

## **TITLE PAGE**

**Title:** Are the true impacts of adverse events considered in economic models of antineoplastic drugs? A systematic review.

**Running title:** Modelling the true impacts of antineoplastic drug adverse events

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### ***Contributorship***

**Alison Pearce:** Contributed to the planning of the study, designed the search strategy, conducting the literature searches, reviewed the retrieved articles for eligibility, completed and documented data extraction, and wrote the paper for publication. Alison Pearce is the guarantor for the overall content of the paper.

**Marion Haas:** Contributed to the planning of the study, advised on the design of the search strategy, reviewed eligibility of articles where eligibility was uncertain, advised on data extraction and interpretation of results and reviewed the publication

**Rosalie Viney:** Contributed to the planning of the study, advised on the design of the search strategy, advised on data extraction and interpretation of results and reviewed the publication

**Liz Chinchen:** Contributed to advising on search strategy techniques, conducting the literature searches and retrieved the eligible articles

### ***Conflicts of interest:***

Alison Pearce: Nil

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### ***Previous versions of this work***

The work described in this paper has not been presented or published elsewhere. The systematic literature review described was used to answer additional research questions, and these have been presented as posters at two conferences, the references for which are below.

1. **PEARCE A, HAAS M, VAN GOOL K, ON BEHALF OF EMCaP INVESTIGATORS (2010).** The cost of chemotherapy side effects: Recommendations for local modelling and economic evaluation [Poster]. *International Society of Pharmacoeconomics and Outcomes Research, Thailand.*
2. **PEARCE A, HAAS M, VAN GOOL K, HAYWOOD P, ON BEHALF OF EMCAP INVESTIGATORS (2010).** Can we calculate the costs of haematological side effects of systemic therapy? [Poster] *Sydney Cancer Conference, Sydney.*

## **Abstract** (270 words)

**Background:** Antineoplastic drugs for cancer are often associated with adverse events, which influence patients' physical health, quality of life and survival. However, the modelling of adverse events in cost effectiveness analyses of antineoplastic drugs has not been examined.

**Aims:** This article reviews published economic evaluations which include a calculated cost for adverse events of antineoplastic drugs. The aim is to identify how existing models manage four issues specific to antineoplastic drug adverse events: the selection of adverse events for inclusion in models, the influence of dose modifications on drug quantity and survival outcomes, the influence of adverse events on quality of life, and the consideration of multiple simultaneous or recurring adverse events.

**Methods:** A systematic literature search was conducted using MESH headings and key words in multiple electronic databases, covering the years 1999 to 2009. Inclusion criteria for eligibility were papers covering a population of adults with solid tumour cancers, the inclusion of at least one adverse event, and the resource use and / or costs of adverse event treatment.

**Results:** From 4985 citations, 26 eligible articles were identified. Studies were generally of moderate quality and addressed a range of cancers and treatment types. While the four issues specific to antineoplastic drug adverse events were addressed by some studies, no study addressed all of the issues in the same model.

**Conclusion:** This review indicates that current modelling assumptions may restrict our understanding of the true impact of adverse events on cost effectiveness of antineoplastic drugs. This understanding could be improved through consideration of the selection of adverse events, dose modifications, multiple events and quality of life in cost effectiveness studies.

## **Key points for decision makers**

- Current models of antineoplastic drug cost effectiveness may underestimate the incidence, cost and flow on effects of adverse events.
- Decision makers should examine whether issues such as the selection of adverse events for inclusion, the implications of dose modifications, the impact of adverse events on quality of life, and the potential for multiple adverse events have been considered in models of antineoplastic drug cost effectiveness.
- Models that address all of these issues relating to adverse events are feasible, and would allow decision makers to make better informed decisions about the cost effectiveness of antineoplastic treatments.

## 1. Background

Antineoplastic drugs, which include chemotherapy, are a common cancer treatment. In 2007-08 there were 260,000 separations for chemotherapy in Australian public and private hospitals combined [1]. However, antineoplastic drugs cause adverse events (side effects). More than 750 adverse events are listed in the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) which is used to define and grade the seriousness of adverse events associated with cancer treatments [2]. Adverse events have been estimated to contribute up to 60% of the total cost of chemotherapy [3].

Willingness to pay for cancer treatments in the community is high, due to a widespread public perception of cancer as a hidden and feared disease [4, 5]. This may lead to a 'treat at all costs' attitude with little consideration given to the economic impacts of these treatments [4, 5]. Economic evaluation is increasingly used to provide information to decision makers in the health care system about the relative value of alternative treatment strategies [4]. While 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 [6].

Economic evaluation requires consideration of both the *costs* and *benefits* of a treatment, with data used to populate these costs and benefits in the model referred to as *inputs*. Typically, antineoplastic drugs include three broad *cost* components – purchasing the antineoplastic products, time and resources for administration of the drugs, and managing adverse events. On the *benefit* 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 antineoplastic drug outcomes are often readily available through clinical trials, while product purchase costs can be obtained from pricing lists. Less information is available estimating the costs of administration [7] and adverse events related to antineoplastic drugs [8].

There are a number of issues which are specific to the adverse events of antineoplastic drugs, that need to be considered in economic evaluations.

### *Adverse event selection*

The inclusion of adverse events in models of antineoplastic drugs is important as these events can influence both sides of the economic evaluation equation. Many economic evaluations of antineoplastic drugs are conducted for the purpose of reimbursement. In this case awareness of the cost-effectiveness threshold is important, as well as the impact of model structure and inputs. The 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.

### *Dose modifications*

As well as incurring a cost to manage the adverse event itself, the experience of an adverse event changes the way a patient receives antineoplastic therapy. In many cases, when a patient experiences an adverse event, their drug dose is either delayed or the dose reduced until they have recovered from the adverse event [9]. The antineoplastic treatment may then continue at the reduced dose to lessen the chance of the adverse event re-occurring [9]. This influences the total amount of antineoplastic drug the patient receives [10], and therefore the amount of product purchased.

The amount of an antineoplastic drug received by a patient can also impact on the outcomes of their treatment. The relative dose intensity of chemotherapy is the ratio of the delivered chemotherapy to the planned chemotherapy dose over a specified period of time [11]. There is evidence that patients who receive a relative dose intensity of less than 85% have significant reductions in survival [10, 12-18]. Retrospective studies have found that up to 56% of people have a relative dose intensity less than 85% due to dose adjustments in response to adverse events [19].

### *Adverse events and quality of life*

While adverse events differ between individuals, almost all patients on antineoplastic drugs will experience at least one adverse event [20]. Many patients report adverse events to be very distressing, with quality of life significantly impacted [21-23]. 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 antineoplastic therapy.

### *Multiple adverse events*

The final consideration when including antineoplastic drug related adverse events in 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 antineoplastic therapy, or 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 dose modifications may change, resulting in different costs and outcomes for the model [9]. The occurrence of more than one adverse event at the same time impacts on the management of each adverse event in terms of treatment, prevention and antineoplastic drug dose [9], and may also change the quality of life impact of an event.

While there are generic guidelines for the development of economic evaluation models [24], these do not consider cancer-specific issues which may bias results [8]. 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 adverse events, discounting and assessing uncertainty [8]. However, the authors are unaware of any published reviews of the modelling techniques used specifically for evaluating the costs and consequences of adverse events associated with antineoplastic drugs.

Adverse events have the potential to have a significant impact on models of antineoplastic drug cost effectiveness through not only the cost of managing the event itself, but also in terms of the quantity of antineoplastic 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 antineoplastic drugs to ensure accurate estimates of cost effectiveness are obtained.

## **1.1 Aim**

This article reviews published economic evaluations which include a method for determining resource use and/or have a method for calculating a cost for adverse events of antineoplastic drugs, to identify how these existing models manage potentially problematic areas specific to antineoplastic drug adverse events. The primary areas of interest are model structure and inputs related to:

- The selection of adverse events for inclusion in models
- The influence of dose modifications
  - on antineoplastic drug product quantity
  - on survival outcomes
- The influence of adverse events on quality of life
- The influence of multiple adverse events, including
  - the same event occurring multiple times during a course of antineoplastic drug therapy
  - multiple events occurring at the same point in time.

## **2. Methods**

A systematic literature search was conducted to identify relevant papers reporting research involving modelling the cost of antineoplastic drug adverse events. Inclusion criteria for eligibility were papers covering a population of adults with solid tumour cancers, the inclusion of at least one antineoplastic drug related adverse event, the resource use and/or calculated costs of adverse event treatment, as well as a stated method or assumptions for determining the resource use and/or costs of adverse events. Studies were excluded if they presented clinical guidelines or were not original research. Conference abstracts were excluded as the information within them was too limited for the purposes of this review.

The following electronic databases were searched to identify relevant articles published in English from January 1999 to September 2009: Medline, EMBASE, PubMed, EBM Reviews, CINAHL, Cochrane Library, Business Source Premier, Academic Search Premier, Econlit, NHS EED, York HTA, ASCO, and the TUFTS CEA Registry. A search strategy was developed for each database using MESH headings (neoplasms, drug therapy, antineoplastic agents, drug toxicity, adverse effect, costs and cost analysis, cost benefit analysis, economics, length of stay, health resources), and relevant keywords (carcinoma, chemotherapy, adverse event, adverse reaction, toxicity, side effect, complication, undesired effect, cost, resource, hospitalisation). The search strategies for Medline, NHS EED and York HTA are provided in Online Resource 1.

Titles and abstracts of the retrieved citations were screened to identify potentially eligible papers. Final assessment of eligibility was based on review of full text articles. Additional papers identified from personal files and the reference lists of included papers were hand searched. Assessment of eligibility was completed by one reviewer for all citations. For studies where eligibility was unclear, a second opinion was sought.

Study quality was assessed for all eligible articles using the checklist developed by Graves [25]. This checklist covers four aspects of study quality, primarily related to costing; costing issues, methods to determine quantities of resources used, valuing of resources and data reporting [25, 26]. Papers were scored from zero to twelve based on the number of criteria which were met.

Data extraction was completed by one reviewer for all articles, using the NHS EED annotated abstract template (<http://www.crd.york.ac.uk/CRDWeb/AboutNHSEED.asp>). 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 (either over time or consecutively) were considered.

### **3. Results**

The search yielded 4985 citations, with 26 eligible articles identified which described the use of economic models including methods or assumptions for resource use and/or the costs of adverse events associated with antineoplastic drugs. Figure I presents a flow chart of study selection.

Table I(a-f) provide the details of each study included in the review. 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 and important approaches to answering the questions relevant to this review, it was decided to include both study types, but to consider them separately.



Table II summarises the characteristics of the included studies. Generally studies were of moderate quality, with a mean Graves score of seven and a range of three to ten (Table 1a-f). Six studies [19] [27] [28] [29] [30] [31] included multiple cancer types, with the remaining focussing on a specific cancer, the most common being breast cancer (12 studies). Over half of the studies were based in the United States, with no studies from Australia or New Zealand.

### ***3.1 General model design***

Table III shows the modelling methods used by the included studies. Cost effectiveness analyses of antineoplastic treatments primarily used Markov models, while decision trees were used in studies of the costs of treating adverse events. 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 [32] [33] and a hospital perspective in the other [34].

### ***3.2 Adverse event selection***

The 26 studies examined 21 different adverse events. Eleven studies [32] [35] [28] [36] [37] [27] [31] [29] [30] [38] [39], mostly adverse event treatment studies, considered a single adverse event. Of the remaining studies, nine [33, 34, 40-46] included between two and five adverse events, while six [47-52] examined more than five, with 15 being the most adverse events costed in a single study [52].

A number of studies (n=6) did not specify on what basis specific adverse events were selected for inclusion in the models. Five studies [33, 38, 41-43] 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 1% or 5% level) [41, 42], potential to impact on cost [45, 47, 49, 52], or the potential to impact on patient quality of life [51]. Twenty studies included any grade of the event, while six [34, 41, 45, 47, 49, 52] restricted inclusion to only grade III/IV events (high cost/low volume events) or those resulting in hospitalisation.

### ***3.3 Dose modifications***

The impact of adverse events on the individual's dose of antineoplastic therapy was specifically examined in five studies [41-43, 49, 52], all of which were evaluations of costs and effectiveness of antineoplastic drugs, with access to primary data regarding dose modifications during treatment. This allowed researchers to include the actual dose received in the models. An additional five antineoplastic drug evaluations [39, 44, 45, 47, 51] indirectly examined 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 antineoplastic drug evaluations and all of the adverse event treatment studies assumed patients received 100% of the planned dose, regardless of the experience of adverse events. In one study this was justified as being a conservative estimate of antineoplastic therapy cost [48].

While early cessation of antineoplastic therapy was sometimes considered in terms of the amount of drug delivered, the impact of dose reduction and delays on survival was not. Two studies, both based on the same neutropenia treatment model, included the scenario where improved adverse event management resulted in lower probability of receiving less than 85% of relative dose intensity, with resulting long-term survival benefits [36, 37]. In this model, the impact of relative dose intensity on long term survival was modelling using a Markov process in which the patient was followed until death [36, 37]. Long term survival was modelled as a function of patient's age, cancer stage, and relative dose intensity (RDI) [36, 37]. Inputs for the proportion of patients who received less than 85% RDI, and the associated relative risk of death for those with an RDI <85% (compared to those with over 85%) were based on literature [36, 37].

### ***3.4 Adverse events and quality of life***

Measurements of quality of life for various states of cancer and cancer treatment were used in 18 of the 26 studies (six adverse event treatment studies and 12 antineoplastic drug evaluations, see Table 1a-f). Thirteen of these studies included a utility decrement associated with antineoplastic drug adverse events (six adverse event treatment studies and seven antineoplastic drug evaluations), and thus had the potential to calculate a cost per quality-adjusted life year (QALY). Some of these estimates included unique decrements for adverse events at different grades, or requiring different treatment, such as hospitalisation compared to out-patient management, but others included a common estimate for the adverse event that was not related to grade or treatment.

Utility estimates for cancer and antineoplastic therapy health states were usually obtained from previous 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 empirical evidence [34, 46, 53]. For example, Lidgren et al simply reduced the utility value by 50% for six months in those experiencing symptomatic heart failure [46].

### ***3.5 Multiple adverse events***

While most models (n=14) allowed for people experiencing the same event multiple times during a period of antineoplastic therapy, only two studies [36, 37] (both adverse event treatment evaluations) specifically considered multiple events over time. These studies, both based on the same febrile neutropenia treatment model, added the cost of subsequent care for febrile neutropenia to the cost of initial hospitalisation. This was based on the assumption that having experienced one episode of febrile neutropenia, an individual is at increased risk of developing febrile neutropenia in the future [36, 37].

In two studies, models were developed which allowed for multiple events to occur at the same time, (one antineoplastic drug evaluation and one adverse event treatment evaluation). Touchette et al (2006) modelled febrile neutropenia, anaemia and thrombocytopenia, and allowed for any combination of the three to be experienced in each cycle of a Markov model [40]. The costs and incidences of adverse events were averaged using a simple decision tree prior to being entered into the model [40]. However, the incidence and cost of each adverse event do not appear to differ based on the combination of events experienced.

Delea et al [48] created a model in which health states were characterised by all combinations of adverse events. The model included endometrial cancer, venous thromboembolism, myocardial infarction, unstable angina, heart failure, hip fracture, other fractures, arthralgia, and hypercholesterolemia [48]. Again, whilst the model allows for 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 do not appear to have changed with the experience of multiple events.

### **3.6 Overall**

No studies included all of the concepts of interest in their models; three studies included none of the concepts of interest in their models [31, 32, 35]. 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 which included the most factors were those by Danova [36] and Lui [37]. Both studies used the same model for management of neutropenia using granulocyte colony-stimulating factors (G-CSFs) in women with breast cancer [36, 37]. The model includes the impact of dose modifications on survival, the impact of neutropenia and its treatment on quality of life, and the potential for one episode of neutropenia to increase risk of multiple future episodes of neutropenia [36, 37]. As this was a model of neutropenia management, the cost of chemotherapy was assumed to be the same in both arms [36, 37]. This means that the influence of dose modifications on the total cost of chemotherapy is not accounted for, and may bias the results. However, this model provides an example of how many of the important components of antineoplastic drug related adverse events can be incorporated into a cost effectiveness model.

## **4. Discussion**

This review of the literature identified two types of economic studies which considered the costs of antineoplastic drug related adverse events; cost effectiveness analyses of antineoplastic treatments, and assessments of the costs or cost effectiveness of treatments for antineoplastic drug related adverse events. Whilst 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 a health care system or hospital perspective, with only direct costs included.

Selection of adverse events for inclusion in models was based on incidence, cost or impact on quality of life.

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

The adverse events related to antineoplastic therapy are complex, and 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 antineoplastic therapy cost effectiveness. The results of this review suggest that many published models which include information regarding adverse events associated with antineoplastic therapy underestimate the incidence, costs and flow on effects of adverse events.

In considering the issues of adverse event selection, dose modifications, quality of life and multiple adverse events, the results of this review provide an opportunity to present recommendations for the modelling of adverse events in antineoplastic therapy cost effectiveness studies. These recommendations have been presented as broad statements, as they are likely to be new considerations for modellers, and to require additional complexity and data in the models. However, they provide a starting point for the inclusion of all relevant impacts of adverse events on the costs and outcomes of antineoplastic drug therapy.

#### ***4.1 Existing comparisons of adverse event models in antineoplastic therapy economic evaluations***

Existing reviews of adverse events in economic evaluations of antineoplastic therapy report similar results to those of this review.

An NHS Health Technology Assessment reviewed economic evidence from four studies of topotecan, doxorubicin and paclitaxel for ovarian cancer [54]. 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 [54]. The review concluded that different model assumptions about adverse event management had the potential to both over-estimate costs through the inclusion of specialised treatment of high volume / low cost events, and underestimate chemotherapy adverse event incidence and costs through assumptions regarding multiple hospital admissions per cycle [54].

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 variety of people [55]. The different models

produced marked variations in results, with a range of between £190,000 and £9,000 per Quality Adjusted Life Year (QALY) gained [55]. This variation in results highlights the influence model design and assumptions can have on the outcomes of economic evaluation.

Finally, a number of cost of illness (COI) studies have examined the costs associated with antineoplastic drug induced neutropenia, 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 [56-62]. Alternatively, some studies have utilised the information available from hospital and health insurance databases to determine the additional cost of healthcare attributable to treating a specific adverse event [63, 64]. Again, different model inputs resulted in significant variation in outcomes.

#### ***4.2 Adverse event selection***

The selection criteria used to identify which adverse events to include in models may lead to under-estimation of the base rate of adverse events. While the inclusion of only events with rates which differ between arms may not have an impact on the incremental cost effectiveness ratio for particular antineoplastic drug alternatives, the overall cost of adverse events (and therefore its impact on the relevant budget) may be higher than that implied by the results. This influences whether the alternative interventions are considered cost effective at an acceptable threshold level. The importance of this will depend on the decision making context that the evaluation is considered within.

Similarly, adverse events which are considered to be low cost or low severity, may be excluded from the analysis. While a low incidence of adverse events may not influence cost effectiveness, high rates 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 agents such as cetuximab for colorectal cancer. The pivotal study of cetuximab found 88% of patients experienced a rash, including 76.8% at the less serious grade I or II [65]. The economic analysis of this study excluded any adverse events less than grade III severity, as they were not thought to contribute significantly to resource use, despite occurring at any grade in only 16% of individuals in the control arm [66].

A non-significant difference in incidence between treatment arms for a specific adverse event does not necessarily indicate that there is no difference in global adverse event profiles between treatment arms in terms of the overall toxicity profile. By assuming conditional independence of the frequency of events, the potential for the sum of adverse events to differ between treatments is removed.

The inclusion of all relevant adverse events in models of antineoplastic therapy cost effectiveness is consistent with recommendations for the modelling of adverse effects for all health interventions [67] [68]. However, including all adverse events will require additional

complexity in the model, and additional data to populate these components of the model. The use of Markov modelling techniques may provide a way to address this additional complexity [6], and clinical trials would be the most likely source of additional information about the costs and consequences of adverse events. Further work is required to identify how the inclusion of all adverse events will impact results.

*Recommendation: All relevant adverse events which are associated with antineoplastic drug treatment should be included in models of antineoplastic therapy cost effectiveness.*

#### **4.3 Dose modifications**

While some studies did consider the impact that dose modifications would have on the total dose of antineoplastic drugs received, many assumed all patients received one hundred per cent of the recommended dose. In the context of a cost effectiveness evaluation, this would result in an overestimation of the costs, as some cost savings are ignored. In the area of cancer treatments, where new antineoplastic drugs are increasingly expensive, the cost of purchasing the drugs may be a significant contributor to costs, and therefore overall cost-effectiveness. Intravenous treatments may have the additional complexity of wastage, as once a vial is opened it often must be used immediately or 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 a full vial has been used.

Clinical trial reports may provide details of the dose modifications and drug wastage during the trial. Information on planned dose, dose dispensed, dose received, and reasons for dose modifications would be ideal for economic modelling. Where this information is not available, data from observational studies, such as information regarding the frequency of dose modifications may be used to provide inputs to the model regarding the incidence of dose modifications. The potential cost savings associated with dose modifications can be estimated using the input price and incorporated into the estimates of product cost per treatment arm. Practice guidelines for the administration of antineoplastic drugs may provide some guidance to the modelling of product wastage.

*Recommendation: The cost savings resulting from dose modifications due to adverse events should be accounted for in models of antineoplastic therapy cost effectiveness.*

Only two studies considered the impact of dose modifications on survival. With survival often the primary outcome of effectiveness in cost effectiveness studies, changes to it as a result of 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 the cost effectiveness of antineoplastic therapy select adverse events for inclusion on the basis of there being a significant difference in incidence between treatments.

It is interesting that although there is a body of literature which examines the cost effectiveness of treatments for neutropenia in relation to their ability to maintain chemotherapy dose intensity [69], there appears to be little transfer of this information into models of antineoplastic drug cost effectiveness, despite many of these models including neutropenia and the costs of its management.

There is relatively little evidence available for the influence of dose modifications on the effectiveness of specific antineoplastic drug treatments. This makes inclusion of these outcomes within the model difficult, as no data are available to populate the model. Economic models based on the results of a clinical trial which has followed patients to death will have implicitly considered the impact of dose modifications on survival. However, where follow up is not complete or data are insufficient, the growing body of evidence across a range of chemotherapy treatments that receiving less chemotherapy reduces efficacy could be used within a sensitivity analysis of the estimated antineoplastic drug efficacy. This would allow the potential impact of uncertainty around the estimates of antineoplastic drug efficacy to be tested.

*Recommendation: The impact of dose modifications due to adverse events on the outcomes of antineoplastic therapy should be considered and included in the sensitivity analysis of models of cost effectiveness.*

#### **4.4 Adverse events and quality of life**

The impact on quality of life of cancer and antineoplastic therapy are generally well considered in cost effectiveness studies of antineoplastic drugs and new adverse event treatments. It is less common for the additional utility decrements associated with adverse events to be included, and these are often difficult to identify [70]. Part of the difficulty in including additional utility decrements (or improvements) associated with adverse events is how these should be considered in relation to the quality of life impacts of having cancer and undergoing antineoplastic drug therapy. While there are studies which have estimated specific utility decrements for adverse events independent of treatment [71], in many cases the decrement associated with antineoplastic treatment may include a component related to adverse events. If this was the case, the addition of a decrement associated with an adverse event may lead to double counting [8]. It is therefore important that the original source of utility scores and the basis for the applied utility weights for both antineoplastic drugs and adverse events be understood before they are incorporated into an economic evaluation. In cases where adequate evidence to populate the specific utility decrements associated with adverse events are not available, utility measures for the experience of cancer and antineoplastic therapy which include the impact of adverse events should be sought.

*Recommendation: The impact of adverse events on quality of life should be considered, and included in models of antineoplastic therapy cost effectiveness, where adequate evidence to populate these components is available.*

#### **4.5 Multiple adverse events**

As the usual sources of information about the incidence of adverse events, clinical trials, report events separately and very rarely provide information about patterns of multiple adverse events. Thus it is not surprising that models of antineoplastic therapy 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 resulted in which resource use (eg hospitalisation) or outcomes (eg reduced quality of life) and therefore the impact on cost effectiveness is difficult to gauge. The use of clinical trial data to examine patterns of multiple adverse events would provide an ideal resource for the modelling of multiple adverse events.

In relation to the influence of multiple events on utility, there has been significant interest in developing quantitative methods to account for comorbidities when assessing health interventions [72]. In studies of cancer, adverse events are commonly considered individually, however the high prevalence of simultaneous adverse events is increasingly recognised as important [73]. Whilst direct elicitation of the utility of these simultaneous events 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 simultaneous events makes conducting these assessments impractical [73]. Modelling approaches have therefore been investigated. The original additive approach to modelling combined utilities has been identified as overly simplistic, and techniques such as multiplicative and minimum modelling are now being studied and used [72, 73].

*Recommendation: Further research is required to allow the consideration of concurrent or consecutive multiple adverse events in models of antineoplastic therapy cost effectiveness.*

#### **4.6 Limitations of the review**

Whilst a systematic review of the literature was undertaken, there may be published economic models incorporating antineoplastic drug related adverse events which were missed. The relatively small proportion of economic evaluations of antineoplastic drugs which were eligible for inclusion in the review appears to be a factor of the inclusion criteria requiring papers to present the methods for determining the resource use and/or cost of adverse events. The exclusion of those papers which simply report a cost without justification allows this review to focus on the methods used to include adverse events, but may result in it not be representative of all studies of antineoplastic drug cost effectiveness.



In addition, the exclusion of papers in languages other than English and conference abstracts may have biased the types of models which were included. Similarly, given that many economic evaluations are conducted for the purpose of policy decision making, there may be economic evaluations of antineoplastic agents which have been developed, but are not available in the peer-reviewed economic literature. These evaluations may differ systematically from those identified in this review, which may have biased the results.

A final potential limitation of the search strategy is that it identified two distinct types of economic evaluations – those assessing the cost effectiveness of antineoplastic drugs, and those assessing the cost effectiveness of adverse event treatments. While both of these are appropriate to answer the questions posed by this review, separate search strategies may have resulted in more efficient identification of eligible papers in these two areas.

For many of the economic evaluations identified, particularly those assessing the cost effectiveness of antineoplastic drugs, the costs of adverse events 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 model builders' best efforts, the results of analysis are not designed to represent real life, but rather to provide information about the likely outcomes of a decision. This means that while there may be many aspects of the disease pathway, treatment choices, and patient characteristics which may influence the outcomes of a decision, they cannot all be incorporated into a model. It may be that for some of the models included in this review detailed modelling of adverse events was a lower priority than evaluations of other areas of the treatment pathway.

## **5. Conclusion**

A number of components are important to the rigorous modelling of antineoplastic drug adverse events, including the selection of all relevant events, the impact of adverse events on antineoplastic drug dose, cancer outcomes and quality of life, and the consideration of multiple adverse events. This literature review systematically searched for all relevant articles which included adverse events in a model of costs and consequences of antineoplastic drugs. There were no models which incorporated all of components discussed above. Two models addressed all but one of the issues, and these models provide an indication of how adverse events can be incorporated into economic evaluations in a rigorous way. Given that there were at least two examples of papers which considered each issue in their model development, it would appear that it is possible to build models of antineoplastic drug adverse events which consider all of these issues.

The adverse events related to antineoplastic therapy 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 antineoplastic drug cost effectiveness, and it appears that many published models may under estimate the incidence, cost and flow on effects of adverse events.

Rigorous modelling of antineoplastic drug adverse events will require the development of more complex models and the availability of additional data. Clinical trials are in a unique position to collect data on many aspects of antineoplastic drug adverse events. However, the inclusion of questions relating to economic evaluation needs to be considered in the study design phase. In the absence of trial data, or for information relating to the experience of antineoplastic drug adverse events outside the trial setting, data from observational or administrative datasets can contribute to economic evaluations. Again, careful consideration of the data available, the economic question being posed and the implications of using observational data is required.

Given that modelling adverse events with appropriate consideration of: the inclusion of all events, dose modifications, quality of life and multiple events appears feasible, future models of antineoplastic drug adverse events should consider these issues.

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**Table I(a) Adverse event treatment studies of neutropenia**

Reference	Cancer type, cancer stage and antineoplastic agents	Perspective	Graves Quality score	AEs and grade	Model and economic analysis	Dose modifications - antineoplastic drug dose	Dose modifications - survival	Quality of life - impact of AEs considered	Multiple AEs over time	Multiple consecutive AEs
Lyman, 2003 (USA) [19]	Any cancer, any stage, any chemotherapy	Not described	6	Neutropenia 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 (USA) [35]	Ovarian, any stage, any chemotherapy	Societal	10	Neutropenia any grade	Cost minimisation, CMA	No	No	No	No	N/A - only considered one AE
Eldar-Lissai, 2008 (USA) [28]	Any cancer, any stage, any chemotherapy	Societal	7	Neutropenia any grade	Decision analysis, multiple - CUA and CEA	No	no	Yes - utilities for febrile neutropenia with and without hospitalisation	No	N/A - only considered one AE
Donova, 2009 (Italy) [36]	Breast cancer, any stage, any adjuvant chemotherapy	National Health System in Italy	8	Febrile neutropenia any grade	Decision analysis, CEA	N/A - cost of chemotherapy excluded from the model	Yes	Yes - utility scores for febrile neutropenia hospitalisation	Yes - pts with one episode of neutropenia are at higher risk of neutropenia in subsequent cycles	N/A - only considered one AE
Liu, 2009 (USA) [37]	Breast cancer, early stage, any myelosuppressive therapy	UK National Health Service	9	Neutropenia any grade	Decision analysis, CEA	No - cost of chemotherapy excluded from the model (same between two arms)	Yes	Yes - utility scores for febrile neutropenia hospitalisation	Yes - pts with one episode of neutropenia are at higher risk of neutropenia in subsequent cycles	N/A - only considered one AE

AE - adverse event, CEA - cost effectiveness analysis, CMA - cost minimisation analysis, CUA - cost utility analysis, N/A - not applicable



**Table I(b) Adverse event treatment studies of anaemia, thrombocytopenia and multiple adverse events**

Reference	Cancer type, cancer stage and antineoplastic agents	Perspective	Graves Quality score	AEs	Model	Dose modifications - antineoplastic drug dose	Dose modifications - survival	QoL impact of AEs considered	Multiple AEs over time	Multiple consecutive AEs
Borg, 2008 (Sweden) [27]	Any cancer, any stage, any chemotherapy	Health care perspective	9	Anaemia, any grade	Markov model, CEA	No	No	Yes - during each cycle of the model the Hb level, EPO and RBCT increments/decrements is used to determine the utility weight	No	N/A - only considered one AE
Cantor, 2003 (USA) [31]	Any cancer, any stage, any chemotherapy	Payers perspective	9	Thrombocytopenia, any grade	Decision analysis model, CMA	No	No	No	No	N/A - only considered one AE
Touchette, 2006 (USA) [40]	Non-small cell lung cancer, any stage, cisplatin, carboplatin or paclitaxel	Health system provider	6	Febrile neutropenia, thrombocytopenia, 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 neutropenia, anaemia and thrombocytopenia

AE - adverse event, CEA - cost effectiveness analysis, CMA - cost minimisation analysis, CUA - cost utility analysis, EPO – erythropoietin, Hb – haemoglobin, RBCT – red blood cell transfusion, N/A - not applicable

**Table I(c) Adverse event treatment studies of nausea and vomiting**

Reference	Cancer type, cancer stage and antineoplastic agents	Perspective	Graves Quality score	AEs	Model	Dose modifications - antineoplastic drug dose	Dose modifications - survival	QoL impact of AEs considered	Multiple AEs over time	Multiple consecutive AEs
Annemans, 2008 (Belgium) [29]	Any cancer, any stage, cisplatin, cyclophosphamide	Health care payers perspective.	5	Nausea and vomiting, any grade	Decision analysis model, CEA	No	No	Yes - utilities for complete response and incomplete response to anti-emetics	No	N/A - only considered one AE
Lordick, 2007 (Germany) [30]	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

AE - adverse event, CEA - cost effectiveness analysis, CMA - cost minimisation analysis, CUA - cost utility analysis, N/A - not applicable

**Table I(d) Antineoplastic cost effectiveness studies of early or primary breast cancer**

Reference	Cancer type, cancer stage and antineoplastic agents	Perspective	Graves Quality score	AEs	Model & economic analysis	AE Selection (summary)	Dose modifications - antineoplastic drug dose	Dose modifications - survival	QoL impact of AEs considered	Multiple AEs over time	Multiple consecutive AEs
Kurian, 2007 (USA) [38]	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 QoL associated with cardiac toxicity included	Assumed - multiple time periods in cardiac toxicity state possible	No- only one AE considered
Lundkvist, 2007 (Sweden) [33]	Early breast cancer, exemestane vs tamoxifen	Not specified	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) [50]	Early breast cancer, letrozole vs tamoxifen; anastrozole vs tamoxifen	UK National Health Service	7	Endometrial cancer, hip fracture, other fracture, cardiac (MI, unstable angina, heart failure), VTE, arthralgia/ arthritis; any grade	Markov, CUA	"Key adverse events"	No	No	Yes	Assumed - AES modelled on incidence	No
Wolowicz 2008 (UK) [41]	Early breast cancer, TAC vs FAC	UK National Health Service	6	Anaemia, diarrhoea, febrile neutropenia, stomatitis, vomiting; grade 3/4 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 difference of greater than 2% between arms	Yes - patients discontinuing chemo as a result of adverse events received fewer cycles of the planned regimen	No	Yes - utility decrements were derived from the published literature	Assumed - AES modelled on incidence	No

Delea 2007 (USA) [48]	Early breast cancer, Letrozole vs tamoxifen	US health care system	7	Endometrial cancer, cardiac (VTE, MI, unstable angina, heart failure), hip fracture, other fracture, arthralgia, hypercholesterolemia; any grade	Markov, CEA	Not specified	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
Riseborough, 2007 (Canada) [42]	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
Lidgren 2008 (Sweden) [46]	Early breast cancer, standard adjuvant chemo 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

AE - adverse event, CEA - cost effectiveness analysis, CMA - cost minimisation analysis, CUA - cost utility analysis, MI – myocardial infarction, VTE – venous thromboembolism, N/A - not applicable

**Table I(e) Antineoplastic cost effectiveness studies of metastatic or advanced breast cancer**

Reference	Cancer type, cancer stage and antineoplastic agents	Perspective	Quality score	AEs	Model	AE Selection (summary)	Dose modifications - antineoplastic drug dose	Dose modifications - survival	QoL impact of AEs considered	Multiple AEs over time	Multiple consecutive AEs
Norum, 2005 (Norway) [39]	Metastatic breast cancer, trastuzumab	Third-party payer	3	Cardiac (congestive heart failure), any grade	Not specified, 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) [43]	Metastatic breast cancer, paclitaxel +/- bevacizumab	Swiss health system	7	Cardiac (hypertension), Infection, CVA; any grade	Markov cohort simulation, CEA	Side effects which showed statistically significant differences in occurrence between treatment arms	Yes - Assumed that patients with chemotherapy discontinuation switched to another agent instead of waiting to the resolution of neuropathy	No	No	Assumed - patients may be able to experience multiple AEs over time.	No
Le, 2008 (USA) [44]	Metastatic breast cancer, capecitabine +/- lapatinib	US Societal perspective	8	Diarrhoea, cardiac event; any grade	Markov , CEA	Taken from trials (not specified)	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

AE - adverse event, CEA - cost effectiveness analysis, CMA - cost minimisation analysis, CUA - cost utility analysis, CVA – cerebrovascular accident, N/A - not applicable

**Table I(f) Antineoplastic cost effectiveness studies of cancers other than breast**

Reference	Cancer type, cancer stage and antineoplastic agents	Perspective	Graves Quality score	AEs	Model & economic analysis	AE Selection (summary)	Dose modifications - antineoplastic drug dose	Dose modifications - survival	QoL impact of AEs considered	Multiple AEs over time	Multiple consecutive AEs
Tumeh, 2009 (USA) [34]	Metastatic colorectal cancer, FOLFOX vs FOLFIRI	Unknown	3	Neutropenia, febrile neutropenia, diarrhea; Grade 3/4 only	Markov, CEA	Grade III/IV in pivotal trials	No	No	Yes - utility for diarrhea and neutropenia from the literature	Assumed - pts can move through multiple AE states	No - patients can only be in one state at a time
Hillner 2005 (USA) [49]	Metastatic colorectal cancer, FOLFOX vs irinotecan & bolus fluorouracil	Medicare as a 3rd party payer	7	Diarrhea, volume depletion, nausea and vomiting, febrile neutropenia, pneumonia, pulmonary embolism/ deep vein thrombosis; Grade 3/4 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 was used.
Bristow, 2007 (USA) [45]	Metastatic ovarian cancer, adjuvant IV paclitaxel vs IP cisplatin & 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) [51]	Metastatic ovarian cancer, pegylated liposomal doxorubicin hydrochloride vs topotecan	Spanish hospitals	6	Anaemia, thrombocytopenia, neutropenia, sepsis, fever, stomatitis/pharyngitis, nausea and vomiting, diarrhea, PPE; Any grade	Not specified - pharmacoeconomic 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 (USA) [74]	Metastatic head and neck cancer, erlotinib, docetaxel, pemetrexed	US Payer	8	Febrile neutropenia, non-febrile neutropenia, anaemia, rash, diarrhoea, infection, nausea, asthenia, pulmonary AEs, fatigue, anorexia, cardiac (dyspnea, chest pain), infection without neutropenia; Grade 3/4 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 (USA) [52]	Advanced non-small cell lung cancer, Docetaxel, Pemetrexed, Erlotinib	Private US Health Insurer	4	Neutropenia, leukopenia, anaemia, febrile neutropenia, infection, nausea, asthenia, pulmonary AEs, fatigue, anorexia, cardiac (chest pain, dyspnea), infection, rash, diarrhoea; Grade 3/4 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

AE - adverse event, CEA - cost effectiveness analysis, CMA - cost minimisation analysis, CUA - cost utility analysis, FOLFIRI – folinic acid fluorouracil and irinotecan, FOLFOX – folinic acid fluorouracil and oxaliplatin, IP – intraperitoneal, IV – intravenous, N/A - not applicable, PPE – palmar-plantar erythrodysesthesia

**Table II Characteristics of included studies**

	<b>Studies of antineoplastic drug costs and effectiveness</b>	<b>Studies of adverse event treatments</b>	<b>Total</b>
<b>n =</b>	<b>16</b>	<b>10</b>	<b>26</b>
<b>Cancers</b>			
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
<b>Cancer stage</b>			
Any stage / stage not specified	0	7	7
Locally advanced / metastatic	9	1	10
Early	7	2	9
<b>Country</b>			
Europe	5	4	9
United States of America	8	6	14
United Kingdom	2	0	2
Canada	1	0	1
Asia	0	0	0
<b>Industry involvement</b>			
Yes – funded or authorship	11	8	19
No, or none specified	5	2	7



**Table III Modelling methods used by included studies**

	<b>Studies of antineoplastic drug costs and effectiveness</b>	<b>Studies of adverse event treatments</b>	<b>Total</b>
<b>n =</b>	<b>16</b>	<b>10</b>	<b>26</b>
<b>Economic analysis</b>			
Cost effectiveness / consequence	11	7	18
Total cost	1	0	1
Cost minimisation	1	2	3
Cost utility	1	0	1
Cost of illness	0	0	0
Cost benefit	0	0	0
Cost effectiveness and cost utility	2	1	3
<b>Perspective</b>			
Health care system / hospital	6	7	13
Third party payer	4	0	4
Society	4	2	6
Not specified	2	1	3
<b>Model</b>			
Decision tree	2	7	9
Markov model	11	2	13
Other models	3	1	4
<b>Costs included</b>			
Direct	12	7	19
Indirect	0	0	0
Direct and indirect	4	3	7
<b>Sensitivity analysis</b>			
Univariate	15	8	23
Multivariate	6	2	8
Probabalistic	10	3	13

**Figure I Flow chart of study selection**

