercept		1	–3.2297	0.3233	99.7957	< .0001
Gender	Female	1	0.1074	0.1536	0.4884	0.4847
Age category	< 70	1	-0.5967	0.1833	10.6029	0.0011
	70–79	1	0.3578	0.1330	7.2402	0.0071
RxRisk category	0–7	1	–0.6961	0.1710	16.5674	< .0001
	8–9	1	–0.2995	0.1719	3.0373	0.0814
	10–12	1	–0.2014	0.1584	1.6171	0.2035
Cancer category (condensed)	Breast	1	–0.6373	0.3724	2.9275	0.0871
	Colorectal	1	1.2029	0.3202	14.1145	0.0002
	Genital	1	–0.4369	0.3268	1.7871	0.1813
	Lung	1	–0.3146	0.4200	0.5611	0.4538
	Non-solid	1	–0.3475	0.3613	0.9252	0.3361
	Other	1	–0.2921	0.3418	0.7299	0.3929
Total doses		1	0.0113	0.00427	6.9925	0.0082
Dose number		1	0.1142	0.00721	251.0882	< 0.0001

Note: DF = degrees of freedom;

Odds ratio estimates			
Effect	**Point estimate**	**95% Wald confidence limits**	
Gender female vs. male	1.113	0.824	1.504
Age category < 70 vs. 80+	0.551	0.384	0.789
Age category 70–79 vs. 80+	1.43	1.102	1.856
RxRisk 0–7 vs. 13+	0.499	0.357	0.697
RxRisk 8–9 vs. 13+	0.741	0.529	1.038
RxRisk 10–12 vs. 13+	0.818	0.599	1.115
Breast vs. urinary cancer	0.529	0.255	1.097
Colorectal vs. urinary cancer	3.33	1.778	6.237
Genital vs. urinary cancer	0.646	0.34	1.226
Lung vs. urinary cancer	0.73	0.32	1.663
Non-solid vs. urinary cancer	0.706	0.348	1.434
Other vs. urinary cancer	0.747	0.382	1.459
Total doses	1.011	1.003	1.02
Dose number	1.121	1.105	1.137

Note: vs. = versus

Nausea and vomiting

There were 7,822 observations used for the analysis, with 20 being deleted (using listwise deletion method) due to a missing value for the dependent or an independent variable. Of these observations, 1,534 had a '1' for 'any nausea or vomiting treatment'. Table 4.13 presents the logistic regression model fit statistics. The likelihood ratio, score test and Wald chi-squared statistics all had probabilities < 0.0001, indicating that the model as a whole fits significantly better than an empty model. When examining the type-3 analysis of effects, it can be seen that all variables other than total number of doses of chemotherapy significantly improve model fit.

Table 4.13: Model fit statistics—nausea and vomiting

Model fit statistics		
Criterion	**Intercept only**	**Intercept and covariates**
AIC	7,745.267	5,755.94
SC	7,752.231	5,860.411
–2 Log L	7,743.267	5,725.94

Testing global null hypothesis: beta = 0			
Test	**Chi-square**	**DF**	**Pr > ChiSq**
Likelihood ratio	2,017.3263	14	< .0001
Score	1973.19	14	< .0001
Wald	1,070.0556	14	< .0001

Type3 analysis of effects			
Effect	**DF**	**Wald chi-square**	**Pr > ChiSq**
Gender	1	21.0361	< .0001
Age category	2	35.818	< .0001
RxRisk category	3	45.8846	< .0001
Cancer category (condensed)	6	417.4084	< .0001
Total number of doses	1	0.0185	0.8918
Dose number when adverse event occurred	1	607.7608	< .0001

Note: DF = degrees of freedom;

Table 4.14 presents the results of the logistic regression displayed as both an analysis of maximum likelihood and an odds ratio. The results of the logistic regression show that females are 48 per cent more likely to have treatment for nausea and vomiting than are males. The same pattern as that for diarrhoea—of a non-ordered relationship between age groups—is seen, with both the younger and middle-age categories significantly different from the oldest age group. Those in the youngest age group are again less likely to have treatment for nausea and vomiting (30 per cent reduction), while the middle-aged category are more than 30 per cent more likely to be treated.

The lowest RxRisk category is significantly less likely to have treatment for an adverse event, and although this trend continues for the other RxRisk categories, it is not significant. Individuals with a diagnosis of colorectal, lung and non-solid cancers are significantly more likely to be treated for nausea and vomiting than are those with urinary cancer. Lung cancer has the highest increase in risk (5.6 times higher). Although the total number of doses of chemotherapy does not significantly increase the risk of being treated for nausea and vomiting, each additional dose of chemotherapy increases the risk of being treated for nausea and vomiting by 19 per cent.

Table 4.14: Analysis of maximum likelihood and odds ratio estimates—nausea and vomiting

Analysis of maximum likelihood estimates						
Parameter		**DF**	**Estimate**	**Standard error**	**Wald chi-square**	**Pr > ChiSq**
Intercept		1	–2.4272	0.2075	136.8446	< .0001
Gender	Female	1	0.3941	0.0859	21.0361	< .0001
Age category	< 70	1	–0.361	0.0998	13.09	0.0003
	70–79	1	0.284	0.0791	12.9085	0.0003
RxRisk category	0–7	1	–0.4849	0.101	23.0454	< .0001
	8–9	1	–0.00526	0.104	0.0026	0.9597
	10–12	1	0.084	0.0981	0.7338	0.3917
Cancer category (condensed)	Breast	1	–0.2873	0.2295	1.5673	0.2106
	CRC	1	1.0338	0.2093	24.3971	< .0001
	Genital	1	–0.3513	0.2076	2.8622	0.0907
	Lung	1	1.7377	0.2198	62.4928	< .0001
	Non-solid	1	1.0215	0.21	23.6543	< .0001
	Other	1	0.2206	0.2106	1.0978	0.2948
Total doses		1	0.00045	0.00331	0.0185	0.8918
Dose number		1	0.1954	0.00792	607.7608	< .0001

Odds ratio estimates			
Effect	**Point estimate**	**95% Wald confidence limits**	
Gender female vs. male	1.483	1.253	1.755
Age category < 70 vs. 80+	0.697	0.573	0.848
Age category 70–79 vs. 80+	1.328	1.138	1.551
RxRisk 0–7 vs. 13+	0.616	0.505	0.751
RxRisk 8–9 vs. 13+	0.995	0.811	1.22
RxRisk 10–12 vs. 13+	1.088	0.897	1.318
Breast vs. urinary cancer	0.75	0.479	1.176
Colorectal vs. urinary cancer	2.812	1.866	4.238
Genital vs. urinary cancer	0.704	0.468	1.057
Lung vs. urinary cancer	5.684	3.695	8.746
Non-solid vs. urinary cancer	2.777	1.84	4.192
Other vs. urinary cancer	1.247	0.825	1.884
Total doses	1	0.994	1.007
Dose number	1.216	1.197	1.235

Note: DF = degrees of freedom; vs. = versus

Anaemia

There were 7,822 observations used for the analysis, with 20 being deleted (using listwise deletion method) due to a missing value for the dependent or an independent variable. Of the total observations, 329 had a '1' for 'any anaemia treatment'. Table 4.15 presents the logistic regression model fit statistics. The likelihood ratio, score test and Wald chi-squared statistics all had probabilities < 0.0001, indicating that the model as a whole fits significantly better than an empty model. When examining the type-3 analysis of effects, it can be seen that all variables other than gender and total number of doses of chemotherapy significantly improve model fit.

Table 4.15: Model fit statistics—anaemia

Model fit statistics		
Criterion	**Intercept only**	**Intercept and covariates**
AIC	2,730.927	2,051.097
SC	2,737.892	2,155.568
–2 Log L	2,728.927	2,021.097

Testing global null hypothesis: beta = 0			
Test	**chi-square**	**DF**	**Pr > ChiSq**
Likelihood ratio	707.8303	14	< .0001
Score	1,619.3185	14	< .0001
Wald	474.1977	14	< .0001

Type-3 analysis of effects			
Effect	**DF**	**Wald chi-square**	**Pr > ChiSq**
Gender	1	0.6830	0.4086
Age category	2	39.4562	< .0001
RxRisk category	3	23.5555	< .0001
Cancer category (condensed)	6	102.1645	< .0001
Total number of doses	1	2.9339	0.0867
Dose number when adverse event occurred	1	226.0091	< .0001

Note: AIC = Akaike Information Criteria; SC = Schwarz Criterion; DF = degrees of freedom;

Table 4.16 presents the results of the logistic regression displayed as both an analysis of maximum likelihood and an odds ratio. The results of the logistic regression show that there is no significant difference between males and females in terms of the risk of being treated for anaemia. In this analysis, only the youngest age group has a significantly different risk of being treated compared with the oldest age group, with the youngest age group having an 80 per cent reduction in the odds of being treated for anaemia. The coefficients for RxRisk show an ordered relationship, with lower RxRisk scores having lower odds of treatment for anaemia compared with the highest RxRisk category. Only individuals with a diagnosis of non-solid cancer have significantly different odds of being treated for anaemia, with a 20 per cent increase in odds. Although the total number of doses of chemotherapy does not significantly increase the risk of being treated for anaemia, each additional dose of chemotherapy increases the risk of being treated for anaemia by 11 per cent.

Table 4.16: Analysis of maximum likelihood and odds ratio estimates—anaemia

Analysis of maximum likelihood estimates						
Parameter		**DF**	**Estimate**	**Standard error**	**Wald chi-square**	**Pr > ChiSq**
Intercept		1	–3.0425	0.3614	70.8527	< .0001
Gender	Female	1	–0.145	0.1754	0.683	0.4086
Age category	< 70	1	–1.5968	0.2576	38.4265	< .0001
	70–79	1	–0.3079	0.156	3.8926	0.0485
RxRisk category	0–7	1	–0.914	0.1893	23.3015	< .0001
	8–9	1	–0.3962	0.1812	4.7795	0.0288
	10–12	1	–0.4537	0.1707	7.066	0.0079
Cancer category (condensed)	Breast	1	–0.6331	0.439	2.0799	0.1492
	CRC	1	0.078	0.3953	0.039	0.8435
	Genital	1	–0.1239	0.3661	0.1145	0.7351
	Lung	1	0.497	0.4233	1.3787	0.2403
	Non–solid	1	1.1968	0.3657	10.7084	0.0011
	Other	1	–0.5841	0.4036	2.0939	0.1479
Total doses		1	0.00873	0.0051	2.9339	0.0867
Dose number		1	0.1111	0.00739	226.0091	< .0001

Odds ratio estimates			
Effect	**Point estimate**	**95% Wald confidence limits**	
Gender female vs. male	0.865	0.613	1.22
Age category < 70 vs. 80+	0.203	0.122	0.336
Age category 70–79 vs. 80+	0.735	0.541	0.998
RxRisk 0–7 vs. 13+	0.401	0.277	0.581
RxRisk 8–9 vs. 13+	0.673	0.472	0.96
RxRisk 10–12 vs. 13+	0.635	0.455	0.888
Breast vs. urinary cancer	0.531	0.225	1.255
Colorectal vs. urinary cancer	1.081	0.498	2.346
Genital vs. urinary cancer	0.883	0.431	1.811
Lung vs. urinary cancer	1.644	0.717	3.768
Non-solid vs. urinary cancer	3.309	1.616	6.777
Other vs. urinary cancer	0.558	0.253	1.23
Total doses	1.009	0.999	1.019
Dose number	1.117	1.101	1.134

Note: CRC = colorectal cancer; DF = degrees of freedom;

Neutropoenia

There were 7,822 observations used for the analysis, with 20 being deleted (using listwise deletion method) due to a missing value for the dependent or an independent variable. Of the total observations, 241 had a '1' for 'any neutropoenia treatment'. Table 4.17 presents the logistic regression model fit statistics. The likelihood ratio, score test and Wald chi-squared statistics all had probabilities < 0.0001, indicating that the model as a whole fits significantly better than an empty model. When examining the type-3 analysis of effects, it can be seen that all variables other than gender and total number of doses of chemotherapy significantly improve model fit, although RxRisk category is close to the $p < 0.05$ threshold.

Table 4.17: Model fit statistics—neutropoenia

Model fit statistics		
Criterion	**Intercept only**	**Intercept and covariates**
AIC	2,153.808	1,677.665
SC	2,160.773	1,782.136
–2 Log L	2,151.808	1,647.665

Testing global null hypothesis: beta = 0			
Test	**Chi-square**	**DF**	**Pr > ChiSq**
Likelihood ratio	504.1429	14	< .0001
Score	1,208.217	14	< .0001
Wald	393.5706	14	< .0001

Type-3 analysis of effects			
Effect	**DF**	**Wald chi-square**	**Pr > ChiSq**
Gender	1	0.9637	0.3262
Age category	2	21.344	< .0001
RxRisk category	3	7.8876	0.0484
Cancer category (condensed)	6	163.5501	< .0001
Total number of doses	1	0.3067	0.5797
Dose number when adverse event occurred	1	138.3514	< .0001

Note: AIC = Akaike Information Criteria; SC = Schwarz Criterion; DF = degrees of freedom;

Table 4.18 presents the results of the logistic regression displayed as both an analysis of maximum likelihood and an odds ratio. The results of the logistic regression show that there is no significant difference between males and females in the risk of being treated for neutropoenia. In this analysis, only the youngest age group has a significantly different risk to the oldest age group, with the youngest age group having a 71 per cent reduction in odds of being treated for neutropoenia. The lowest RxRisk category is nearly half as likely to experience treatment for neutropoenia as the highest category; however, the other RxRisk categories are not significantly different from the highest category. Only individuals with a diagnosis of genital cancer or non-solid cancer have significantly different odds of being treated for neutropoenia, with a fourfold increase in odds for those with non-solid cancer. Although the total number of doses of chemotherapy does not significantly increase the risk of being treated for neutropoenia, each additional dose of chemotherapy increases the risk of being treated for neutropoenia by 10 per cent.

Table 4.18: Analysis of maximum likelihood and odds ratio estimates—neutropoenia

Analysis of maximum likelihood estimates						
Parameter		**DF**	**Estimate**	**Standard error**	**Wald chi-square**	**Pr > ChiSq**
Intercept		1	–3.3119	0.3858	73.7065	< .0001
Gender	Female	1	–0.1852	0.1887	0.9637	0.3262
Age category	< 70	1	–1.2231	0.2868	18.1942	< .0001
	70–79	1	0.1477	0.1627	0.8248	0.3638
RxRisk category	0–7	1	–0.5803	0.2083	7.7567	0.0054
	8–9	1	–0.3447	0.2116	2.6547	0.1032
	10–12	1	–0.2907	0.1962	2.1964	0.1383
Cancer category (condensed)	Breast	1	–0.2352	0.4453	0.279	0.5973
	CRC	1	–0.6544	0.4562	2.0581	0.1514
	Genital	1	–0.8305	0.4015	4.279	0.0386
	Lung	1	0.1202	0.4629	0.0675	0.7951
	Non-solid	1	1.3695	0.38	12.985	0.0003
	Other	1	–0.6567	0.4263	2.3722	0.1235
Total doses		1	0.00357	0.00644	0.3067	0.5797
Dose number		1	0.0983	0.00835	138.3514	< .0001

Odds ratio estimates			
Effect	**Point estimate**	**95%Wald confidence limits**	
Gender female vs. male	0.831	0.574	1.203
Age category < 70 vs. 80+	0.294	0.168	0.516
Age category 70–79 vs. 80+	1.159	0.843	1.594
RxRisk 0–7 vs. 13+	0.56	0.372	0.842
RxRisk 8–9 vs. 13+	0.708	0.468	1.072
RxRisk 10–12 vs. 13+	0.748	0.509	1.098
Breast vs. urinary cancer	0.79	0.33	1.892
Colorectal vs. urinary cancer	0.52	0.213	1.271
Genital vs. urinary cancer	0.436	0.198	0.957
Lung vs. urinary cancer	1.128	0.455	2.794
Non-solid vs. urinary cancer	3.933	1.868	8.284
Other vs. urinary cancer	0.519	0.225	1.196
Total doses	1.004	0.991	1.016
Dose number	1.103	1.085	1.121

Note: CRC = colorectal cancer; DF = degrees of freedom

4.3.6 **Results: GEE**

Diarrhoea

There were 5,414 events in the 78,151 observations used in the model. Of these, 6,740 observations (8.6 per cent) were dropped due to missing values for any one of the independent or dependent variables. Table 4.19 shows there were 7,842 clusters (individuals), the largest cluster size (number of chemotherapy doses) being 132. According to the QIC statistic, the best working correlation structure is the autoregressive model.

Table 4.19: Comparison of GEE correlation structures—diarrhoea

GEE model information: diarrhoea				
Correlation structure	**Exchangeable**	**Independent**	**AR(1)**	**Unstructured**
GEE model information				
Subject effect	PPN	PPN	PPN	PPN
Number of clusters	7,842	7,842	7,842	7,842
Clusters with missing values	1,772	1,772	1,772	1,772
Correlation matrix dimension	144	144	144	144
Maximum cluster size	132	132	132	132
Minimum cluster size	0	0	0	0
Algorithm converged	Yes	Yes	Yes	Error
GEE fit criteria				
QIC	8,796.7357	8,792.5778	8,784.3248	0
QICu	8,725.9976	8,685.2661	8,687.0743	0
Exchangeable working correlation				
Correlation	0.148695762	N/A	N/A	N/A

Note: AR = Autoregressive; N/A = not applicable; QIC = quasi-likelihood under the independence model criterion; QICu = simplified quasi-likelihood under the independence model criterion

The autoregressive working correlation structure was therefore selected as the best model. The exchangeable working correlation structure provides an estimate of the correlation within individuals. The result of 0.15 indicates that the correlation between observations of an individual is not strong in this model. Under the autoregressive correlation structure, the QIC and QICu were further calculated for valid variations of the full model.

As seen in Table 4.20, none of the model variations resulted in a lower QIC or QICu than the original model (Model 1), and therefore this is the model that has the best fit and for which results are presented.

Table 4.20: Comparison of model structures—diarrhoea

Diarrhoea	Number of levels		
	Model 1	Model 2	Model 3
Variables			
Gender (no change)	2	2	2
RxRisk category (no change)	4	4	4
Age	Continuous	4	Continuous
Cancer category (no change)	7	7	7
Chemo category	8	8	8 (adjusted)
Model fit statistics			
QIC	8,784.3248	8,905.5128	8,872.0441
QICu	8,687.0743	8,799.8964	8,760.4872

Note: QIC = quasi-likelihood under the independence model criterion; QICu = simplified quasi-likelihood under the independence model criterion

Table 4.21 presents the results of the GEE analysis for diarrhoea. The results indicate that there is no significant difference between the odds of the average female being treated for diarrhoea compared with the odds of the average male. For every year of increasing age, the odds of being treated for diarrhoea decrease by four per cent. Moving from the highest to the lowest RxRisk category reduces the odds of being treated for diarrhoea by 40 per cent. Although the results for the other two RxRisk groups are not significant, a trend of increasing RxRisk score being associated with increased odds of being treated for diarrhoea is observed. Lung cancers and non-solid cancers were the only cancers with significantly different odds of being treated for diarrhoea compared with urinary cancers; lung cancer odds were reduced by 70 per cent, while non-solid cancer odds were reduced by 60 per cent. Only chemotherapy types antimetabolites, plant alkaloids and immune-stimulants did not have significantly decreased odds of being treated for diarrhoea than the comparison, category 8. The greatest decrease was seen for individuals receiving chemotherapy category 1, who had more than 70 per cent less treatment for diarrhoea.

Table 4.21: GEE results—diarrhoea

Analysis of GEE parameter estimates						
Empirical standard error estimates						
Parameter		**Estimate**	**Standard error**	**95% confidence limits**		**Pr > |Z|**
Intercept		0.830	2.252	0.169	4.078	0.819
Gender	Female	1.024	1.189	0.729	1.438	0.893
	Male	–	–	–	–	–
Age		0.964	1.009	0.947	0.981	< .0001
RxCat	0–7	0.590	1.258	0.376	0.925	0.022
	8–9	0.684	1.250	0.442	1.058	0.088
	10–12	0.793	1.226	0.532	1.182	0.255
	13+	–	–	–	–	–
sitecatb	Breast	0.648	1.610	0.255	1.647	0.362
	CRC	1.521	1.466	0.718	3.219	0.274
	Genital	0.642	1.561	0.268	1.537	0.320
	Lung	0.303	1.606	0.120	0.768	0.012
	Non-solid	0.390	1.526	0.170	0.894	0.026
	Other	0.686	1.514	0.304	1.548	0.365
	Urinary	–	–	–	–	–
chemocatb	Alkylating agents	0.269	1.540	0.115	0.627	0.002
	Antimetabolites	0.922	1.430	0.457	1.859	0.820
	Plant alkaloids and other natural	0.415	1.658	0.154	1.119	0.082
	Cytotoxic antibiotics	0.333	1.734	0.113	0.979	0.046
	Other antineoplastic	0.370	1.444	0.180	0.759	0.007
	Endocrine treatment	0.383	1.515	0.170	0.865	0.021
	Immunostimulants	0.500	1.746	0.168	1.492	0.214
	Immunosuppressants	–	–	–	–	–

Note: CRC = colorectal cancer; Pr = probability

Nausea

There were 5,414 events in the 84,164 observations used in the model. Of these, 214 (less than one per cent) were dropped due to missing values for any one of the independent or dependent variables. Table 4.22 shows there were 7,842 clusters (individuals), the largest cluster size (number of chemotherapy doses) being 131.

According to the QIC statistic, the best working correlation structure is the independent model. However, the independent model assumes each observation from an individual is uncorrelated with every other observation of that individual, in effect reducing the GEE to the generalised linear model. It has been noted that this assumption is often incorrect, and there is substantial clinical reasoning to support the correlation of this data. For example, the incidence of anticipatory nausea and vomiting makes a good case for the correlation of nausea and vomiting incidence between individuals, although as nausea and vomiting is often managed through prevention, the correlation may be less than with other adverse events. Overall, the clinical reasoning to suggest some correlation between individuals with incidence of nausea and vomiting led to the selection of the model identified as second by the QIC statistic – the autro-regressive structure.

Table 4.22: Comparison of GEE correlation structures—nausea and vomiting

GEE model information: nausea				
Correlation structure	**Exchangeable**	**Independent**	**AR(1)**	**Unstructured**
GEE model information				
Subject effect	PPN	PPN	PPN	PPN
Number of clusters	7,842	7,842	7,842	7,842
Clusters with missing values	1,772	1,772	1,772	1,772
Correlation matrix dimension	131	131	131	131
Maximum cluster size	122	122	122	122
Minimum cluster size	0	0	0	0
Algorithm converged	Yes	Yes	Yes	Error
GEE Fit Criteria				
QIC	31,524.2686	31,402.4105	31,425.9355	0
QICu	31,323.559	31,044.5535	31,134.6051	0
Exchangeable Working Correlation				
Correlation	0.279105402	N/A	N/A	N/A

Note: AR = autoregressive; N/A = not applicable; QIC = quasi-likelihood under the independence model criterion; QICu = simplified quasi-likelihood under the independence model criterion

The autoregressive working correlation structure was therefore selected as the best model. The exchangeable working correlation structure provides an estimate of the correlation within individuals. The result of 0.28 indicates that there is moderate correlation between observations of an individual in this model. Under the autoregressive correlation structure, the QIC and QICu were further calculated for valid variations of the full model. As seen in

Table 4.23, none of the model variations resulted in a lower QIC or QICu than the original model (Model 1), and therefore this is the model that has the best fit and for which results are presented.

Table 4.23: Comparison of model structures—nausea and vomiting

	Number of levels		
	Model 1	**Model 2**	**Model 3**
Variables			
Gender (no change)	2	2	2
RxRisk category (no change)	4	4	4
Age	Continuous	4	Continuous
Cancer category	7	16	16
Chemo category	8	8	8 (adjusted)
Model fit statistics			
QIC	31,675.8288	32,186.768	32,222.0879
QICu	31,467.9872	31,883.4702	31,925.487

Note: QIC = quasi-likelihood under the independence model criterion; QICu = simplified quasi-likelihood under the independence model criterion

Table 4.24 presents the GEE results for nausea and vomiting. The results indicate that the average female is 1.6 times more likely to be treated for nausea than is the average male. For every year of increasing age, the odds of being treated for nausea decrease by three per cent. Moving from the highest to the lowest RxRisk category reduces the odds of being treated for nausea by more than 25 per cent. Breast cancers and non-solid cancers were the only cancers with significantly different odds of being treated for nausea compared with urinary cancers; breast cancer odds were reduced by nearly half, while non-solid cancers had odds of more than 60 per cent less. Only chemotherapy categories 6 and 7 did not have significantly increased odds of being treated for nausea than the comparison—category 8. The highest increase was for individuals using cytotoxic antibiotics, which resulted in a 13-fold increase in the odds of being treated for nausea.

Table 4.24: GEE results—nausea and vomiting

Analysis Of GEE parameter estimates						
Empirical standard error estimates						
Parameter		**Estimate**	**Standard error**	**95% limits**	**confidence**	**Pr > |Z|**
Intercept		0.62257	2.073214	0.149135	2.59893	0.5157
Gender	Female	1.643618	1.10153	1.359749	1.986551	< .0001
	Male	–	–	–	–	–
Age		0.972583	1.00632	0.960693	0.98462	< .0001
RxCat	0–7	0.746619	1.13678	0.580712	0.959925	0.0227
	8–9	0.977653	1.140082	0.756162	1.26415	0.8633
	10–12	0.987578	1.125357	0.783409	1.244956	0.9157
	13–26	–	–	–	–	–
sitecatb	Breast	0.510278	1.31798	0.297007	0.876692	0.0148
	CRC	1.308655	1.299397	0.783253	2.186495	0.3044
	Genital	0.629959	1.29706	0.378401	1.048856	0.0756
	Lung	1.660137	1.303301	0.987775	2.789884	0.0557
	Non-solid	0.380298	1.296541	0.228596	0.632674	0.0002
	Other	0.683451	1.295763	0.411313	1.135644	0.1418
	Urinary	–	–	–	–	–
chemocatb	Alkylating agents	9.025916	1.416799	4.560353	17.86601	< .0001
	Antimetabolites	2.245886	1.402561	1.157196	4.358814	0.0168
	Plant alkaloids and other natural	6.61606	1.414251	3.354155	13.05015	< .0001
	Cytotoxic antibiotics	13.43012	1.430752	6.65521	27.1018	< .0001
	Other antineoplastic	4.337074	1.417791	2.188245	8.596886	< .0001
	Endocrine treatment	0.573957	1.407197	0.293846	1.120976	0.104
	Immunostimulant	1.835836	1.55566	0.772209	4.364921	0.1692
	Immunosuppressant	–	–	–	–	–

Note: CRC = colorectal cancer; Pr = probability

Anaemia

There were 5,414 events in the 84,872 observations used in the model. Of the total observations, 6,740 (7.9 per cent) were dropped due to missing values for any one of the independent or dependent variables. Table 4.25 shows there were 7,842 clusters (individuals), the largest cluster size (number of chemotherapy doses) being 132. According to the QIC statistic, the best working correlation structure is the autoregressive model.

Table 4.25: Comparison of GEE correlation structures—anaemia

GEE model information: anaemia				
Correlation structure	**Exchangeable**	**Independent**	**AR(1)**	**Unstructured**
GEE model information				
Subject effect	PPN	PPN	PPN	PPN
Number of clusters	7,842	7,842	7,842	7,842
Clusters with missing values	1,772	1,772	1,772	1,772
Correlation matrix dimension	144	144	144	144
Maximum cluster size	132	132	132	132
Minimum cluster size	0	0	0	0
Algorithm converged	Yes	Yes	Yes	Error
GEE fit criteria				
QIC	7,201.5806	7,196.9367	7,192.4169	0
QICu	7,137.1834	7,119.8467	7,121.9319	0
Exchangeable Working Correlation				
Correlation	0.077635613	N/A	N/A	N/A

Note: AR = autoregressive ; N/A = not applicable; QIC = quasi-likelihood under the independence model criterion; QICu = simplified quasi-likelihood under the independence model criterion

The autoregressive working correlation structure was therefore selected as the best model. The exchangeable working correlation structure provides an estimate of the correlation within individuals. The result of 0.08 indicates that there is very low correlation between observations of an individual in this model. Under the autoregressive correlation structure, the QIC and QICu were further calculated for valid variations of the full model. As seen in Table 4.26, Model 3 resulted in a lower QIC or QICu than the original model (Model 1), and therefore this is the model that has the best fit and for which results are presented.

Table 4.26: Comparison of model structures—anaemia

Anaemia	Number of levels		
	Model 1	**Model 2**	**Model 3**
Variables			
Gender (no change)	2	2	2
RxRisk category (no change)	4	4	4
Age	Continuous	4	Continuous
Cancer category (no change)	7	7	7
Chemo category	8	8	8 (adjusted)
Model fit statistics			
QIC	7,192.4169	7,265.8202	7,190.7760
QICu	7,121.9319	7,189.9376	7,115.2317

Note: QIC = quasi-likelihood under the independence model criterion;
QICu = simplified quasi-likelihood under the independence model criterion

Table 4.27 presents the GEE results for anaemia. The results indicate that there is no difference between the odds of the average female receiving treatment for anaemia and the odds of the average male, nor for increasing age. Moving from the highest to the lowest RxRisk category reduces the odds of being treated for nausea by 55 per cent. There were no cancers that had significantly different odds of being treated for anaemia than the comparison urinary cancer. Only chemotherapy categories 3, 5 and 6 had significantly reduced odds of being treated for anaemia than the comparison category 8. The greatest decrease was for individuals using endocrine chemotherapy, which resulted in a decrease in odds of 84 per cent.

Table 4.27: GEE results—anaemia

Analysis of GEE parameter estimates						
Empirical standard error estimates						
Parameter		**Estimate**	**Standard error**	**95% confidence limits**		**Pr > |Z|**
Intercept		0.009	3.347	0.001	0.100	0.000
Gender	Female	0.936	1.256	0.598	1.464	0.772
Gender	Male	–	–	–	–	–
Age		1.014	1.012	0.990	1.039	0.248
RxCat	0–7	0.451	1.234	0.299	0.681	0.000
	8–9	0.759	1.222	0.512	1.123	0.168
	10–12	0.758	1.213	0.519	1.107	0.152
	13–26	–	–	–	–	–
sitecatb	Breast	0.641	1.905	0.181	2.269	0.491
	CRC	0.928	1.576	0.381	2.261	0.869
	Genital	1.204	1.518	0.532	2.726	0.656
	Lung	0.800	1.568	0.331	1.933	0.620
	Non-solid	1.733	1.508	0.774	3.878	0.181
	Other	0.873	1.559	0.365	2.083	0.759
	Urinary	–	–	–	–	–
chemocatc	Alkylating agents	0.522	1.516	0.231	1.181	0.119
	Antimetabolites	0.262	2.203	0.056	1.231	0.090
	Plant alkaloids and other natural	0.259	1.531	0.113	0.597	0.002
	Cytotoxic antibiotics	0.432	1.774	0.141	1.330	0.144
	Other antineoplastic	0.213	1.572	0.088	0.517	0.001
	Endocrine treatment	0.161	2.088	0.038	0.680	0.013
	Immunostimulants	1.228	1.719	0.425	3.548	0.705
	Immunosuppressants	–	–	–	–	–

Note: CRC = colorectal cancer; Pr = probability

Neutropoenia

There were 600 events in the 77,754 observations used in the model. Of the total observations, 6,741 (8.4 per cent) were dropped due to missing values for any one of the independent or dependent variables. Table 4.28 shows there were 7,842 clusters (individuals) with the largest cluster size (number of chemotherapy doses) being 132.

The model was run with all variables at the least aggregated level of categorisation possible, to test for the best correlation structure to maximise model fit. None of the models was able to run with the unconsolidated categorisation of cancer site, and therefore the consolidated categorisation of cancer site was used as the base case. The unstructured model did not converge, because the limit of the iterations was reached. According to the QIC statistic, the best working correlation structure is the autoregressive model.

Table 4.28: Comparison of GEE correlation structures—neutropoenia

GEE model information: neutropoenia				
Correlation structure	**Exchangeable**	**Independent**	**AR(1)**	**Unstructured**
GEE model information				
Subject effect	PPN	PPN	PPN	PPN
Number of clusters	7,842	7,842	7,842	7,842
Clusters with missing values	1,772	1,772	1,772	1,772
Correlation matrix dimension	144	144	144	144
Maximum cluster size	132	132	132	132
Minimum cluster size	0	0	0	0
Algorithm converged	Yes	Yes	Yes	Iteration limit
GEE fit criteria				
QIC	4,326.5212	4,327.4831	4,323.5252	4,389.6091
QICu	4,720.7796	4,267.4930	4,268.9744	4,292.7313
Exchangeable working correlation				
Correlation	0.016522194	N/A	N/A	N/A

Note: AR = autoregressive; N/A = not applicable; QIC = quasi-likelihood under the independence model criterion; QICu = simplified quasi-likelihood under the independence model criterion

The autoregressive working correlation structure was therefore selected as the best model. The exchangeable working correlation structure provides an estimate of the correlation within individuals. The result of 0.17 indicates that there is low

correlation between observations of an individual in this model. Under the autoregressive correlation structure, the QIC and QICu were further calculated to test valid variations of the full model. As seen in Table 4.29, none of the model variations resulted in a lower QIC or QICu than the original model (Model 1), and therefore Model 1, as the model with the best fit, is presented in the results.

Table 4.29: Comparison of model structures—neutropoenia

Neutropoenia	Number of levels		
	Model 1	**Model 2**	**Model 3**
Variables			
Gender (no change)	2	2	2
RxRisk category (no change)	4	4	4
Age	Continuous	4	Continuous
Cancer category (no change)	7	7	7
Chemo category	8	8	8 (adjusted)
Model fit statistics			
QIC	4,323.5252	4,382.7543	4,356.2605
QICu	4,268.9744	4,324.664	4,297.0947

Note: QIC = quasi-likelihood under the independence model criterion; QICu = simplified quasi-likelihood under the independence model criterion

Table 4.30 presents the GEE results for neutropoenia. The results indicate that there is no difference between the odds of the average female receiving treatment for neutropoenia and the odds of the average male. Age also does not make a significant difference to the odds of being treated for neutropoenia. Moving from the highest to the lowest RxRisk category reduces the odds of being treated for neutropoenia by 60 per cent. All cancers had significantly increased odds of being treated for neutropoenia when compared with urinary cancer. The increase in odds was largest for non-solid cancers, with a nearly 50-fold increase, and lung cancers, with a 20-fold increase. Only chemotherapy categories 6 and 2 were not at significantly increased odds of being treated for neutropoenia in comparison to chemotherapy type 8. The largest increase was for the odds of those on chemotherapy treatment 7, which had a 700-fold increase.

Table 4.30: GEE results—neutropoenia

Analysis of GEE parameter estimates						
Empirical standard error estimates						
Parameter		**Estimate**	**Standard error**	**95% confidence limits**		**Pr > |Z|**
Intercept		0.000	3.708	0.000	0.001	< .0001
Gender	Female	1.067	1.287	0.651	1.750	0.7965
	Male	–	–	–	–	–
Age		1.005	1.012	0.981	1.030	0.6726
RxCat	0–7	0.415	1.359	0.228	0.758	0.0042
	8–9	0.624	1.274	0.388	1.004	0.0518
	10–12	0.855	1.275	0.531	1.376	0.5189
	13–26	–	–	–	–	–
sitecatb	Breast	7.969	1.804	2.507	25.330	0.0004
	CRC	8.051	1.768	2.636	24.596	0.0003
	Genital	5.433	1.664	2.002	14.739	0.0009
	Lung	20.456	1.814	6.367	65.726	< .0001
	Non-solid	49.353	1.634	18.854	129.192	< .0001
	Other	9.669	1.702	3.409	27.429	< .0001
	Urinary	–	–	–	–	–
chemocatb	Alkylating agents	6.078	2.104	1.415	26.117	0.0153
	Antimetabolites	3.037	2.143	0.682	13.526	0.145
	Plant alkaloids and other natural	10.620	2.135	2.402	46.955	0.0018
	Cytotoxic antibiotics	18.254	2.118	4.194	79.448	0.0001
	Other antineoplastic	5.328	2.078	1.270	22.352	0.0222
	Endocrine treatment	4.152	2.142	0.933	18.478	0.0616
	Immunostimulants	700.994	2.161	154.795	3174.483	< .0001
	Immunosuppressants	–	–	–	–	–

Note: CRC = colorectal cancer; Pr = probability

Summary across adverse events

Table 4.31 presents a summary of the GEE results across adverse events, highlighting the variables which have consistent effects. This is most strongly seen with the variable RxRisk, where having fewer comorbidities is associated with a significantly lower risk for all four adverse events.

Table 4.31: Summary of GEE results

Variable	Diarrhoea	Nausea and vomiting	Anaemia	Neutropoenia
Gender (female)	ND	Increase***	ND	ND
Age (younger)	Increase***	Increase***	ND	ND
RxRisk (fewer comorbidities)	Decrease*	Decrease*	Decrease***	Decrease**
Breast cancer	ND	Decrease*	ND	Increase***
Colorectal cancer	ND	ND	ND	Increase***
Genital cancer	ND	ND	ND	Increase***
Lung cancer	Decrease*	ND	ND	Increase***
Non-solid tumours	Decrease*	Decrease***	ND	Increase***
Other	ND	ND	ND	Increase***
Antineoplastic	Decrease***	Increase***	ND	Increase*
Progestogens	ND	Increase*	ND	ND
LHRH agonists	Decrease***	Increase***	Decrease**	Increase***
Anti-estrogens	Decrease*	Increase***	ND	Increase***
Anti-androgens	Decrease**	Increase***	Decrease***	Increase*
Aromatase inhibitors	Decrease*	ND	Decrease*	ND
Immunostimulants	ND	ND	ND	Increase***

* < 0.05; **< 0.01; ***< 0.001
Note: ND = Nil difference

4.3.7 **Discussion**

In this sample of people with a diagnosis of cancer treated with chemotherapy, the adverse events diarrhoea, nausea and vomiting, anaemia and neutropoenia are more commonly treated in individuals who are older or who have more comorbidities. There are some adverse events that may be influenced by the specific cancer the individual has, or the specific chemotherapy with which they are being treated. The analysis is based on the proxy of having experienced an

adverse event, and therefore the interpretation is limited to individuals likely to have been treated for an adverse event.

In the models using a summary statistic to remove the correlation from the data, all models were found to be better than an empty model. In most cases, not gender nor the total number of doses, nor both of these variables, were found to improve model fit. However, given the potential clinical relevance of these factors and the fact that the sample size was large enough to account for additional variables, these variables were included in each of the models. For diarrhoea and nausea and vomiting, the type-3 analysis shows that age overall and RxRisk overall are significant predictors of diarrhoea and of nausea and vomiting. However, it is unclear why these effects are not ordered when specific levels within the variable are examined.

For all GEE models, the autoregressive model was selected as the most appropriate working correlation structure. Clinically, this can be interpreted as indicating that specific individuals are more likely to experience a specific adverse event in general, and an additional time effect suggests that having been treated for an adverse event recently will increase the risk of being treated for one again.

The GEE analysis utilises all data rather than removing correlated observations through use of a summary statistic. There were between 77,754 and 84,164 observations used in the GEE models, compared with 7,822 in the analysis using a summary statistic. Although the results of the two models for each adverse event were very similar, more confidence can be placed in the GEE-based results. This is because the GEE methodology gives a more-accurate estimation of the associations for the reason that the analysis looks for an association at every observation, rather than simply overall. In addition, the extra observations in the GEE analysis increases the power of the analysis to detect an effect. Finally, in this case, the question answered by the GEE is more clinically relevant for the research question than that which is possible by using a summary measure.

Although the intra-cluster correlation coefficients obtained through the exchangeable models structure of the GEE analysis found that correlation was low

(0.02–0.28), the relationship between observations of the same patient remains clinically important, and thus the GEE model remains the most appropriate analysis technique.

4.4 Resource-use associated with chemotherapy adverse events in clinical practice

Many economic evaluations use expert opinion or estimation to determine the resource-use associated with chemotherapy adverse events. This analysis provides a more rigorous estimate of the true costs associated with adverse events in a clinical practice setting.

4.4.1 Methods

Multiple linear regression was used to identify whether those who had been treated for a likely adverse event had higher resource-use than those who were not treated for an adverse event, with resource-use measured as healthcare costs.

Healthcare costs were defined as the total healthcare expenditure during the six months following the commencement of new chemotherapy treatment. The 6-month period commenced on 1 January 2005. A *new chemotherapy* was defined as one that had not been supplied during November or December 2004. This resulted in individuals having different start dates, but a consistent period in the treatment cycle is used for each person in the analysis. It is not known whether the new chemotherapy was the first chemotherapy for an individual, or a new regimen.

To calculate total healthcare expenditure, the following components were included:

- Medical service use as recorded in the MBS database. Prices for each medical service were taken from the database to reflect the costs to MBS at the time the service was delivered. As the medical service use for this analysis was all incurred during a 12-month period, no conversion to a common year was required.

- Hospitalisations as recorded in the APDC linked dataset. AR-DRGs were used to identify a cost for each admission, with the national weighted costs used. It is not known whether patients were admitted to a public or private hospital; therefore, the public price was used. Direct and overhead costs were included. As the hospitalisations included in this analysis were all incurred during a 12-month period, no conversion to a common year was required.

- Pharmaceutical items were extracted from the PBS dataset. All pharmaceutical items were included in the analysis, including chemotherapy drugs.

4.4.2 Issues with cost data

Data distribution

Cost data are typically positively skewed (due to a small number of patients with very high costs) and are truncated at zero (i.e. no patients have negative costs) (259-261). This is because most patients will undergo standard medical care with similar relatively low costs, but a small proportion of patients will have complications and require additional treatment resulting in a disproportionate amount of the costs (261). This skew and outliers means that it is more-accurate to report median cost and interquartile range for patients, because this describes the 'typical cost' (rather than mean, range and standard deviation) (260). However, for decision-makers, the mean cost is required, because the overall cost for a group of patients is necessary information in the decision-making process (260, 261).

These properties of cost data also make the use of parametric tests difficult (260). Statistical theory says that if the sample size is large enough (> 150), the central limit theorem will hold, and parametric assumptions will also hold (260, 262). To assess whether this is the case, the sample distribution should be examined (260). If the skewness of the sample is sufficiently low to indicate normality for the sampling distribution of the mean, parametric statistics can be used (260). However, this method should be used with caution, and the results may be sensitive to extreme observations (259).

In modelling these data, ordinary least square (OLS) regression is often used; however, if the data are not normally distributed, this can lead to biased parameters (263). An additional issue with the use of OLS regression for cost data is that it can predict negative costs, which are not possible in reality (263).

If the sample is too small or too skewed, there are a number of options for analysis, including nonparametric tests, transformation or bootstrapping (260) and, more recently, GLM using the gamma distribution and log-link (261).

The conventional biostatistical approach is to use nonparametric tests (260, 264). However, nonparametric tests are better suited to hypothesis testing than to estimation (260). In addition, parametric tests usually use medians for comparisons, and thus may be considered inappropriate by many economists who are interested in the mean costs of treatment for decision-making (260). It is now generally accepted that nonparametric techniques for the analysis of cost data are inappropriate, although they continue to be used in many published studies (260, 261).

Taking a classic econometric approach (264), transforming cost data by means of log, square root or reciprocal transformations, the skew in the data is reduced, and a normal distribution is approximated (259, 260). This results in geometric means being compared rather than arithmetic means and therefore will often underestimate the true costs due to the positive skew of cost data (260). The other major factor in the transformation of cost data is that it is difficult to retransform costs back to the original scale after analysis (259, 260). Because the linear regression of log-transformed costs models the expected mean of the log cost rather than the log of the expected mean, simple exponentiation back to the natural scale results in biased estimates of the intercept (261, 263). This can be corrected using bias correction factors in the retransformation, or smear techniques, which apply nonparametric factors (261); however, these techniques assume a constant error and therefore are not suitable for data that are heteroskedastic (263). This makes interpretation of results difficult (260).

Nonparametric bootstrapping is a data-based simulation method for assessing statistical precision (260). Random values are selected from the original sample with replacement to yield a bootstrap sample of the same size as the original (260, 261). This is repeated a number of times, typically 1,000 times, to create a sample of bootstrapped means with its own distribution (260). This mean and other parametric statistics may be calculated for the bootstrapped distribution (260). It allows the comparison of arithmetic means without making assumptions about the distribution of costs (260). Nonparametric bootstrapping can be used either for primary analysis or as a check on the robustness of using parametric tests with non-normal data (260, 261). Although a number of authors recommend this method for analysing cost data (260), it has been argued that this method, although valid, will tend to produce estimates similar to those based on the assumptions of normality and that more robust results will be obtained by actually modelling the skewness of the data, as is done in gamma distributions, described below (261).

GLM is an extension of linear regression methods; it allows the response to be distributed in non-normal ways, including Poisson, gamma and binomial distributions (261, 264). For the analysis of cost data, the gamma distribution is often appropriate, given the typical pattern of variation observed (261). A log-link is often used in the analysis of cost data with GLM because it guarantees non-negative outcomes, but unlike a logarithmic transformation, the original scale of the data is maintained, making interpretation of results easier (259, 261, 264).

Censored data

Cost data are often analysed as costs incurred during a set period of observation for individuals in a group (261). However, this type of study often includes censored data, because patients may die or be lost to follow-up (261). This censoring may be addressed using traditional survival analysis; however, because the total costs at the end of the observation period are likely to be highly correlated with the total costs at censoring, the assumptions of survival analysis are generally not met (261). Some survival analysis techniques have been

developed for the analysis of lifetime costs; however, these only account for censoring due to death, not due to patients lost to follow-up (261).

Standardisation of costs is a technique used to account for patients for whom only short-term cost data are available (261). The available short-term costs are scaled up to estimate the costs that would have been incurred if all patients had been followed for the full duration of the study (261). However, this may be inaccurate because initial care costs may be different from those experienced over the longer term of a disease (261). The use of standardisation of cost data is more acceptable in studies of chronic disease where deaths due to disease are rare and other causes of loss to follow-up can be considered to be missing at random (261).

For other types of studies, it may be appropriate to only include in the analysis those patients who were followed for the full period, although this does result in a reduced sample size (261). For studies where death is part of the disease, and could be considered an important part of the disease process in the time frame selected for analysis, a 'complete case analysis' that includes censored costs in their unstandardised form can be conducted (261).

Analysis

The analysis of the costs of adverse events was undertaken using multiple regression, using the model formula:

Equation 3

$$total\ cost = a + gender + age + RxRisk + cancer + doses + any\ adverse\ event + e$$

Equation 4

$$total\ cost = a + gender + age + RxRisk + cancer + doses + diarrhea + anemia + nausea\ \&\ vomiting + neutropenia + e$$

To assess the model for suitability for regression analysis, descriptive analysis was undertaken with particular focus on the dependent variable total cost. The log-transformed total costs were also assessed, because this is the most commonly used transformation for skewed cost data. Finally, the mean of total cost was

compared with the standard deviation in a plot, with the data grouped by age category and cancer type. This was done to assess if the data had an approximate constant coefficient of variation, which demonstrates the appropriateness of the data for modelling using a gamma distribution.

Based on these results, three analysis methods for the cost data were assessed: OLS regression, OLS regression using log-transformed total cost, and a generalised linear model using a gamma distribution and log-link.

To account for the possible impact of censored data due to individuals dying during the 6-month observation period, the number of these individuals was identified. Given the small incidence of death during the observation period, the regression was run with all patients included; however, the final selected model was re-run using the censored data to assess if this significantly affected the results. Given that the data are administrative and data capture should therefore be complete for all patients, censoring due to loss to follow-up was not thought to be of great concern. Table 4.32 lists the variables included in the various models analysed.

Table 4.32: Variables included in the DVA models of costs associated with adverse events

Variable	Type	Levels
Total cost	Continuous	Raw total healthcare cost over 6-month period
Log cost	Continuous	The (natural) log of the total cost
Total cost censored	Continuous	Raw total healthcare cost over 6-month period for only those individuals who did not die during the observation period
Log cost censored	Continuous	The log (10 or natural) of the total cost for only those individuals who did not die during the observation period
Gender	Categorical	Male/Female
Age	Continuous	Age calculated from DOB to the first day of the 6-month observation period
Rx Risk	Continuous	Overall RxRisk score, calculated using all pharmaceutical data
Cancer	Categorical	Consolidated to 7 levels based on ICD classification (breast, colorectal, genital, lung, non-solid, urinary, other)
Any adverse event	Binary	Whether during the 6-month observation period the individual was treated for diarrhoea OR anaemia OR nausea/vomiting OR neutropoenia
Any diarrhoea	Binary	Whether during the 6-month observation period the individual was treated for diarrhoea

Variable	Type	Levels
Any nausea and vomiting	Binary	Whether during the 6-month observation period the individual was treated for diarrhoea
Any anaemia	Binary	Whether during the 6-month observation period the individual was treated for diarrhoea
Any neutropoenia	Binary	Whether during the 6-month observation period the individual was treated for neutropoenia

Note: DOB = date of birth; ICD = international classification of disease

4.4.3 Results

There were 5,619 individuals included in the analysis. Of these, 683 individuals died during the 6-month observation period, leaving 4,936 individuals remaining for the analysis, excluding censored individuals.

Figure 4.2 displays the distribution of total costs in this group of 5,619 patients. The costs are highly skewed, with a mean (median) of $13,511 ($7,126), and range between $0.00 and $225,949. In the dataset without censored individuals, the costs are lower but remain highly skewed (coefficient of skewness 3.05, coefficient of kurtosis 14.00) with a mean (median) total cost of $12,403 ($6,479), and a range between $0 and $184,055. Total costs for the group are highly skewed, as expected.

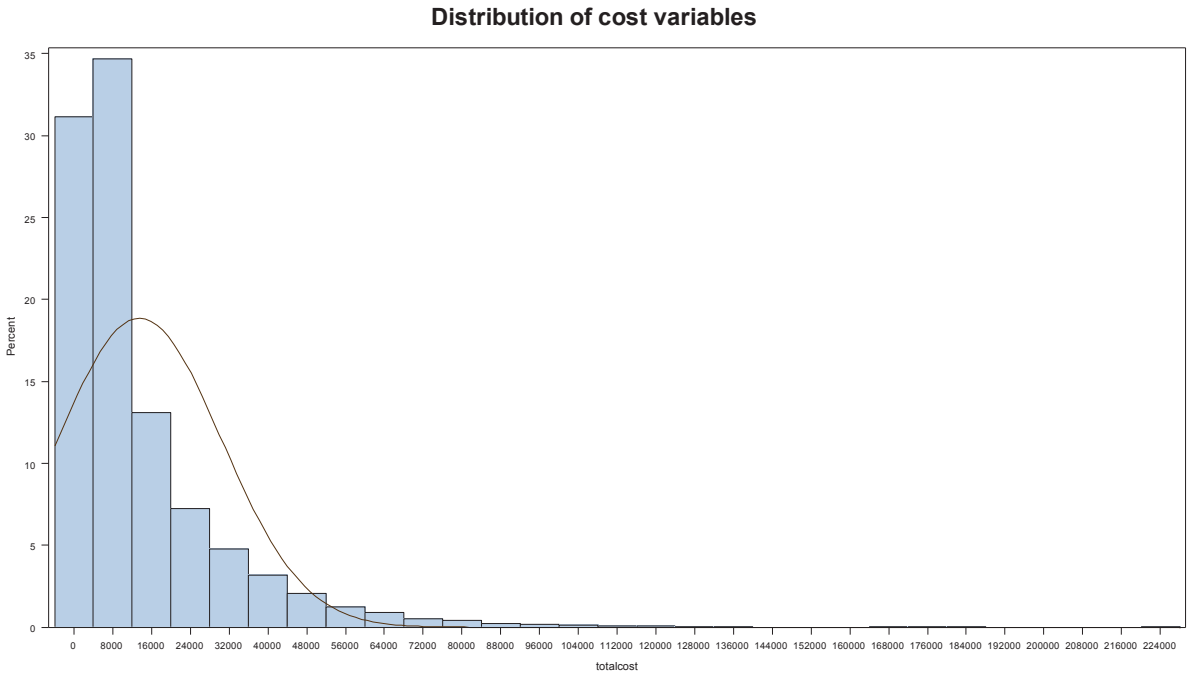


Figure 4.2: Distribution of total costs for the first six months of a new chemotherapy treatment

Figure 4.3 shows a histogram of the log-transformed costs, which appear to be approximately normal although now left skewed (coefficient of skewness = –1.23) and rather leptokurtic (peaked with heavy tails) (coefficient of kurtosis = 7.12).

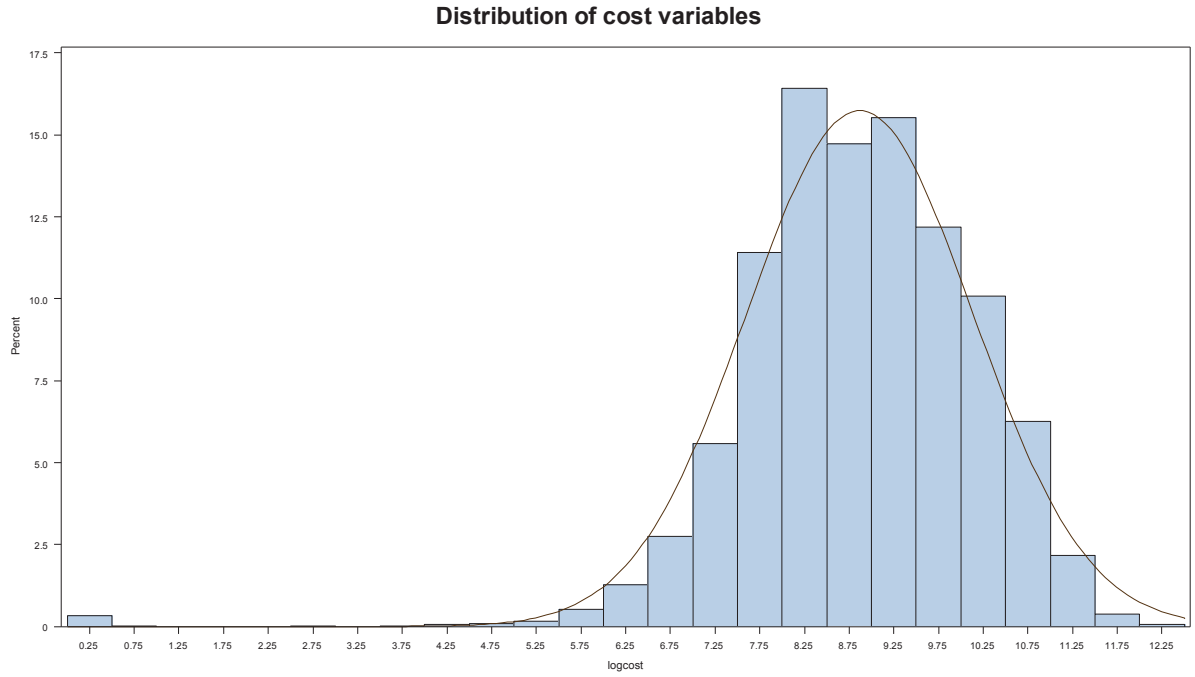


Figure 4.3: Distribution of log-costs associated with adverse events in the first six months of a new chemotherapy treatment

Figure 4.4 compares the average raw cost per person with the standard deviation of average raw cost per person, when grouped by age categories and by cancer type. The approximately linear relationship demonstrates that there is an approximate constant coefficient of variation, indicating that the gamma distribution is appropriate for analysis of these data.

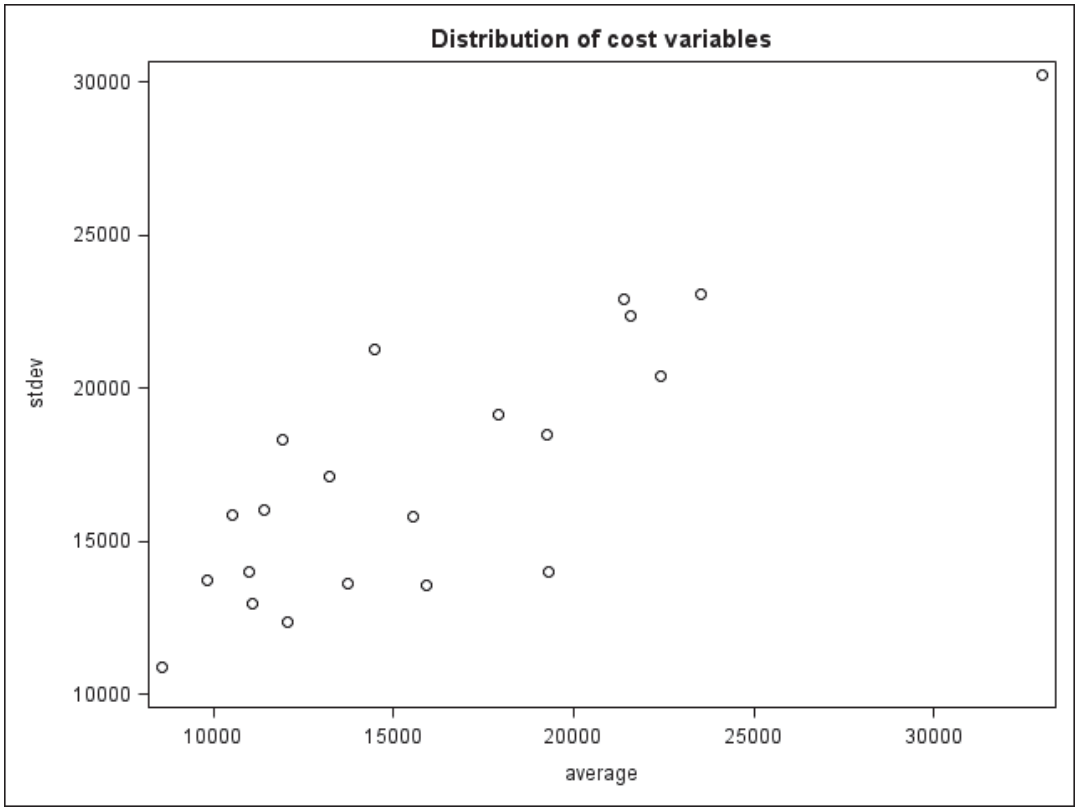


Figure 4.4: Distribution of cost variables—mean raw cost vs. standard deviation of raw cost per person by age group and gender

The use of OLS regression with raw cost as the dependent variable has the advantage of being easy to interpret, and given the relatively large number of observations, an argument can be made for using OLS regression despite the presence of skew in the cost data.

Table 4.33 displays the significance levels of the following variables when used to predict costs: gender (baseline category male), age (continuous), RxRisk (continuous), Sitecatb (baseline category urinary cancer), any diarrhoea, any nausea, any anaemia, any neutropoenia (all baseline category 'Yes' (1)). The variables age, RxRisk, any nausea, any anaemia and any neutropoenia are significant predictors of costs ($p < 0.001$). All other variables have p-values greater than 0.01 but less than 0.05, with the exception of colorectal and lung cancers. However, the results of type-3 tests of fixed effects show that each categorical variable, when analysed as a group (with the exception of gender and any diarrhoea), are significant predictors of cost ($p < 0.001$).

Overall cost is $1,418 lower on average for women than for men. For every additional year of age, there appears to be a $140 saving in overall costs. As RxRisk category increases, costs increase by $552. Breast, genital and other cancers are all associated with lower overall cost in comparison with urinary cancer, while non-solid tumours are the only cancer associated with a significantly increased cost compared with urinary cancer. Being treated for nausea and vomiting, anaemia and neutropoenia all result in statistically significant additional costs, with neutropoenia resulting in the greatest cost increase at more than $10,000. Diarrhoea has a weaker association; however, this is of significance because it appears to predict a lower overall cost, which is inconsistent with the clinical hypothesis.

Interpretation of these results should take into consideration the skewed data on which they are based. The analysis of skewed data often results in heteroskedastic results, which may not be accurate or may result in biased interpretation (173, 265).

Table 4.33: Results of simple linear regression of costs and each adverse event

Solution for fixed effects: simple linear regression of costs and each adverse event						
Effect	**Category**	**Estimate**	**Standard error**	**DF**	**t value**	**Pr > |t|**
Intercept		39,705	3,131.98	5,596	12.68	< .0001
Gender	Female	–1,418.69	599	5,596	–2.37	0.0179
	Male	0	–	–	–	–
Age		–140.26	30.3976	5,596	–4.61	< .0001
RxRisk		552.77	59.6786	5,596	9.26	< .0001
sitecatb (cancer site)	Breast	–4,148.06	1,299.15	5,596	–3.19	0.0014
	Colorectal	616.02	1,206.16	5,596	0.51	0.6096
	Genital	–3,231.73	1,097.67	5,596	–2.94	0.0033
	Lung	237.14	1,395.47	5,596	0.17	0.8651
	Non-solid	4,655.44	1,214.67	5,596	3.83	0.0001
	Other	–2,693.62	1,150.71	5,596	–2.34	0.0193
	Urinary	0	–	–	–	–
Any diarrhoea	0	2,498.68	977.5	5,596	2.56	0.0106
	1	0	–	–	–	–
Any nausea	0	–7,511.1	543.34	5,596	–13.82	< .0001
	1	0	–	–	–	–
Any anaemia	0	–4,724.43	1,042.62	5,596	–4.53	< .0001
	1	0	–	–	–	–
Any neutropoenia	0	–10,631	11,41.47	5,596	–9.31	< .0001
	1	0	–	–	–	–

Type-3 tests of fixed effects				
Effect	**Num DF**	**Den DF**	**F value**	**Pr > F**
Gender	1	5,596	5.61	0.0179
age	1	5,596	21.29	< .0001
RxRisk	1	5,596	85.79	< .0001
sitecatb	6	5,596	26.96	< .0001
Any diarrhoea	1	5,596	6.53	0.0106
Any nausea	1	5,596	191.1	< .0001
Any anaemia	1	5,596	20.53	< .0001
Any neutropoenia	1	5,596	86.74	< .0001

Note: DF = degrees of freedom

Table 4.34 displays the significance levels of the same variables to predict log-costs. The variables gender, RxRisk, other cancer, any nausea, any anaemia and any neutropoenia are all significant predictors of costs ($p < 0.001$). All other variables have p-values more than 0.01 but less than 0.05, with the exception of colorectal and lung cancers, and any diarrhoea. The results of type-3 tests of fixed effects show that only age and any diarrhoea are not significant predictors of cost ($p < 0.001$). Interpretation of these results is difficult because these are the log-costs, and it is not possible to retransform these to natural units without using smear techniques, which may result in biased results.

Table 4.34: Results of linear regression with log-costs and each adverse event

Solution for fixed effects: regression of log-costs—3 x adverse events						
Effect	**Category**	**Estimate**	**Standard error**	**DF**	**t Value**	**Pr > |t|**
Intercept		10.2124	0.2335	5,596	43.74	< .0001
Gender	F	–0.2062	0.04466	5,596	–4.62	< .0001
	M	0	–	–	–	–
Age		–0.00565	0.002266	5,596	–2.49	0.0127
RxRisk		0.06941	0.004449	5,596	15.6	< .0001
Sitecatb (cancer site)	Breast	–0.3471	0.09686	5,596	–3.58	0.0003
	CRC	–0.077	0.08992	5,596	–0.86	0.3919
	Genital	–0.1911	0.08184	5,596	–2.34	0.0195
	Lung	–0.167	0.104	5,596	–1.61	0.1084
	Non-solid	0.1749	0.09056	5,596	1.93	0.0535
	Other	–0.3751	0.08579	5,596	–4.37	< .0001
	Urinary	0	–	–	–	–
Any diarrhoea	0	–0.01491	0.07288	5,596	–0.2	0.8379
	1	0				
Any nausea	0	–0.5665	0.04051	5,596	–13.98	< .0001
	1	0	–	–	–	–
Any anaemia	0	–0.3472	0.07773	5,596	–4.47	< .0001
	1	0	–	–	–	–
Any neutropoenia	0	–0.5458	0.0851	5,596	–6.41	< .0001
	1	0	–	–	–	–

Type-3 tests of fixed effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Gender	1	5,596	21.33	< .0001
Age	1	5,596	6.21	0.0127
RxRisk	1	5,596	243.37	< .0001
sitecatb	6	5,596	17.98	< .0001
Any diarrhoea	1	5,596	0.04	0.8379
Any nausea	1	5,596	195.54	< .0001
Any anaemia	1	5,596	19.95	< .0001
Any neutropoenia	1	5,596	41.14	< .0001

Note: DF = degrees of freedom

Table 4.35 shows the significance levels of the same variables to predict costs using a gamma model with a log-link function. The reference case is a male with colorectal cancer who experiences no adverse events. Similar to the previous models, all variables except gender, breast cancer, lung cancer, non-solid tumours and any diarrhoea are significant predictors of cost ($p < 0.001$). When running gamma/log models in SAS, the general code drops observations with an outcome of '0' (264), resulting in an additional 18 individuals being removed from the analysis.

The intercept is the estimated log mean of the fitted gamma distribution (254), so that the mean cost over the 6-month period is the exponential of 9.5636, which is $14,237 (95% confidence interval $10,514, $19,274).

In GLM analysis, the scale parameter is sometimes called the *gamma index parameter* (254). A value of '1' for the index parameter corresponds to the exponential distribution (254). In this analysis, the estimated value of the scale parameter is 1.0824, with a 95 per cent confidence interval (1.0474, 1.1186). Given that this does not contain '1', the hypothesis of an exponential distribution for the data is rejected at the 0.05 level, indicating that the use of a simple linear regression is not appropriate.

Table 4.35: Results of gamma model of the additional cost associated with each adverse event

Analysis of maximum likelihood parameter estimates								
Parameter		**DF**	**Estimate**	**Standard error**	**Wald 95% confidence limits**		**Wald chi-square**	**Pr > ChiSq**
Intercept		1	9.5636	0.1546	9.2606	9.8665	3,828.08	< .0001
Gender	Female	1	–0.0995	0.0365	–0.171	–0.028	7.45	0.0064
Age		1	–0.0065	0.0018	–0.0101	–0.0029	12.51	0.0004
RxRisk		1	0.0473	0.0036	0.0403	0.0544	173.04	< .0001
sitecatb (cancer site)	Breast	1	–0.4071	0.058	–0.5208	–0.2934	49.28	< .0001
	Genital	1	–0.2713	0.0448	–0.3591	–0.1834	36.65	< .0001
	Lung	1	0.0918	0.0678	–0.041	0.2247	1.84	0.1754
	Non-solid	1	0.2214	0.0533	0.1168	0.3259	17.22	< .0001
	Other	1	–0.277	0.0485	–0.372	–0.182	32.64	< .0001
	Urinary	1	0.0073	0.0741	–0.138	0.1526	0.01	0.9216
Any diarrhoea	1	1	–0.1139	0.0599	–0.2314	0.0035	3.61	0.0573
Any nausea	1	1	0.4763	0.0333	0.411	0.5415	204.4	< .0001
Any anaemia	1	1	0.2883	0.0631	0.1647	0.412	20.89	< .0001
Any neutropoenia	1	1	0.4293	0.0697	0.2926	0.566	37.89	< .0001
Scale		1	1.0824	0.0181	1.0474	1.1186	–	–

Note; DF = degrees of freedom

The results of the GLM with the exponential of the estimate and confidence intervals are shown in Table 4.36. Once the exponential value of the estimate is taken, the cost results have a simple interpretation (263). For example, being female results in a nine per cent reduction in cost. Each additional RxRisk category results in a five per cent increase in cost. Breast, genital and other cancers all have lower overall costs than the baseline category of colorectal cancer. Treatment for nausea and vomiting, anaemia or neutropoenia all significantly increase costs, whereas diarrhoea is non-significant.

Table 4.36: GLM results with exponential values

Parameter		Exp (estimate)	Exp (Wald 95% confidence limits)	
Intercept		14,237.01	10,515.44	19,273.76
Gender	F	0.91	0.84	0.97
Age		0.99	0.99	1.00
RxRisk		1.05	1.04	1.06
sitecatb (cancer site)	Breast	0.67	0.59	0.75
	Genital	0.76	0.70	0.83
	Lung	1.10	0.96	1.25
	Non-solid	1.25	1.12	1.39
	Other	0.76	0.69	0.83
	Urinary	1.01	0.87	1.16
Any diarrhoea	1	0.89	0.79	1.00
Any nausea	1	1.61	1.51	1.72
Any anaemia	1	1.33	1.18	1.51
Any neutropoenia	1	1.54	1.34	1.76
Scale		2.95	2.85	3.06

SAS allows the assessment of cumulative residuals as a way of assessing the goodness of link in the model. This technique uses plots of cumulative residuals to assess model fit, and it can be used to assess the fit of covariates or the appropriateness of the link function. The analysis is based on whether the simulated residual patterns that would be generated by the model under the specified assumptions are statistically different from the one actually generated.

Figure 4.5 shows the actual pattern of residuals with a log-link printed in bold, while 20 simulations are represented with dotted lines. Interpretation of these results is based on the shape of the line and its relationship to the simulations (a closer match is better), as well as the p-value (254, 266). A low p-value, such as $p < 0.05$ indicates that the actual functional form being used is less than optimal (266). This is caused by a residual pattern that differs from the expected patterns generated by the simulation (266). P-values greater than 0.2 are preferred (266).

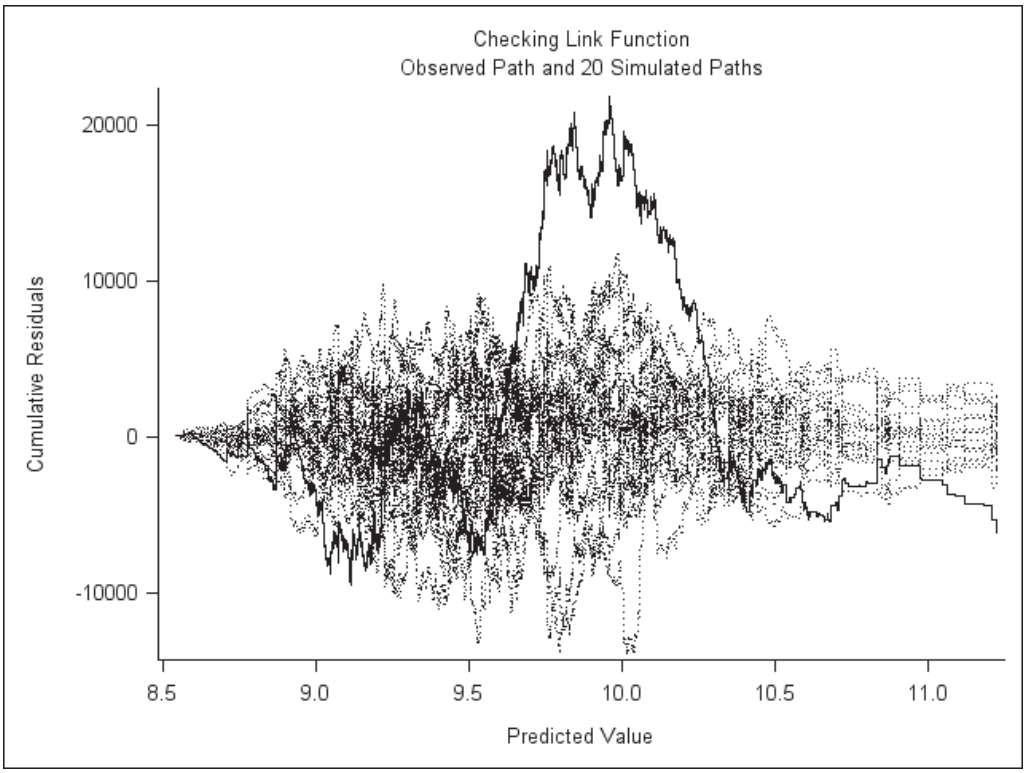


Figure 4.5: Pattern of residuals—actual with 20 simulations

This plot indicates that there is an artefact in the data at around the predicted value of 10.0. One possible reason for this may be interactions in the data between the independent variables. An exploratory analysis was conducted to run the model with interaction terms included. The clinically relevant potential interactions were identified as follows:

- **Interaction between the adverse event**s. It is possible that individuals who experience multiple adverse events have associated costs that are not simply additive for the two (or more) events. There may be some cost

savings associated with multiple events being treated simultaneously (e.g. one hospitalisation for multiple events), or the treatment costs may be increased as adverse events that are not serious in isolation become more significant when experienced in combination. For example, diarrhoea alone may not be serious, but when combined with nausea and vomiting the risks of dehydration would be significantly increased, and thus treatment may be more aggressive than expected for low-grade diarrhoea alone.

- **Interactions between the type of cancer and the adverse event**s. Specific types of cancer may be more likely to be associated with specific adverse events. For example, individuals with colorectal cancer may be more likely to experience diarrhoea because they have an already compromised digestive system. This may also mean that in those individuals with colorectal cancer, the treatment for diarrhoea is different from the treatment for diarrhoea in individuals with other types of cancer, resulting in a difference in costs.

- **Interactions between age and comorbidities**. It is likely that older people have more comorbidities; however, the implications of comorbidities in the older population may be more serious. This may mean that treatment costs are higher due to the complexity of managing multiple medical conditions simultaneously.

The interactions between the adverse events were added to the model first, as these were considered the most important. All six combinations of adverse events occurring in doubles (e.g. diarrhoea and vomiting, diarrhoea and anaemia) were included in the model initially. Of these, only two of the three anaemia interactions were significant at the $p < 0.05$ level (any anaemia with any diarrhoea or any neutropoenia). The three anaemia interactions were therefore kept in the model, with the remaining adverse-event interactions removed.

The interactions between cancer type and adverse events were then added. The high number of levels in these variables led to a large number of coefficient estimates. The interactions between anaemia and neutropoenia and between anaemia and diarrhoea remained significant. In relation to the interaction of cancer type with adverse events, it appeared that nausea and vomiting was the most significant, with interactions at the $p < 0.05$ level for nausea and vomiting and non-solid tumours, nausea and vomiting and lung cancer, and nausea and vomiting and genital cancers. Nausea and vomiting and other cancers had a stronger association ($p < 0.07$), although this was not statistically significant. In addition, a significant interaction between urinary cancer and neutropoenia was identified. It was decided to keep the interaction of nausea and vomiting and cancer type in the model, and remove the others.

Finally, the interaction of age and comorbidities was assessed. This was not significant, and was consequently removed from the model. The final model therefore contained the main effects and the additional interactions for anaemia with the other adverse events and nausea and vomiting with cancer type. This model (see Table 4.37) shows that the inclusion of these interaction terms makes little difference in the significance of the main effects on the total cost. However, a number of interactions do appear to influence total cost significantly.

Table 4.37: Results of gamma model with main effects and interaction terms

Analysis of maximum likelihood parameter estimates								
Parameter			**DF**	**Estimate**	**Standard Error**	**Wald 95% Confidence limits**		**Wald chi-square**	**Pr > ChiSq**
Intercept			1	9.3929	0.1581	9.0829	9.7028	3,527.6	< .0001
Gender	F		1	–0.0881	0.0364	–0.1595	–0.0167	5.85	0.0155
Age			1	–0.0055	0.0018	–0.0091	–0.0019	8.98	0.0027
RxRisk			1	0.0493	0.0036	0.0422	0.0564	186.84	< .0001
sitecatb (cancer site)	Breast		1	–0.359	0.066	–0.4883	–0.2297	29.62	< .0001
	Genital		1	–0.1853	0.0519	–0.2871	–0.0835	12.73	0.0004
	Lung		1	0.3008	0.0914	0.1217	0.48	10.83	0.001
	Non-solid		1	0.3485	0.0638	0.2234	0.4736	29.82	< .0001
	Other		1	–0.2777	0.0558	–0.3871	–0.1683	24.77	< .0001
	Urinary		1	0.0952	0.0822	–0.0659	0.2564	1.34	0.2467
Any diarrhoea	1		1	–0.1079	0.0626	–0.2305	0.0148	2.97	0.0848
Any nausea	1		1	0.6617	0.0792	0.5064	0.817	69.74	< .0001
Any anaemia	1		1	0.3947	0.0905	0.2173	0.5722	19.01	< .0001
Any neutropoenia	1		1	0.5258	0.0774	0.374	0.6775	46.13	< .0001
Any diarrhoea*Any anaemia	1	1	1	–0.4917	0.2229	–0.9286	–0.0549	4.87	0.0274
Any nausea*Any anaemia	1	1	1	0.016	0.1292	–0.2372	0.2692	0.02	0.9016
Any anaemia*Any neutropoenia	1	1	1	–0.4567	0.1859	–0.8212	–0.0923	6.03	0.014
sitecatb*any nausea	Breast	1	1	–0.1627	0.119	–0.396	0.0706	1.87	0.1718
sitecatb*any nausea	Genital	1	1	–0.3156	0.0976	–0.507	–0.1242	10.45	0.0012
sitecatb*any nausea	Lung	1	1	–0.4854	0.1371	–0.7542	–0.2167	12.54	0.0004

Analysis of maximum likelihood parameter estimates								
Parameter			**DF**	**Estimate**	**Standard Error**	**Wald 95% Confidence limits**		**Wald chi-square**	**Pr > ChiSq**
sitecatb*any nausea	Non-solid	1	1	–0.4015	0.1125	–0.622	–0.181	12.74	0.0004
sitecatb*any nausea	Other	1	1	0.1805	0.1141	–0.0431	0.4042	2.5	0.1136
sitecatb*any nausea	Urinary	1	1	–0.3522	0.1945	–0.7333	0.0289	3.28	0.0701
Scale			1	1.0908	0.0183	1.0555	1.1273		

Note: DF = degrees of freedom

Table 4.38 shows the exponentiated results of the GLM with interaction terms included. The interaction effects represent the combined effects of the two variables on the cost of chemotherapy. The inclusion of interaction terms in the models results in a different interpretation of the effects for all of the coefficients, compared with the interpretation when only main effects are included (267). The value of each parameter is now interpreted based on the value of the interaction parameter (267). For example, the five per cent increase in costs associated with moving up one RxRisk category is now conditional on the value of the interaction terms being zero, that is, having no anaemia and having no nausea and vomiting.

Table 4.38: Results of gamma model with interaction terms—exponentiated

Parameter		Exp(estimate)	Exp(Wald 95% confidence limits)	
Intercept		12,002.86	8,803.46	16,363.36
Gender	Female	0.92	0.85	0.98
Age		0.99	0.99	1.00
RxRisk		1.05	1.04	1.06
Sitecatb (cancer site)	Breast	0.70	0.61	0.79
	Genital	0.83	0.75	0.92
	Lung	1.35	1.13	1.62
	Non-solid	1.42	1.25	1.61
	Other	0.76	0.68	0.85
	Urinary	1.10	0.94	1.29
Any diarrhoea	1	0.90	0.79	1.01
Any nausea	1	1.94	1.66	2.26
Any anaemia	1	1.48	1.24	1.77
Any neutropoenia	1	1.69	1.45	1.97
Any diarrhoea*any anaemia	1	0.61	0.40	0.95
Any nausea*any anaemia	1	1.02	0.79	1.31
Any anaemia*any neutropoenia	1	0.63	0.44	0.91
sitecatb*any nausea	Breast	0.85	0.67	1.07
sitecatb*any nausea	Genital	0.73	0.60	0.88
sitecatb*any nausea	Lung	0.62	0.47	0.81
sitecatb*any nausea	Non-solid	0.67	0.54	0.83
sitecatb*any nausea	Other	1.20	0.96	1.50
sitecatb*any nausea	Urinary	0.70	0.48	1.03
Scale		2.98	2.87	3.09

Note: Exp = exponential

When the plots of cumulative residuals are examined for the model with the interaction terms included, it can be seen in Figure 4.6 that while the peak at the predicted value of ten remains, the simulated paths now more often follow the peak although this is not a consistent pattern. It is therefore concluded that the generalised linear model with main effects is the most appropriate technique for this analysis of the costs of chemotherapy adverse events.

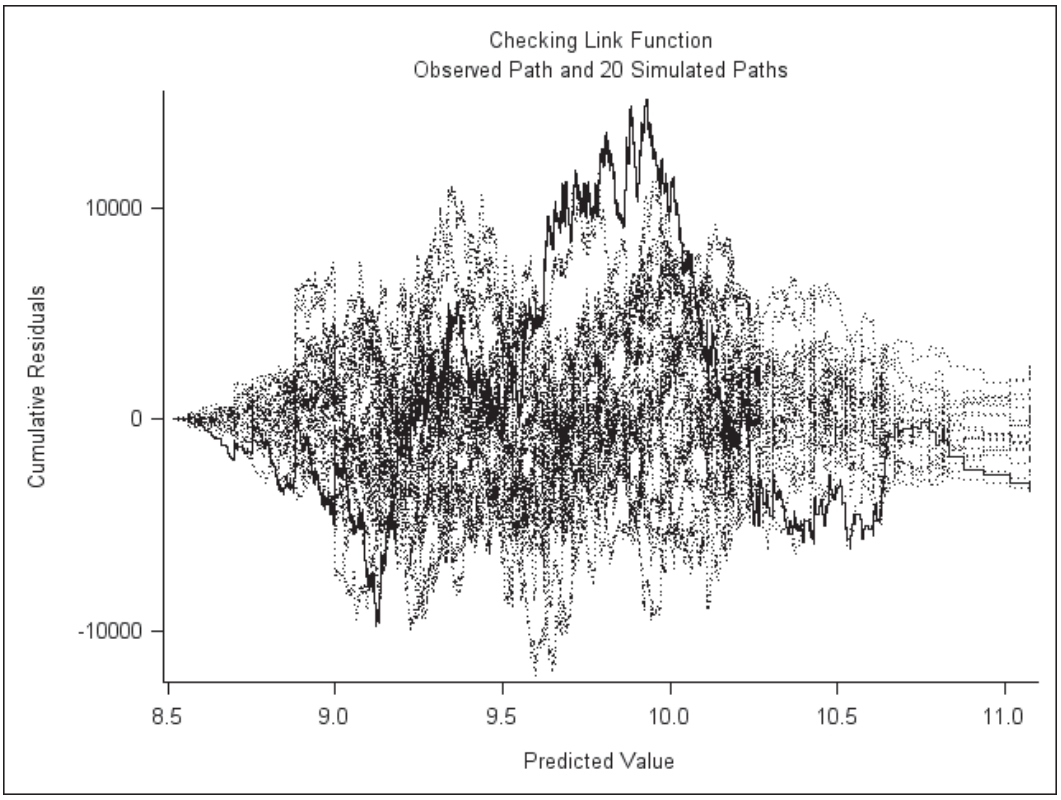


Figure 4.6: Pattern of residuals—actual with 20 simulations

4.4.4 Discussion

A number of methods of analysing skewed data are presented in relation to the costs associated with experiencing treatment for a likely adverse event in the first six months of a new chemotherapy treatment. All models have similar results, with significant additional costs associated with nausea and vomiting, anaemia and neutropoenia.

The simple linear regression provides easily interpretable results, showing increased costs of between $4,700 for anaemia and $10,600 for neutropoenia.

However, caution should be used in interpreting these results because the skewed distribution of the data is not accounted for, based on the assumption that the sample size is large enough for the central limit theorem to account for the skew.

Repeating the analysis using the log of the raw costs provides a method for removing the skew from the data, and similar results are obtained for the statistical significance of the variables. However, the interpretation of the coefficients is difficult, and therefore this approach is not suitable from a decision-maker's perspective.

The use of generalised linear models provides a method to account for the skew in the data while still providing results that can be easily interpreted. These results are consistent with those of simple linear regression, although the coefficient for neutropoenia is reduced. In an attempt to improve goodness of link, the model was adjusted to include interaction terms related to anaemia and nausea and vomiting. This produced little change in the main effects results of the regression and did not substantially improve model fit.

Additional assessments of goodness of fit for the distribution selected in generalised linear models have been suggested, including the Pregiborn link test (268), modified Hosmer and Lemeshow test, Pearson's correlation test (264), and the modified Park test (269). However, for the purposes of this analysis, the model structure is based on clinical reasoning. The model structure is therefore based on the fact that the standard deviation of cost is proportional to the mean, which indicates a gamma distribution, and the log-link ensures non-zero results and retains the original units for interpretation. This model structure is commonly recommended in the literature for analysis of cost data (263, 264, 269, 270) .

It is therefore proposed that the generalised linear model with main effects only is the most appropriate technique for this analysis.

4.5 DVA Discussion

The current inputs for the incidence of chemotherapy adverse events for models of chemotherapy cost-effectiveness are typically based on clinical trials. Clinical trials have been shown to underestimate the incidence of chemotherapy adverse events through the low external validity of the clinical trial environment, the poor reporting of adverse events in clinical trials, and the exclusion from clinical trials of older sicker individuals (52-55, 217-220).

This chapter has used a large administrative dataset to examine the incidence, the factors that influence the incidence, and the resources associated with chemotherapy adverse events. By using administrative data to estimate the incidence of chemotherapy adverse events, this analysis has provided an opportunity to estimate the incidence of adverse events in a clinical practice population. This cohort has high external validity and primarily includes older individuals with multiple comorbidities.

The four adverse events examined in this analysis—diarrhoea, nausea and vomiting, anaemia and neutropoenia—had lower incidences than reported in previous observational studies of heterogeneous cohorts (77). However, the factors that influence the incidence of these adverse events are generally consistent with clinical expectations, in that those who have more comorbidities are more likely to experience adverse events. Finally, the additional resource-use associated with nausea and vomiting, anaemia and neutropoenia are all significant, ranging from $7,500 to $10,600.

Similarly, the use of expert opinion or estimates of the resources associated with chemotherapy adverse events in models of chemotherapy cost-effectiveness introduces a source of potential bias. By using data to estimate the additional costs associated with adverse events in a clinical practice cohort, additional evidence is available for estimating the costs associated with chemotherapy adverse events.

The low incidence of adverse events identified in this cohort could be an underestimation of the rate of adverse events in this cohort, or it may be that this older cohort with multiple comorbidities is less likely to experience an adverse

event. In the case of underestimation, the use of prescribed pharmaceuticals, medical services received and hospitalisations to identify cases of treatment for a likely adverse event may not be sensitive to the actual incidence of an adverse event, and may therefore result in underestimates. This may be the case if individuals receive one script for an adverse-event treatment, such as diarrhoea, which they fill at the beginning of treatment, but which then covers them for multiple cycles of chemotherapy. In this case, it would not be possible to know for which doses of chemotherapy the medication had been used. Similarly, for less-severe events, such as nausea and diarrhoea, over-the-counter medications may be available, which individuals could substitute for prescription treatments. If the use of the proxy was responsible for an underestimation of adverse events, this would be consistent with work in the US, which found that the use of diagnostic and procedure codes may be of only limited value in measuring severe chemotherapy adverse events in elderly Medicare beneficiaries (271).

It is also possible that older individuals and those with multiple comorbidities do indeed experience fewer adverse events. This may be because the perceived frailty of these patients leads oncologists to treat them conservatively; they may be less likely to prescribe highly toxic chemotherapy treatment, or may prescribe them at a lower dose than usual to prevent adverse events from occurring.

It is not possible to determine which of these two provide an explanation for the case; it may be a combination of the two. The examination of adverse events in a prospective cohort of cancer patients in NSW, described in Chapter 5, further examines this issue.

The factors that influence the incidence of treatment for a likely adverse event are examined in two ways to address the correlation of observations within the data. First, a logistic regression using a summary statistic to remove the correlation was undertaken. This found that having more doses of chemotherapy leads to higher odds of being treated for a likely side effect. Consistent with the literature, nausea and vomiting was more likely to occur in women (175). Of interest is the inverted U-shaped relationship between age and the adverse events diarrhoea and nausea and vomiting. This implies that younger patients are least likely to have an

adverse event, possibly because they are healthier and/or stronger. However, the oldest age group is also less likely to have an adverse event (in comparison with the middle-age group), indicating that older age may indeed have a protective effect, possibly due to the prescription of less-toxic chemotherapies and to chemotherapies at lower doses. Neither the specific chemotherapy regimen nor the dose intensity of the chemotherapy regimen is known in this cohort, and therefore this issue cannot be investigated further here.

GEEs are a more efficient method of identifying the factors that influence the incidence of treatment for a likely adverse event. By accounting for correlation between observations, all the observations are used and more-accurate results are obtained. This analysis found that although the correlation between observations was generally low, the autoregressive correlation structure was consistently the best fit. This implies that the correlation between observations of the same individual is higher when the observations are closer together in time than those separated by a longer period. The results of these models indicate that as comorbidities increase so do the odds of being treated for a likely adverse event. The same adverse events that demonstrated the inverted U relationship between age and adverse events in the regression using a summary statistic have a significant relationship in this analysis. However, because age was used as a continuous variable, the interpretation is that each additional year of age reduces the odds of having diarrhoea or nausea. Consistent with the clinical expectations of observational research in a heterogeneous cohort, the effects of type of cancer and type of chemotherapy on each adverse event are varied.

The additional resources associated with experiencing treatment for a likely adverse event in the first six months of a new chemotherapy treatment were explored. As is typical for cost data, in this cohort the cost data were heavily right-skewed. Given the large sample size, it was considered possible to continue with a simple linear regression regardless of the skew, and these results identified the saving associated with not having nausea and vomiting as $7,500, for not having anaemia as $4,700 and for not having neutropoenia as $10,600.

When a typical econometric approach is taken, the log-costs are used in the analysis to reduce the skew in the data. Although this analysis results in similar significance of each of the parameters, it is more difficult to interpret the results without using complex retransformation techniques. This makes these results less useful from the decision-maker's perspective.

Finally, the use of GLM with a gamma distribution allows the skewed data to be accounted for while maintaining the interpretability of the results. This analysis produced an intercept (average total cost) of $14,237 in the first six months of a chemotherapy treatment. Nausea and vomiting increases this by 61 per cent ($8,684), anaemia by 33 per cent ($4,698) and neutropoenia by 54 per cent ($7,687). These results are broadly consistent with the results from the simple regression analysis, although the magnitude of the result for neutropoenia is somewhat reduced.

An assessment of the goodness of link of the model showed that there was an artefact in the data at the predicted value of 10.0. An exploratory analysis of interactions within the data found that many of the interactions between anaemia and other adverse events and between nausea and the type of cancer were significant. With the addition of the interaction terms, the magnitude and significance of the main effects remained similar, although the magnitude of the coefficient for nausea and vomiting was further increased. However, the artefact remained in the data, which indicates that this exploratory analysis did not account for it.

The addition of interaction terms did not appear to address the issue of the artefact in the data. Overall, the GLM model with only main effects provides a model that takes account of the skewed data while providing results that can be interpreted easily by decision-makers. Therefore, this is the preferred model for interpretation.

In considering to whom the results of this analysis could be applied, the characteristics of the cohort must be considered. When compared to the general NSW population, the cancer rates and chemotherapies are generally comparable

but the cohort is older and has more comorbidities. This limits the generalisability of the results to older NSW residents receiving chemotherapy for cancer. This population is of specific interest because they are often excluded from clinical trials, and therefore are underrepresented in economic evaluations of chemotherapy.

Limitations of the dataset and analysis

Administrative data has many advantages in terms of efficiency, cost and size, but there are limitations. The sample may be biased due to patient selection or to data-collection procedures. For this specific dataset, the population included is older than the general population in Australia, and this means caution must be taken in generalising the results to the general population. In addition, the available data is limited in that it is only that which is required for the purposes of administration In the case of DVA, the incidence of adverse events is not specifically collected, and therefore a proxy measure based on pharmaceutical and medical services received was required. The data collection methods and linkage technique used are in general of excellent quality, however there is the potential for some missing data or incorrect linkages to be included in the dataset.

The use of the proxy is one of the major limitations of the analysis presented in this chapter. While the methods themselves are suitable for the type of data, there is a strong dependence on the proxy being an accurate measure of adverse event incidence. This assumption will be tested in Chapter 5, where the self-reported incidence of adverse events is compared to the incidence calculated using the proxy.

The final analysis, that of costs associated with adverse events, identifies the first occurrence of a chemotherapy treatment in a specified time period. However, it is not possible to differentiate between those for whom this is the first chemotherapy treatment and those for whom previous chemotherapy regimens have been used. It is not known whether either the experience of adverse events or the management of individuals in subsequent chemotherapy treatments may differ, resulting in bias within the analysis.

Finally, the multiple methods of assessing the additional cost associated with chemotherapy adverse events resulted in similar results, and were a useful demonstration of the different methods for the purpose of this thesis. In general however, multiple assessments of the same outcome should be avoided.

These analyses provide a top-down examination of the incidence of chemotherapy adverse events in older people in a clinical practice setting. They confirm that being of increasing age and having comorbidities increases the probability of experiencing treatment for a likely adverse event. The use of clinical practice data to inform chemotherapy cost-effectiveness analyses is important to ensure that adverse events are not underestimated and that results are informative to decision-makers. Although it is believed that the use of a proxy in all likelihood contributed to this analysis underestimating the incidence of adverse events in this cohort, it remains clear from this research that there are significant additional costs associated with experiencing an adverse event. This research indicates the importance of obtaining accurate estimates of the costs of chemotherapy adverse events from sources other than expert opinion. Given that this dataset does not appear to provide accurate estimates of the incidence of chemotherapy adverse events, this research clearly highlights the need for prospectively collected data on the incidence of chemotherapy adverse events in clinical practice settings. An analysis of this type of data is described in Chapter 5.

4.5.1 **Conclusion**

This chapter investigated the incidence and resources associated with chemotherapy adverse events in a clinical practice setting. An administrative dataset was used, which had the advantages of being large and representative of clinical practice in NSW, although the cohort was older and had more comorbidities than the general population of NSW. It appears that the treatment-based proxy developed to identify those who experienced an adverse event may have underestimated the incidence of chemotherapy adverse events. Despite this, the results suggest that those with multiple comorbidities are more likely to experience an adverse event and that age is also related to adverse events, although the exact relationship is unclear. The results of this analysis using a

treatment-based proxy suggest that it is difficult to obtain accurate estimates of the incidence of adverse events in clinical practice from administrative data. This provides a strong case for the use of prospectively collected data on patients' reported chemotherapy adverse events, and this analysis is reported in Chapter 5.

The additional costs identified in this analysis associated with experiencing treatment for a likely adverse event are significant and consistent with or higher than those reported in the cost-of-illness literature. However, they are likely to be lower than the costs generally used in economic evaluations of chemotherapies, and thus this chapter supports the use of more rigorous estimation methods for these inputs than expert opinion or estimation.

Chapter 5: Incidence and consequences of chemotherapy adverse events in a prospective cohort study

Chapter summary

This chapter explores the incidence, management and costs of chemotherapy adverse events in a second standard-practice cohort: the Elements of Cancer Care study. The models described in Chapter 3 drew from information about best-practice guidelines and clinical trials to estimate the costs associated with adverse events. However, the literature suggests that clinical practice guidelines and clinical trials do not necessarily reflect clinical practice.

The Elements of Cancer Care study, which has collected data from a prospective cohort of individuals with breast, lung or colorectal cancer undergoing chemotherapy, provides data that reflect clinical practice. This chapter explores how information about self-reported adverse events contributes to the understanding of chemotherapy adverse events.

The focus is on using this bottom-up data source in two ways: 1) to build a picture of the experience of adverse events in a standard-practice cohort, including the incidence and management of adverse events, and to compare the incidence in the cohort with that in clinical trials and 2) to use the data to validate the proxy measure of adverse-event incidence that was developed in Chapter 4.

This work produces the first Australian estimates of the incidence of chemotherapy adverse events in a standard-practice setting. Adverse events are common in this cohort, stressing their importance in models of chemotherapy cost-effectiveness. It is also demonstrated that adverse events are more common in clinical practice than are reported in clinical trials. There is little previous work both quantifying and providing a direction for these differences—this work provides information about both.

It is also demonstrated that the proxy developed in Chapter 4, that is, using administrative data to identify individuals who experience a chemotherapy adverse event, is likely to underestimate the incidence of adverse events. The proxy is therefore not recommended for use in estimating the adverse events associated with chemotherapy. This signifies the value of observational data of the experience of adverse events in clinical practice to the accurate modelling of the costs and consequences of chemotherapy for decision-makers.

The work undertaken for this chapter provides the basis for using data for the modelling of chemotherapy cost-effectiveness that is more relevant to the perspective of the decision-maker. In Chapter 6, the effect of using the rates of adverse events from the Elements of Cancer Care cohort rather than from clinical trial data to populate one of the models developed in Chapter 3 is examined. This illustrates the potential for the application of the results of this work.

5.1 Background

The models developed and described in earlier chapters used data on the incidence of adverse events from clinical trials, management of adverse events from clinical practice guidelines, and resource-use and costs from administrative data. However, the literature suggests that the incidence of adverse events in standard practice is different from that in clinical trials. The literature suggests that clinical practice does not always meet best-practice standards and that administrative data is not always reflective of standard clinical practice. If this is the case, it has implications for models of chemotherapy cost-effectiveness and for health-policy decision-makers, because incidence and resource-use (and therefore costs), are not reflective of clinical practice in the real world.

There is often discussion of the adverse events associated with chemotherapy in the clinical trial reports about new treatments, but there is little evidence about the incidence and management of adverse events in the clinical practice setting. The existing observational studies of chemotherapy adverse events have often examined only a specific chemotherapy regimen (272, 273), cancer type and stage (217, 274-276) or adverse event (77, 219, 272). There have been very few

observational studies of how adverse events are experienced in heterogeneous cohorts with different types of cancer and chemotherapy treatments (77), none of them in Australia.

Clinical practice guidelines are designed to improve the quality of care by ensuring the best evidence is used consistently in clinical practice (277). However, despite guidelines being available for many aspects of cancer care, compliance or adherence remains less than optimal (278-284),resulting in variations in practice that can lead to reduced outcomes for patients (280), reduced treatment of patients (283), over-treatment of patients (282) and additional costs to the healthcare system (281). A survey of oncologists suggests some reasons for this non-compliance with cancer treatment guidelines, including a lack of awareness of guidelines, difficulty applying guidelines in practice and difficulty reading or interpreting guidelines (279).

The ISPOR Real-World Data Task Force published a report on the use of real-world data in health policy, particularly for coverage and payment decisions (285). This report provides an excellent summary of the issues associated with data collected outside clinical trials and, of most use to this work, includes discussions of observational study data and administrative data (285). Both these data sources provide better external validity than do clinical trials; however, both data sources suffer from a lack of randomisation to minimise bias in comparisons (285). Observational studies tend to provide more information than do administrative data, although, due to time and cost, there are usually fewer patients in observational studies (although often more than enrolled in a typical clinical trial) (285).

The Elements of Cancer Care study is a prospective cohort study of individuals with breast, lung or colorectal cancer who are undergoing chemotherapy in NSW. The Elements of Cancer Care study provides the opportunity to analyse self-reported adverse-event information, prospectively collected from a cohort of individuals undergoing chemotherapy, to examine the experience of chemotherapy adverse events in a standard-practice setting. By examining the frequency and management of self-reported adverse events in the Elements of

Cancer Care cohort, a more-accurate estimation of the incidence of adverse events in the standard-practice setting can be obtained. In addition, the way in which adverse events are managed in practice, and whether this conforms to best-practice guidelines can be assessed. These more-accurate estimates are important for decision-makers, who are usually considering a decision for the standard-practice setting rather than for a clinical trial environment.

The analysis in Chapter 4 used a proxy measure of the incidence of adverse events and developed models of the factors likely to influence adverse events and the additional costs associated with having an adverse event. However, it is important to test and validate proxy measures and models where possible, because this allows an assessment of the reliability, validity and generalisability of the proxy and the models for use in real-world decision-making. The Elements of Cancer Care data allow for the validation of the proxy developed in Chapter 4, because the same administrative data are available for the Elements of Cancer Care patients, along with their self-reported adverse-event incidence.

5.1.1 Aims and objectives

The aim of this chapter is to investigate the frequency and management of chemotherapy adverse events in a population receiving standard care. Using the Elements of Cancer Care cohort a series of descriptive analyses were undertaken to address the following objectives:

1. Identify the frequency of common adverse events in a sample of people with cancer being treated with chemotherapy in a standard-practice setting.
2. Validate use of adverse-event treatments as a proxy for experiencing adverse events in administrative data, such as that described in Chapter 4.
3. Explore the management of diarrhoea, nausea and vomiting, neutropoenia and anaemia in a standard-practice sample.
4. Compare rates of adverse events in standard practice to that reported in clinical trials.

5.1.2 **Data**

The Elements of Cancer Care study was designed to prospectively track patients undergoing chemotherapy for the treatment of breast, colorectal and lung cancer, and utilises both primary and secondary data (63). It was developed to collect comprehensive data about the full spectrum of care and costs associated with cancer treatment (63). The study recruited patients from 12 cancer treatment centres in NSW, aiming to represent metropolitan and regional settings and the public and private hospital sectors (63).

The primary aims of the Elements of Cancer Care study were to:

1. Identify the individual care elements involved in administering specific chemotherapy treatment protocols (including hospitalisations, emergency department attendances and doctor visits, imaging, procedures, chemotherapy and other supportive medicines) (63).
2. Estimate the resource-use and costs associated with each care element and determine where these costs are borne (Commonwealth and state governments, private healthcare payers and/or patients) (63).

Elements of Cancer Care patient recruitment

Field staff attended medical oncology clinics and reviewed clinic appointment lists to identify patients undergoing chemotherapy for breast, colorectal or lung cancer at each site (63). Once a patient's oncologist confirmed their eligibility for the study, patients were approached when they attended the clinic for an appointment or for chemotherapy (63). The eligibility criteria were that patients be aged over 18 years, be able to comprehend written and spoken English (or have an interpreter available), be able to give informed consent, and not be participating in a clinical trial (63). The exclusion of patients participating in a clinical trial was important as this ensured the cohort was representative of a standard-practice setting.

Patient consent was obtained through a face-to-face interview with study field staff (63). Patients were able to consent to a combination of medical-record review, monthly interviews and data linkage (63). Overall, 83 per cent of patients

consented to full data collection through record review, monthly interviews and data linkage (63).

The study was approved by St Vincent's Hospital Human Research Ethics Committee in December 2007, and site-specific approvals were obtained from each of the participating centres (63).

Elements of Cancer Care data collection

The primary data collection included medical-record reviews undertaken throughout the study until cessation of chemotherapy or study withdrawal (63). Information collected through record reviews included demographics, history of cancer and cancer treatment, current treatment, and health-service use in the previous month (63). In addition, monthly interviews were conducted with patients for six months, unless chemotherapy ceased earlier or the patient withdrew from the study (63). The interviews covered any changes to socioeconomic status, costs incurred for medical bills or travel related to treatment in the previous month, and any adverse events experienced in the previous month (63).

In relation to adverse events, participants were asked if they had experienced chest pain, angina, constipation, diarrhoea, dyspnoea, fatigue (including duration), mucositis, pain (including duration and location: abdomen, back, chest, limbs or other), rash, thrombosis or vomiting (63). The questions were designed to elicit information about whether an adverse event had been experienced, along with the grade at which it was experienced (see Appendix Q for wording of the adverse-event questions) (63). Grading was categorised according to the NCI Common Toxicity Criteria (CTC) version 4 (31).

The NCI CTC is a standardised system for describing and grading the severity of adverse events related to cancer or its treatment (31). The grades range from Grade 1 to Grade 5, with Grade 1 indicating a mild event, and Grade 5 being death related to an adverse event (where appropriate) (31). The questions in the Elements of Cancer Care surveys relating to adverse events were worded in such a way as to elicit the grade of each adverse event according to the NCI CTC. There

is evidence that versions of the NCI CTC that have been adapted for completion by patients result in ratings consistent with those provided by their clinicians (which is how clinical trial adverse event reporting and grading is completed) (286).

A final interview was conducted three months after cessation of treatment to obtain information about additional out-of-pocket costs incurred in the time following cessation of chemotherapy (63).

For secondary data, Medicare Australia provided data for individuals from the PBS and the MBS, and the NSW CHeReL performed a linkage of the following data sources:

- NSW CCR
- NSW APDC
- NSW EDDC
- NSW Registry of Births, Deaths & Marriages (63).

The NSW CCR is a population-based registry that records all new cancer diagnoses and all cancer deaths in NSW. The database captures basic demographic information and cancer details. Degree of spread is collected at diagnosis, but no ongoing collection of information about disease progression is undertaken. This field is therefore not necessarily reflective of current cancer stage. Each unique cancer diagnosis in an individual is recorded as a separate record in the database.

The APDC covers all inpatient admissions to public and private hospitals in NSW, including demographic-related and admission-related data. The EDDC covers all emergency department presentations in NSW. While the APDC includes diagnosis codes that are identified by trained clinical information managers using the Australian ICD coding system, the EDDC has diagnosis codes generated by medical, nursing or clerical personnel at the point of care. Therefore, these may not be consistent between records of an individual who presents to emergency and is then admitted (225).

The NSW Registry of Births Deaths & Marriages is a state government authority with the role of registering NSW life events, including births, deaths, marriages, changes of name and changes of gender. These data are then used to establish a range of legal entitlement, and is provided to the Australian Institute of Health and Welfare and the Australian Bureau of Statistics for planning and research purposes (287).

A pilot study was undertaken in 2008, with the main study recruitment commencing in January 2009 and completed in October 2010 (63). The main study comprised two patient cohorts based on time of recruitment: 2009 and 2010 (63). For this analysis, the cohorts were combined, and only variables that were common between the two cohorts were used.

In addition, for patients who attended hospitals in the South Eastern Sydney and Illawarra Area Health Service (SESIAHS), a network of hospitals and health services in the east and south of Sydney operated by the NSW Department of Health, and responsible for public health services within the defined area, the results of all blood chemistry and haematology tests undertaken during the Elements of Cancer Care data-collection period were collected.

5.2 Analysis

An analysis data set was created from the 2009 adverse events data and the 2010 adverse events data, using those variables that were in common between the two cohorts. Table 5.1 describes the adverse-event variables included in the analysis dataset.

Table 5.1: Adverse-event variables in the Elements of Cancer Care analysis

Variable name	Variable type	Variable description
Survey number	Character e.g. ABH10	Unique patient identifier
Recruitment date	Date	Date of first interview or record review
Form 1 – Form 8	Text	The type of form that was completed at each time point; options include patient follow-up, completed treatment and record review
Follow-up date 1 to follow-up date 8	Date	Date of follow-up at each time point
Chest 1–10	Numeric (1–4)	Grade of chest pain at each time point
Constipation 1–8	Numeric (1–4)	Grade of constipation at each time point
Diarrhoea 1–8	Numeric (1–4)	Grade of diarrhoea at each time point
Dyspnoea 1– 8	Numeric (1–4)	Grade of dyspnoea at each time point
Fatigue 1–8	Numeric (1–4)	Grade of fatigue at each time point
Mucositis 1–8	Numeric (1–4)	Grade of mucositis at each time point
Pain 1–8	Numeric (1–4)	Grade of pain at each time point
Rash 1–8	Numeric (1–4)	Grade of rash at each time point
Vomiting 1–8	Numeric (1–4)	Grade of vomiting at each time point
Any chest	Binary (0 = *no*, 1 = *yes*)	Was any chest pain experienced during study?
Any constipation	Binary (0 = *no*, 1 = *yes*)	Was any constipation experienced during study?
Any diarrhoea	Binary (0 = *no*, 1 = *yes*)	Was any diarrhoea experienced during study?
Any dyspnoea	Binary (0 = *no*, 1 = *yes*)	Was any dyspnoea experienced during study?
Any fatigue	Binary (0 = *no*, 1 = *yes*)	Was any fatigue experienced during study?
Any mucositis	Binary (0 = *no*, 1 = *yes*)	Was any mucositis experienced during study?
Any pain	Binary (0 = *no*, 1 = *yes*)	Was any pain experienced during study?
Any rash	Binary (0 = *no*, 1 = *yes*)	Was any rash experienced during study?
Any vomiting	Binary (0 = *no*, 1 = *yes*)	Was any vomiting experienced during study?
Max. chest	Numeric (0–4)	Worst grade of chest pain reported during study
Max. constipation	Numeric (0–4)	Worst grade of constipation reported during study
Max. diarrhoea	Numeric (0–4)	Worst grade of diarrhoea reported during study
Max. dyspnoea	Numeric (0–4)	Worst grade of dyspnoea reported during study
Max. fatigue	Numeric (0–4)	Worst grade of fatigue reported during study
Max. mucositis	Numeric (0–4)	Worst grade of mucositis reported during study
Max. pain	Numeric (0–4)	Worst grade of pain reported during study
Max. rash	Numeric (0–4)	Worst grade of rash reported during study
Max. vomiting	Numeric (0–4)	Worst grade of vomiting reported during study

As only those variables that the two cohorts had in common were used for the analysis, follow-up time points 9 and 10 were excluded because these were only available for the 2010 cohort.

The new variable for 'any AE' (any adverse event) was calculated for each adverse event based on an individual having experienced that adverse event at any grade at any time point during follow-up. The new variable for 'max. AE' (maximum AE) was calculated for each adverse event based on the highest (worst) grade of each adverse event the individual experienced at any time point during follow-up.

Although participants were asked whether they experienced thrombosis during follow-up interviews, this was not collected in a way that was compatible with the CTCAE criteria, and therefore could not be coded in grades. These data were therefore excluded from the analysis.

SAS 9.3 was used for all data analysis. Despite extensive data cleaning processes undertaken for the study dataset in general, some additional data cleaning was required specifically for this analysis. A number of errors were identified in data entry for grade of chest pain, with two grades entered simultaneously for the same patient at the same time point. It was clarified that this was a data entry error, and there were very few occurrences; these two observations were excluded from the analysis of chest pain.

5.2.1 Demographics and clinical characteristics

There were 482 individuals in the Elements of Cancer Care study. The general demographic variables of the cohort were examined to assess the suitability of the variable for inclusion in the regression analyses. Based on an assessment of data spread, average, skew and missing values all variables were assessed suitable for analysis.

In general, the demographic and clinical characteristics of the cohort are similar to those seen in a NSW population of individuals with cancer. The sample comprised more women than men due to the high number of people with breast cancer in the cohort (Table 5.2). Consistent with people who have cancer, the

majority of participants were aged more than 50 years. Most participants were from Australia; however, a number of patients were from the UK or New Zealand, and there was a wide variety of other countries of origin identified. The countries were consolidated into regions using the United Nations Statistics Division classifications (288). The sample is well educated, with two-thirds having completed higher education.

More than 50 per cent of the sample had breast cancer; only 13 per cent of enrolled participants had lung cancer. More than half of the participants had cancer which had spread (metastasised) beyond the original tumour (*advanced cancer*).

Table 5.2: Demographic and clinical characteristics of the Elements of Cancer Care cohort

Characteristic	Frequency	%
Gender		
Female	356	73.86
Male	126	26.14
Age group (years)		
< 30	2	0.41
30–39	20	4.15
40–49	88	18.26
50–59	124	25.73
60–69	169	35.06
70–79	64	13.28
> 79	15	3.11
Country classification		
Oceania	285	73.64
Europe	72	18.60
North America	5	1.29
South America	3	0.78
Asia	16	4.13
Africa	6	1.55
Higher education		
Yes	255	66.93
No	126	33.07
Site of cancer		
Breast	261	54.15
Colorectal	157	32.57
NSCLC	64	13.28
Stage of cancer		
Stage I	8	1.66
Stage IA	3	0.62
Stage IB	10	2.07
Stage IC	9	1.87
Stage II	27	5.6
Stage IIA	31	6.43
Stage IIB	32	6.64
Stage III	46	9.54
Stage IIIA	32	6.64
Stage IIIB	27	5.6
Stage IIIC	8	1.66
Stage IV	249	51.66

5.3 Frequency of common adverse events

The aim of this analysis was to identify the frequency of common adverse events in a sample of people with cancer being treated with chemotherapy in a standard-practice setting.

5.3.1 Methods

Overall frequency was determined by the number of patients in the analysis population who recorded a *Yes* for the selected adverse event at any grade at least once during their period of follow-up.

Frequency by grade was determined by identifying the worst grade of each event each individual experienced, and then calculating the number of patients in the cohort who recorded a *yes* for each grade level as the highest grade experienced (*worst AE*) for each adverse event. This is consistent with the way that adverse events are often published in the clinical trial literature, where adverse events are often reported at overall frequency and then 'serious adverse events' are those reported at Grade III/IV. The same analysis of *ever AE* and *worst AE* was conducted for haematological adverse events using blood-test-result data for patients from the SESIAHS.

The cumulative incidence of adverse events was graphed to depict the incidence pattern of each adverse event over time.

5.3.2 Results

Eighty-six per cent of participants reported at least one adverse event during the study period. The highest grade of adverse event experienced during the study period was spread between less-serious events (Grade I or II) and serious events (Grade III or IV) as shown in Table 5.3. More than one-quarter of individuals reported having had a very serious (Grade IV) adverse event.

Table 5.3: Highest grade of adverse event experienced during Elements of Cancer Care study period

Max. grade of adverse event	Frequency	%
0	64	14.13
I	30	6.62
II	78	17.22
III	159	35.1
IV	122	26.93

Note: max. = maximum

The incidence of each adverse event at any time during the data-collection period is shown in Table 5.4. With the exception of chest pain, the incidence rates for all adverse events examined were more than 70 per cent, with fatigue being the most common at 85 per cent. The rates of any anaemia and any neutropoenia were calculated using the haematology and biochemistry results for those patients seen at the SESIAHS.

Table 5.4: Self-reported adverse events—any adverse event during the Elements of Cancer Care study period

Adverse event	Frequency	%
Chest pain	54	12
Constipation	333	74
Diarrhoea	335	74
Dyspnoea	321	71
Fatigue	384	85
Mucositis	321	71
Pain	339	75
Rash	320	71
Vomiting	284	63
Anaemia*	92	75
Neutropoenia*	20	16

* Calculated using haematology and biochemistry results for patients seen at SESIAHS

The worst grade of each adverse event experienced by each individual over the course of the study was calculated, and the frequencies are shown in Table 5.5. In most cases, the less-serious events (Grade I or Grade II) are the most frequent, with relatively few instances of more-serious adverse events reported. The exceptions to this are dyspnoea, fatigue and pain for which Grade III or IV events are more common.

The worst grade of anaemia and the worst grade of neutropoenia were calculated using the haematology and biochemistry results, and are shown in Table 5.6. The NCI CTCAE criteria for grading neutropoenia uses the laboratory result for ANC to diagnose neutropoenia as either present or absent. When present and in the presence of fever, it is considered to be Grade III febrile neutropoenia. The Elements of Cancer Care study did not record whether fever was present at the time of the blood test. For the purpose of this analysis, it is assumed that every case of neutropoenia is a case of febrile neutropoenia; however, this may be an overestimate of the presence of febrile neutropoenia.

Table 5.5: Self-reported adverse events—worst grade reported during Elements of Cancer Care study period

	Grade 0		Grade I		Grade II		Grade III		Grade IV	
Adverse event	**Freq.**	**%**	**Freq.**	**%**	**Freq.**	**%**	**Freq.**	**%**	**Freq.**	**%**
Chest pain	399	88	34	8	16	4	4	1	0	0
Constipation	120	26	179	40	112	25	31	7	11	3
Diarrhoea	118	26	210	46	99	22	21	5	5	1
Dyspnoea	132	29	179	40	60	13	49	11	33	7
Fatigue	69	15	52	11	95	21	165	36	72	16
Mucositis	132	29	184	40	92	20	41	9	4	1
Pain	114	25	158	35	66	45	82	18	33	7
Rash	133	29	199	44	72	16	44	10	5	1
Vomiting	169	37	226	50	34	8	20	4	4	1

Note: Freq. = frequency

Table 5.6: Haematological adverse events—worst grade during Elements of Cancer Care study period

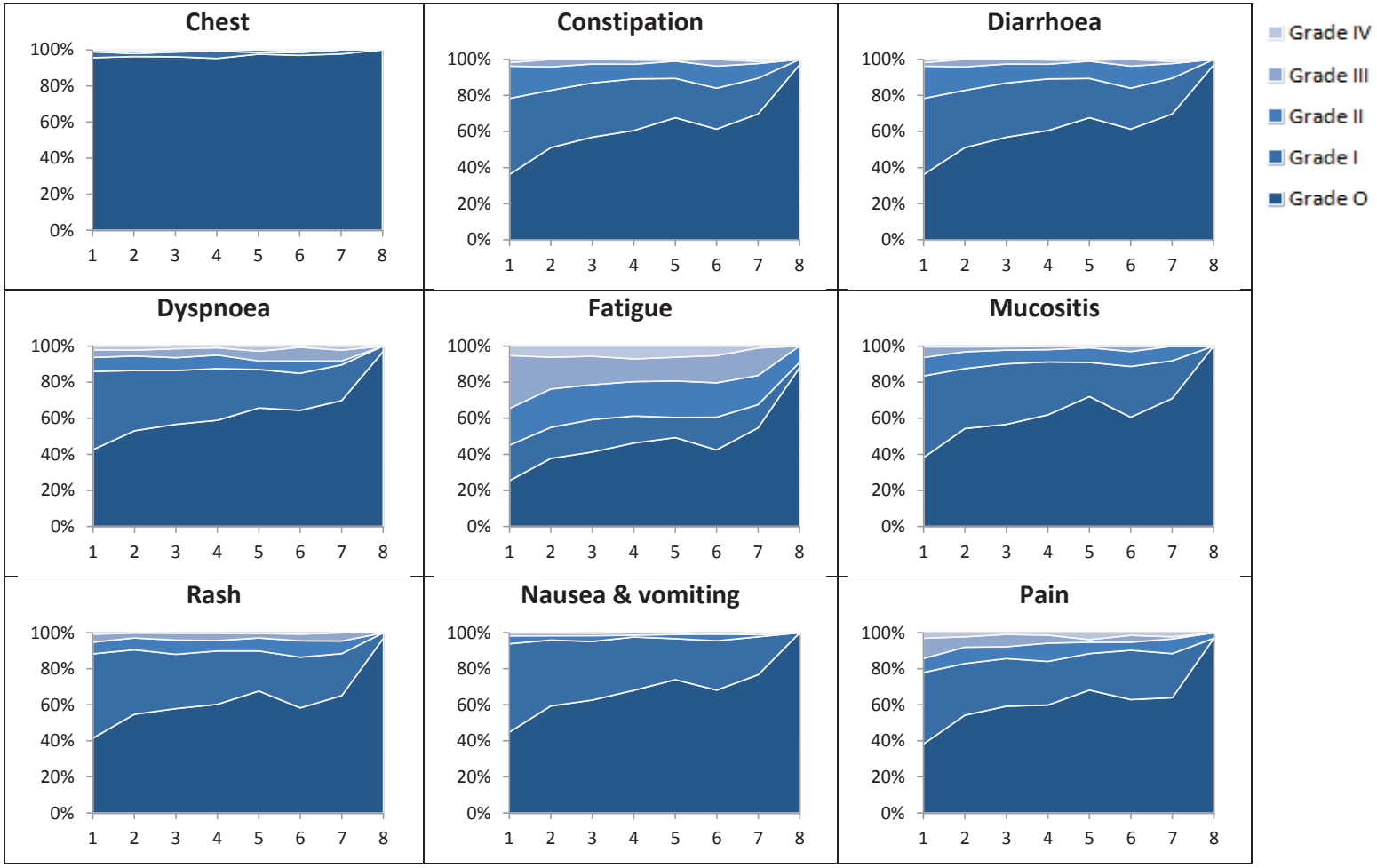
	Grade 0		Grade I		Grade II		Grade III		Grade IV	
Adverse event	**Freq.**	**%**	**Freq.**	**%**	**Freq.**	**%**	**Freq.**	**%**	**Freq.**	**%**
Anaemia	29	24	50	41	34	28	8	7	0	0
Neutropoenia	100	83	N/A	N/A	N/A	N/A	20	17	N/A	N/A

Note: Freq = frequency; N/A = not applicable

To obtain an estimate of the cumulative frequency of adverse events during the study period, a cumulative frequency graph was generated for each adverse event (see Figure 5.1). Each graph shows the percentage of individuals at each time point (monthly follow-up) that had the specific adverse event at each grade level. Individuals who ceased chemotherapy were excluded from the following months' calculations.

For each of the adverse events, the proportion of people experiencing no adverse event increased as time progressed. This may indicate that individuals with adverse events tend to have them early in the treatment regime and that the adverse event is managed with prevention or dose modifications for future doses. However, a proportion of individuals experienced adverse events in the first month, in some cases serious events (Grade III or IV). This proportion dropped in the second observation period (month two), but then remained relatively steady for the next four to five months of treatment.

Figure 5.1: Cumulative frequency of self-reported adverse events during Elements of Cancer Care study period



5.3.3 **Discussion**

Although the incidence of adverse events associated with chemotherapy is often reported in clinical trials of new treatments, there are few examinations of chemotherapy adverse events in a community or standard-practice setting. A large survey by Henry et al. of individuals currently undergoing chemotherapy or radiotherapy treatment for cancer was conducted in the US, and questions about adverse events from treatment were asked, but the time frame for these adverse events is not clear (77). Similar to the estimate in this cohort (86 per cent), the survey by Henry et al. found that 88 per cent of the 814 respondents reported at least one adverse event of their cancer treatment (87).

The incidence of specific self-reported adverse events in this standard-practice cohort appears higher than the incidence reported in the survey by Henry et al. (see Table 5.7). This higher rate of reported adverse events may be due to the nature of the questions in the Elements of Cancer Care survey. In requesting that the specific grade of an adverse event be selected, individuals were given examples of each adverse event, including at less-severe levels. This may have encouraged individuals to report less-severe events that they may otherwise have excluded from their reporting.

Although there is little available literature for comparison, the proportion of severe adverse events is also higher than would perhaps be expected. This too may be a function of the nature of the questions used to elicit the grade of the event from an individual, and it is possible that the wording (which has not been specifically validated) encouraged individuals to select higher grades for events than a medical professional may have.

Table 5.7: Comparison of incidence of adverse events in Elements of Cancer Care study with Henry et al. 2008 (87)

Adverse event	Henry et al. (77) %	Elements of Cancer Care %
Chest pain	–	12
Constipation	42	74
Diarrhoea	45	74
Dyspnoea	–	71
Fatigue	80	85
Mucositis	28	71
Pain	48	75
Rash	–	71
Vomiting	48	63
Anaemia	37	75
Neutropoenia	–	16

The cumulative frequency of each adverse event shows a similar pattern. A large proportion of individuals reported having an adverse event in the first month. There was a 10–20 per cent reduction in the number of people reporting an adverse event in the second month. The incidence then levelled until after the fifth or six month when adverse events became less common. The numbers of individuals participating in these last months are much smaller than in the initial months, and so care should be taken with interpretation of these figures.

There is no comparative literature available that examines the cumulative incidence of adverse events over time during chemotherapy treatment in a standard-practice setting. This pattern may demonstrate that a number of individuals who experience an adverse event on commencing chemotherapy are treated (with preventative strategies or a change to the chemotherapy treatment) to avoid re-occurrence of the adverse event. However, for many patients, there are ongoing adverse events during chemotherapy, and for a small proportion of these, the events are serious.

5.4 Validate use of an adverse-event treatment proxy

The second aim of this analysis was to determine whether the proxy for receiving treatment for a likely adverse event, which was developed in Chapter 4, was suitable for identifying individuals who have experienced an adverse event. The proxy was based on identifying from administrative records whether an individual had either received a prescription for a pharmaceutical product or had a medical service that may be used to treat an adverse event, in the three days after a dose of chemotherapy.

5.4.1 Methods

The analysis of the DVA data described in Chapter 4 identified specific treatments for adverse events of chemotherapy from the PBS and MBS data. The presence of one or more of these treatments within three days of a dose of chemotherapy was considered a proxy for the patient having experienced an adverse event. For example, if a patient received an anti-diarrhoeal medicine on the day following chemotherapy, they were considered to have been treated for chemotherapy-induced diarrhoea. It was recognised that the use of treatments as a proxy for incidence would likely result in underestimates of treatment frequency, because many cases of adverse events may not be treated or may be treated in ways not captured by the MBS or PBS.

The Elements of Cancer Care data includes the same administrative information available with the DVA data to create the proxy for having been treated for a likely adverse event (see Chapter 4 for details). In addition to this, the Elements of Cancer Care study collected self-reported data on whether an individual experienced an adverse event related to chemotherapy during the previous month. This allows a comparison of the proxy identified rates of adverse events with self-reported adverse event rates in the same cohort.

The comparison was done using a 2x2 contingency table, and the significance of any difference was calculated using the odds ratio and a chi-square statistic.

The odds ratio is calculated by dividing the probability of the event occurring by the probability of the event not occurring. In this case, it is the probability of the

proxy identifying an adverse event, when the individual self-reported having had the adverse event, divided by the probability of the proxy identifying an adverse event despite the individual not reporting experiencing the event.

5.4.2 Results

The incidence of each of the four adverse events examined in the DVA data was identified in the Elements of Cancer Care data using the proxy method based on treatments for adverse events. These results are presented by dose and by person in Table 5.8. With the exception of nausea and vomiting, the rates of adverse events are relatively low, both by dose of chemotherapy, and by individual. These rates are similar to those obtained using the proxy method in the DVA dataset, with the exception of nausea and vomiting, which is far more common in the Elements of Cancer Care data, both per dose and per person, and neutropoenia per person, which is also more common in the Elements of Cancer Care data.

Table 5.8: Incidence of adverse events by dose identified using proxy in the Elements of Cancer Care dataset and the DVA dataset

	By dose				By person			
	Elements of Cancer Care		DVA		Elements of Cancer Care		DVA	
Adverse event	Freq.	%	Freq.	%	Freq.	%	Freq.	%
Nausea and vomiting	3261	26	879	1	390	46	396	5
Diarrhoea	99	< 1	638	< 1	41	8	330	4
Anaemia	42	< 1	5415	6	24	5	1535	17
Neutropoenia	273	2	601	< 1	73	14	242	3

Note: Freq. = frequency

The four contingency tables (Table 5.9, Table 5.10, Table 5.15 and Table 5.12) show that the odds of individual self-reporting diarrhoea are twice that when the proxy identifies treatment for diarrhoea. The odds of an individual self-reporting nausea and vomiting are 26 per cent higher when the proxy also identifies treatment for nausea and vomiting. The odds of an individual being identified through blood test results as having anaemia are more than doubled when the proxy also identifies treatment for anaemia. In contrast, the opposite is seen in neutropoenia, where the odds of an individual being identified in blood test results

as having neutropoenia are 60 per cent less when the proxy identifies treatment for neutropoenia.

Table 5.9: Self-reported diarrhoea compared with proxy-diarrhoea

Self-reported adverse events compared with proxy-identified diarrhoea			
Proxy-identified diarrhoea	**Self-reported diarrhoea**		
	No	**Yes**	**Total**
No	12,268	1,473	13,741
Yes	79	20	99
Total	12,347	1,493	13,840

Note: Odds ratio (95 per cent CI): 2.11 (1.29, 3.45)

Table 5.10: Self-reported nausea and vomiting compared with proxy- nausea and vomiting

Self-reported N&V compared with proxy-identified N&V			
Proxy-identified N&V	**Self-reported N&V**		
	No	**Yes**	**Total**
No	8,520	850	9,370
Yes	2,912	365	3,277
Total	11,432	1,215	12,647

Notes: Odds ratio (95 per cent CI): 1.26 (1.10, 1.13); N&V = nausea and vomiting

Table 5.11: Blood-test-identified anaemia compared with proxy-anaemia

Blood-test-identified anaemia compared with proxy-identified anaemia			
Proxy-identified anaemia	**Blood-test-identified anaemia**		
	No	**Yes**	**Total**
No	14,107	3,387	17,494
Yes	38	20	58
Total	14,145	3,407	17,552

Odds ratio (95 per cent CI): 2.12 (1.27, 3.77)

Table 5.12: Blood-test-identified neutropoenia compared with proxy-neutropoenia

Blood-test-identified neutropoenia compared with proxy-identified neutropoenia			
Proxy-identified neutropoenia	**Blood–test-identified neutropoenia**		
	No	**Yes**	**Total**
No	16,825	205	17,030
Yes	272	1	273
Total	17,097	206	17,303

Odds ratio (95 per cent CI): 0.30 (0.04, 2.16)

To assess whether there was a pattern in the severity of events that the proxy correctly identified, the grade of self-reported adverse event was compared with the proxy-identified adverse-event rates. From the results (Table 5.13, Table 5.14, Table 5.15, Table 5.16) there does not appear to be a pattern in the grade of adverse events that the proxy is more likely to identify.

Table 5.13: Self-reported diarrhoea by grade compared with proxy-identified diarrhoea

Self-reported diarrhoea compared with proxy-identified diarrhoea						
Proxy-identified diarrhoea	**Grade of self-reported diarrhoea**					
	0	**I**	**II**	**III**	**IV**	**Total**
No	12,268	1,118	306	43	6	13,741
Yes	79	3	17	0	0	99
Total	12,347	1,121	323	43	6	13,840

Table 5.14: Self-reported nausea and vomiting by grade compared with proxy-identified nausea and vomiting

Self-reported N&V compared with proxy-identified N&V						
Proxy-identified N&V	**Grade of self-reported N&V**					
	0	**I**	**II**	**III**	**IV**	**Total**
No	8,520	742	81	26	1	9,370
Yes	2912	329	24	11	1	3,277
Total	11,432	1,071	105	37	2	12,647

Note: N&V = nausea and vomiting

Table 5.15: Blood-test-identified anaemia by grade compared with proxy-identified anaemia

Blood–test-identified anaemia compared with proxy-identified anaemia					
Proxy-identified anaemia	**Grade of blood-test-identified anaemia**				
	0	**I**	**II**	**III**	**Total**
No	1,568	2,534	790	63	4,955
Yes	1	4	16	0	21
Total	1,569	2,538	806	63	4,976
Frequency missing = 12576					

Table 5.16: Blood–test-identified neutropoenia by grade compared with proxy-identified neutropoenia

Blood-test-identified neutropoenia compared with proxy-identified neutropoenia			
Proxy-identified neutropoenia	**Grade of blood-test-identified anaemia**		
	0	**III**	**Total**
No	4,493	205	4,698
Yes	1	1	2
Total	4,494	206	4,700
Frequency missing = 12603			

Finally, the grade of self-reported adverse event was compared to the treatments identified by the proxy in the administrative datasets to see if the proxy was more likely to pick up any particular pattern in treatments (Table 5.17, Table 5.18, Table 5.19 and Table 5.20). Again, there does not appear to be a pattern in the grade of adverse events that the proxy was more likely to identify based on the treatment received.

Table 5.17: Proxy-identified diarrhoea treatments compared with self-reported diarrhoea by grade

Proxy-identified treatments by self-reported diarrhoea grade						
Proxy-identified treatment	**Self-reported grade of diarrhoea**					
	0	**I**	**II**	**III**	**IV**	**Total**
Hospitalisation	22	0	0	0	0	22
Loperamide	49	3	17	0	0	69
No treatment	12,246	1,118	306	43	6	13,719
Other anti-diarrhoeals	30	0	0	0	0	30
Total	12,347	1,121	323	43	6	13,840

Table 5.18: Proxy-identified nausea and vomiting treatments compared with self-reported nausea and vomiting by grade

Proxy-identified treatments by self-reported nausea and vomiting grade						
Proxy-identified treatment	**Self-reported grade of nausea and vomiting**					
	0	**I**	**II**	**III**	**IV**	**Total**
A04AD	147	12	0	1	0	160
HT3	2,530	287	21	10	1	2,849
Hospitalisation	39	1	0	0	0	40
No treatment	8481	741	81	26	1	9,330
Other antiemetics	235	30	3	0	0	268
Total	1,1432	1,071	105	37	2	12,647

Note: A04AD = 'Other antiemetics' class of drug, HT3 = HT3-receptor antagonist

Table 5.19: Proxy-identified anaemia treatments compared with laboratory-test-identified anaemia by grade

Proxy-identified treatments by laboratory–test-identified grade of anaemia					
Proxy- identified treatment	**Laboratory-test-identified grade of anaemia**				
	0	**I**	**II**	**III**	**Total**
Iron	0	0	0	0	0
No treatment	1,568	2,534	790	63	4,955
Transfusion	1	4	16	0	21
Total	1,569	2,538	806	63	4,976
Frequency missing = 12576					

Table 5.20: Proxy-identified neutropoenia treatments compared with laboratory-test-identified neutropoenia by grade

Proxy-identified treatments by Laboratory-test-identified grade of neutropoenia			
Proxy-identified treatment	**Laboratory-test-identified grade of neutropoenia**		
	0	**III**	**Total**
Antibiotics	0	1	1
G-CSF	1	0	1
Hospitalisation	8	10	18
No treatment	4,485	195	4,680
Total	4,494	206	4,700
Frequency missing = 12603			

Note: G-CSF = Granulocyte colony-stimulating factor

5.4.3 Discussion

This analysis identified that the odds of the proxy identifying someone as being treated for a likely adverse event was lower than the odds of someone self-reporting an adverse event. Overall, there was poor congruence between the two measures. Given that there was little pattern between the proxy and the severity of the event or the treatment for the event, it would appear that this proxy measure developed using administrative data is not suitable for identifying individuals who have had an adverse event related to chemotherapy.

The proxy appears to underestimate the number of individuals who experience an event. This implies that patients are reporting adverse events which are not identified through the proxy measures used. There could be a number of reasons

for this. It may be that individuals are experiencing adverse events but that these are not being treated. There is evidence that a number of adverse events routinely go untreated; with a US survey of individuals in the community receiving chemotherapy or radiotherapy finding approximately half of the individuals who reported an adverse event received no treatment for it (77). This may be because for many adverse events, such as fatigue or anxiety, there are few treatments available other than reductions in chemotherapy doses.

It may also be that individuals are being treated for the adverse event, but the treatment is not being captured by the proxy measure. This would be the case if people were being treated with pharmaceutical products or medical services not considered to be either best practice or common practice in Australia, because these were the basis of the proxy method. Similarly, if individuals are obtaining treatments in a way that is not captured by the administrative datasets, these will not be captured. Examples may be over-the-counter medications, or medications dispensed while the patient is an inpatient.

In addition, it is possible that individuals are receiving a prescription for adverse-event treatments, such as anti-diarrhoeals or anti-nausea treatments at the commencement of chemotherapy. This prescription may provide enough treatment for multiple cycles of chemotherapy, even when the adverse event is experienced each time. In this case, the treatment would be captured only once—when the prescription is filled at the commencement of treatment—and, although the individual continues to use the dispensed medication after each dose of chemotherapy, it is not identified by the proxy. This would fit the pattern that is seen with the cumulative incidence of adverse events, with individuals filling a script at the beginning of chemotherapy and then using the dispensed medications throughout the chemotherapy regimen.

Finally, it may be that there are errors in the selection of treatments for inclusion in the proxy measure. For example, if incorrect item numbers have been selected, or the three-day rule is not appropriate, these would potentially reduce the ability of the proxy to identify relevant treatments for likely adverse events.

Given these potential issues with the use of the proxy to identify individuals who have been treated for a likely adverse event, it is not recommended that administrative data be used to identify the incidence of chemotherapy adverse events in a clinical practice sample.

5.5 Explore the management of adverse events

The fourth aim of this analysis was to examine the use of various guidelines' recommended treatments for chemotherapy-related adverse events. Evidence suggests that guidelines for best practice are not always followed in the standard-practice setting (278-284). The specific management strategies for adverse events for which there was sufficient evidence of utilisation included:

- the use of antiemetics in individuals who reported vomiting
- the use of anti-diarrhoeals in individuals who reported having diarrhoea
- the use of blood transfusions in individuals who have anaemia
- the use of ESAs in individuals who have anaemia.

5.5.1 Methods

For people who reported diarrhoea or vomiting, the use of anti-diarrhoeals (for diarrhoea) or antiemetics (for vomiting) within the month of the self-reported adverse event were identified, along with presentations to emergency departments or admissions to hospital for a diarrhoea- or vomiting-related diagnosis.

The management of diarrhoea was examined by identifying the recommended treatments from clinical practice guidelines. Loperamide and octreotide are recommended internationally, although octreotide is not approved in Australia for chemotherapy-related diarrhoea. Therefore, the PBS data were used to identify the prescription of loperamide, octreotide and drugs in the 'anti-diarrhoeals' ATC class (excluding loperamide) within the month after an individual reported experiencing diarrhoea.

Preventative management of nausea and vomiting is strongly recommended in clinical practice guidelines. The use of 5-HT3RA, neurokinin-1 receptor antagonists and corticosteroids are best-practice pharmaceutical management for

the prevention of chemotherapy-induced nausea and vomiting. The PBS data was used to identify the prescription of any of these drugs within the month after an individual reported experiencing nausea and vomiting.

The haematological adverse events identified through the blood-test results are the actual rates of those adverse events, rather than the self-reported adverse events. For individuals who were identified in the blood-test data as having experienced anaemia or neutropoenia, the use of best-practice treatments including blood transfusions, ESAs and G-CSFs at the time of the blood-test result were identified. Clinical practice guidelines provide guidance on the grade of event at which these treatments should be implemented, and this was assessed using cross-tabulation contingency tables.

5.5.2 Results

The frequency of each diarrhoea treatment in the PBS dataset is shown in Table 5.21. Although loperamide and other anti-diarrhoeals are present, it can be seen that octreotide is not used. Octreotide is recommended by a number of international guidelines for the management of chemotherapy-induced diarrhoea but is not approved or used in standard practice for outpatients in Australia. If it were used in Australia, octreotide would be for patients whose diarrhoea was serious enough to warrant hospital admission, and its use would therefore not be captured in this data.

Table 5.21: Proxy-identified diarrhoea treatments compared with self-reported diarrhoea by grade

Proxy-identified treatments by self-reported diarrhoea grade						
Proxy-identified treatment	**Self-reported grade of diarrhoea**					
	0	**I**	**II**	**III**	**IV**	**Total**
Hospitalisation	22	0	0	0	0	22
Loperamide	49	3	17	0	0	69
No treatment	12,246	1,118	306	43	6	13,719
Other anti-diarrhoeals	30	0	0	0	0	30
Total	12,347	1,121	323	43	6	13,840

The prevention of nausea and vomiting is strongly recommended in clinical practice guidelines. This may explain the high number of individuals who have received treatment for nausea and vomiting, despite having reported not experiencing this event, as shown in Table 5.22.

Table 5.22: Proxy-identified nausea and vomiting treatments compared with self-reported nausea and vomiting by grade

Proxy-identified treatments by self-reported nausea and vomiting grade						
Proxy-identified treatment	**Self-reported grade of nausea and vomiting**					
	0	**I**	**II**	**III**	**IV**	**Total**
NK1 receptor antagonists	147	12	0	1	0	160
5-HT3RA	2,530	287	21	10	1	2849
Hospitalisation	39	1	0	0	0	40
No treatment	8,481	741	81	26	1	9330
Other antiemetics	235	30	3	0	0	268
Total	11,432	1,071	105	37	2	12,647

Note: 5-HT3RA = 5-HT3 receptor antagonist

The haematological adverse events are actual rates rather than self-reported rates. This means that the patients themselves may not be aware of having an adverse event, particularly with less-serious events of anaemia or neutropoenia. The low numbers of individuals receiving iron and transfusions (Table 5.23) are surprising, and require further investigation.

Table 5.23: Proxy-identified anaemia treatments compared with blood-test-identified anaemia by grade

Proxy-identified treatments by blood-test-identified grade of anaemia					
Proxy-identified treatment	**Blood-test-identified grade of anaemia**				
	0	**I**	**II**	**III**	**Total**
Iron	0	0	0	0	0
No treatment	1,568	2,534	790	63	4,955
Transfusion	1	4	16	0	21
Total	1,569	2,538	806	63	4,976
Frequency missing = 12576					

Febrile neutropoenia can only be graded as Grade III or higher. It is defined by an ANC < 1000/mm3 and the presence of a fever. It was not possible to identify whether an individual experienced a fever; therefore, it is feasible that a proportion of those individuals identified as having an ANC < 1000/mm3 did not experience a fever and therefore did not require treatment. The results for neutropoenia are shown in Table 5.24.

Table 5.24: Proxy-identified neutropoenia treatments compared with blood-test-identified neutropoenia by grade

Proxy-identified treatments by blood-test-identified grade of neutropoenia			
Proxy-identified treatment	**Blood-test-identified grade of neutropoenia**		
	0	**III**	**Total**
Antibiotics	0	1	1
G-CSF	1	0	1
Hospitalisation	8	10	18
No treatment	4,485	195	4,680
Total	4,494	206	4,700
Frequency missing = 12603			

Note: G-CSF = Granulocyte colony-stimulating factor

5.5.3 Discussion

This analysis has attempted to illustrate how the adverse events of chemotherapy are managed in a clinical practice setting. For each event, the analysis has highlighted the number of people who reported having experienced an adverse event, but who appeared to have received no treatment for it, according to the administrative data. Although this appears to demonstrate that the management of adverse events in clinical practice does not follow best-practice guidelines, the generally poor performance of the proxy has made it difficult to ascertain whether individuals were not being treated or whether the administrative data were unable to identify the treatments being received.

5.6 Compare rates of adverse events in standard practice to clinical trials

Most cost-effectiveness analyses of chemotherapy are designed to compare specific chemotherapy regimens. However, the preceding analyses report the rates

of adverse events in a heterogeneous cohort of patients receiving chemotherapy for cancer. By identifying the chemotherapy treatments that were most common in the Elements of Cancer Care data, the rates of adverse events in a standard-practice setting could be compared with those reported in clinical trials.

5.6.1 Methods

The frequency of each chemotherapy regimen was calculated for each type and grade of cancer. Chemotherapy regimens that could be associated with a cancer and a specific stage of disease and had sufficient numbers (n >25) for meaningful analyses were selected. The evi-Q website was searched to identify the pivotal clinical trials which guide the use of these chemotherapy treatments. The peer-reviewed publication(s) reporting these trials were obtained. The incidence of adverse events at each grade level were extracted from the clinical trial reports for the analysis. Additional documentation of adverse events was sourced where available or necessary.

5.6.2 Results

The most common treatment regimen in the Elements of Cancer Care cohort was single-agent trastuzumab for metastatic breast cancer, which was administered to 35 women. This can be delivered in weekly or three-weekly doses (39), and these two regimens were combined for this analysis. No other regimens were seen frequently enough in the Elements of Cancer Care cohort to provide a large enough sample for this type of analysis.

The eviQ website lists the rate of adverse events in the three-weekly regimen from a Phase II clinical trial of efficacy, safety and pharmacokinetics of trastuzumab monotherapy (289). However, this trial publication does not break down adverse-event incidence by grade and is therefore not suitable for use in this analysis. For the once-weekly regimen, the rate of adverse events in a multinational single arm study of trastuzumab (290) was presented on the eviQ website. This is the same study used in the Australian Public Assessment Report for trastuzumab published by the TGA in February 2011. The Roche Product Information Sheet provides a summary of adverse reactions recorded during all pivotal trials of trastuzumab (at different dose levels and for different disease types). However, specific rates are

not presented, making it unsuitable for this analysis. Therefore, the Cobleigh et al. paper (290) was used for comparison in this analysis. Table 5.25 shows a comparison between rates of any adverse event and rates of severe adverse events reported by Cobleigh et al. (290) and identified in the Elements of Cancer Care data. For every adverse event that is in both studies, the rate in the Elements of Cancer Care data is higher than that reported by Cobleigh et al. This is so both for any event and for severe events.

Table 5.25: Comparison of trastuzamab adverse events—Cobleigh et al (290) and Elements of Cancer Care study.

	Cobleigh et al. (290)*				EoC results**	
	Any grade		Severe adverse events		Any grade	Severe adverse events
Adverse event	No. of patients	%	No. of patients	%	%	%
Pain	103	48	17	8	77	20
Vomiting	60	28	1	0.5	77	6
Diarrhoea	55	26	3	1	77	6
Dyspnoea	49	23	10	5	77	14
Chest pain	44	21	3	1	4	0
Constipation	27	13	1	0.5	77	9
Rash	26	12	0	0	77	3

Note: EoC = Elements of Cancer Care;
*Trastuzumab adverse events were reported in Cobleigh as adverse events in > 10 per cent of 213 patients treated with at least one dose of trastuzumab, including those not related to treatment,
**Adverse events in the Elements of Cancer Care study were self-reported by women taking trastuzumab in a clinical practice setting

5.6.3 Discussion

This comparison of the rates of adverse events reported in the pivotal clinical trial for a chemotherapy regimen and a standard-practice sample of women receiving that same chemotherapy provides evidence that chemotherapy adverse events are more common in clinical practice than reported in clinical trials. Both for any adverse event and for serious adverse events, the rates were higher in the Elements of Cancer Care cohort than in the clinical trial.

This may be a factor of the stricter environment in clinical trials. For clinical trials, individuals must generally be younger and fitter than are those typically seen in clinical practice. This may mean that patients in clinical trials are physically better able to cope with chemotherapy and therefore less likely to experience adverse events. In addition, the typical clinical trial is conducted in a large high-quality teaching hospital, where there may be best-practice management of adverse events in place to reduce both the incidence of any adverse events and the likelihood of an adverse event becoming serious. In addition, clinical trials often involve more frequent monitoring and follow-up than is seen in clinical practice, and this again may contribute to individuals' adverse events being better managed.

Alternatively, the rates of adverse events may be similar in the two cohorts, but the method of reporting results in the differing rates. It is possible that when oncologists and research nurses are relied upon to collect adverse-event information, they may be less likely to have a full picture of the experience of chemotherapy for the individual and may therefore unknowingly underreport the number or type of adverse events individuals are experiencing. By being asked whether they have experienced each of a series of adverse events—as was the method in the Elements of Cancer Care study—patients may be prompted to report adverse events that they may not report to a physician who is asking in general about progress following chemotherapy.

It is unfortunate that there was only one regimen with a sufficient sample size upon which to conduct this analysis. Although there were a number of colorectal cancer protocols received by similar numbers of patients, these patients varied widely in terms of the stage of disease, which could influence the adverse events experienced, and thus make this analysis inappropriate. In larger studies, this would provide an excellent avenue for further research.

5.7 Overall discussion of Elements of Cancer Care

The incidence of adverse events in this clinical practice-based cohort of individuals undergoing chemotherapy for breast, lung and colorectal cancer is high, with 85 per cent of participants reporting at least one adverse event. In

addition, most adverse events occurred in more than 70 per cent of participants, with fatigue being the most common. These estimates represent the first Australia-based estimates of the incidence of common chemotherapy adverse events in a clinical practice setting, and they improve upon previous similar international estimates by estimating incidence by grade of event. Similarly, the presentation of cumulative incidence of adverse events has not previously been seen, and provides an insight into the pattern of adverse events over the course of chemotherapy. In contrast to clinical expectations, the incidence of adverse events over time appears to be relatively stable.

The rates observed in this cohort are consistent with those seen in other observational studies of heterogeneous cancer and chemotherapy groups in a clinical practice setting, but they are significant in that they highlight the importance of adverse events in any consideration of chemotherapy cost-effectiveness. Adverse events that occur in such a high proportion of individuals receiving chemotherapy will influence the overall cost—even when the cost is relatively low per event.

The Elements of Cancer Care data provided an ideal opportunity to validate the proxy and the related models described in Chapter 4 by using administrative data to identify individuals who have a chemotherapy-related adverse event. When a treatment for likely adverse event was received within three days of a dose of chemotherapy, this was used as the proxy for having an adverse event. When this proxy was used with the administrative data collected in the Elements of Cancer Care study, low rates of adverse events were observed, and these were in similar ranges to those seen in the DVA study described in Chapter 4.

However, when this proxy-based measure of the incidence of adverse events was compared with the self-reported rates of adverse events, it became clear that the proxy was underestimating the incidence of chemotherapy adverse events. It is not clear why this is the case, with no pattern observed related to the severity or the treatment of an adverse event and whether it was identified by the proxy. Given the poor performance of the proxy, additional validation of the models developed in Chapter 4 was not undertaken in the Elements of Cancer Care data. If an

appropriate proxy was identified, this type of analysis could use the betas derived from DVA models to develop predicted values for individuals in the Elements of Cancer Care study, and then compare predicted with actual values. This would enable an assessment of how well the models would perform with a different dataset, and thus allow for an examination of their generalisability.

Therefore, there is an opportunity to use the self-reported incidence of adverse events to run models similar to those developed in the DVA analysis described in Chapter 4, to investigate whether other factors contribute to the likelihood of an individual having an adverse event and to identify the additional cost related to an adverse event during chemotherapy.

Despite the poor performance of the proxy, this analysis appears to confirm that modelling the costs and consequences of chemotherapy adverse events based on the incidence reported in clinical trials may not be appropriate. The treatment of adverse events, although not clearly described by this cohort data, does appear to differ from best practice in some ways. Similarly, administrative data do not reflect clinical practice and therefore they should be avoided when modelling chemotherapy adverse events.

Limitations

This is a relatively large cohort of individuals with cancer in NSW, however the data and analysis have some limitations which need to be considered in interpreting the results. There was a relatively small proportion of individuals in the sample with non-small cell lung cancer, which makes analysis of these individuals as a sub-group difficult. Similarly, the sub-group of individuals for whom blood test results were available was relatively small, making this analysis less robust.

The classification of chemotherapy regimens was a particularly difficult component of the data cleaning process, and it is possible that some individuals may have had their chemotherapy regimen incorrectly coded, although the numbers of these are thought to be small.

Relying on self-reported data of adverse events may have introduced bias into the study, as there is some evidence that different approaches to eliciting this information can lead to different responses. The inclusion of comprehensive record reviews is hoped to have minimised this effect, but there may still be some bias.

The self-reported incidence of chemotherapy adverse events in this observational cohort was compared to the incidence identified in the administrative dataset presented in the previous chapter. While this comparison provides an interesting contrast, it should be noted that the populations in the two cohorts are different. While both cohorts are of NSW residents, the DVA cohort is a group of older individuals who have numerous comorbidities. In contrast, the Elements of Cancer Care cohort is more representative of the general population. This may have the effect of biasing the comparison of adverse events, particularly if older individuals with multiple comorbidities are more likely to experience adverse events overall, and may be treated differently.

The difference identified between the reported rates of adverse events in clinical trials compared to clinical practice highlights a challenge for decision makers and modellers. While observational data appears to be preferable to inform decision making, this data is time and resource intensive to gather. While it is not feasible for an observational study to be conducted for every economic evaluation, the conduct of large, well-designed, prospective observational studies with the needs of modellers and decision makers in mind could provide valuable input to models.

In conclusion, the first Australia-based comparison of rates of self-reported chemotherapy adverse events in a clinical practice setting with rates of chemotherapy adverse events reported in the pivotal trial of a specific chemotherapy regimen, has confirmed that chemotherapy adverse events are more common in clinical practice than in clinical trials. This analysis could only be conducted with one chemotherapy protocol, and additional similar analysis with a range of chemotherapy treatments and cancer types is necessary.

This work highlights a number of areas for future research. It appears that the use of administrative data is not suitable for assessing the adverse events of chemotherapy, and therefore observational studies of chemotherapy in clinical practice are paramount. At the very least, pragmatic clinical trials should be encouraged, especially when cost-effectiveness analysis is being conducted alongside. Future research in this area will enable more-robust assessments to be made of the types of treatments individuals receive for adverse events to assess the extent to which these align with clinical practice guidelines.

5.7.1 Conclusion

This chapter has explored the incidence, management and costs of chemotherapy adverse events in a standard-practice cohort. The first Australian estimates of the incidence of chemotherapy adverse events in a heterogeneous cohort in a standard-practice setting are described. It is found that adverse events are not only common in this cohort but also more common than reported in clinical trials.

In addition, the data from the Elements of Cancer Care study were used to validate the proxy (see Chapter 4) developed to analyse adverse events in the DVA administrative dataset. It was found that the proxy can identify only a small proportion of self-reported adverse events, and it is therefore not recommended that administrative data be used to examine adverse events of chemotherapy.

The work described in this chapter confirms the importance of the role of observational data in providing information for decision-makers that is relevant to the clinical practice setting.

Chapter 6: Discussion

Chapter summary

This thesis has explored the incidence, costs and consequences of chemotherapy adverse events as they relate to cost-effectiveness analysis. This final chapter describes the contribution of this work to the existing literature in this area and the implications for various key stakeholders. In addition, it considers the potential areas for future research indicated by these results.

The development of new chemotherapy drugs is an important part of developing more effective treatments for cancer. With the cost and complexity of drug development increasing, and the evolution of personalised medicine shrinking market size (1, 8-11), chemotherapy drugs are one of the fastest growing components of Australia's PBS (a federal government-funded scheme to provide affordable medicines to Australians) (3). With healthcare budgets under strain, decision-makers increasingly rely on cost-effectiveness analysis to determine the most efficient use of the limited healthcare dollars, including chemotherapy drugs (16). In order to accurately inform policymaking, cost-effectiveness analysis needs to be based on an assessment of all relevant costs and consequences (16).

When undertaking economic evaluation of chemotherapy, three aspects are usually considered: the costs of the chemotherapy drugs, the costs of administering the chemotherapy drugs, and the costs of adverse events (side effects). This thesis focused on the costs and consequences of chemotherapy adverse events, for which there is little previous research.

There are more than 250 adverse events that are considered as commonly associated with cancer treatment (31). Adverse events associated with chemotherapy are an important component of treatment, because they impact on an individual's quality of life (32, 33, 78) and the costs of treatment. In addition, there is evidence that the chemotherapy dose modifications used to manage adverse events may reduce the efficacy of chemotherapy treatment (67, 69-75). To ensure that models of chemotherapy cost-effectiveness are accurate, it is necessary

to include all the costs and consequences of chemotherapy adverse events; however, this is rarely achieved (65).

The overall objective of this research was to investigate the incidence, costs and consequences of chemotherapy adverse events. This research has addressed the need for Australia-based models of the costs and consequences of chemotherapy adverse events that take into account the complexities of managing adverse events. These models allow decision-makers to base decisions on evidence that includes all relevant information. In addition, the type of data used as inputs to these models was explored, because this has the potential to affect whether the results of cost-effectiveness analyses are reflective of clinical practice—the setting in which decision-makers are operating.

Different methodologies and data sources were used to investigate the incidence, costs and consequences of chemotherapy adverse events. These were guided by a review of the literature covering previous work in modelling chemotherapy adverse events. The incidence of chemotherapy adverse events was explored in two clinical practice settings using administrative data and the Elements of Cancer Care cohort study. The costs of chemotherapy adverse events were assessed in two ways. First, the costs of four common chemotherapy adverse events were modelled using decision analysis. Second, the additional costs associated with managing adverse events in clinical practice were estimated using administrative data.

The consequences of chemotherapy adverse events were then explored in terms of the management and treatment strategies used in the Elements of Cancer Care study. In addition, the models of adverse events considered the consequences of chemotherapy beyond the associated financial costs by considering consequences such as effects on quality of life and on the efficacy of chemotherapy.

This research identified that adverse events have not been included in chemotherapy cost-effectiveness models to date in any rigorous or systematic way. However, the models developed as part of this research and described in Chapter 3 demonstrate that it is possible to model chemotherapy adverse events in

a rigorous and systematic way. These models identified that when all relevant costs and consequences are included even adverse events that are low probability or low cost can have a significant impact on the overall cost of chemotherapy. This cost not only includes a direct financial cost but also an impact on individuals' quality of life and the proportion of individuals receiving adequate dose intensity of chemotherapy.

This research has also demonstrated that the type of data used to populate models of chemotherapy cost-effectiveness is important. Analysis of observational data identified higher rates of adverse events in clinical practice than reported in clinical trials. In addition, the types of individuals who are typically excluded from clinical trials, such as older people or those with multiple comorbidities, are more likely to be treated for a likely adverse event.

Contribution to the literature

A major contribution of this work is the development of models of four common chemotherapy adverse events that address many of the complexities of the costs and consequences usually ignored in existing models. Modelling not only the best-practice treatments for adverse events but also their impacts on quality of life and dose modifications represents a significant improvement in the way adverse events are considered in the context of cost-effectiveness analyses. These models will be available as a resource to anyone building a model of chemotherapy cost-effectiveness analysis to ensure that common adverse events are included in a rigorous way.

There are few studies describing the incidence of chemotherapy adverse events in heterogeneous populations of individuals undergoing chemotherapy (77), and none in Australia. The analysis of the Elements of Cancer Care data presented here provides the first estimates of the incidence of common chemotherapy adverse events in Australian clinical practice. The results demonstrate that adverse events are common and often serious.

There have been a number of studies examining the experience of chemotherapy and adverse events in clinical practice (53, 54, 218).This research confirms that in

the case of trastuzumab for metastatic breast cancer in Australia, adverse events are more common in clinical practice than reported in the pivotal clinical trial(s). This has important implications for both clinical practice and economic evaluation.

The use of observational and administrative data to examine the costs of various treatments is increasing (48). In this research, analysis of the linked DVA data used a proxy to identify individuals who were treated for a likely adverse event. The results showed that individuals who were older or had multiple comorbidities were more likely to be treated for a likely adverse event, and that being treated for a likely adverse event significantly increased total expenditure on chemotherapy. This provides an Australian estimate based on a large sample that is consistent with clinical expectations. These findings confirm that individuals typically excluded from clinical trials are more likely to experience adverse events, indicating that the exclusion of these individuals from trials may lead to biased results in cost-effectiveness analyses based on the results from clinical trials.

The validation of the proxy used to identify individuals treated for a likely adverse event was undertaken by comparing the self-reported adverse events with those identified through the proxy. This demonstrated that the use of this linked administrative dataset to estimate the incidence of adverse events, based on pharmaceuticals products and medical services received within three days of chemotherapy, underestimates the incidence of adverse events. This provides a valuable contribution to the understanding of the strengths and limitations of the administrative data in general, and the DVA data specifically.

Implications

The findings of this research will be of interest to model-builders, those undertaking economic evaluations, decision-makers, clinicians and patients.

Those undertaking economic evaluations require accurate and robust estimates of the costs and consequences of chemotherapy. Adverse events are an important but complex component of chemotherapy and need to be taken account of. The decision analytic models developed in this research provide model-builders with

convenient and efficient 'plug ins' for their cost-effectiveness analysis. This will allow not only a rigorous approach to the inclusion of adverse events in economic evaluations of chemotherapy but also a consistent approach across chemotherapy models, increasing transparency and comparability.

In addition, it is important for those undertaking economic evaluations to consider the work demonstrating the increased incidence of adverse events in clinical practice because many cost-effectiveness analyses are currently based on data from clinical trials. Given that the purpose of cost-effectiveness analyses is to inform decision-makers of the likely impacts of health-service decisions in clinical practice, it is important that model-builders acknowledge the potential for the inputs in their models to result in biased estimates, and to investigate methods of incorporating clinical practice data into models, even if only as values for the purpose of sensitivity analysis.

Box B: Implications of more common adverse events

This research identified that adverse events are more common in clinical practice than reported in clinical trials. To demonstrate the potential impact of this, the model of chemotherapy-induced diarrhoea described in Chapter 3 and populated with diarrhoea incidence from a clinical trial is compared with the results of the same model populated with self-reported diarrhoea rates from the Elements of Cancer Care study.

For women with metastatic breast cancer receiving trastuzumab, the average cost of diarrhoea based on the incidence rates from the pivotal clinical trial was $53 per diarrhoea event. The Elements of Cancer Care study reported higher rates of adverse events at all severity levels for women with the same cancer and chemotherapy. When these self-reported diarrhoea rates were used (keeping the costs for each grade constant), the average cost of diarrhoea was $303 per diarrhoea event.

This demonstrates the significant impact that the difference between clinical trial reported incidence and clinical practice incidence can have on the estimations of the cost of chemotherapy treatments.

Similarly, for decision-makers using the results of models of cost-effectiveness to determine future funding of chemotherapy treatments, an awareness of the limitations of existing models of chemotherapy cost-effectiveness in relation to adverse events will increase their knowledge about the issues that need to be considered. The results of this research indicate that current models are likely to underestimate the true costs of chemotherapy, because they do not include comprehensive information about the impacts of adverse events on costs, quality of life or chemotherapy efficacy. Making decision makers aware of this underestimation may not ensure researchers develop rigorous models, however, it is likely to lead to a more informed consideration of the evidence available, and an improved decision-making process.

Clinicians and patients may also be interested in the results of this research. For many patients, adverse events are the way in which they experience cancer and chemotherapy, and additional information about the likelihood of experiencing an adverse event, how it will be managed, and the full spectrum of consequences of having an event are all crucial to making informed treatment decisions. This means that oncologists need to be aware of these issues and involve patients in interactive discussions about how these results might apply to the individual.

Limitations

There are a number of limitations to the research presented, which may influence how it is implemented in practice. The literature review provides an overall examination of models in the peer-reviewed literature. However, many models are prepared for reimbursement submissions and may never be published in the academic arena. These unpublished models could be systematically different from those which are published. This could mean that the recommendations resulting from the review may not be applicable to the models which are prepared purely for reimbursement submission, which is the primary type of model seen by decision makers.

The models presented provide a ‘plug-in’ approach to the inclusion of adverse events in models of chemotherapy cost-effectiveness. While this standardised approach has advantages in terms of consistency and transparency, there are a

number of potential difficulties with this approach. These four adverse event models represent some of the common adverse events associated with chemotherapy, but is certainly not exhaustive. For each chemotherapy cost effectiveness model a decision will need to be made on which adverse events are applicable, and which should be included in the model. With the current models all being independent of each other, inclusion of more than a handful of models could result in high levels of complexity. The development of models which include the interaction between adverse events and acknowledge adverse event clusters will go some way to addressing this, but will still run the risk of not being appropriate to the specific chemotherapy under investigation.

The models are also based on best practice treatment pathways. These may these not be consistent with day to day clinical practice, for a variety of reasons. The availability of drugs and medical services differs across jurisdictions, as does the patient profile, and model of service provision. These may all influence how best practice guidelines are implemented, and may make the results of the models presented in this thesis less applicable to the local setting.

Similarly, the data inputs used were selected on the basis of methodological quality. For some settings there may have been evidence that was based on more representative populations or in more similar settings. Again this has implications for the generalisability of the model results, and highlights the trade off between developing models based on top down data which are generalisable across settings, and using a bottom up approach to developing models which are locally specific. The aim for these models is that they are transparent enough that if locally applicable bottom up data are available, they could be used as inputs to the model rather than the top down data presented here.

The analysis of adverse events in a large administrative dataset is limited by the need to use a proxy for the incidence of adverse events. It would appear that the proxy developed has relatively low sensitivity to the identification of adverse events, and thus understimates the incidence of adverse events. This means the findings regarding this incidence, factors associated with and costs of adverse events should be interpreted with caution.

The analysis of the adverse events in the Elements of Cancer Care study provides more detailed, Australian specific information about adverse events in clinical practice. However, the relatively small numbers of individuals receiving the same chemotherapy regimen for the same cancer type means that sub-group analysis was difficult.

Overall these limitations provide areas where caution should be used in the interpretation and potential implementation of the results in the decision making process. Nevertheless the results provide an important contribution to the literature of the economic evaluation of chemotherapy adverse events. Together with the results of the research presented in this thesis, these limitations also highlight a number of areas for future research.

Areas for future research

A number of areas for future research arise from this work. Four common adverse events were chosen to form the focus of this research, because they provided a mix of low and high severity, short- and long-term events, low and high treatment costs and management through prevention or treatment. It was beyond the scope of this thesis to model additional adverse events, but many common adverse events would benefit from the development of rigorous models like those presented here. This would result in a suite of adverse event models that could be used by chemotherapy cost-effectiveness model-builders in Australia. Research is not only obtaining and disseminating results; a significant component is implementing the research— putting it into practice. This research and the resultant work could be further developed by promoting these models as the preferred method for modelling chemotherapy adverse events. Ideally, these models would be recommended by bodies such as the PBAC and the Medical Services Advisory Committee. The modelling of multiple simultaneous adverse events is an area with the potential to impact significantly on the outcomes of chemotherapy cost-effectiveness analysis, but it was beyond the scope of this research. There is some evidence that adverse events occur in clusters (291) and that the incidence and management of specific adverse events would be different when they occur in combination with a second event. These clusters could be

investigated using data such as that from the Elements of Cancer Care study to determine which adverse events tend to occur together, or through analysis of clinical trial data. Once common clusters are identified, regression analysis could be conducted to identify the impact of each adverse event on the costs and management in clinical practice. These interactions could then be modelled, so that the impacts of multiple simultaneous events could be accurately estimated.

There are a number of gaps in the models described in Chapter 3. Those models for which a utility decrement could not be specified for each grade could be improved by the inclusion of a Markov process for calculating the impact on quality of life. This would ensure the accurate capture of the impact of the adverse event on quality of life, by accounting for the time the individual spends in each health state as well as the utility weight associated with that health state. In addition, specific research to obtain better estimates for the utility decrements associated with adverse events would be a valuable addition to the rigorous modelling of chemotherapy. Finally, the use of clinical practice data, such as the Elements of Cancer Care data, could provide evidence about the proportion of people whose dose of chemotherapy is modified as a result of adverse events.

Some questions are best answered by study designs that include randomisation to minimise bias. However, the potential underestimation of the incidence of adverse events in this setting needs to be recognised. This type of research could be further developed by the investigation of the reasons for rates of adverse events in clinical trials being lower. Potential reasons include that the individuals in clinical trials are younger and fitter, or the structured environment of a trial provides closer follow-up and stricter treatment protocols, or a combination of both.

It is possible that administrative data, such as the DVA dataset, could provide valuable information about the experience of chemotherapy adverse events; however, the proxy developed for the analysis in this thesis was insufficient. Additional research could identify the variables in the dataset that would contribute to the development of a better proxy of adverse events.

The analysis of the Elements of Cancer Care study data could be extended to include an estimate of the costs associated with the delivery of chemotherapy. This could be done by identifying the total cost per month for each patient and conducting a comparison between the costs during months when an adverse event was recorded and the costs during the months when there was no adverse event. Such an analysis would need to account for the high proportion of months in which an adverse event is reported and the clustering of events.

Finally, larger studies of the incidence and management of chemotherapy adverse events in clinical practice are required. There have been examples of these in Australia (166); however, they have focused on a specific adverse event rather than on the range of events experienced. The advantage of examining more than one event is the potential to examine the experience of multiple events occurring simultaneously, which remains a gap in the modelling of chemotherapy adverse events.

Large scale observational studies are typically time and resource intensive; new technologies may provide an opportunity to conduct larger-scale clinical practice studies with increasing ease, enabling ongoing patient reporting of events, resulting in accurate detailed data collection while minimising patient recall error. For example, some research has used mobile-phone data entry for adverse events during chemotherapy (23). If this were implemented widely, it would provide a rich source of data for the investigation of adverse events in clinical practice.

There is clearly a challenge for decision analysts wishing to construct and populate economic models in a timely manner for decision making, if prospective studies are the preferred data source. However**,** a separate observational study is not required for each economic evaluation if large, well designed, generalisable studies are designed and conducted with the needs of model builders and decision makers in mind.

6.1.1 **Conclusion**

The treatment of cancer is an important component of the healthcare system; however, it is an increasingly expensive one. Decision-makers must rely on tools

such as economic evaluation to inform their decisions and assist prioritisation of limited healthcare funds. In the case of chemotherapy treatments for cancer, the cost of chemotherapy drugs, the resources for chemotherapy administration and the impacts of adverse events need to be considered. However, the incidence, costs and consequences are generally not well understood. This is partially due to a lack of awareness of the issues, which results in a lack of data, particularly relating to the experience of adverse events in clinical practice settings. These deficiencies lead to a lack of rigorous modelling of the incidence, costs and consequences of adverse events in assessments of chemotherapy cost-effectiveness.

This thesis has provided rigorous, Australia-based models of the costs and consequences of chemotherapy adverse events. These models provide a demonstration of model structures that take account of the complexities of the management of adverse events in clinical practice. They also provide the opportunity for the resulting cost estimates to be incorporated into any model of chemotherapy cost-effectiveness, thus providing a tool for transparent and rigorous modelling. In addition, this thesis has explored two new data sources as means to provide better information about the incidence and impact of adverse events in the clinical practice setting. These are unique Australia-based estimates, and provide the opportunity for model-builders and decision-makers to consider carefully the implications of using clinical trial data in economic evaluations of chemotherapy.

Overall, this thesis contributes a better understanding of the incidence, costs and consequences of chemotherapy adverse events and how these should be considered when modelling chemotherapy cost-effectiveness.

APPENDICES

Appendix A: PRISMA Checklist

Section/topic	#	Checklist item	Where reported
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 27
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 27
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 27-28
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 31-32
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	n/a
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 32 & 34
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 33
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix B
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 34

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 34
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 34
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 35-36
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	n/a
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	n/a
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 2.1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2.1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 2.1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2.1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 2.1 & Figure 2.2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Section 2.3

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 58
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Section 2.4
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page iii

Appendix B: Search strategies for literature review

Search conducted 03/Aug/2009
FINAL - saved as Chemo AE costs

Search Results

EMBASE, CLHTA, CDSR, ACP Journal Club, DARE, CCTR, CLCMR, CLEED, Ovid MEDLINE(R)

#	Searches	Results
1	Neoplasms/	104030
2	carcinoma$.mp. [mp=ti, ot, ab, sh, hw, kw, tn, dm, mf, tx, ct, nm]	500242
3	cancer$.mp. [mp=ti, ot, ab, sh, hw, kw, tn, dm, mf, tx, ct, nm]	1206077
4	drug therapy/	9593
5	antineoplastic agents/	158823
6	chemotherap$.mp. [mp=ti, ot, ab, sh, hw, kw, tn, dm, mf, tx, ct, nm]	329349
7	drug toxicity/	5478
8	adverse effect/	2289
9	adverse event$.mp. [mp=ti, ot, ab, sh, hw, kw, tn, dm, mf, tx, ct, nm]	93629
10	adverse effect$.mp. [mp=ti, ot, ab, sh, hw, kw, tn, dm, mf, tx, ct, nm]	110828
11	adverse reaction$.mp. [mp=ti, ot, ab, sh, hw, kw, tn, dm, mf, tx, ct, nm]	22103
12	adverse drug.mp. [mp=ti, ot, ab, sh, hw, kw, tn, dm, mf, tx, ct, nm]	27684
13	toxic$.mp. [mp=ti, ot, ab, sh, hw, kw, tn, dm, mf, tx, ct, nm]	417148
14	side?effect$.mp. [mp=ti, ot, ab, sh, hw, kw, tn, dm, mf, tx, ct, nm]	83917
15	undesired effect$.mp. [mp=ti, ot, ab, sh, hw, kw, tn, dm, mf, tx, ct, nm]	549
16	complication$.mp. [mp=ti, ot, ab, sh, hw, kw, tn, dm, mf, tx, ct, nm]	702074
17	cost analysis/	44823
18	cost-benefit analysis/	70141
19	economics/	8418
20	length of stay/	55946
21	health resources/	23323
22	cost$.mp. [mp=ti, ot, ab, sh, hw, kw, tn, dm, mf, tx, ct, nm]	454615
23	resource$.mp. [mp=ti, ot, ab, sh, hw, kw, tn, dm, mf, tx, ct, nm]	171552
24	hospitali?ation$.mp. [mp=ti, ot, ab, sh, hw, kw, tn, dm, mf, tx, ct, nm]	146605
25	1 or 2 or 3	1431967
26	4 or 5 or 6	430978
27	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	1333983
28	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	745231
29	25 and 26	285284
30	27 and 28 and 29	5372
31	limit 30 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained]	5013
32	limit 31 to human [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained]	4942
33	limit 32 to yr="1999 -Current" [Limit not valid in DARE; records were retained]	4133
34	limit 33 to humans [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained]	4133
35	remove duplicates from 34	3347
36	from 35 keep 1	1

Results of your search: **from 35 [remove duplicates from 34] keep 1**

Results Available: **1**
Results Displayed: **#1**

Centre for Reviews and Dissemination

NHS
National Institute for Health Research

Help | Why log in? | Login

Search

(•) All these words
( ) Any of these words

(Searches using AND/OR/NOT combinations override the above)

Year published From - search restrictions info

10 results per page

Home
Results
MeSH
Search history

History Saved searches

Search history

	Search	Matching records
# 1	cancer	5373
# 2	neoplasms	1106
# 3	carcinoma	766
# 4	drug AND therapy	3343
# 5	chemotherapy	1522
# 6	antineoplastic	31
# 7	"side effect"	248
# 8	"adverse event"	445
# 9	"adverse effect"	214
# 10	toxicity	742
# 11	cost	25963
# 12	"cost analysis"	2797
# 13	"cost benefit"	707
# 14	economic	27607
# 15	"length of stay"	1184
# 16	resource	7158
# 17	#1 AND #2 AND #3	191
# 18	#1 OR #2 OR #3	5867
# 19	#4 OR #5 OR #6	4574
# 20	#7 OR #8 OR #9 OR #10	1550
# 21	#11 OR #12 OR #13 OR #14 OR #15 OR #16	31499
# 22	#18 AND #19 AND #20 AND #21	195

Clear history | Save history | Export history

- DARE = 44
- NHS EED = 137
- HTA = 14

Using the search history

Each search (and MeSH search) that you do is stored in a search history. If you enter a search while this history page is displayed, the history display will be updated to show the search line just run.

You can view the results of any search line in a history by clicking on the search terms in that line.

The search history lists each search you have entered: each search has a line number; the search terms used; and the number of records found.

Appendix C: NHS EED annotated abstract

Library id

1st Author:

Title:	
Cancer & stage	
Chemotherapy	
Adverse event(s)	
AE treatment(s)	
Population & setting	
Objective	
Economic study type	
Modelling and statistical extrapolation	
Dates to which data relate	
Clinical and epidemiological data	
Data sources	
Methods used to obtain data	
Measure of benefits used in the economic evaluation	
Direct costs	
Indirect costs	
Currency	

Library id

NHS EED annotated abstract continued…

Statistical analysis of costs	
Methods used to allow for uncertainty	
Estimated benefits used in the economic analysis	
Cost results	
Synthesis of costs and benefits	
Authors conclusions	
Commentary	
Implications of the study	
Other publications of interest	

Appendix D: Graves checklist (49)

General costing issues
Q1. Was the perspective of the cost analysis stated?
Q2. Was the perspective of the cost analysis justified?
Q3. Were cost data included that satisfied the stated perspective?
Q4. Did the authors make a distinction between short and long run costs?
Methods to determine quantities of resources
Q5. Were methods given for estimating the quantities of resources used per participant (variable costs)?
Q6. Were methods given for allocating the time of human resources (semi-fixed costs) between participants?
Q7. Were methods given for allocating the use of other resources (fixed costs) between participants?
Methods used to determine value of resources consumed
Q8. Were methods given for the estimation of any prices, unit costs or charges?
Q9. Were data other than third-party charges used?
Reporting of data
Q10. Was the year(s) reported in which the cost data were collected?
Q11. Was the base cost year reported?
Q12. Were adjustments made for costs incurred in different time periods?

Appendix E: Tables of all studies in the literature review, shown by adverse-event type or cancer type

(i) Adverse-event treatment studies of neutropoenia

Reference	Cancer type, cancer stage and chemotherapy	Perspective	Graves quality score	Adverse event and grade	Model and economic analysis	Dose modifications: chemotherapy dose	Dose modifications: survival	Quality of life: impact of adverse events considered	Multiple adverse events over time	Multiple concurrent adverse events
Lyman 2003 (US) (86)	Any cancer, any stage, any chemotherapy	Not described	6	Neutropoenia any grade	Decision analysis, CEA	No; discussed, but not included	No; discussed, but not included	No; discussed, but not included	No	N/A; only considered one AE
Cosler 2004 (US) (292)	Ovarian, any stage, any chemotherapy	Societal	10	Neutropoenia any grade	Cost-minimisation, CMA	No	No	No	No	N/A; only considered one AE
Eldar-Lissai 2008 (US) (293)	Any cancer, any stage, any chemotherapy	Societal	7	Neutropoenia any grade	Decision analysis, multiple - CUA and CEA	No	No	Yes; utilities for febrile neutropoenia with and without hospitalisation	No	N/A; only considered one AE
Danova 2009 (Italy) (92)	Breast cancer, any stage, any adjuvant chemotherapy	National Health System in Italy	8	Febrile neutropoenia any grade	Decision analysis, CEA	N/A; cost of chemotherapy excluded from the model	Yes	Yes; utility scores for febrile neutropoenia hospitalisation	Yes; episode of neutropoenia means higher risk in subsequent cycles	N/A; only considered one AE
Liu 2009 (US) (91)	Breast cancer, early stage, any myelosuppressive therapy	UK National Heath Service	9	Neutropoenia any grade	Decision analysis, CEA	No; cost of chemotherapy excluded from the model (same between two arms)	Yes	Yes; utility scores for febrile neutropoenia hospitalisation	Yes; episode of neutropoenia means higher risk in subsequent cycles	N/A; only considered one AE

Note: AE = adverse event; CEA = cost-effectiveness analysis; CMA = cost-minimisation analysis; CUA = cost-utility analysis; N/A = not applicable; pts = patients; UK = United Kingdom; US = United States

(ii) Adverse-event treatment studies of anaemia, thrombocytopenia and multiple events

Reference	Cancer type, cancer stage and chemotherapy	Perspective	Graves quality score	Adverse events	Model	Dose modifications: chemotherapy dose	Dose modifications : survival	Quality of life: impact of adverse events considered	Multiple adverse events over time	Multiple concurrent adverse events
Borg 2008 (Sweden) (94)	Any cancer, any stage, any chemotherapy	Healthcare perspective	9	Anaemia, any grade	Markov model, CEA	No	No	Yes; each cycle of the model the Hb level, EPO and RBCT increments/ decrements are used to determine the utility weight	No	N/A; only considered one AE
Cantor 2003 (US) (294)	Any cancer, any stage, any chemotherapy	Payers' perspective	9	Thrombo-cytopenia, any grade	Decision-analysis model, CMA	No	No	No	No	N/A; only considered one AE
Touchette 2006 (US) (95)	NSCLC, any stage, cisplatin, carboplatin or paclitaxel	Health system provider	6	Febrile neutropoenia, thrombo-cytopenia, anaemia, any grade	Markov model, CEA	No	No	No	Assumed - could accrue costs due to adverse events once at each cycle	Yes; any combination of febrile neutropoenia, anaemia and thrombocyto penia

Note: AE = adverse event; CEA = cost-effectiveness analysis; CMA = cost-minimisation analysis; CUA = cost-utility analysis; EPO = erythropoietin; Hb = haemoglobin; N/A = not applicable; NSCLC = non-small-cell lung cancer; RBCT = red blood cell transfusion.

(iii) Adverse-event treatment studies of nausea and vomiting

Reference	Cancer type, cancer stage and chemotherapy	Perspective	Graves quality score	Adverse events	Model	Dose modifications: chemo dose	Dose modifications: survival	Quality of life: impact of adverse events considered	Multiple adverse events over time	Multiple concurrent adverse events
Annemans 2008 (Belgium) (295)	Any cancer, any stage, cisplatin, cyclophosphamide	Healthcare payers' perspective	5	Nausea and vomiting, any grade	Decision-analysis model, CEA	No	No	Yes; utilities for complete response and incomplete response to antiemetics	No	N/A; only considered one AE
Lordick 2007 (Germany) (97)	Any cancer, any stage, cisplatin	Unit cost from the statutory health-insurance perspective	8	Nausea and vomiting, any grade	Decision-analysis model, CEA	No	No	Yes; utilities for chemotherapy with some nausea, and nausea with emesis/nausea	No	N/A; only considered one AE

Note: AE = adverse event; CEA = cost-effectiveness analysis; CMA = cost-minimisation analysis; CUA = cost-utility analysis; N/A = not applicable.

(iv) Chemotherapy cost-effectiveness studies of early or primary breast cancer

Reference	Cancer type, cancer stage and chemotherapy	Perspective	Graves quality score	Adverse events	Model and economic analysis	Adverse events selection (summary)	Dose mods: chemo dose	Dose mods: survival	Quality of life: impact of adverse events considered	Multiple adverse events over time	Multiple concurrent adverse events
Kurian 2007 (US) (296)	Early breast cancer, adjuvant therapy: anthracyclines vs. trastuzumab	Society	7	Cardiac toxicity, any grade	Markov, CEA	'Major difference between the alternative regimens'	No	No	Yes; previously published adjustments for quality of life associated with cardiac toxicity included	Assumed: multiple time periods in cardiac toxicity state possible	No; only one AE considered
Lundkvist 2007 (Sweden) (87)	Early breast cancer, exemestane vs. tamoxifen	NS	7	Osteoporosis, thromboembolic event, any grade	Markov, CEA	AEs with statistically significant different occurrence rates between arms of the trial, with rare, mild, and negligible cost events excluded	No	No	No; because utility loss from adverse events was expected to be low	Assumed; AEs modelled by incidence, so possible for patients to experience multiple AEs over time	No
Karnon 2008 (UK) (297)	Early breast cancer, letrozole vs. tamoxifen; anastrazole vs. tamoxifen	UK National Heath Service	7	Endometrial cancer, hip or other fracture, Cardiac, VTE, arthritis; any grade	Markov, CUA	'Key adverse events'	No	No	Yes	Assumed; AEs modelled on incidence	No
Wolowacz (UK) (298)	Early breast cancer, TAC vs FAC	UK National Heath Service	6	Anaemia, diarrhoea, febrile neutropoenia, stomatitis, vomiting; Grade III/IV only	Markov, CEA and CUA	Grade III/IV or severe life-threatening events that occurred in more than 1% of patients in either trial arm and at a	Yes; patients stopping chemo due to adverse events received fewer cycles	No	Yes; utility decrements were derived from the published literature	Assumed; AEs modelled on incidence	No

Reference	Cancer type, cancer stage and chemotherapy	Perspective	Graves quality score	Adverse events	Model and economic analysis	Adverse events selection (summary)	Dose mods: chemo dose	Dose mods: survival	Quality of life: impact of adverse events considered	Multiple adverse events over time	Multiple concurrent adverse events
						difference of greater than 2% between arms	of the planned regimen				
Delea 2007 (US) (90)	Early breast cancer, letrozole vs. tamoxifen	US healthcare system	7	Endometrial cancer, cardiac, hip fracture, other fracture, arthralgia, hypercholesterolemia; any grade	Markov, CEA	NS	No; assumed that compliance with therapy is 100%	No	Yes; utilities were assessed for a range of breast cancer adverse events using standard gamble	Assumed; AEs modelled on incidence	Yes; for disease-free patients, states are also characterised by all possible combinations of adverse events
Risebrough 2007 (Canada) (299)	Primary breast cancer, 5 years tamoxifen vs. 2–3 years tamoxifen + 3–2 years exemestane	Canadian provincial payer perspective	8	Osteoporosis, hypercholesterolemia, cardiac event, thromboembolism, fracture; any grade	Markov, CEA	cumulative incidence > 1%, significant difference between arms or clinically important differences AND a suspected significant impact on costs	Yes; discontinuation due to AEs was included in drug acquisition costs	No	No	Assumed; AEs modelled on incidence	No

Reference	Cancer type, cancer stage and chemotherapy	Perspective	Graves quality score	Adverse events	Model and economic analysis	Adverse events selection (summary)	Dose mods: chemo dose	Dose mods: survival	Quality of life: impact of adverse events considered	Multiple adverse events over time	Multiple concurrent adverse events
Lidgren 2008 (Sweden) (93)	Early breast cancer, standard adjuvant chemotherapy vs. one additional year of Herceptin®	Societal perspective in Swedish setting	9	Cardiac toxicity, and associated monitoring; any grade	Markov, CEA	Cardiac events only	No; assumed patients followed full treatment schedule	No	Yes; utility reduced by 50% for 6 months for patients experiencing symptomatic heart failure	No	No

Note:AE = adverse event; CEA = cost-effectiveness analysis; CMA = cost-minimisation analysis; CUA = cost-utility analysis; FAC = 5-fluorouracil, doxorubicin, cyclophosphamide; MI = myocardial infarction; N/A = not applicable; TAC = taxotere, adriamycin and cyclophosphamide; VTE = venous thromboembolism ; vs. = versus.

(v) Chemotherapy cost-effectiveness studies of metastatic or advanced breast cancer

Reference	Cancer type, cancer stage and chemotherapy	Perspective	Quality score	Adverse events	Model	Adverse events selection (summary)	Dose modifications: chemo dose	Dose modifications: survival	Quality of life: impact of adverse events considered	Multiple adverse events over time	Multiple concurrent adverse events
Norum 2005 (Norway) (300)	Metastatic breast cancer, trastuzumab	Third-party payer	3	Cardiac (congestive heart failure), any grade	NS, CEA	Most important	Indirect; used actual number of doses delivered in a study, which may have accounted for dose delays	No	No	No	No
Dedes 2009 (Switzerland) (301)	Metastatic breast cancer, paclitaxel +/– bevacizumab	Swiss health system	7	Cardiac (hypertension), infection, CVA; any grade	Markov cohort simulation, CEA	Side effects that showed statistically significant differences in occurrence between treatment arms	Yes; assumed that patients with chemotherapy discontinuation switched to another agent instead of waiting for the resolution of neuropathy	No	No	Assumed; patients may be able to experience multiple AEs over time	No
Le 2009 (US) (143)	Metastatic breast cancer, capecitabine +/– lapatinib	US societal perspective	8	Diarrhoea, cardiac event; any grade	Markov, CEA	Taken from trials (NS)	Indirect; average dose per patient per day from published data	No	No	Assumed; AEs modelled by incidence, so possible for patients to experience multiple AEs over time	No

Note: AE = adverse event; CEA = cost-effectiveness analysis; CMA = cost-minimisation analysis; CUA = cost-utility analysis; CVA =cerebrovascular accident ; N/A = not applicable; NS = not stated.

(vi) Chemotherapy cost-effectiveness studies of cancers other than breast

Reference	Cancer type, cancer stage and chemotherapy	Perspective	Graves quality score	Adverse events	Model and economic analysis	Adverse events selection (summary)	Dose modifications: chemotherapy dose	Dose mods: survival	Quality of life: impact of adverse events considered	Multiple adverse events over time	Multiple concurrent adverse events
Tumeh 2009 (US) (88)	Metastatic colorectal cancer, FOLFOX vs. FOLFIRI	Unknown	3	Neutropoenia, febrile neutropoenia, diarrhoea; Grade III/IV only	Markov, CEA	Grade III/IV in pivotal trials	No	No	Yes; utilities from the literature	Assumed; patients can move through multiple AE states	No; patients can only be in one state at a time
Hillner 2005 (US) (214)	Metastatic colorectal cancer, FOLFOX vs. irinotecan and bolus fluorouracil	Medicare as a third-party payer	7	Diarrhoea, volume depletion, nausea and vomiting, febrile neutropoenia, pneumonia, pulmonary embolism/ DVT; Grade III/IV only	Markov, CEA	Treatment-induced toxicity requiring hospitalisation	Yes; actual doses delivered were used for drug acquisition costs	No	No	No	No; if multiple toxicities occurred in a cycle, then only the most severe results were used
Bristow 2007 (US) (302)	Metastatic ovarian cancer, adjuvant IVT paclitaxel vs. IP cisplatin and IP paclitaxel	Society	8	Neutropenic fever, gastrointestinal toxicity, metabolic events, renal failure, thrombocytopenia; any grade requiring hospitalisation	Decision analysis, CEA	Events most likely to result in hospitalisation; Grade III/IV only	Indirect; treatment completion rates from pivotal studies used to model dose of chemotherapy received	No	No	Assumed; patients may be able to experience multiple AEs over time	No

Ojeda 2003 (Spain) (98)	Metastatic ovarian cancer, PLD vs. topotecan	Spanish hospitals	6	Anaemia, thrombocytopenia, neutropoenia, sepsis, fever, stomatitis/pharyngitis, nausea and vomiting, diarrhoea, PPE; any grade	NS; pharmaco economic model, CMA	Chosen on the basis of patient perception, frequency and clinical importance; included all grades	Indirect; total amount of drug used per patient during the pivotal trial was used to calculate drug costs	No	No	Assumed; AEs modelled by incidence, so possible for patients to experience multiple AEs over time	No
Carlson 2008 (US) (119)	Metastatic head and neck cancer, erlotinib, docetaxel, pemetrexed	US payer	8	Febrile neutropoenia, non-febrile neutropoenia, anaemia, rash, diarrhoea, infection, nausea, asthenia, pulmonary AEs, fatigue, anorexia, cardiac (dyspnoea, chest pain), infection without neutropoenia; Grade III/IV or requiring hospitalisation	Decision analysis, CEA and CUA	Grade III/IV events greater than 5% or those requiring hospitalisation	Indirect; all drug utilisation estimates were adjusted for dose intensity received	No	Yes; disutility for adverse events was applied during the first month of therapy	Assumed; model not described, but assume patients may be able to experience multiple AEs over time	No
Ramsey 2006 (US) (89)	Advanced NSCLC, docetaxel, pemetrexed, erlotinib	Private US health insurer	4	Neutropoenia, leukopenia, anaemia, febrile neutropoenia, infection, nausea, asthenia, pulmonary AEs, fatigue, anorexia, cardiac (chest pain, dyspnoea), infection, rash, diarrhoea; Grade III/IV or requiring hospitalisation	Budget impact, total costs	Grade III/IV adverse events with an incidence rate of 5% or greater or AEs requiring hospitalisation	Yes; dose reductions observed in the clinical trials for each agent were accounted for in the analysis	No	No	Assumed; AEs modelled by incidence, so possible for patients to experience multiple AEs over time	No

Note: AE = adverse event; CEA = cost-effectiveness analysis; CMA = cost-minimisation analysis; CUA = cost-utility analysis; IP = intraperitoneal; IVT = intravenous therapy; NSCLC = non-small-cell lung cancer; N/A = not applicable; PLD = pegylated liposomal doxorubicin; US = United States.

Appendix F: Principles of Good Practice for Decision Analytic Modelling in Health Care Evaluations

In assessing the quality of the models presented in this thesis, the Principles of Good Practice for Decision Analytic Modelling in Health Care Evaluations (215)were used. These present criteria for assessing the quality of models in three areas: model structure, data inputs and model validation. The section of the thesis presented here in which each of the criteria are addressed is presented in the table below.

Principles of Good Research Practice for Decision Analytic Modelling	**Where addressed in thesis**
Model Structure	
The model should reflect the chosen decision-making perspective. If a perspective narrower than societal is used, then the implications of broadening the perspective to the societal should be discussed.	Section 3.2: Modelling methods
The structure of the model should be consistent both with a coherent theory of the health condition being modelled and with available evidence regarding causal links between variables.	Section 3.2: Modelling methods
The limitations of the evidence supporting the chosen model structure should be acknowledged.	Section 3.2: Modelling methods
The structure of the model should be as simple as possible, while capturing underlying essentials of the disease process and interventions.	Section 3.2: Modelling methods
Options and strategies should not be strictly limited by the availability of direct evidence from clinical trials or currently accepted clinical practice.	Section 3.2: Modelling methods
Data availability may affect choices regarding model structure.	Section 3.2: Modelling methods

When appropriate, modelled populations should be disaggregated according to strata that have different event probabilities, quality of life, and costs.	Section 3.2: Modelling methods
The time horizon of the model should be long enough to reflect important and valued differences between the long run consequences and costs of alternative options and strategies.	Section 3.1.1 Economic modelling
Data identification	
A model should not be faulted because existing data fall short of idea standards of scientific rigor. Decisions will be made, with or without the model.	Box A: Priorities for research to improve parameter estimates
Systematic reviews of the literature should be conducted on key model inputs. Evidence that such reviews have been done should accompany the model.	Section 3.2: Modelling methods and Appendix D
Ranges (ie upper and lower bounds) should accompany base-case estimates of all input parameters for which sensitivity analyses are performed.	Tables of Parameters and values tested in sensitivity analysis for each model
Specification of probability distributions for input parameters based on sampling uncertainly and/or between study variations may be incorporated into formal probabilistic sensitivity analysis. This is not always necessary or cost effective.	Probabalistic sensitivity analysis was not necessary for these models
If known data sources are excluded from consideration in estimating parameters, the exclusion should be justified.	Not applicable
Data sources and results should not be rejected solely because they do not reach generally accepted probability thresholds defining ‘statistical significance’.	Section 3.2: Modelling methods
Expert opinion is a legitimate method for assessing parameters, provided either that these parameters are shown not to affect the results importantly or that a sensitivity analysis is reported on these parameters with a clear statement that results are conditional upon this/these subjective estimate/s.	Section 3.2: Modelling methods

A case should be made that reasonable opportunities to obtain new additional data prior to modelling have been considered.	Not applicable
Data Modeling	
Data modelling assumptions should be disclosed and supported by evidence of their general acceptance and, preferably, of their empirical validity. Key steps taken in developing the model should be carefully documented and recorded.	Structure of the decision model section of each model includes a referenced list of assumptions
When alternative, equally defensible, data modelling approaches may lead to materially different results, sensitivity analysis should be performed to assess the implications of these alternatives	Not applicable
Data modelling methods should follow generally accepted methods of biostatistics and epidemiology.	Not applicable
Data incorporation	
Measurement units, time intervals, and population characteristics should be mutually consistent throughout the model	Throughout the description of each model
All modelling studies should include extensive sensitivity analysis of key parameters. Either deterministic or probabilistic sensitivity analyses are appropriate	Deterministic sensitivity analysis conducted for each model
Validation	
Models should be subjected to thorough internal testing and debugging.	Section 3.2: Modelling methods
Models should be calibrated against population data where available	Section 3.2: Modelling methods
Copies of models with reasonable user interface should be made available for peer review purposes	Section 3.2: Modelling methods

Models should be developed independent from one another	Section 3.2: Modelling methods
If a model's outputs differ appreciably from other available results, then explanation of the discrepancies should be made	Section 3.2: Modelling methods
Modellers should cooperate with each other in comparing results and articulating reasons for discrepancies	Section 3.2: Modelling methods
Models should be based on the best evidence available at the time they are built	Section 3.2: Modelling methods
It is not necessary that every data estimate or structural assumption be tested in prospective studies in advance of model use	Section 3.2: Modelling methods
Models should never be regarded as complete or immutable. They should be repeatedly updated and sometimes replaced, as new evidence becomes available to inform their structure and input values.	Section 3.2: Modelling methods and 3.8: Modelling Discussion.

Appendix G: Search strategies for adverse event models

Diarrhoea search strategies

Cochrane Library search strategy—diarrhoea best practice

Number	Search strategy
1	Chemotherapy
2	Diarrhoea OR diarrhoea
Result	11 guidelines identified, 0 included in the review

Medline search strategy—diarrhoea best practice

Number	Search strategy
1	Neoplasms*
2	Drug Therapy*
3	Chemotherapy
4	Diarrhoea*
5	Diarrhoea
6	Practice guideline*
7	Practice guideline as topic*
8	Best practice
9	Gold standard
10	1 AND (2 OR 3) AND (4 OR 5) AND (6 OR 7 OR 8 OR 9)
Result	172 guidelines identified, 4 included in the review

* MeSH heading

National Guidelines Clearinghouse search strategy—diarrhoea best practice

Number	Search strategy
1	Diarrhoea, in 'Neoplasms'
2	Diarrhoea, in 'Neoplasms'
Result	36 guidelines identified, 1 included in the review

Web-based searches using the internet engines Google and Google Scholar were conducted using the search terms *chemotherapy*, *diarrhoea*, *diarrhea* and *practice guidelines*. The bibliographies of retrieved publications were hand-searched for any relevant references missing in the database search.

Cochrane Library search strategy—diarrhoea inputs

Number	Search strategy
1	Chemotherapy AND Diarrhoea
2	Cancer AND Octreotide
3	Cancer AND Loperamide
4	Antibiotics AND Cancer AND Diarrhoea
Result	36 papers identified, 10 included in the review

Medline search strategy—diarrhoea inputs

Number	Search strategy
1	Neoplasms*
2	Drug Therapy*
3	Chemotherapy
4	Diarrhoea*
5	Diarrhoea
6	Octreotide*
7	Loperamide*
8	Anti-bacterial agents*
9	Quality of Life*
10	Utilities
11	Choice Behaviour*
12	1 AND (2 or 3) AND (4 or 5)
13	12 AND 6
14	12 AND 7
15	12 AND 8
16	12 AND (9 or 10 or 11)
Result	10 papers identified, 2 included in the review

* MeSH heading

Web-based searches using the internet engines Google and Google Scholar were conducted using the search terms *chemotherapy*, *diarrhoea*, *diarrhea* and *practice guidelines*. The bibliographies of retrieved publications were hand-searched for any relevant references missing in the database search.

Anaemia search strategies

Cochrane Library search strategy—anaemia best practice

Number	Search strategy
1	Chemotherapy
2	Anaemia OR Anaemia
Result	13 guidelines identified, 3 included in the review

Medline search strategy—anaemia best practice

Number	Search strategy
1	Neoplasms*
2	Drug Therapy*
3	Chemotherapy
4	Anaemia*
5	Anaemia
6	Practice guideline*
7	Practice guideline as topic*
8	Best practice
9	Gold standard
10	1 AND (2 OR 3) AND (4 OR 5) AND (6 OR 7 OR 8 OR 9)
Result	42 guidelines identified

* MeSH heading

National Guidelines Clearinghouse search strategy—anaemia best practice

Number	Search strategy
1	Anaemia, in 'Neoplasms'
2	Anaemia, in 'Neoplasms'
Result	6 guidelines identified, 4 included in the review

Web-based searches using the internet engines Google and Google Scholar were conducted using the search terms *chemotherapy*, *anaemia*, *anemia* and *practice guidelines*. The bibliographies of retrieved publications were hand-searched for any relevant references missing in the database search.

Cochrane Library search strategy—anaemia inputs

Number	Search strategy
1	Chemotherapy AND (Anaemia or anaemia)
2	Cancer AND transfusion
Result	13 reviews identified, 2 included in the review

Two large systematic reviews examining the effects of erythropoietin and darbepoetin for patients with cancer in terms of anaemia and survival (published in 2009 and 2010 respectively) were identified in the Cochrane Collaboration, which provides high-quality systematic reviews of evidence. Therefore, the Medline search was limited to articles published between 2009 and the date of the search.

Medline search strategy—anaemia inputs

Number	Search strategy
1	Neoplasms*
2	Drug Therapy*
3	Chemotherapy
4	Anaemia*
5	Anaemia
6	Erythropoietin*
7	Darbepoetin
8	Blood Transfusion*
9	'Quality of Life'*
10	Utilities
11	Choice Behaviour*
12	1 AND (2 or 3) AND (4 or 5)
13	12 AND 6
14	12 AND 7
15	12 AND 8
16	12 AND (9 or 10 or 11)

* MeSH inputs

Web-based searches using the internet engines Google and Google Scholar were conducted using the search terms chemotherapy, *anaemia*, *anemia* and *practice* guidelines. The bibliographies of retrieved publications were hand-searched for any relevant references missing in the database search

Nausea and vomiting search strategies

Cochrane Library search strategy—nausea and vomiting best practice

Number	Search strategy
1	Chemotherapy
2	Nausea
3	Vomiting
4	1 AND (2 or 3)
Results	35 papers identified, 5 included in the review

Medline search strategy—nausea and vomiting best practice

Number	Search strategy
1	Neoplasms*
2	Drug Therapy*
3	Chemotherapy
4	Nausea*
5	Vomiting*
6	Emesis
7	Practice guideline*
8	Practice guidelines as topic*
9	Guideline*
10	Best practice
11	Gold standard
12	1 AND (2 OR 3) AND (4 OR 5 OR 6) AND (7 OR 8 OR 9 OR 10 OR 11)
Result	42 papers identified, 33 included in the review

* MeSH heading

National Guidelines Clearinghouse search strategy—nausea and vomiting best practice

Number	Search strategy
1	Nausea, in 'Neoplasms'
2	Vomiting, in 'Neoplasms'
Result	85 papers identified, 2 included in the review

Web-based searches using the internet engines Google and Google Scholar were conducted using the search terms *chemotherapy*, *nausea*, *vomiting* and *practice guidelines*. The bibliographies of retrieved publications were hand-searched for any relevant references missing in the database search.

Cochrane Library search strategy—nausea and vomiting inputs

Number	Search strategy
1	Chemotherapy AND (nausea or vomiting)
2	Cancer AND serotonin antagonist
3	Cancer AND dexamethasone
4	Cancer and aprepitant
5	Cancer AND corticosteroids

Medline search strategy—nausea and vomiting inputs

Number	Search strategy
1	Neoplasms*
2	Drug Therapy*
3	Chemotherapy
4	Nausea*
5	Vomiting*
6	Emesis
7	Serotonin antagonists*
8	Dexamethasone*
9	Aprepitant
10	Antiemetics*
11	Adrenal cortex hormones*
12	'Quality of Life'*
13	Utilities
14	Choice Behaviour*
15	1 and (2 or 3) and (4 or 5 or 6)
16	15 AND (7 or 8 or 9 or 10 or 11)
17	15 AND (12 or 13 or 14)
Result	224 papers identified

* MeSH headings

Web-based searches using the internet engines Google and Google Scholar were conducted using the search terms *chemotherapy*, *nausea*, *vomiting* and *practice guidelines*. The bibliographies of retrieved publications were hand-searched for any relevant references missing in the database search

Neutropoenia search strategies

Cochrane Library search strategy—neutropoenia best practice

Number	Search strategy
1	Chemotherapy
2	Neutropoenia
3	Febrile neutropoenia
4	Infection
5	1 AND (2 or 3 or 4), limited to reviews

Medline search strategy——neutropoenia best practice

Number	Search strategy
1	Neoplasms*
2	Drug Therapy*
3	Chemotherapy
4	Neutropoenia*
5	Febrile neutropoenia
6	Practice guideline*
7	Practice guidelines as topic*
8	Guideline*
9	Best practice
10	Gold standard
11	1 AND (2 OR 3) AND (4 OR 5) AND (6 OR 7 OR 8 OR 9 OR 10)
Result	36 papers identified, 4 included in the review

* indicates MeSH headings

National Guidelines Clearinghouse search strategy—neutropoenia best practice

Number	Search strategy
1	Chemotherapy AND neutropoenia
Result	85 papers identified, 2 included in the review

Web-based searches using the internet engines Google and Google Scholar were conducted using the search terms chemotherapy, neutropoenia and practice guidelines. The bibliographies of retrieved publications were hand-searched for any relevant references missing in the database search.

Cochrane Library search strategy—neutropoenia inputs

Number	Search strategy
1	Chemotherapy AND neutropoenia
2	Cancer AND filgrastim
3	Cancer AND pegfilgrastim
4	Cancer AND sargramostim
5	Cancer AND fluoroquinolones

Medline search strategy—neutropoenia inputs

Number	Search strategy
1	Neoplasms*
2	Drug Therapy*
3	Chemotherapy
4	Neutropoenia*
5	Febrile neutropoenia
6	Granulocyte Colony-Stimulating Factor*
7	Filgrastim
8	Pegfilgrastim
9	Sargramostim
10	Fluoroquinolones*
11	Antibiotics
12	'Quality of Life'*
13	Utilities
14	Choice Behaviour*
15	1AND (2 or 3) AND (4 or 5)
16	15 AND (6 or 7 or 8 or 9 or 10 or 11)
17	15 AND (12 or 13 or 14)

* = MeSH headings

Web-based searches using the internet engines Google and Google Scholar were conducted using the search terms *chemotherapy*, *neutropoenia* and *practice guidelines*. The bibliographies of retrieved publications were hand-searched for any relevant references missing in the database search.

Appendix H: Previous studies that included a cost of diarrhoea

Reference	Study design	Cancer and stage	Diarrhoea management resource categories	Diarrhoea treatment costs (International$ 1999)	Summary of diarrhoea costs
Tumeh (2009) US (88)	Markov decision model designed to compare the efficacy and cost-effectiveness of FOLFOX (folinic acid, fluorouracil and oxaliplatin) with FOLFIRI (folinic acid, fluorouracil and irinotecan)	Metastatic colorectal cancer	Outpt visits, laboratory tests, medication	$150.60 per incidence	The cost of diarrhoea was included in a model of chemotherapy cost-effectiveness, based on reimbursement costs
Carlson (2008) US (119)	Decision-analysis model designed to evaluate incremental costs of, and QALYs gained from, erlotinib, docetaxel or pemetrexed	Stage IIIb/IV head and neck cancer	Hospitalisation, inpt doctor visits, outpt visits, medications	$155 per event	The cost of diarrhoea was included in a model of cost-effectiveness and cost-utility, based on clinical trials and DRGs
Danese (2008) US (127)	Budget impact model of adding erlotinib to a US health-plan insurer's formulary	Locally advanced, nonresectable or metastatic pancreatic cancer	Outpt visits, hospitalisation, inpt doctor visits, medications	Low-grade: $144 per AE; High-grade: $773.24 per AE	The cost of Grade III/IV diarrhoea was included in the model, based on US Medicare reimbursement rates to the insurer
Douillard (2007) France (142)	Cost consequences analysis of capecitabine, de Gramont and Mayo Clinic regimens	Stage III colorectal cancer	Outpt visits, medications, hospitalisations	Ambulatory: $49.48 per AE; Hospitalisation: $1,148.30 per AE	The cost of Grade III/IV diarrhoea was included in the model, based on DRG tariffs and expert opinion
Ojeda (2003) Spain (98)	Cost-minimisation of PLD vs. topotecan	Recurrent epithelial ovarian cancer	NS	Mild: $0 per AE; Mod: $69.20 per AE; Severe: $654.60 per AE; Life-threatening: $1,438.39 per AE	Cost of diarrhoea at all grades was included using an expert panel to estimate resource-use and administrative data for unit costs
Hillner (2005) US (214)	Markov model of the cost-effectiveness of FOLFOX vs. irinotecan and bolus fluorouracil	Metastatic colorectal cancer	Hospitalisations, inpt doctor visits	$8,662.64 per treatment cycle with Grade III/IV diarrhoea	Costs of Grade III/IV diarrhoea were included, based on Medicare reimbursement for DRG codes

Reference	Study design	Cancer and stage	Diarrhoea management resource categories	Diarrhoea treatment costs (International$ 1999)	Summary of diarrhoea costs
Le (2009) US(143)	Markov model of the cost-effectiveness of capecitabine +/– lapatinib	Advanced breast cancer	NS	$6,713.10: base-case cost of treating an event	A range for the cost of Grade III/IV diarrhoea was included, based on published literature
Wolowacz (2008) UK (298)	Markov model of cost-effectiveness and cost-utility of Taxotere®, Adriamycin® and cyclophosphamide vs. 5-FU, doxorubicin, cyclophosphamide as adjuvant therapy	Early node-positive breast cancer	NS	$3,972.19 per episode	The cost of Grade III/IV diarrhoea was included, based on published literature
Dranitsaris (2009) Canada (303)	Cost consequences and cost-effectiveness analysis of nab-paclitaxel or docetaxel vs. paclitaxel	Metastatic breast cancer	Medications	$2,198.27 per event	The cost of Grade III/IV toxicity, based on oncology literature. Utilities collected through TTO with nurses and pharmacists
Ramsey (2006) US (89)	Budget impact model to assess total cost of docetaxel, pemetrexed and erlotinib	Advanced NSCLC	Medications, hospitalisation, inpt doctor visits	Expected cost to plan: no hospital $84.40; hospital $1,520.43	Costs for Grade III/IV diarrhoea included, based on prescribing information (incidence) and Medicare reimbursements rates
Ward (2007) UK (304)	State transition model to assess cost-effectiveness of three adjuvant chemotherapies	Early breast cancer	Hospitalisation	Total cost: $1,716.51	Based on results of three randomised controlled trials with economic components
Takeda (2007) UK (305)	Markov model of cost-effectiveness of gemcitabine + paclitaxel as second-line therapy	Metastatic breast cancer	NS	Expected cost per cycle: $238.73	Cost data, based on a single clinical trial, not fully published
Jansman (2004) Netherlands (306)	Cost–benefit analysis of capecitabine vs. Mayo Clinic regimen	Palliative and adjuvant colorectal cancer	Travel, hospitalisation, medications	Mean cost per patient: palliative $4,311.81; adjuvant $1,153.07	Cost of diarrhoea based on travel, inpt days and medication, although source not specified

Reference	Study design	Cancer and stage	Diarrhoea management resource categories	Diarrhoea treatment costs (International$ 1999)	Summary of diarrhoea costs
Tampellini (2004) Italy (102)	Cost-minimisation of FOLFOX vs. modified FOLFOX	Metastatic colorectal cancer	Medications, hospitalisation	$2.34–$176.68 per event	Costs of toxicities were estimated from the literature
Dranitsaris (2005a) Canada (107)	Cost-of-illness study of diarrhoea	Adjuvant or palliative colorectal cancer	Hospitalisation, lab. tests, diagnostic tests, nursing time, inpt doctor visits, outpt visits	Mean cost per patient: $6,766.11	Cost of diarrhoea treatment items based on local costs and literature
Dranitsaris (2005b) Canada (108)	Cost-of-illness study of diarrhoea	Adjuvant or palliative colorectal cancer	Hospitalisation, lab. tests, diagnostic tests, nursing time, inpt doctor visits, outpt visits	Mean cost per patient: $2,081.07	Cost of diarrhoea treatment items based on local costs and literature
Arbuckle (2000) US (110)	Total cost of diarrhoea	Colorectal cancer	Medications, outpt visits, hospitalisation	Total for 100 patients: $93,593.70	Costs based on local values for direct resource-use
Chu (2009) US (159)	Total cost of diarrhoea with various fluorouracil regimens	Colorectal cancer	Outpt visits, hospitalisation, medications	Mean monthly expenditure during treatment episode, depending on chemotherapy: $31.65–$55.10	Cost of complications included in model based on total claim amount and direct healthcare expenditure
Smith (2002) Europe & North America (160)	Cost-minimisation analysis of PLD vs. topotecan	Second-line ovarian cancer	Medications, outpt visits, hospitalisation	Mean cost per person depending on chemotherapy: $35.14–$62.02	Costs from national formularies and/or authorities

Reference	Study design	Cancer and stage	Diarrhoea management resource categories	Diarrhoea treatment costs (International$ 1999)	Summary of diarrhoea costs
Levy-Piedbois (2000) France (162)	Cost-effectiveness analysis of second line irinotecan vs. fluorouracil	Metastatic colorectal cancer	Hospitalisation, outpt visits	Diarrhoea only: $20,773 total cost for 7 patients; Diarrhoea + infection: $17,805 total cost for 6 patients; Diarrhoea + other: $15,435 total cost for 9 patients	Costs derived from the accounting system at local hospitals
Capri (2003) Italy (99)	Cost-minimisation analysis of PLD vs. topotecan	Second-line ovarian cancer	Outpt visits, lab. tests, hospitalisation, medications	Mean cost per patient: Grade I $11.83; Grade II $26.02; Grade III $1,089.40; Grade IV $1,441.88	Unit costs were based on national formulary and DRG reimbursement rates

Note: DRGs = diagnosis related groups; AE = adverse event; G = grade; inpt = inpatient; lab. = laboratory; NS = not stated; outpt = outpatient; NSCLC = non-small-cell lung cancer; PLD = pegylated liposomal doxorubicin; QALYs = quality adjusted life years; TTO = time trade-off.

Appendix I: Diarrhoea TreeAge model

Appendix J: Previous studies that included a cost of anaemia

Reference	Study design	Cancer and stage	Anaemia management resource categories	Anaemia treatment costs (International$ 1999)	Summary of anaemia costs
Carlson (2008) US **(119)**	Decision analytic model to evaluate incremental costs and QALYs of erlotinib, docetaxel or pemetrexed	Stage IIIb/IV NSCLC	Medication, transfusions	$3,695.07 per AE	The cost of anaemia was included in a model of chemotherapy cost-effectiveness, based on costs reported in the literature (source not provided)
Ojeda (2003) Spain **(98)**	Cost-minimisation decision model of PLD vs. topotecan	Metastatic ovarian cancer	NS	Mild: $0 Moderate: $983.37 Severe: $489.76 Life-threatening: $733.91 (All costs per AE)	The cost of anaemia was included in a cost-minimisation model of chemotherapy cost-effectiveness. The resources used to manage anaemia were obtained from an expert panel
Wolowacz (2008) UK **(298)**	Markov model of the cost-effectiveness and cost-utility of Taxotere®, Adriamycin® and cyclophosphamide vs. fluorouracil, doxorubicin and cyclophosphamide as adjuvant therapy	Early breast cancer	NS	$3,088.78 per episode	The cost of anaemia was included in a model of chemotherapy cost-effectiveness, based on costs reported in the literature
Dranitsaris (2009) Canada **(303)**	Cost consequences and cost-effectiveness analysis of nab-paclitaxel or docetaxel vs. paclitaxel	Metastatic breast cancer	Transfusions, medications	$2,237.28 per patient	The cost of anaemia was included in a model of chemotherapy cost-effectiveness, based on costs reported in the literature
Ramsey (2006) US **(89)**	Budget impact model to assess total cost of docetaxel, pemetrexed and erlotinib	Metastatic NCSLC	Outpt visit, medications, transfusions	$295.41 expected cost to plan	The cost of anaemia was included in a model of chemotherapy total cost.

Reference	Study design	Cancer and stage	Anaemia management resource categories	Anaemia treatment costs (International$ 1999)	Summary of anaemia costs
Wilson (2007) UK **(105)**	Independent sampling model to assess the cost-effectiveness of epoetin treatment compared with standard care with blood transfusion alone	Any cancer, any stage	Medications, transfusions, administration and adverse events of epoetin and blood transfusions	$23,2648.80 ICER	The cost-effectiveness of two treatments for chemotherapy-induced anaemia was compared
Ward (2007) UK **(304)**	State transition model to assess cost-effectiveness of docetaxel vs. paclitaxel vs. non-taxane anthracycline-containing chemotherapy (adjuvant)	Early breast cancer	Transfusions, hospitalisation	$1,217.55 total initial cost to manage event	The cost of anaemia was included in a model of chemotherapy cost-effectiveness, based on costs reported in the literature
Takeda (2007) UK **(305)**	Markov model for cost-effectiveness of gemcitabine + paclitaxel as 2nd line therapy	Metastatic breast cancer	NS	$964.04 expected cost per cycle per person	The cost of anaemia was included in a model of chemotherapy cost-effectiveness, based on costs reported in the literature
Borg (2008) Sweden **(94)**	Markov model to estimate the incremental costs and QALY gains associated with erythropoietin stimulating agent treatment compared with RBC transfusion for anaemia	Any cancer, any stage	Transfusions, medication, hospitalisation	$2,701.56 per QALY	The cost-effectiveness of two treatments for chemotherapy-induced anaemia was compared

Reference	Study design	Cancer and stage	Anaemia management resource categories	Anaemia treatment costs (International$ 1999)	Summary of anaemia costs
Touchette (2006) US **(95)**	Markov model of cost-effectiveness of amifostine from a hospital's perspective	Stage IIIb/IV NSCLC	RBC	$198.45 per month of chemotherapy	The cost of anaemia was included in a model of adverse-event chemoprevention, based on costs from unspecified sources
Tampllini (2004) Italy **(102)**	Cost-minimisation of FOLFOX vs. FOLFOX chronotherapy	Metastatic colorectal cancer	Medications, hospitalisation	$269.37 per AE	The cost of anaemia was included in a cost-minimisation model of chemotherapy, with costs based on the literature (source not specified)
Liu (2008) Taiwan **(113)**	Regression analysis of the medical resource utilisation of people with chemotherapy-induced anaemia	Any stage gastric, colorectal, lung or breast cancer	Hospitalisation, outpt visits	$9,920.21 total cost with anaemia; $8,580.70 total cost with no anaemia (2001–02) $9,928.80 total cost with anaemia; $8,518.18 total cost with no anaemia (2002–03)	A population representative claims database was used to analyse the differences in resource utilisation and economic burden of patients receiving chemotherapy who experience anaemia compared with those who do not
Martin (2003) UK **(96)**	Incremental cost-utility analysis of survival with erythropoietic stimulating agents vs. placebo	Stage IV breast cancer	Medications, diagnostic tests, hospitalisation, outpt visits	$16,909.04 mean cost per patient	The costs of anaemia were included in a cost-utility analysis, based on data from a randomised controlled trial
Fagnoni (2006) France **(156)**	Retrospective before-and-after case-study analysis of erythropoietic stimulating agents in adjuvant chemotherapy	Breast cancer	Medications, transfusions, hospitalisation	$36.16 mean cost per patient with no erythropoietic stimulating agents treatment; $1,753.70 mean cost per patient with erythropoietic stimulating agents when required	The direct costs of erythropoietic stimulating agents to manage chemotherapy-induced anaemia were included in this cost-effectiveness analysis.

Reference	Study design	Cancer and stage	Anaemia management resource categories	Anaemia treatment costs (International$ 1999)	Summary of anaemia costs
Novello (2005) Italy **(157)**	Cost-minimisation analysis of gemcitabine and/or cisplatin vs. paclitaxel and/or carboplatin vs. vincristine and/or cisplatin	Locally advanced, recurrent or metastatic NSCLC	Hospitalisation, transfusions, medications, lab. tests	$3,973.79 per AE	Resource consumption during a clinical trial, including for anaemia, was calculated for a cost-minimisation analysis
Groener (1999) Netherlands **(158)**	Cost-effectiveness analysis of raltitrexed and 5-FU + leucovorin	Advanced colorectal cancer	Hospitalisation, lab tests, outpt visits, travel, medications, diagnostic tests	$2,328.00 per patient	The costs of anaemia were included in a cost-effectiveness analysis, based on data from a randomised controlled trial
Chu (2009) US **(307)**	Regression analysis of patient database to assess frequency and costs of chemotherapy-related complications	Colorectal cancer	Outpt visits, hospitalisation and medication	$250.87 mean monthly expenditure during treatment episode with capecitabine alone, to $661.16 mean monthly expenditure during treatment episode with 5-FU + oxaliplatin	Regression analysis was used to predict the frequency and costs of chemotherapy complications, including anaemia.
Smith (2002) Europe and North America **(160)**	Cost-minimisation of PLD vs. topotecan	Second line treatment for ovarian cancer	Medications, outpt visits and hospitalisation	$5,355.15 (US topotecan) $481.66 (US PLD) $1480.13 (UK topotecan) $195.35 (UK PLD)	The cost of anaemia was included in a cost-minimisation model of chemotherapy, with costs based on the literature
Persson (2005) Sweden **(161)**	Retrospective chart review of utilisation, outcomes and cost of erythropoietic stimulating agents to treat anaemia	Any stage of any solid tumour cancer	Medications, hospitalisations, transfusions	$8,001.89 mean cost per patient with epoetin alpha; $9,135.64 mean cost per patient with darbepoetin alpha	The cost of anaemia was determined by a retrospective analysis of patient records

Reference	Study design	Cancer and stage	Anaemia management resource categories	Anaemia treatment costs (International$ 1999)	Summary of anaemia costs
Annemans (1999) Netherlands, Belgium, France and Spain **(103)**	Cost-effectiveness of paclitaxel and cisplatin compared with teniposide and cisplatin	Advanced, previously untreated NSCLC	Medication, diagnostic tests, lab. tests, inpt doctor visits	Netherlands: $426 cost of one moderate or severe episode; Belgium: $345 cost of one severe episode, $73 cost of one moderate episode; Spain: $300 cost of one severe episode, $89 cost of one moderate episode; France: $561 cost of one severe episode, $33 cost of one moderate episode	The cost of anaemia was included in a model of chemotherapy cost-effectiveness, using trial-based resources for anaemia management
Levy-Piedbois (2000) France **(162)**	Cost-effectiveness of irinotecan vs. 5-FU	Metastatic colorectal cancer	Hospitalisation, outpt visits	$7,075 total cost for 7 patients	The cost of anaemia was included in a model of chemotherapy cost-effectiveness, using trial-based resources for anaemia management
Capri (2003) Italy **(99)**	Cost-minimisation analysis of PLD	Failed first-line treatment for ovarian cancer	Outpt visits, lab. tests, hospitalisation, medications	$24.84 mean per patient: Grade I; $1,620.49 mean per patient: Grade II; $2,780.86 mean per patient: Grade III; $3,481.10 mean per patient: Grade IV	The cost of anaemia was included in a model of chemotherapy cost-effectiveness, using trial-based resources for anaemia management

Note: AE = adverse event; ICER = incremental cost-effectiveness ratio; inpt = inpatient; lab. = laboratory; NS = not stated; NSCLC = non-small-cell lung cancer; outpt = outpatient; PLD = pegylated liposomal doxorubicin; QALY = quality adjusted life year; RBC = red blood cell; UK = United Kingdom; US = United States of America

Appendix K: Anaemia TreeAge model

Appendix L: Previous studies that included a cost of nausea and vomiting

Reference	Study design	Cancer and stage	Nausea and vomiting management resource categories	Nausea and vomiting treatment costs (International$)	Summary of nausea and vomiting costs
Carlson 2008 US (119)	Decision analytic model to evaluate the incremental costs and QALYs of erlotinib, docetaxel and pemetrexed	Advanced NSCLC	Outpt visits	$152 per event (Grade III/IV only)	The cost of nausea and vomiting was included in a model of chemotherapy cost-effectiveness, based on incidence rates in clinical trials and assumed treatments with reimbursement costs
Danese 2008 US (127)	Budget impact model of adding erlotinib to gemcitabine	Metastatic pancreatic cancer	Outpt visits, hospitalisation, inpt doctor visits	$5,563 per event	The cost of nausea and vomiting was included in a model of chemotherapy cost-effectiveness, based on cancer registry and clinical trial data
Douillard 2007 France (142)	Cost consequences analysis of capecitabine, Mayo Clinic and de Gramont regimens	Stage III colorectal cancer	Outpt visits, medications, hospitalisations	$137 unit cost for ambulatory care; $1,385 unit cost for hospitalisation	The cost of nausea and vomiting was included in an analysis of the costs of chemotherapy, based on clinical trial data and expert opinion
Ojeda 2003 Spain (98)	Cost-minimisation analysis of PLD hydrochloride vs. topotecan	Recurrent epithelial ovarian cancer	NS	Per event: Mild $0.02, Moderate $0.43, Severe $357, Life-threatening $1,513	The cost of nausea and vomiting was included in a model of chemotherapy cost-effectiveness, based on incidence rates in clinical trials, and costs estimated by expert opinion
Hillner 2005 US (214)	Incremental cost-effectiveness projection using simulated cohorts starting FOLFOX or starting irinotecan, leucovorin and fluorouracil	Metastatic colorectal cancer	Hospitalisation, inpt doctor visits	$5,102 per event (Grade III/IV only)	The cost of nausea and vomiting was included in a model of chemotherapy cost-effectiveness, based on clinical trial data and reimbursement costs

Reference	Study design	Cancer and stage	Nausea and vomiting management resource categories	Nausea and vomiting treatment costs (International$)	Summary of nausea and vomiting costs
Wolowacz 2008 UK (298)	Markov model estimating the cost and outcomes from initiation of adjuvant chemotherapy to death	Early breast cancer	NS	$3,472 per episode (Grade III/IV only)	The cost of nausea and vomiting was included in a model of chemotherapy cost-effectiveness, based on clinical trial data, observational data and hospital costs
Dranitsaris 2009 Canada (303)	Economic analysis comparing nab-paclitaxel and docetaxel with paclitaxel	Metastatic breast cancer	Medications	$706 per event (Grade III/IV only)	The costs of nausea and vomiting were included in a model of chemotherapy cost-effectiveness based on a meta-analysis of trial data and oncology literature
Ward 2007 UK (304)	Clinical and cost-effectiveness of docetaxel and paclitaxel compared with non-taxane anthracycline-containing chemotherapy regimens	Early stage breast cancer	Hospitalisation	$1,717 per event (Grade III/IV only)	The costs of nausea and vomiting were included in a model of chemotherapy cost-effectiveness based on trial data and UK reference costs
Takeda 2007 UK (305)	Clinical and cost-effectiveness of gemcitabine	Metastatic breast cancer	NS—sourced from literature	$671 per cycle (Grade III/IV only)	The costs of nausea and vomiting were included in a model of chemotherapy cost-effectiveness based on trial data and other published studies
Annemans 2008 Belgium (295)	Cost-effectiveness analysis using a decision analytic model of aprepitant in the prevention of chemotherapy-induced nausea and vomiting	Any cancer, any stage	Medications	Cisplatin: $73 incremental cost; cyclophosphamide: $20 incremental cost. Greater differences seen when assessed with real-life data	A decision analytic model was used to assess the cost of nausea and vomiting when aprepitant was used, compared with standard prevention strategies. A comparison of trial-based vs. observational-data approaches to estimating resource-use was undertaken

Reference	Study design	Cancer and stage	Nausea and vomiting management resource categories	Nausea and vomiting treatment costs (International$)	Summary of nausea and vomiting costs
Lordick 2007 Germany (97)	Outcomes and cost-effectiveness of aprepitant for high-emetogenic-risk chemotherapy	Any cancer, any stage	Medications	$32,248 per QALY	A decision analytic model developed to assess the cost-effectiveness of aprepitant vs. a control regimen for prevention of chemotherapy-induced nausea and vomiting. Inputs based on trial data and costs from health-insurance perspective
Jansman 2004 Netherlands (306)	Cost–benefit analysis of capecitabine vs.5-FU + leucovorin	Colorectal cancer, any stage	Travel, inpt days, medications	$1,727 mean cost per patient	A decision analytic model was constructed to assess the cost–benefit of chemotherapy, based on single-centre retrospective file review for resource-use
Tampellini 2004 Italy (102)	Cost-minimisation of chrono-chemotherapy and FOLFOX	Metastatic colorectal cancer	Medications and hospitalisation	Chronotherapy $163.43 per cycle for prevention; FOLFOX $238.45 per cycle for prevention	The costs of nausea and vomiting were included in a chemotherapy cost-minimisation analysis, based on direct costs of drugs and incidence of adverse events from clinical trials
Barrajon 2000 Spain (308)	Cost–benefit analysis comparing ondansetron, granisetron and tropisetron in preventing chemotherapy-induced nausea and vomiting	Multiple cancers	Drug purchase, materials for infusion, nursing time, doctor time, hospitalisation	Minimum cost per patient: tropisetron $27; granisetron $43.23; ondansetron $31.67	A randomised double-blind crossover study of three treatments to prevent chemotherapy-induced nausea and vomiting, including a cost–benefit analysis. Inputs were based on direct and indirect costs obtained during the trial
Novello 2005 Italy (157)	Cost-minimisation analysis of gemcitabine & cisplatin, paclitaxel & carboplatin and vinorelbine & cisplatin	Metastatic NSCLC	Hospitalisation, transfusions, medication, lab. tests	$2,919 per event	The cost of nausea and vomiting was included in a retrospective chemotherapy cost-minimisation analysis. Resource-use and costs were based on clinical trial data

Reference	Study design	Cancer and stage	Nausea and vomiting management resource categories	Nausea and vomiting treatment costs (International$)	Summary of nausea and vomiting costs
Chu 2009 US (159)	Generalised linear models were used to predict monthly complication costs of 5-FU chemotherapy treatments	Colorectal cancer	Outpt, hospitalisation, medications	$197–$475 mean monthly expenditure during treatment episode, depending on chemotherapy	The contribution of nausea and vomiting to total monthly costs during chemotherapy treatment was estimated using regression analysis of an administrative database
Smith 2002 US and UK (160)	Comparative economic analysis of PLD vs. topotecan	Ovarian cancer	Medications, clinic visits, hospitalisation	US mean costs per person: topotecan $86 PLD $51 UK mean costs per person: topotecan $308 PLD $156	The cost of nausea and vomiting was included in a chemotherapy cost-minimisation analysis, based on clinical trial data and previously reported economic analyses
Geling 2005 Canada (309)	Estimate clinical efficacy and drug acquisition costs of administering 5-HT3RAs beyond 24 hrs to prevent delayed nausea and vomiting	Any cancer, any stage	Medication	$256 drug acquisition costs per patient protected from delayed nausea and vomiting per cycle	The costs of nausea and vomiting were estimated based on a meta-analysis of 5-HT3RA efficacy in preventing nausea and vomiting related to chemotherapy
Capri 2003 Italy (99)	Cost minimisation analysis of PLD vs. topotecan	Ovarian cancer	Outpt, lab. tests, hospitalisation, medications	Grade I $11 Grade II $84 Grade III $96 Grade IV $1,184	The cost of nausea and vomiting was included in a chemotherapy cost-minimisation analysis, based on Phase III trials and expert opinion derived from the Delphi method

Notes; 5-FU = 5-fluorouracil; inpt = inpatient; lab. = laboratory; NSCLC = non-small-cell lung cancer; outpt = outpatient; PLD = pegylated liposomal doxorubicin; US = United States

Appendix M: Nausea and vomiting TreeAge model

Appendix N: Previous studies that included a cost of neutropoenia

Reference	Study design	Cancer and stage	Neutropoenia management resource categories	Neutropoenia treatment costs (International $)	Summary of neutropoenia costs
Tumeh 2009 US **(88)**	Markov model assessing the effectiveness and cost-effectiveness of fluorouracil, with folinic acid and oxaliplatin vs. fluorouracil with folinic acid and irinotecan	Metastatic colorectal cancer	Outpt visits, hospitalisation	Neutropoenia $171 per incidence; febrile neutropoenia $4,535 per incidence	The cost of neutropoenia and febrile neutropoenia were included in a model of chemotherapy cost-effectiveness, based on incidence rates from trial data and reimbursement costs
Carlson 2008 US **(119)**	Decision analytic model to evaluate the incremental costs and QALYs of erlotinib, docetaxel or pemetrexed	Advanced NSCLC	Hospitalisation, inpt doctor visits	Neutropoenia $7,791 per event; febrile neutropoenia $15,156 per event	The cost of neutropoenia was included in a model of chemotherapy cost-effectiveness, based on incidence rates in clinical trials and reimbursement costs
Douillard 2007 France **(142)**	Cost consequences analysis of capecitabine, Mayo Clinic and de Gramont regimens	Stage III colorectal cancer	Hospitalisation	$2,684.63 unit cost	The cost of neutropoenia was included in an analysis of the costs of chemotherapy, based on clinical trial data and expert opinion
Bristow 2007 US **(302)**	Cost-effectiveness of intraperitoneal vs. intravenous chemotherapy	Stage III ovarian cancer	Hospitalisation, staff costs	$8,265 per hospitalisation	The cost of neutropoenia was included in a model of chemotherapy cost-effectiveness, based on incidence rates in clinical trials and actual charges from a health service
Ojeda 2003 Spain **(98)**	Cost-minimisation analysis of PLD hydrochloride vs. topotecan	Recurrent ovarian cancer	NS	Cost per adverse event: Mild $0 Moderate $0.54 Severe $202 Life-threatening	The cost of neutropoenia was included in a model of chemotherapy cost-effectiveness, based on incidence rates in clinical trials and costs estimated by expert opinion

Reference	Study design	Cancer and stage	Neutropoenia management resource categories	Neutropoenia treatment costs (International $)	Summary of neutropoenia costs
				$554	
Hillner 2005 US **(214)**	Incremental cost-effectiveness projection using simulated cohorts of patients starting fluorouracil, folinic acid and oxaliplatin vs. irinotecan, leucovorin (folinic acid) and fluorouracil	Metastatic colorectal cancer	Hospitalisation, inpt doctor visits	$11,339 cost per event	The cost of neutropoenia was included in a model of chemotherapy cost-effectiveness, based on incidence rates in trial data and reimbursement costs
Wolowacz 2008 UK **(298)**	Markov model estimating the cost and outcomes from initiation of adjuvant chemotherapy to death	Early breast cancer	NS	$2,220 cost per episode	The cost of neutropoenia was included in a model of chemotherapy cost-effectiveness, based on trial data, observational data and hospital costs
Dranitsaris 2009 Canada **(303)**	Economic analysis comparing nab-paclitaxel and docetaxel with paclitaxel	Metastatic breast cancer	Medications, hospitalisation, dose delay	Neutropoenia $1,020 per event; febrile neutropoenia $5,245 per event	The cost of neutropoenia was included in a model of chemotherapy cost-effectiveness based on a meta-analysis of trial data and oncology literature
Main 2006 UK **(100)**	A systematic review and economic evaluation of topotecan, PLD hydrochloride and paclitaxel	Advanced ovarian cancer	Outpt visits, medication, hospitalisation	$80.69 (units unknown)	The cost of neutropoenia was included in a model of chemotherapy cost-effectiveness, based on incidence rates from trial data and UK reference costs
Ward 2007 UK **(304)**	Clinical and cost-effectiveness of docetaxel and paclitaxel compared with non-taxane, anthracycline-containing chemotherapy regimens	Early stage breast cancer	Hospitalisation	$3,387 total initial cost to manage febrile neutropoenia event; $1,677 total cost of neutropoenia per	The cost of neutropoenia was included in a model of chemotherapy cost-effectiveness, based on incidence rates from trial data and UK reference costs

Reference	Study design	Cancer and stage	Neutropoenia management resource categories	Neutropoenia treatment costs (International $)	Summary of neutropoenia costs
				subsequent cycle	
Takeda 2007 UK **(305)**	Clinical and cost-effectiveness of gemcitabine	Metastatic breast cancer	NS—sourced from literature	$1,721 expected cost per cycle	The cost of neutropoenia was included in a model of chemotherapy cost-effectiveness based on trial data and other published studies
Liu 2009 UK **(91)**	Decision analytic model of the cost-effectiveness of pegfilgrastim vs. filgrastim primary prophylaxis	Early stage breast cancer	Medication	$6,572 ICER per episode of febrile neutropoenia avoided	A decision analytic model was developed to assess the cost-effectiveness of two treatments to prevent febrile neutropoenia, based on data from a review of the literature and expert opinion
Danova 2009 Italy **(92)**	Cost-effectiveness of pegfilgrastim vs. 6 days of filgrastim for preventing febrile neutropoenia	Early stage breast cancer	Medication, hospitalisation	$429 ICER for QALYs gained	A decision analytic model was developed to assess the cost-effectiveness of two treatments to prevent febrile neutropoenia, based on data from a review of the literature
Eldar-Lissai 2008 US **(293)**	Cost-utility model of prophylactic pegfilgrastim	Any solid tumour cancer, any stage	Medication	$1,984 mean estimated cost per day for surviving patients; $3,139 mean estimated cost per day for dying patients	A decision analytic model was developed to assess the cost-effectiveness of three treatments to prevent febrile neutropoenia, based on data from claims data and published literature
Lyman 2003 US **(86)**	Decision analytic model to determine the population risk threshold for neutropoenia at which prophylactic colony-stimulating factors become	Any cancer, any stage	Hospitalisation, medication	18% to 23% population risk is the threshold for cost-saving use	A decision analytic model was developed to determine the threshold for population risk of neutropoenia at which prophylactic treatment would become cost-effective. Inputs were based on a retrospective analysis of patient costs at

Reference	Study design	Cancer and stage	Neutropoenia management resource categories	Neutropoenia treatment costs (International $)	Summary of neutropoenia costs
	cost-effective				one hospital
Touchette 2006 US **(95)**	Markov model of amifostine to reduce or prevent chemotherapy toxicities, including neutropoenia	NSCLC	Hospitalisation	$9,309 per month of chemotherapy	A Markov model was developed to assess the cost-effectiveness of using amifostine to prevent chemotherapy toxicities, including neutropoenia. Inputs were based on clinical patient registry, medication dispensing records, clinical literature and costing catalogues
Cosler 2004 US **(292)**	A re-estimation of a decision analytic model to determine the population risk threshold for neutropoenia at which prophylactic colony-stimulating factors become cost-effective	Ovarian cancer	Medication, outpt visits, hospitalisation, lab. costs, phone calls, carer time, carer costs, patient time	$5,869 mean additional cost attributable to severe neutropoenia	A decision tree was re-estimated using addition direct and indirect costs to assess the threshold for population risk of neutropoenia at which prophylactic treatment would become cost-effective. Inputs were based on questionnaires of 26 patients
Bennett 2007 US **(106)**	Total cost of chemotherapy-induced febrile neutropoenia	Any cancer, any stage	Hospitalisation, outpt visits, lab. costs, phone calls, medication, patient time, carer time	$2,056 mean direct costs per patient; $1,652 mean indirect costs per patient	A cost-of-illness study of chemotherapy-induced febrile neutropoenia, with data collected using patient questionnaires
Jansman 2004 Netherlands **(306)**	Cost–benefit analysis of capecitabine vs.5-fluorouracil and leucovorin	Colorectal cancer, any stage	Travel, inpt days and medications	Palliative patients: $1,713 mean per patient Adjuvant patients: $2,969 mean per patient	A decision analytic model was constructed to assess the cost–benefit of chemotherapy, based on single-centre retrospective file review for resource-use

Reference	Study design	Cancer and stage	Neutropoenia management resource categories	Neutropoenia treatment costs (International $)	Summary of neutropoenia costs
Tampellini 2004 Italy **(102)**	Cost-minimisation of chrono-chemotherapy and fluorouracil, folinic acid and oxaliplatin	Metastatic colorectal cancer	Medication, hospitalisation	$281 per event	The cost of neutropoenia as included in a chemotherapy cost-minimisation analysis, based on direct costs of drugs and incidence of adverse events from clinical trials
Minisini 2005 Belgium and Italy **(109)**	Incidence and direct costs of febrile neutropoenia and neutropenic infections	Breast cancer	Hospitalisation, medication, diagnostic tests, nurse time	$3,781 mean cost per patient	The direct costs of neutropoenia were collected from a retrospective analysis of patient records
Fortner 2004 US **(111)**	Impact of medical visits for chemotherapy and chemotherapy-induced neutropoenia on patient time and activities	Any cancer, any stage	Outpt visits, lab. tests, medications, hospitalisations, staff costs	$110 per hospitalisation per patient	The amount of time required for treatment of neutropoenia was measured through patient surveys
Novello 2005 Italy **(157)**	Cost-minimisation analysis of gemcitabine/cisplatin, paclitaxel/carboplatin and vinorelbine/cisplatin	Locally advanced, recurrent or metastatic NSCLC	Hospitalisation, transfusions, medication, lab. tests	$3,409 per event	The cost of neutropoenia was included in a retrospective chemotherapy cost-minimisation analysis. Resource-use and costs were based on data collected during a clinical trial
Calhoun 2001 US **(112)**	Evaluating the total costs of chemotherapy-induced toxicity	Ovarian cancer	Hospitalisation, inpt doctor visits, outpt visits, medications, lab. tests, phone calls, patient time, carer time, carer	$12,097 mean total costs per patient	The cost of neutropoenia was included in a resource estimate of total costs for chemotherapy toxicities based on detailed patient surveys

Reference	Study design	Cancer and stage	Neutropoenia management resource categories	Neutropoenia treatment costs (International $)	Summary of neutropoenia costs
			costs		
Chu 2009 US **(159)**	Generalised linear models were used to predict monthly complication costs of 5-fluorouracil chemotherapy treatments	Colorectal cancer	Outpt visits, hospitalisation, medications	$1,090 mean monthly expenditure during treatment episode for patients receiving 5-FU and oxaliplatin	The contribution of neutropoenia to the total monthly costs during chemotherapy treatment were estimated using regression analysis of an administrative database
Cagianno 2005 US **(114)**	Incidence, cost and mortality of neutropoenia hospitalisations	Any cancer	Hospitalisation	$8,000 mean cost per hospitalisation for high prevalence cancers; $8,600 mean cost per hospitalisation for low- prevalence cancers	Neutropoenia hospitalisation rates were obtained from hospital discharge data in 7 states, with national cancer registry data then used to calculate nation rates and costs
Timner-Bonte 2006 Netherlands **(310)**	Cost-effectiveness of adding G-CSFs to antibiotics for prophylaxis of neutropoenia	Small-cell lung cancer	Medication	$3,642 mean cost per episode	Economic analysis was conducted alongside a clinical trial to identify the difference in mean total costs per patient with two different prophylactic strategies
Smith 2002 US and UK **(160)**	Comparative economic analysis of PLD vs. topotecan	Ovarian cancer	Medication, outpt visits, hospitalisation	Mean cost per person: US topotecan $3,882 US PLD $514 UK topotecan $781	The cost of neutropoenia was included in a chemotherapy cost-minimisation analysis, based on clinical trial data and previously reported economic analyses

Reference	Study design	Cancer and stage	Neutropoenia management resource categories	Neutropoenia treatment costs (International $)	Summary of neutropoenia costs
				UK PLD $37	
Annemans 1999 Europe **(103)**	Cost-effectiveness of paclitaxel and cisplatin vs. teniposide and cisplatin in multiple European countries	Advanced NSCLC	Medication, diagnostic tests, lap tests, inpt doctor visits	Neutropoenia cost per episode: $291 in France $1,624 in Belgium Febrile neutropoenia cost per episode: $2,706 in Spain $4,613 in France	The cost of neutropoenia was included in a chemotherapy cost-effectiveness analysis, based on clinical trial data, patient chart analysis and expert opinion obtained with the Delphi method
Levy-Piedbois 2000 France **(162)**	Cost-effectiveness of irinotecan vs. 5-fluorouracil	Metastatic colorectal cancer	Hospitalisation, outpt visits	$8,903 total cost for 3 patients	The cost of neutropoenia was included in a chemotherapy cost-effectiveness analysis, based on clinical trial data and accounting systems of two hospitals
Capri 2003 Italy **(99)**	Cost-minimisation analysis of PLD vs. topotecan	Ovarian cancer	Outpt visits, lab. tests, hospitalisation, medication	Mean cost per patient: Grade I/II $0 Grade III $335.93 Grade IV $1,838	The cost of neutropoenia was included in a chemotherapy cost-minimisation analysis, based on Phase III trials and expert opinion derived from the Delphi method

Notes; G-CSFs = granulocyte colony-stimulating factors; ICER = incremental cost-effectiveness ratio; inpt = inpatient; lab. = laboratory; NS = not stated; NSCLC= non-small-cell lung cancer; outpt = outpatient; PLD = pegylated liposomal doxorubicin; vs. = versus

Appendix O: Neutropoenia TreeAge model

Appendix P: DVA dataset size

Dataset size: A significant issue in the analysis of the data was the size of the dataset. Not only are there a large number of individuals in the dataset, the collection of every pharmaceutical product and medical service they have received over a five-year period means there is a large number of observations for each individual. The PBS dataset had a total of 28,875,615 observations, resulting in a dataset that was 63GB.

Careful consideration of efficient data management and analysis techniques were required to ensure that analysis was possible. Ensuring the same network location of the data and the analysis software on the computer and network provided an opportunity to reduce processing time, because removing the need for the software to call and send data over the network produced significant savings in processing speed. For example, with the SAS program located on the local computer hard drive and the data on a network drive, a simple *proc means* command took 85 seconds of CPU time and 41 minutes of real time to process. The same procedure with both SAS and the data on the local hard drive took eight seconds of CPU time and less than two minutes of real time to process. This is illustrated in Figure A.1.

Management of the data to reduce the need for text variables, particularly those with long strings, was another valuable way of reducing dataset size and improving processing speed. As each character in a dataset is 1 byte of information, variables such as the PBS form and generic name, which allowed up to 1024 bytes/characters, had the potential to increase the size of the data set significantly. Separating these from the dataset resulted in a reduction in dataset size from 63Gb to approximately 3Gb.

Finally, the use of SQL programming language rather than basic SAS programming provided significant efficiencies. SQL language influenced efficiency in a number of areas, including CPU time, by consolidating the number of steps, improved input/output efficiency through consolidated code, and reduced programming time through simplified code structure (254) perhaps the biggest

gain in efficiency for this analysis was using SQL to remove the need to sort variables for merging or other data management activities.

```
libname apdva 'H:\zMEDACPGuest\Alison Pearce';
110  proc means data=apdva.PBSGCcancer noprint nway;
111       class PPN;
112       var Service_Paid_Amount;
113       output out=apdva.cancerpbscost
114           mean=M_Service_Paid_Amount;
115  RUN;
NOTE: There were 5277778 observations read from the data set
APDVA.PBSGCCANCER.
NOTE: The data set APDVA.CANCERPBSCOST has 29787 observations
and 4 variables.
NOTE: PROCEDURE MEANS used (Total process time):
      real time           41:26.81
      cpu time            1:25.00
************************************************************
libname apdva 'D:\Alison Pearce\SAS Datasets';
17   proc means data=apdva.PBSGCcancer noprint nway;
18    class PPN;
19     var Service_Paid_Amount;
20     output out=apdva.cancerpbscost
21           mean=M_Service_Paid_Amount;
22   RUN;
NOTE: There were 5277778 observations read from the data set
APDVA.PBSGCCANCER.
NOTE: The data set APDVA.CANCERPBSCOST has 29787 observations
and 4 variables.
NOTE: PROCEDURE MEANS used (Total process time):
      real time           1:54.87
      cpu time            8.26 seconds
```

Figures A.1 Screenshot of processing time using local vs. network drives

Appendix Q: Elements of Cancer Care patient questionnaires

Side-effects Information

For the following questions, please select one option.

In the last month have you had:

1. Dyspnoea

☐ Shortness of breath at rest

☐ Shortness of breath on exertion, with minimal impact on activities of daily living

☐ No shortness of breath except on exertion, unable to walk a flight of stairs or one city block without stopping

☐ No shortness of breath except on exertion, able to walk a flight of stairs without stopping

☐ No shortness of breath

2. Diarrhoea

☐ Diarrhoea resulting in severe fluid losses (shock) or other severe complications

☐ Diarrhoea to the point where hospitalisation was required

☐ Mild-to-moderate diarrhoea, requiring IVT fluids

☐ Mild diarrhoea

☐ No diarrhoea

3. Constipation

☐ Constipation resulting in obstruction or other severe complication

☐ Constipation, which significantly interfered with your usual activities

☐ Mild-to-moderate constipation occasionally interfering with your usual activities, persistent symptoms requiring the use of laxatives on most days

☐ Mild-to-moderate constipation not interfering with your usual activities, occasional symptoms with occasional use of laxatives

☐ No constipation

4. Mucositis

☐ Hospitalisation resulting from severe bleeding or other complication

☐ Extremely troublesome mouth or throat ulcers, with difficulty eating and drinking, and requiring intravenous fluids

☐ Mildly troublesome mouth or throat ulcers, making eating or drinking difficult

☐ Inflamed mouth or throat, not interfering with eating

☐ No mouth or throat ulcers

Vomiting

☐ Vomiting severe enough to result in perforation or other severe complication

☐ Six or more episodes of vomiting in 24 hours, IVT fluids required

☐ Two to five episodes of vomiting in 24 hours, may need IVT fluids

☐ One episode of vomiting in 24 hours

☐ No vomiting

5. Rash

☐ Severe life-threatening rash requiring hospital admission

☐ Severe rash covering more than 50 per cent of the body

☐ Minimal to moderate rash, may involve blistering, covering less than 50 per cent of the body

☐ Mild rash (redness of skin) anywhere on the body

☐ No rash

6. Pain

☐ Disabling pain

☐ Severe pain where either the pain or the medication you're taking for the pain interferes with your daily activities

☐ Moderate pain where either pain or the medication you're taking for the pain interferes with function but you can still get on with daily activities

☐ Minimal pain, not interfering with daily activities

☐ No pain in the last month

7. **If you had pain, how long did it last?** _____

8. **What part of the body did you have the pain?** _____

9. Fatigue?

☐ Disabling fatigue

☐ Severe fatigue interfering with daily activities

☐ Minimal to moderate fatigue with some impact on activities of daily living

☐ Mild fatigue

☐ No fatigue over the month

10. **If you suffered from fatigue, how long did it last?** _____

For the following questions please select all options that are applicable (more than one option may apply)

11. Thrombosis

☐ A blood clot (legs or lungs) which resulted in a hospital admission

☐ A blood clot (legs or lungs) which resulted in a review in the emergency department

☐ A blood clot (legs or lungs) which resulted in you taking Warfarin

☐ A blood clot (legs or lungs) which resulted in you having Clexane/ heparin injections

☐ A blood clot (legs or lungs) which resulted in you wearing pressure stockings

☐ A blood clot (legs or lungs) for which you had no treatment

☐ No blood clots (legs or lungs)

•

12. Chest pain

☐ Chest pain or angina, which resulted in a hospital admission

☐ Chest pain or angina, which resulted in a review in the emergency department

☐ Chest pain or angina and was seen by local doctor

☐ Chest pain or angina and did not seek medical advice or used own medication

☐ No chest pain or angina

Do you have a medical history of angina or heart disease?

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