CANCER TREATMENT PATHWAYS: AML A DETAILED COSTING STUDY EXAMPLE

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THESIS ABSTRACT

Background

AML is one of the most common and acute diseases among the types of leukaemia. The treatment costs for AML/APML are considerably high as it involves the use of expensive treatments (such as stem cell transplantation). Over the past 20 years, the topic has attracted the interest of an increasing number of economic evaluation researchers, with the goal of reducing the related costs without compromising the quality of care and the clinical outcomes. However, no relevant overall/lifetime treatment cost study has been carried out yet, mainly due to UK data availability constraints. Taking the above into consideration, the aim of the study was to calculate the overall/lifetime treatment costs by applying the bottom-up method.

Methods

In order to obtain overall/lifetime cost for AML/APML treatments, an innovative three-phase costing study was conducted on 239 newly diagnosed (during September 2004 to September 2006) adult AML/APML patients in Haematological Malignancy Research Network (HMRN). The study employed the bottom-up costing method and the retrospective treatment pathway. The involved patients were followed from diagnosis date onwards, until death or cure. Treatment pathways, and all the relevant clinical information (including treatments, tests, and duration) were extracted from patients' medical notes on a regular basis by well trained research nurses. Unit costs were determined from various sources, including the British National Formulary and the unit costs of health and social care from the Personal Social Services Research Unit (PSSRU). Finally, an exploratory analysis was carried out on the obtained cost results in order to uncover potential cost predictors.

Results

The average overall treatment cost per patient was found to be £27290. This cost was mainly the result of the first-line treatment cost and the number of AML recurrences. The major cost driver throughout all disease phases was hospitalization, followed by drug and complication treatment. Age, death or not, number of treatments, type of primary induction treatment, and response to induction treatment were found to be highly associated with overall treatment costs.

Conclusion

The results of the current study showed that the lifetime/overall costs of AML/APML treatments was considerably high (although variance between patients was high as well), and uncovered the potential existence of a number of cost predictors. It is expected that these findings could help to bridge the gap between the actual cost and the NHS reference costs, while the potential cost predictors could assist decision makers in relation to health policy or clinical guideline issues.

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ABBREVIATIONS

ADE	Cytarabine, Daunorubicin, Etoposide
AlloBMT	Allogeneic bone marrow transplant
AML	Acute myeloid leukemia
ANLL	Acute non-lymphocytic leukaemia
APML	Acute promyelocytic leukemia
AraC (HD)	High dose Cytarabine
AraC (LD)	Low dose Cytarabine
ATO	Arsenic trioxide
AutoBMT	Autologous bone marrow transplant
BCSH	The British Committee for Standards in Haematology
BMT	Bone Marrow Transplantation
BNF	British National Formulary
CEA	Cost-effectiveness analysis
CR	Complete remission
CRR	Complete remission rate
CUA	Cost-utility analysis
DA	Cytarabine, Daunorubicin
ENT	Ear, Nose and Throat
ETI	Etoposide, Tioguanine, Idarubicin
FAB	French-American-British classification
FC	Fludarabine, Cyclophosphamide
FLA	Fludarabine, Cytarabine
FLAG	Fludarabine, Cytarabine ,G-CSF
FLAG-Ida	Fludarabine, Cytarabine ,G-CSF, Idarubicin
G-CSF	Granulocyte Colony-Stimulating Factor
GM-CSF	Granulocyte/macrophage colony stimulating factor
HAM	Cytarabine, Mitoxantrone
HILIS	HMDS Integrated Laboratory Information System
HMDS	Haematological Malignancy Diagnostic Service
HMRN	Haematological Malignancy Research Network
HRG	Healthcare Resource Group
HSCT	Hematopoietic stem cell transplantation
ICD	International Classification of Diseases
IV	Intra-venous
MACE	Metoclopramide, Amsacrine, Cytarabine, Etoposide

MidAC	Mitoxantrone, Cytarabine
NCI	National Cancer Institution
NHS EED	NHS Economic Evaluation Database
NHS	National Health Service
NHSCR	National Health Service Central Register
PBSCT	Peripheral blood stem cell transplants
PCD	Palliative Care Database
PSSRU	Personal Social Services Research Unit
RCT	Randomized controlled trial
RVU	Relative value units
SPC	Specialist palliative care
WHO	World Health Organization

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This thesis is dedicated to my mother.

AUTHOR'S DECLARATION

I declare that this thesis is original work of the author. The research contained in this thesis has been undertaken under the supervison of the Research Group of Haematological Malignancy Research Network (HMRN) at the University of York.

Han-I Wang 2010

Chapter 1 Introduction

Background, objectives, and study outline

CHAPTER 1 INTRODUCTION

1.1 Research Motivation

1.1.1 Why AML/APML?

Cancer care is often associated with intensive, ongoing treatment regimens and consequently has high associated costs. In this context, an important issue within the health care industry is the reduction of related costs without compromising the quality of care and the clinical outcomes. Better understanding of treatment costs facilitates evidence based decision making.

Among all cancers, haematological malignancies are one of the most costly to treat, as it involves expensive treatments (such as stem cell transplantation). Traditionally, the haematological malignancies are classified into three groups, namely lymphoma, leukaemia, and myeloma. Over the past 20 years, leukaemia treatments have advanced rapidly and, additional therapies are also expected to be introduced in the near future. Because of these developments, a number of economic evaluation researchers have increasingly focused on 'leukaemia' and the high costs associated with new treatments [1, 2].

Following the increased interest in leukaemia it was decided that acute myeloid leukaemia (AML) was the target disease to study here. This was because AML is one of the most common and acute diseases among different types of leukaemia (acute lymphocytic leukaemia (ALL), chronic myeloid leukaemia (CML), and chronic lymphocytic leukaemia (CLL)) [3-5]. The current work was planned and carried out with the support of the Haematological Malignancy Research Network, (HMRN) [6].

1.1.2 What is AML/APML?

Acute Myeloid Leukaemia (AML) is a form of cancer that affects the myeloid blood cells produced in the bone marrow. This includes red blood cells, platelets, and all white cells except lymphocytes. For the above reason, in some American publications, AML is also referred as acute non-lymphocytic leukaemia (ANLL) [7, 8]. In AML, blast cells start to accumulate in the bone marrow and can not differentiate properly. This leads to a large number of immature white blood cells in blood and bone marrow, with the amount of normal white blood cells significantly decreased. Therefore, this type of AML is also referred to acute myeloblastic leukaemia [9]. In cases where abnormal cells are red blood

cells or platelet, the term erythroleukaemia or acute megakaryocytic leukaemia are used respectively [8].

a. Classification

AML is not a single disease but a set of phenotypically similar diseases [10]. The traditional French-American-British (FAB) classification divides AML into eight subtypes ranging from M0 to M7 [11]. However, the more recent World Health Organization (WHO) classification sub-categorizes AML into five groups, in order to increase prognostic utility [10, 12-15]. In HMRN, which is the network involved in the current study, the WHO classification system was used. Further details on the above can be found in **Appendix 1.1**.

b. AML epidemiology in the UK

AML and APML account for approximately 6.7% of all newly diagnosed haematological neoplasms in the UK, with an incidence rate of 4.0 per 100,000 [16]. There are approximately 2000 new cases of AML diagnosed in the UK every year, with over 1400 of these cases involving patients over 60 years of age [16-19]. AML can occur at any age, but the incidence rate increases with age. The median age of the AML is 68 [16]. It is the most common type of leukemia in adults and accounts for approximately 15-20% of childhood leukaemia [3].

c. Treatment

AML is a quickly progressing disease. If left untreated, AML often lead to death within a few months from diagnosis [20, 21]. AML treatment can be divided into two phases: induction (remission induction) and consolidation (post-remission / maintenance / remission continuation) therapy.

- **Induction therapy**

  Induction therapy is the first phase of treatment. Its purpose is to destroy the leukaemia cells in the blood and bone marrow, and to put the leukaemia into remission [9]. The conventional induction therapy for patients with good risk features is intensive chemotherapy (in combination with anthracycline and cytarabine) [22, 23]. To decrease the incidence and severity of infections induced by chemotherapy, sometimes additional cytotoxic agents (such as G-CSF) are used as adjuncts/supportive care [24, 25]. For some elderly relapsing patients (with poor risk features), no intervention has

been proven to be better than others. Under such circumstance, low intensity chemotherapy may be given [24, 25].

- **Consolidation therapy**

This is the second phase of treatment. It begins after the leukaemia is in remission. Its purpose is to destroy the remaining leukaemia cells, which might be inactive but they can potentially begin to re-grow leading to relapsed disease [26]. A number of types of interventions are used as consolidation therapies including intensive chemotherapy and allogeneic or autologous hematopoietic stem cell transplantation (HSCT) [24, 25]. However, relapsing patients are more likely to be candidates for hematopoietic stem cell transplantation [26].

- **Supportive care/therapy**

Supportive care can be used as a main treatment option when patients' conditions ccould not tolerate intensive therapies with cure intent, or as a treatment that is given in addition to the primary therapy. Supportive care contains a number of sub-type treatments, including blood or platelet transfusion, erythropoietin, granulocyte colony-stimulating factor, and steroids.

d. Prognosis

Prognosis is dependent on age, cell type, and the therapy given to patient [23-25]. It is generally accepted that older age is an adverse prognostic factor [23, 24, 27, 28]. Leukemic cell type is another strong prognostic factor in terms of both response to induction therapy and survival [29, 30]. Patients with t(15;17), t(8;21), or inv(16) are expected to have better response to induction therapy and better overall survival [24, 31-33]. Type of treatment also has an important role in prognosis. AML is known for its rapid progress, leading to death within weeks or months if untreated [34, 35]. However, approximately 60-70% of adults with AML are expected to achieve complete remission after induction therapy. More than 25% of adults with AML (about 45% of those who achieve complete remission) can be expected to survive 3 or more years [24, 36].

1.1.2 Why economic evaluation of AML/APML is important?

Increased emphasis is being placed recently on the economic evaluations of AML/APML. This is mainly due to its progressively increasing cost of treating this disease. This trend is driven by the following three factors:

a. Increasing cases related to incidence

The increasingly aging population in developed countries has resulted in increased incidence of AML. According to predictions based on an extrapolation of UK Leukaemia Research Fund epidemiologic data, the number of AML cases will increase 20% by 2031. This is mainly due to an increase of cases occurring in the elderly [37].

b. Increasing cases related to recurrence

Major advances have occurred in treatment over the last 25 years. Modern therapy ensures that the great majority of patients achieve clinical remission. However, because AML/APML often relapses patients often require further courses of treament [38].

c. Expensive to treat

AML treatments have a very high associated cost, as they involve expensive interventions, such as prolonged hospital care, high level technological medical intervention, and provision of specialized facilities (such as those available on bone marrow transplant units) [39]. Moreover, new treatments/drugs under development often have high costs (such as Mylotarg). As a result AML is one of the most expensive diseases to treat among all cancers.

Since the number of AML cases is expected to increase steadily and treatment costs are expected to remain high, economic evaluation of AML is important and necessary for more efficient healthcare resource allocation. However, only a small number of (three) AML economic evaluation studies have been carried out in the UK, with all of them focusing only on specific treatments (and not on lifetime treatments) due to data constraints. For this reason, the current study aims to explore methods to overcome these constraints and evaluate the lifetime treatment costs of AML, while also determining cost predictors for future health policy decision-making.

1.2 Determining a method for cost calculation

1.2.1 Introduction of costing method

Over the past few decades, researchers have tried to establish a 'gold standard' in order to provide the best estimate of 'true cost'. However, this gold standard was difficult to establish [40] as different costing methods are appropriate to specific situations and no single methodology is appropriate for all circumstances. In the absence of a 'gold standard', the approaches for accurate estimations of the cost of specific healthcare services have been broadly classified into two categories: top-down and bottom-up [41-43].

a. Top-down approach

Top-down methods use relative value units (RVU), such as hospital days, outpatient visits, or other metrics to assign total costs to individual services or healthcare products. They are often used when fine details are not available [43].

The top-down method is an efficient approach. It is easy to conduct, less resource-demanding, and the implied data collection is relatively straightforward. Of greatest importance, the top-down method ensures that all expenses are included and no cost is overseen. This is because in this approach the basis is the "total cost", which is later assigned to end products through a set of distribution formulas [44, 45]. However, the drawback of the top-down approach is that costs derived in this way might not accurately reflect actual resource use because total costs are allocated based on aggregate information [46]. Moreover, the result derived through the top-down costing method lacks a direct cause-and-effect relationship, as the top-down approach assigns the total costs by using "various weighting systems". Therefore, any factor identified using the top-down approach might be associated but not causative [47].

b. Bottom-up approach

The bottom-up approach is a method that assigns costs to health services or products, based on the actual contribution of the resource use and representing their proportion of total costs [43, 48, 49].

This approach has many advantages. Firstly, many different issues can be addressed and the effect of each can be well understood as the conceptual design is built from scratch [47]. Secondly, the cost results are precise and reliable because they are derived in great detail. Thirdly, the bottom-up approach is transparent; it allows tracing and identifying the contribution of each element of the healthcare system to the cost of an individual healthcare service, while it also presents the subtle cost variations [43, 48-50]. Finally, it can reveal the cause and effect relationship [47].

However, there are also a number of disadvantages related with the bottom-up approach. Firstly, the whole analysis procedure is complex and time-consuming, something that make it more expensive to implement and difficult to use [42, 43, 49, 51]. Secondly, the bottom-up method is a resource-demanding approach. It requires a costing model that has to be designed from scratch, a detailed cost database, and analysts who are familiar with the study area involved in order that the method can be correctly applied [47].

1.2.2 Why use the bottom up costing method?

a. Capturing variations in cost

The bottom-up approach emphasizes time and patient differences as it builds up costs based on resource use, which can vary over time and between individuals [43]. In contrast, top-down approaches smooth out cost differences over time and between patients as they apply the same weights to similar products irrespectively of time or patient differences [50]. Furthermore, the transparency and the strong cause-effect relationship associated with the bottom-up approach mean that the cost results can be further analyzed [43, 48-50].

b. Characteristics of the treatment/intervention cost

An important characteristic of the hospital / treatment cost is that departments within the hospital work in collaboration with each other (not completely independent). Therefore, treatments processes are the result of complex interplay between many departments and thus cost units. In this context, the bottom-up costing method can be more precise than the top-down approach, as the former would not compromise the accuracy of the generated costs.

c. Exploring a method to overcome data constraints in the UK

There is an increasing interest in costing life-time treatments for AML/APML patients, as life-time cost provides a clear overview of the total medical resource use for each patient. However, no relevant life-time treatment cost studies have been carried out in the UK. Moreover, in previous related studies, hospital billing systems and administrative claim databases were the main data sources for costing life-time treatments. However, in the UK, neither of the aforementioned data sources are available. The lack of previous data, specifically on life-time costs, and the inability of current top-down information systems to supply the detailed costings restricts the possibility of costing lifetime treatment for AML/APML in the UK. To resolve this issue, it was decided that bottom-up costing should be used, as this method is considered to be an alternative way to obtain the real cost without compromising the quality of the study.

1.3 Why cost the full history of treatment?

Many previous economic evaluation studies of AML/APML have been restricted by setting a fixed time or study time period due to time, workforce, or data constraints. Such studies only use the 'first line treatment phase' or 'induction treatment phase' as study time period. This approach made their results more comparable, but fails to take two facts into consideration. Firstly, first-line treatment does not represent the whole range of treatments. Although cancer treatments generally are centered on the initial treatment episode, the outcome of induction treatment can only partly determine the whole range of treatments on the patient pathway. Secondly, AML/APML is a disease with a high rate of relapse. First line treatment cost therefore only accounts for part of the overall treatment cost. In order to have an overview of the total medical resource use and to uncover the long-term effect of cost predictors, it was decided to cost the entire pathway, including all treatments for AML/APML.

1.4 Aim and objectives of the thesis

The current study is an exploratory cost study, which forms the basis of a methodology for constructing life-time costs and illustrating the complexity of using a bottom-up methodological approach. The overall aim of this thesis is to provide the first detailed lifetime/overall costs of treating patients with AML/APML in the UK.

The general objectives for this thesis are:

a. To apply the bottom-up method in order to overcome the constraints of UK data and provide high-quality longitudinal cost data for economic evaluation studies.
b. To explore phase-specific and lifetime treatment costs in order to identify patterns of resource utilization for AML/APML treatments in the UK.
c. To explore possible cost predictors in order to provide useful information (on AML/APML) to policymakers or expert panels

1.5 Outline of the current thesis

The current study was carried out in three main phases. In the first phase, the cost drivers that were commonly used in previous studies were explored in order that they could be integrated into the costing method of the current study. In the second phase, the bottom-up approach was employed in order to develop a costing method suitable for the UK setting. In the third phase, the costing method that had been developed was applied and the treatment costs were calculated. Finally, the cost results were further analyzed in order to uncover related cost predictors for AML/APML lifetime treatments. The breakdown of chapters is as follows.

In Chapter two, the existing literature on economic evaluations of AML/APML is presented. The costing methods (such as data sources and measurement details) and the results of existing studies are presented.are possible cost drivers for the UK setting are then identified.

In Chapters three and four, the three main databases which provided the data for this study are further discussed. Details related to database handling (such as data cleaning and missing data imputation) can be found in Chapter three. The results from the preliminary analysis of the three databases (such as treatment types and treatment durations) are presented in Chapter four.

Chapter five presents an overview of the study methodology. This includes concepts such as deciding the costs that should be evaluated and determining the data sources to be used for costing.

The three-phase costing method developed for the study is described in Chapters six, seven and eight. Phase one, which relates to the bottom-up costing methods for each cost driver, is presented in Chapter six, while Phase two, which relates to the costing methods for each treatment, is presented in Chapter seven. Finally, Phase three, which relates to the costing method for the overall treatments, is presented in Chapter eight.

In Chapter nine, all the cost results are presented, ordered by treatment phases (including each treatment and overall treatment costs) along with the possible cost predictors. In this chapter, the challenges that arose during the costing and information related to data handling are presented. Also, the study results are further compared with those of other related studies in order to justify/validate the costing method and the cost results.

The final chapter (Chapter ten) summarizes the main findings of each chapter and the contribution of the current study to the existing literature. Finally, issues that require further analysis in the future in relation to the costings are listed.

The structure of the thesis is illustrated below (Figure 1.1)

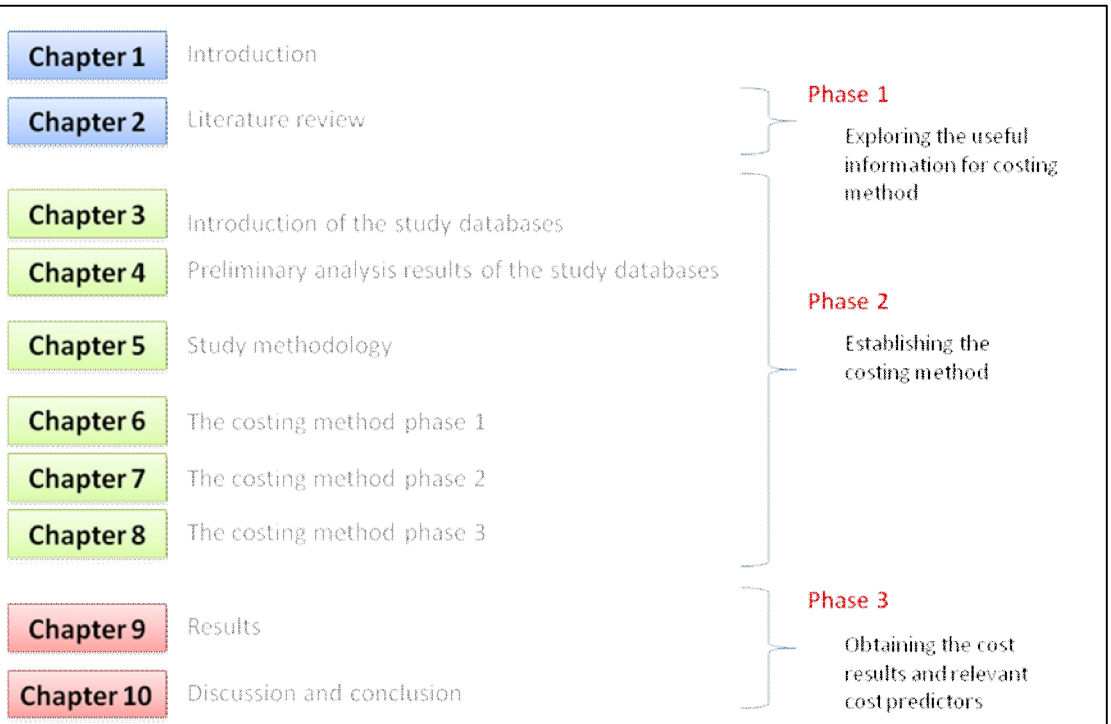


Figure 1.1 Illustration of the structure of the thesis

Chapter 2 Literature Review

CHAPTER 2 LITERATURE REVIEW

2.1 Objectives of the review

Various cost measurement methods are generally available. For the purposes of the current work, it was decided that a systematic review would be conducted to explore the available costing methods for AML/APML and confirm the appropriateness of current practices.

In the systematic review, all the costing studies that were relevant to AML/APML were reviewed. In the process, detailed information about the treatment costing methods, the data sources, and the cost results were extracted and sorted, in order to provide references for the costing methods used at later stages of the current study.

The review questions focused on:

a. The number of relevant cost studies that have been conducted on AML/APML.
b. The costing methods used in the relevant studies (including the study time period, and the involved cost drivers).
c. The results of the relevant studies.

The review process is illustrated in **Figure 2.1**.

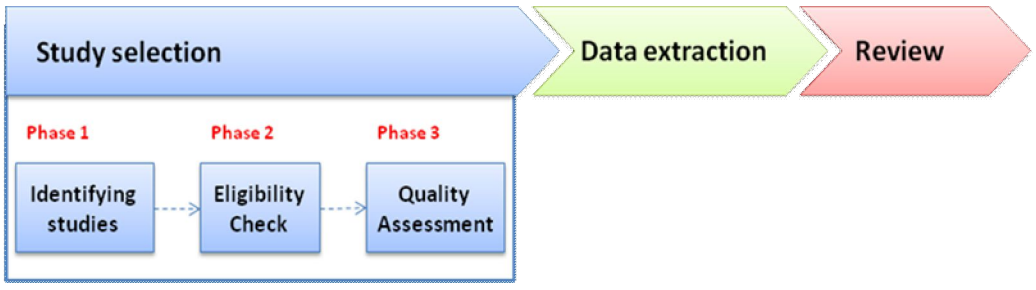


Figure 2.1 The illustration of the review process

2.2 Study selection phase 1: selection criteria

The research was limited to English language articles published between 1995 and 2007. All types of cost studies (such as cost analysis, cost effectiveness analysis, and cost utility analysis studies) on AML/APML were included. The details are discussed in the following sections, while the summarized criteria are listed in **Table 2.1**.

Table 2.1 Summary of the study selection criteria

	Inclusion	Exclusion
Population	Newly diagnosed AML / APL	Not AML / APL studies or only a minor part discusses about AML
Intervention	Economic evaluation analysis	Clinical management analysis
Outcome	Costing method	No relevant methods
Language	English studies	Non-English studies
Publication status	Published and unpublished	-
Publish year	1995-2008	Before 1995

2.2.1 Participants

Inclusion criteria:

Studies in which patients were newly diagnosed with Acute Myeloid Leukemia (AML) and/or Acute Promyelocytic leukemia (APML / APL) were included, regardless of age and treatment phases.

Exclusion criteria:

Studies in which patients who were not diagnosed with AML or APML were excluded.

a. AML /APML

Studies that recruited both AML and APML patients were included. The reason for this was that the treatments and the clinical manifestations of APML were significantly different from the ones of AML, although APML is a common subtype of AML (accounts for 5-10% of cases of AML) [52, 53]. In the current review, studies focusing exclusively on APML or on both AML and APML were all included. It is worth noting that studies that included various haematological cancers (in which only a minor part concerned AML/APML) were excluded, as the relevant study designs, measurement methods, and results had little correlation with AML/APML.

b. Newly diagnosed

Studies that recruited 'newly diagnosed' and 'previously untreated' patients were both included to allow the costing of the complete patient pathway from time of diagnosis. It is worth noting that the newly diagnosed criterion only applied to induction therapy studies. For studies focusing on consolidation therapy, complications of treatment, and supportive or palliative care, the newly diagnosed criteria was not applied, as it is not necessary to restrict with the newly diagnosed and previous untreated criteria.

c. Age

All the relevant economic evaluation studies on AML/APML were included regardless of the age of the study patients. The reason for not taking age into consideration was that AML/APML can occur in the young and the elderly groups [52, 53].

2.2.2 Intervention and comparisons

All AML/APML studies involving cost calculations were included. The reason for this was to reveal how the costing methods were carried out in previous studies. This included cost analysis, cost utility analysis, and cost effectiveness analysis. However, clinic management studies were not included as these studies were not related to cost estimation. Also, previous 'review studies' were excluded. The reason for this was that 'review studies' could not provide information related with the costing methodology, as these studies mainly focused on summarizing the cost results of other original studies. It is worth noting that the economic evaluations for single intervention or for comparison of multiple interventions were all included. The interventions were further categorized at later stages of the review.

2.2.3 Outcome

For the purposes of the current review, the primary outcomes were costing methods and costing details, while the secondary outcomes were cost results.

a. For the objectives of the current review, costing methods and costing details (such as data sources and associated cost drivers) reported in previous studies were regarded as the primary outcomes. These details provided useful references for the costing method that was used at later stages of the current study.

b. Cost results were set as the secondary outcome of the current review. Through the transformation of the cost values to 2007 USD, cost results from studies from different countries, or those using different methods became comparable. The reason for converting currencies to US dollars, and not the opposite, was that most of the cost-study results were published in US dollars.

2.2.4 Language

Only relevant studies written in English were included in the current review. This was for 2 reasons. Firstly, as English journals are a central point of the field in the present day, papers published in them are guaranteed to have been subjected to thorough reviewing. Therefore, papers written in English are considered to be of a higher quality standard than papers written in other languages [54]. Secondly, in most cases articles from non-English journals were very difficult to access/obtain, in contrast to study abstracts written in English that could be easily obtained through the main search engines of electronic databases for health care studies (such as MEDLINE, PUBMED, EMBASE). However, excluding non-English papers might cause language bias. Previous studies have shown that research reporting effective interventions is more likely to be published in English [55-57]. Therefore, it was expected that the costing methods and results for ineffective intervention could be overlooked in the current review.

2.2.5 Publication status

Unpublished studies were considered to be of a lower quality standard than published ones (as they are likely not to have been reviewed thoroughly) and, thus, could bias the review results. However, both published and unpublished studies were included in the current review. This was mainly for two reasons. Firstly, excluding unpublished studies would cause publication bias, which effectively means that studies with significant findings are more likely to be published [58-62]. Therefore, excluding the unpublished studies could bias the results of the current review. Secondly, including the unpublished studies increased the amount of the reviewed studies. Therefore, it was considered that the inclusion of both published and unpublished studies would help in collecting as many relevant studies as possible, while it would also prevent publication bias.

2.2.6 Year of publication

In order to include as many relevant studies as possible, no restriction on the year of publication was generally desirable in the current context. However, only studies

published between 1995 and 2008 were included here. This was for 3 reasons. Firstly, most of the available studies were published after 1994. Secondly, cancer treatments advanced rapidly. Treatments used before 1994 were not applicable in the present day. Thirdly, the Calman Hine Report (1995) introduced into the reconfiguration of cancer services in 1995 in order to ensure the quality of cancer services [63]. Therefore, it was decided the cut-off point of the year of publication to be set to 1995.

2.2.7 Full text versus abstract

Ideally, only full report studies should be included. However, due to the difficulty of full text access, abstracts were also included if they had sufficient relevant PICO information (population, intervention, control, and outcome). This ensured that the highest possible number of studies was identified.

2.3 Study selection phase 1: Search strategies for identifying studies

To identify studies potentially related with the current work, four sources were examined/searched. Details of the search process for each of these sources are presented in the following sections.

2.3.1 Published studies

Published studies were mainly identified via the search engines of the relevant electronic database, namely MEDLINE / PUBMED, EMBASE, and NHS Economic Evaluation Database (NHS EED) of Centre for Reviews and Dissemination. MEDLINE , the U.S. National Library of Medicine's bibliographic database, is one of the most complete databases, as it contains more than 18 million articles (with about 3/4 of these articles being recent) covering biomedicine and health from 1947 to the present day [54, 64, 65]. However, it was not the only database that was examined. This was because previous research has shown that, on average, only 34% of papers are covered by both MEDLINE and EMBASE [66]. This indicated that a large number of studies were not included in MEDLINE. For this reason, it was decided that EMBASE (covering all areas of health care and index journal published from around the world), and the NHS EED (focusing on health economic evaluation) would also be searched/examined, in addition to MEDLINE.

To identify relevant studies, several filters and truncations were used in the search engines, such as the Ovid economic evaluation filter, the filter designed by the SIGN [67], truncated name of treatment regiment intervention, and truncated name of the AML / APL. The key words and truncations of the search strategy are listed in **Appendix 2.1**, while the detailed search strategies for 'AML/APML studies' and 'economic studies' are described below.

a. AML / APML studies

The search strategy for AML / APML studies was derived from 3 sources:

- From three previous AML / APML review papers in the Cochran library [68-70].
- From the full name of the textbook terminology [52, 53].
- From Ovid MEDLINE MeSH for AML / APML (derived from the MeSH search on the Cochran Library website [71].)

The resulting search strategies for AML/APML studies are listed in **Appendix 2.1**.

b. Economic studies

The search strategy for economic studies derived from 3 sources:

- From the use of two filters, namely the Ovid MEDLINE filter and the SIGN's filter. The 'SIGN's economic studies filter' was an adaptation of the strategy designed by the NHS Centre for Reviews and Dissemination at the University of York. It provided less sensitive searches, but enabled retrieval of potentially relevant medical studies [67, 71-73].
- From the relevant MeSH terms [71]
- From previous systematic review papers [74].

The resulting search strategies for economic studies are listed in **Appendix 2.1**.

2.3.2 Grey literature

As mentioned earlier, unpublished studies (grey literatures) were examined in the current work in order to avoid publication bias [59-61, 75-77]. The following 3 types of such studies were examined.

a. PhD and Master Theses: relevant topics were obtained using both electronic and hand searching.
b. Government publication: relevant topics were obtained using both electronic and hand searching.
c. Conference proceedings: relevant topics were obtained from several sources by using both electronic and hand searching (see **Appendix 2.2**).

2.3.3 Ongoing trials

Databases containing the latest trials (see **Appendix 2.2**) were also searched; as such sources can occasionally provide useful albeit incomplete information. Secondly, ongoing trial searching can prevent the introduction of time period bias, which occurs when the search is conducted for an unrepresentative time period.

2.3.4 Hand-search

In order to avoid overlooking related articles, a manual search was performed on key journals, conference proceedings, and reference lists.

a. Key Journal

Key journals are journals that specifically focus on haematology, or leukemia treatment. (Key journals are listed in **Appendix 2.2**). To prevent overlooking important studies, hand-searching was applied to key journals. This helped in retrieving two types of useful information. Firstly, information that was not included in the electronic databases (as sometimes relevant information appeared in news columns, editorials, or letters). Second, relevant articles that were not indexed properly or not indexed with the term used in the search strategies of the current review (as sometimes these articles could be easily overlooked [58]).

b. Conference proceedings

Important conference proceedings were also searched manually. This was because of the following reasons. Firstly, most conference proceedings were not included in MEDLINE or any other electronic database. Secondly, according to previous research, over one-half of the work reported in conferences never reached full publication, while even work that was eventually published in full was observed to be systematically different from work that was not [78]. Thirdly, conference abstract is a type of grey literature that is more likely to generally contain 'negative' results, compared to studies published in journals [79].

c. Reference list of the papers

To avoid overlooking important studies, all the citations found in the identified studies (including the systematic review papers) were screened manually. This approach helped identification of the relevant studies quickly. However, a drawback related to this was that the authors of the identified studies could selectively cite studies with positive or coherent results [80, 81]. Therefore, hand searching the reference list of the related studies was used in combination with other searching approaches to identifypotential studies for the review.

2.4 Study selection phase 2: Eligibility check

Studies obtained during searches were further screened/selected in order to retain the ones that addressed the review questions. For this task, two processes were employed: eligibility checks and quality assessment. Relevant details are presented in the following sections.

The purpose of the eligibility checks was to screen studies and evaluate their relevance to the review purposes. An eligibility check form was built for this purpose, and all the candidate studies were assessed using this form. Studies that met the inclusion criteria were included in the current work.

2.4.1 Building the eligibility form

In order to identify relevant studies, an eligibility form that was built. The form, which can be found in **Appendix 2.3**, contained a number of questions related with the inclusion and the exclusion criteria (please refer to sections 2.1.2, 2.1.2, 2.1.3). Since study selection involved subjective judgments, use of the eligibility form was expected to reduce the study selection bias caused by reviewers' preference [54], and thus make the study selection procedure more transparent [54, 58].

2.4.2 Reviewer

a. One reviewer

Decisions regarding the inclusion and exclusion criteria of individual studies often involve some degree of subjectivity. Therefore, it is generally suggested that having at least two reviewers is desirable in order to reduce the possibility of subjective judgments [54] and the possibility of discarding important and relevant studies because of human errors (such as accidental exclusion, overlooking, or misunderstanding) [54, 58, 82]. However, in the current review, only one reviewer was involved in the candidate studies selection process. This was mainly because of time and workforce constraints. In order to maintain the transparency and reproducibility of the study selection, and to reduce the possibility of human errors, a second reviewer was invited to double-check the selection procedures of twenty random selected abstracts. It was expected that if the selection results of two reviewers were consistent, it would be safe to claim that the selection results of the current review were, by and large, robust.

b. Blind review

The reviewer was unaware of the authors' names, the institutions, the journals, and the results of the candidate studies when the eligibility check was applied. This was expected to help avoiding the introduction of the ascertainment bias, which occurs when false results are produced by a possible subjective selection by the reviewers [54, 58, 83].

2.4.3 Study selection process

After the eligibility form was built, it was used for assessing the eligibility of all candidate studies. In cases where specific information (title and abstract) of the study was sufficient, decisions were made based on the eligibility criteria. When information was insufficient or doubtful, the full text of the study was retrieved and checked for further consideration [84]. However, related studies for which information validity was still doubtful after the examination of the full text, it was decided to be include in the current review. This was because once a study had been excluded it was impossible to be considered again. Also, this allowed doubtful studies to be further examined at later stages of the current work when further information became available [58].

2.4.4 Keeping logs of excluded studies with reasons

All the excluded studies, as well as the reasons for their exclusion, were recorded. This was because keeping logs not only maintained the transparency of the selection process, but also could answer possible question regarding the exclusions [58].

2.5 Study selection phase 3: Quality assessment

Review results can be biased by poor internal and external validities of eligible studies (such as unsuitable interventions and inadequate follow-up time for internal validities, unreliable measurement techniques and inappropriate statistical analysis for external validities [54, 85-87]). Based on suggestions of the Cochrane Collaboration and other experts [83, 88], assessment of quality/validity was conducted by means of a quality assessment checklist. This was in order to minimize possible biases caused by poor validities of the eligible studies

2.5.1 Developing the quality assessment checklist

A number of checklists are available with each of them focusing on specific study designs (such as the checklist for randomized controlled trial and the checklist for observational studies) [54, 89]. In the context of the current review, the quality assessment checklist was constructed according to the following aspects (the checklist can be found in **Appendix 2.5**).

a. Modifying two existing checklists

The quality assessment checklist was mainly based on Drummond's and BMJ study quality checklist [90, 91], as both of these two checklists were capable of assessing the quality of economic evaluation studies. Since economic evaluation studies were not the only type of eligible studies for the current review, the checking questions derived from the aforementioned checklists were further divided into two categories/phases according to their characteristics.

In the first phase, the checking questions focused on the quality of the reported costing method of all the eligible studies. The emphasis was placed on what and how the eligible studies measured the cost (for example: Were the costing measurement methods described comprehensively?). In the second phase, the checking questions focused on the quality of the economic evaluation studies (for example: were all the important and relevant costs and outcomes identified?). This was because the questions were important for economic evaluation studies but inadequate for judging the quality of non-economic evaluation studies.

Considering the above, after the two-phase quality assessment checklist was built, all the eligibility studies were assessed by means of the first-phase checklist, while economic evaluation studies were further assessed by means of the second-phase checklist.

b. Two types of evaluation study

Economic evaluation studies can be further divided into two categories: trial-based studies (using a single source of evidence) and model-based studies (using multiple literature sources) [83]. Generally, most reviewers show preference in designing separate quality checklists for different study bases [54]. However, in some occasions, joint checklists can be also considered [92]. In the current review, a joint checklist was used, as there was a large number of common checking questions. The checking questions were divided into two, only in the study design quality domain. In the part designed for trial-based studies, the checking questions focused on the quality of the study structure (such as inclusion / exclusion criteria, or data collecting method). In the part designed for model-based studies, the checking questions focused on the quality of the literature review (such as the method of deriving input parameters for the model, or the representativeness of the model in terms of clinical practice)[84].

c. Internal and external validity

Internal and external validities are both important for quality assessment. In the current review, more emphasis was put on internal validity, as latter was a prerequisite for external validity [54, 84]. Internal validity focused on whether results of a study were 'correct' for the circumstances being studied. In contrast, external validity focused on whether results of a study were applicable to other circumstances (outside the study) [93]. Therefore, if the results of a study were invalid (internal validity), then the checking questions of its external validity became redundant.

d. Simple checklists rather than quality scales

There are two approaches for assessing the study quality. One is using the summary scores, and the other is examining the influence of the quality components by simple checklists [58, 94]. Although the use of summary quality scores can provide a useful overall quality assessment, it was decided that the simple checklist approach should be used (instead of the summary score) in the current review. This was for the following two reasons. Firstly, different measurement scales may lead to discordant results. Secondly, summary score was difficult to interpret, as associations between score results and quality

were unclear [58, 94]. In order to avoid the aforementioned issues and to ensure the transparency of the study selection process [89], it was decided that the simple checklist approach should be preferred.

2.5.2 Quality assessment process

After the quality assessment checklist was built, it was applied to the full texts in order the quality (validity) of the eligible studies to be assessed, while it was, also, judged by two un-blinded & independent reviewers. Because of time and workforce restrictions, only one reviewer assessed the qualities of all the eligible studies, while another independent reviewer only double-checked the results of twenty random eligible studies. This was in order to reduce possible bias caused by reviewer's preference. Both of the reviewers were un-blinded, as blinded review was not necessary here [54, 58, 83]. It is worth noting that the quality assessment results of the two independent reviewers were consistent. Based on this, it is claimed that the selection results were robust.

2.6 Data extraction

After the study selection, the next step was the extraction of the data. A specially designed data extraction form was used in order the data from the selected studies to be transformed to useful information suitable for further analysis at later stages of the current work.

2.6.1 Rationales of using data extraction form

a. The data extraction form provided clearer summaries than the study abstracts, as the design of the form was based on and linked to review questions [95].
b. The data extraction form was a bridge between what was reported by the original investigators and what was ultimately reported by the review authors [96].
c. The data extraction form prevented collecting low or high amount of information. Collecting too much information might lead the length of the extraction form to be longer than that of the original study. On the contrary, collecting low amounts of information might result in missing important data and introduce a need for revisiting original study at later stages of the review process [96].

2.6.2 Design data extraction form

The design of the data extraction form was based on three important aspects: 1) the review questions, 2) the eligibility criteria of the selected studies, 3) the informal collation of experiences from numerous review authors (published in Cochrane Handbook for Systematic Reviews of Interventions [96]). Moreover, according to suggestions found on the Cochrane Handbook [96], ticking boxes or coded responses were adopted into the data extraction form. This was in order to save time during the data extraction, while it also ensured that the same term was used for data categorization during the extraction. The data extraction form can be found in **Appendix 2.5**, while its components are discussed in the following sections.

a. General information

Information collected from the selected studies included: title, authors' name, source information (year / volume / pages / journal or conference), contact E-mail address, country, the source type, study type (trial / observation / model), and data type (primary / secondary).

- The contact E-mail address was collected as a mean to contact the author regarding possible queries.

- The country information was collected as a mean to identify the differences of the costing methods usage from country to country. Furthermore, the emphasis was put in UK studies, as information related with the costing methods and the data sources used in these studies was expected to be helpful at later stages of the research.

- The 'price year' was collected for comparison reason, as the cost value changes over time because of the inflation (for example, £20 in 1998 has not the same value as £20 in 2008). The price year information was useful for cost comparison at later stages of the current work.

- Information related with the study type and the data type was collected because they could help in assessment of the costing methodologies and the data sources that were used in the selected studies.

b. Participants

The following information was collected from the selected studies: total number (initial sample size / number of AML or APML patients – when AML/APML was not the only one study population), setting of target population (description of inclusion and exclusion criteria / diagnostic criteria / baseline characteristics/treatment phase), study period, outcome sample size (withdrawals and losses to follow-up).

- Three different sample sizes were collected. This was for two reasons. Firstly, the outcome sample size always differs from the initial numbers because of attrition or exclusions [96]. Secondly, if AML/APML was not the only study group (such as in case of hematological malignancy study), it was important to collect the number of AML/APML patients, as this number could affect the review results and its generalization.

- Age information was collected because AML/APML could occurred at any age [52, 53, 97, 98]. Also, since treatment types and treatment tolerance differed between age groups [52, 53, 97, 98], it was expected that differences in cost between age groups could occur. Therefore, it was deemed that age information collection was necessary.

- Treatment phase information was collected because there were great different between treatment types and regimens in different treatments phases [97, 98], something that could the affect cost results.

- Study period' was also collected as it was associated with the costing methods and the cost results.

c. Intervention

Information related with study intervention was also collected from the selected studies. This included treatment type (overall treatment, chemotherapy, adjunctive treatment, transplantation, complication treatment, examination, supportive or palliative care), analysis type (Cost analysis, CEA/CUA), and objectives of selected studies.

- Treatment types information was collected because different treatments required different methods to cost. The information not only helped to categorize the selected studies, but also assisted in uncovering the costing methods/data sources used for costing different treatments.

- Objective information was collected because of its relation to the review questions. It not only helped to double check whether selected the studies were eligible, but also provided overviews of these studies.

d. Outcome (Costing Methods)

According to the review questions, the following information was collected: cost data sources (unit cost / charges / payments), cost drivers, costing methods, and cost results. It is worth noting that selected study results, mainly to be used as notes.

- Cost data source information was collected because it was the main part of the costing methods, and also it determined the cost results. Therefore, the collected information not only helped to uncover the costing methods that were used in the selected studies, but also helped to distinguish whether cost results were comparable.

- Information related with the costing method (such as method types, cost drivers, and data sources) was collected for three reasons. Firstly, it could uncover how previous studies measured the cost, which answered the review questions of the current review. Secondly, it could help to assess whether any costs have been omitted in the selected

studies. Thirdly, it could help to judge whether the study designs of the selected studies were applicable and replicable.

- The results of the selected study were collected because they provided a clear, albeit simple, overview of the studies (irrespectively of how many outcomes were presented). Since variation in study results can be very large [99], it was decided only results that matched the review purposes to be collected.

e. Note

A blank footnote column was left for the purpose of keeping important notes relevant to the study. Also, following suggestions from the Cochrane Systematic review Handbook, another blank space was left for notes. This was placed near the beginning of the form, as opposed to its end, in order to avoid placing notes, questions or reminders in a position less noticeable [96]. Overall, two note-columns were included in the data extraction form. Important notes (such as reminders) were put in the column positioned in the beginning of the form, while less important notes (such as reference to other studies) were put in the column in the end of the form.

2.6.3 Data extraction Process

Using the designed data extraction form, data were extracted from the selected studies individually. It is worth noting that three data extraction principles were followed in order to avoid identified errors. Firstly, ‘raw’ data were preferred for the data extraction. For example, number was preferred to rate. Secondly, value range, confidence interval, or P value was also extracted, if available. This was in order to provide overviews of value variation. Finally, the extracted quantity formats should be consistent for comparison reason.

After data extraction was completed, summaries of the review results were generated. The relevant details are presented in the following sections.

2.7 Results (characteristics of selected studies)

The search strategies were practically applied in January 2008 and resulted in 333 abstracts. After the eligibility check and the quality assessment of these articles in full-text, only 50 papers were found to match the review purposes of the current review. The relevant study selection details are discussed in the following sections.

2.7.1 Number of studies for the review

According to the set search strategies (please refer to section 2.3 for details), three main sources were examined. Relevant details are discussed in the following sections, while the results are summarized in **Table 2.2**.

Table 2.2 The summarized results of study selection

Name of source	Number of papers indentified	Number of papers after abstract screening	Numbers of papers after detailed reviewing in full text
Publish studies			
MEDLINE	277	85	41
PUBMED	277	85	41
EMBASE	279	85	41
NHS EED	28	19	19
Cochrane Library	2	2	2
CancerLit	0	0	0
Cochrane Center Register of Controlled trials	0	0	0
Subtotal	288	85	41
Grey Literature			
Thesis	0	0	0
ZETOC and ISI Conference Search	0	0	0
Conference Proceedings	26	26	2
Subtotal	26	26	2
Hand-searching			
Key journals	5	5	2
Reference list of papers	25	15	6
Subtotal	30	20	8
Total			**51-1=50***

*One Mexico paper couldn't be found because of wrong citation.

a. Published studies

The electronic database searching strategies resulted in the collection of 288 abstracts. After the abstracts were screened using the eligibility form, 85 studies were found to be potentially relevant. The two main reasons for the exclusion of the 203 studies are described below.

- Irrelevant studies
  A number of the obtained studies were found to be irrelevant, due to confusing key words and wrong indexed terms. The irrelevant studies were discarded, as they did not provide any answers to the review questions.

- Case and review studies
  Although database searching confirmed to the inclusion and exclusion criteria (please refer to section 2.2), two case studies and 12 review studies were found in the obtained 288 published studies. According to the exclusion criteria, these studies were considered to be irrelevant to the review purposes. Therefore, they were all excluded.

After the eligibility check, the eligible studies were further evaluated using the quality assessment checklist. Finally, 41 published studies were found to be relevant. The reason for excluding the remaining 44 studies was that costing methods were not included in the contents of these studies, although cost results were referred to briefly in their main body. Overall, 41 published papers were included in the current review study (**Table 2.2**).

b. Grey literature

Twenty-six studies considered through the grey literature electronic database or hand searching for relevant topics from PhD and Master theses, and through conference proceedings, were found to be potentially relevant. However, after the eligibility check and the quality assessment of the full text, only two conference studies were confirmed to be relevant. The two main reasons for excluding the remaining 24 studies are described as following:

- Most of the reports included the term ‘cost-effectiveness’ in the last sentence in the conclusion. However, as a whole, these reports were irrelevant with cost analysis or economic evaluation.

- AML/APML cases only accounted for a minor proportion of the study population. Therefore, the results could not represent the real treatment and/or lifetime cost for AML/APML.

Overall, two unpublished conference proceeding reports were included in the current review study (**Table 2.2**).

c. Hand searching of key journals and reference list of papers

Hand searching the key journals and the reference lists of the selected articles resulted in 20 relevant articles. After excluding the repeated studies and the review studies, only eight articles remained (three conference reports and five published studies). It is worth noting that there were two non-English studies (one German study [100] and one Dutch study [101]) among these eight articles. The reason for the inclusion of these two studies was that they contained important information related with costing methods. In the German study, the bottom-up costing method was used and described, while in the Dutch study, the costing method that was used was described in detail. Since these two articles were considered to be important for the current review study, they were translated into English for further review use (**Table 2.2**).

Overall, there were 51 studies and reports were recruited in the current review study, including two non-English, but important studies. One of the aforementioned studies was a Mexico article [102] that could not be reached due to wrong citation from MEDLINE. Therefore, a total of 50 studies and reports were finally included in the current work. The study selection process is illustrated **Figure 2.2**.

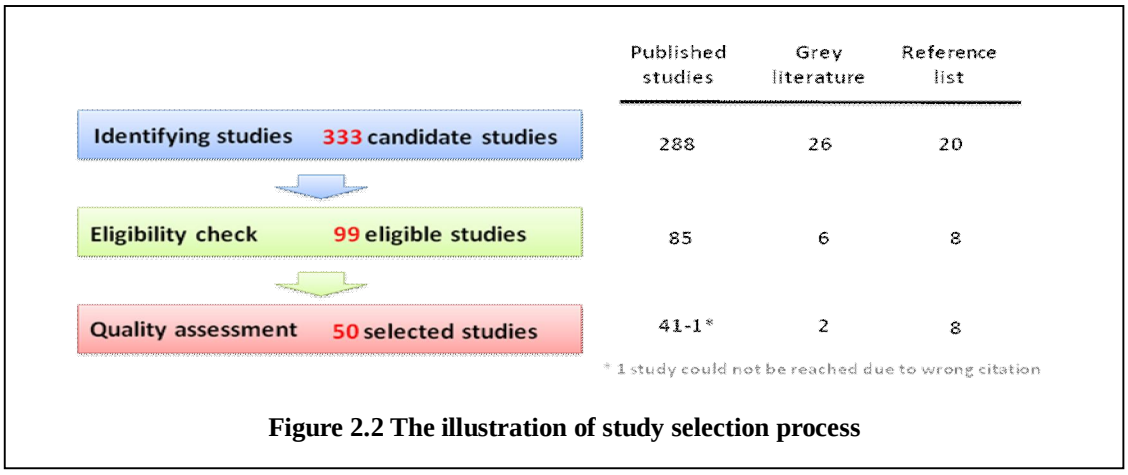


Figure 2.2 The illustration of study selection process

2.7.2 Overview of the selected studies

The details of the study search and selection were approached by three different perspectives. Relevant details can be found in the following sections, while the summarized results are presented in **Table 2.3** below.

Table 2.3 Number of selected studies

Treatment type	Number of studies			
	1995-1999	2000-2004	2005-2008	**Total**
Overall treatment	0	4	3	**7**
Chemotherapy	1	3	4	**8**
Transplantation	6	9	2	**17**
Complication treatment	1	4	3	**8**
Adjunctive trreatment	7	4	0	**11**
Examination	1	0	1	**2**
Palliative or supportive care	2	0	3	**5**
Total	**17**	**24**	**16**	**58***

* Due to five studies that focused on more than one treatment. (1 study compared the costs of overall treatment, chemotherapy, supportive care, palliative care, and transplantation, 1 study estimated overall treatment costs and chemotherapy costs, 1 study estimated the costs of chemotherapy with / without adjunctive care, 1 study estimated the costs of chemotherapy, side effect treatment and supportive treatment, and 1 study estimated the costs of chemotherapy and transplantation.

a. Treatment types

The data extracted from the selected studies were sorted and categorized into seven different treatment groups, namely overall/lifetime treatment (seven studies), chemotherapy (eight studies), transplantation (17 studies), complication treatment (eight studies), supportive /adjunctive care (11 studies), examination (two studies), and palliative or supportive care (five studies). Overall, 58 articles were ready for reviewing. It is worth noting that the additional 8 articles (50 studies in total were included in the current review) were obtained from five studies that compared costs and health outcomes of 13 different treatments. Relevant details can be found in **Table 2.3**.

b. Publish year

The selected studies were further subdivided by publish year (in 5-year intervals), namely 1995-1999, 2000-2004, and 2005-2008. Between 1995 and 1999, 18 studies and report were found to have been published, while 24 and 16 studies were published between 2000 and 2004, and between 2005 and 2008 respectively (**Table 2.3**). It is worth noting that the number of publications related with AML/APML economic evaluations increased

progressively (3.6 papers per year were published during 1995-1999, 4.8 papers per year were published during 2000-2005, and 5.3 papers per year were published during 2005-2008). This also underlined the increasing emphasis on AML/APML treatment cost analysis.

Taking the 'treatment types' into consideration, the results showed that the focus was on different treatment type cost studies during different publish time periods. During 1995-1999, most of the studies focused on growth factor cost saving and transplantation costs. During 2000-2005, most studies focused on transplantation costs. Growth factor cost studies were still highly emphasized, but meanwhile the researchers started paying more attention on overall/lifetime treatment costs and complication treatment costs. Between 2005 and 2008, the emphasis of the related studies started shifting from transplantation and growth factor costs to chemotherapy, complication treatment, and supportive or palliative cares costs (please refer to **Table 2.3** for details).

c. Country

The country information of the selected studies (the location that the selected studies were carried out) was further divided into four main groups: America, Europe, Asia, and others. The relevant details are listed in **Table 2.4** (Only countries with more than two studies are listed; the rest were categorized into 'others').

Table 2.4 Summarized country information of selected studies

Treatment type	Number of papers													
	America			Europe					Asia				Others	
	USA	CA	UK	FRA	ESP	ITA	NED	GER	TUR	IND	JPN	TWN		Total
Overall treatment	4	0	0	0	0	0	1	1	0	0	0	1	0	**7**
Chemotherapy	2	0	0	0	0	2	0	1	0	1	1	1	0	**8**
Transplantation	4	2	0	3	1	0	3	1	0	1	0	1	1 Norway	**17**
Complication	3	0	1*	0	1*	1	1*	0	1	0	1	0	1* Belgium 1 Brazil	**8**
Adjunctive care	4	0	1	1	1	1	1	0	0	0	0	0	1 Australia 1 unknown	**11**
Examination	0	0	0	1	0	0	0	0	1	0	0	0	0	**2**
Palliative or supportive care	0	0	0	0	0	2	0	1	0	0	0	1	1 Mexico	**5**
Total	**16**	**2**	**2**	**5**	**3**	**6**	**6**	**4**	**2**	**2**	**2**	**4**	**4**	**58**

* The study country of this paper covered UK, Spain, Netherlands, and Belgium.

** CA: Canada, FRA: France, ESP: Spanish, ITA: Italy, NED: Netherlands, GER: Germany, TUR: Turkey, IND: India, JPN: Japan, and TWN: Taiwan.

As shown in **Table 2.4**, most of the selected studies (16 articles in total) were carried out in the USA, followed by Italy and Netherlands which had six relevant costing studies each. The rest of the countries had between one and five relevant cost studies since 1995.

Taking the treatment type into account, the results showed that different countries focused on different treatment costs. USA focused on overall/lifetime treatment, transplantation, complication treatment, and adjunctive care cost. Italy focused on chemotherapy and palliative care; while Netherlands and France focused on transplantation costs (**Table 2.4**).

2.8 Results (costing method review)

In order to the review results to be presented systematically, the data extracted from the selected studies were categorized into the following seven groups: overall/lifetime treatment (seven papers), chemotherapy (eight papers), transplantation (17 papers), complication treatment (eight papers), growth factor (11 papers), examination (two papers), and supportive or palliative care (five papers). The review results of each treatment type are discussed in detail in the following sections.

2.8.1 Overall treatment for AML/APML

After categorization and data extraction, seven studies were found to be focusing on overall treatment costs. The summary of these seven studies can be found in **Appendix 2.8**.

a. Overview

Four out of the seven overall treatment cost studies were published during 2001-2002 [103-106], while three of them were published during 2005-2006 [107-109]. More than half of the studies (four papers) were carried out in the USA [103, 104, 108, 109].

In terms of study population, four studies focused on elderly AML/APML patients ($\geqq$60 or $\geqq$65 years old) [103, 104, 108, 109], two studies on adult patients ($\leqq$60 years old) [104, 107], and only one study on pediatric patients [109]. Most of the studies applied cost analysis for costing the overall treatment, while only one study applied cost-effectiveness analysis [107]. In terms of study time period, most of the studies only estimated the inpatient costs either from admission (or diagnosis) to discharge or for a fixed period of time (such as three years). However, there were three studies that measured not only the inpatient costs but also the follow-up costs [103-105]. It is worth noting that most of the studies used hospital charges for costing. Only two studies used the administrative claim payment data for costing [103, 104].

b. Cost drivers

The cost drivers that were used in the selected studies for costing overall AML/AMPL treatments were categorized into two main groups: medical-related and non-medical-related cost drivers. The related summary can be found in **Table 2.5**.

Table 2.5 Cost drivers for costing overall treatments

Cost drivers	Reference No.
Medical cost drivers	
Inpatient condition	
Hospitalization	[109], [103], [104], [105], [106]
Pharmacy / IV therapy	[109], [107]
SNF	[109]
Laboratory / Pathology	[109], [107], [105]
OR / Anesthesia / Recovery room	[109]
Radiology	[109]
Respiratory services / Pulmonary function	[109]
Physical therapy / Occupational therapy	[109]
Skilled nursing facility	[103], [107], [106]
Physician / supplier	[103], [104], [107], [106]
Procedure	[107], [105]
Relapse treatment	[105], [106]
First admission	[108]
Sequent admission	[108]
Outpatient condition	
Outpatient visit	[103], [104], [105]
Follow-up condition	
Home health care	[103], [104]
Hospice	[103], [104]
Overall follow-up cost	[105]
Non-medical cost drivers	
Durable medical equipment payments	[103]
Out-of-pocket	[107]

As shown in **Table 2.5**, the medical cost drivers were divided into three subgroups: inpatient condition, outpatient condition, and follow-up condition.

- In inpatient condition, hospitalization was the most commonly used cost drivers. Personnel cost (such as skilled nurses and physicians) [103, 104, 107] and drug and examination costs [107, 109] followed.
- In outpatient condition, outpatient visit costs was the only cost driver [103, 104].
- In follow-up condition, home health care and hospice were normally used as cost drivers for costing follow-up in the overall AML/APML treatment costs [103, 104].

In relation to non-medical cost drivers, only a few studies took the latter into account for costing the overall treatments. Only Lang et al. [103] used capital overhead as non-medical cost driver, and Yu et al. [107] used out of pocket as non-medical cost drivers.

c. Cost results

By using the historical currency exchange rates [110] and inflation calculator [111], all the overall treatment costs were converted to US dollar's value as of 2007. Relevant conversion information is listed in **Appendix 2.6** and **Appendix 2.7**, while details of the results are presented in **Table 2.6**.

Table 2.6 Cost results for costing overall treatments

Reference No.	Country	Study period	Patients	Year	Cost per patient	cost (in 2007USD)
Rosenman [109]	USA	3 years	AML all ages	1997	$112,200 (13,500 – 217,600) per year	$151,470 per year
Lang [103]	USA	2 years	AML elder	2001	$25,944 ± 27,413 per year	$31,652 per year
Menzin [104]	USA	2 years	AML	1998	$20,795 ± 435 per year	$27,657 per year
Yu [107]	Taiwan	From diagnosis to the end of therapy	AML adult	2003	$43,418 (1,494 – 172,332) per treatment cycle	$51,233 per treatment cycle
Katz [108]	USA	From first admission to the last discharge	AML elder	2003	$115,471 ± 334,581 per treatment cycle	$136,256 per treatment cycle
Uyl-de Groot [105]	Netherlands	From diagnosis to 2 years follow-up	AML adult	1995	$104,386	$148,228
Kuse [106]	Germany	2 inductions+1 consolidation	AML elder	1999	Young adult: 105KDM (63-204 KDM) Elderly patients: 87.6KDM (56-147 KDM)	$65,500 per protocol cycle $54,645 per protocol cycle

As shown in **Table 2.6**, the result presentations were categorized into two groups: 'costs per patient per year' and 'cost per patient per treatment cycle'.

All studies in the 'costs per patient per year' group were from the USA [103-105]. One of them focused on elderly AML patients [104], while the remaining studied all age range of AML patients. It was observed that although only Lang et al. [104] and Menzin et al. [105] took follow-up and outpatient visits into consideration, their costs results were the lowest. On the contrary, although Rosenment et al. [103] only focused on inpatient costs, the cost result was the highest. A possible explanation for this was that different data sources and cost drivers were used in different studies (**Appendix 2.8**).

Both of the studies in the 'cost per patient per treatment cycle' group were from 2003 [107, 108]. One of these studies (Yu's study) focused on adult patients [107], and the other (Katz's study) on the elderly patients [108]. Although the study period of Yu's study [107] was longer than Katz's study [108], the cost result of the former was lower. This might be due to different study populations (elderly patients were considered to be more expensive to treat) and different country settings.

2.8.2 Chemotherapy for AML/APML

After categorization and data extraction, eight studies were found to be focusing on chemotherapy costs. The summary of these studies can be found in **Appendix 2.9**.

a. Overview

Most of the studies were published after 2000 [100, 107, 108, 112-115] (only one study was published before 2000 [116]), and they were mainly carried out in the USA [108, 114], Italy [112, 113], and Asia [107, 116]. In relation to study time period, only Takeshifa et al. [116] and Storti et al. [113] cost chemotherapies in fixed periods of time (first 2 months of hospitalization and one month respectively), while in the remaining studies, chemotherapies were cost by cycles. It is worth noting that 'hospital charges' were the main data source for costing chemotherapies in most of the studies, with only Takeshifa et al. [116] using 'payment data' for the same purpose.

b. Cost drivers

The cost drivers used in the selected studies for costing chemotherapy were categorized into the following two main groups: medical-related and non-medical-related cost drivers. The related summary is shown in **Table 2.7**.

Table 2.7 Cost drivers for costing chemotherapy

Type of cost (cost driver)	(Reference No.)
Medical cost drivers	
Inpatient condition	
Hospitalization	[107], [113], [114], [115], [116]
Pharmacy (drug/regimen)	[107], [112], [113], [114]
G-CSF	[114], [112]
Antiblastic drugs	[112]
Anticoagulants drugs	[116]
Infection treatment / antibiotic treatment	[114], [112], [116], [113]
Blood bank / transfusion	[107], [114], [112], [116], [113]
Laboratory / Pathology	[107], [114], [112], [116]
Surgery	[114], [116]
Radiology	[114], [112], [116]
Skilled nursing facility	[107], [114], [112], [116]
Physician / supplier	[107], [114], [112], [116]
Outpatient condition	
Outpatient visit	[114]
Emergency Room	[114]
Non-medical cost drivers	
Out-of-pocket	[107]

In the medical cost driver groups, the cost drivers were further divided into two subgroups, namely inpatient setting and outpatient setting.

- In inpatient condition, the most commonly used cost drivers were hospitalization, drug/regimen, transfusion, personnel, laboratory test and complication treatment. It is worth noting that the drug costs of chemotherapy were not always presented separately. In 4 of the studies [100, 108, 114, 116], the drug costs were included in the hospitalization cost.
- In outpatient setting, only one study measured the outpatient visit costs and emergency room cost for costing chemotherapy [114].

In relation to the non-medical cost driver group, only Yu et al. [107] used hospital charges to estimate the out of pocket costs for costing chemotherapy.

c. Cost results

The cost results of the 8 chemotherapy cost studies are summarized in **Table 2.8**.

Table 2.8 Cost results for chemotherapy

Study	Country	Study period	Patients	Regimens	Year	Cost per patient per cycle	Cost (in 2007 USD)
Yu [107]	Taiwan	Single therapy cycle	AML adult ≦60 (54)	HidAC	2003	CC: $7,607 (546 – 23,115) HiDAC: $13,668 (1,538 – 29,180)	CC: $8,976 HiDAC: $16,128
Katz [108]	USA	From first admission until last discharge	AML elder ≧ 60 (219)	ADE	2003	Without chemotherapy: $80,541 (388,194) With chemotherapy: $163,159 (236,486)	$97,490
Berman [114]	USA	From diagnosis until the day before the next phrase of chemotherapy	AML (79)	Cytarabine+ Idarubicin	1999	Standard: $124,868 Protocol: $96,571	Standard: $162,328 Protocol: $125,542
Clavio [112]	Italy	Beginning of therapy until discharge	AML adult ≦60 (18)	AML10 FLANG	1997	AML10: $12,424 FLANG: $9,269	AML 10: $16,772 FLANG: $13,513
Jacob [115]**	India	Complete treatment	AML	DA, MidAC	2006	500,000 INR	$11,845
Takeshifa [116]	Japan	First 2 month of hospitalization	APML adult 17-65 (36)	CC ATRA	1993	CC: ¥4,164,026 ± 1,268,026 ATRA: ¥2,906,825 ± 1,122,474	CC: $56,402 ATRA: $39,373
Storti [113]**	Italy	1 month	AML elder 65-80 (17)	CC LDC	2005	CC: €6500 Low dose chemotherapy: €1806	CC: $8,985 LDC: $2,497
Stabler [100]	Germany	3 months	Cancer (66)	Conditioning	2002	-	-

* CC: conventional chemotherapy ; **conference report

As shown in **Table 2.8**, the cost results varied significantly. This was because the related regimens, study periods, and study populations were all different. Therefore, it was not possible for the cost comparisons to be carried out.

2.8.3 Transplantation for AML

There were 17 studies found to be focusing on transplantation costs., a summary of these studies can be found in **Appendix 2.10**.

a. Overview

Only three of the transplantation cost studies were published before 2000 [117-119]. The rest of the studies were published after 2000 [120-127]. The studies were carried out in several countries, since transplantation cost is an important issue on a worldwide basis. The focus of the studies was on adult or pediatric patients or both but elderly patients. It is worth noting that only five studies specifically focused on AML patients [107, 118-120, 127], while the remaining were case-mixed studies (AML/APML were part of the study populations). In relation to study time periods, fixed time period (such as one year and two year) costs were estimated in seven of the studies [118-122, 127], while in the remaining studies the estimation was for costs per cycle/event were [107, 117, 123-126, 128]. It is also worth noting that hospital charges were used for costing in most of the studies, with the bottom-up costing method being used only in four of them [118, 121, 124, 127].

b. Cost drivers

The cost drivers that were used in the selected studies for costing transplantation were categorized into the following three main groups: pre-transplantation, transplantation, and follow-up.

The most commonly used cost drivers for costing pre-transplantation were: screen/laboratory test, harvest, conditioning chemotherapy and radiotherapy, while surgery, hospitalization, drugs, transfusion, and infection treatment were the most commonly used cost drivers for costing transplantation. It is worth noting that stem cell transplantation cost was not always reported separately. In many cases, the transplantation costs were included in the hospitalization cost. Only in five of the studies, the transplantation surgery costs were reported separately [107, 118, 119, 124, 128]. In relation to the follow-up group, only four studies took follow-up cost into consideration [121, 122, 124, 128]. The most commonly used cost drivers for costing follow-up were drugs, outpatient visits, and laboratory tests. Details relevant to the above matters can be found in **Table 2.9**.

Table 2.9 Cost drivers for costing transplantation

Cost drivers	Reference No.
Pre-transplantation	
Screening cost	
Diagnostic test (investigation)	[120], [127], [124], [125], [126], [128], [118], [100]
Laboratory test (culture)	[107], [120], [122], [124], [125], [126], [121], [118]
Radiology evaluation	[120], [124], [125], [128], [118], [122]
Harvest (stem cell collection)	[120], [124], [125], [128], [121], [119], [122]
Pharmacy	[128]
Conditioning chemotherapy	[120], [125], [121], [122], [100]
TBI	[120], [124], [125], [121], [122], [123]
Hospitalization	[121]
Outpatient visit	[120], [121]
Personnel cost	[128]
Overheads: durable equipment & required spaces	[124]
Transplantation	
Inpatient setting	
Surgery	[118], [107], [124], [119] [128], [100]
Care expense	
Hospitalization	[107], [120], [127], [125], [126], [121], [117], [118], [119], [100]
Personnel cost	[126], [128]
Pharmacy	[107], [124], [126], [128], [118], [119], [122]
CSF	[120], [124], [125]
Parenteral nutrition	[107], [120], [124], [125], [121]
Infection treatment	[120], [124], [125]
Transfusion	[107], [120], [124], [125], [126], [128], [121], [119], [122]
Disposables	[126]
Overheads	[127], [120], [107]
Outpatient setting	
Outpatient visit	[124], [121], [117], [122], [100]
Acute care	[118], [122]
Personnel	[127], [118], [100]
Overheads: durable equipment and required space	[127]
Follow-up costs	[119]
Screening test	
Diagnostic test	[124], [128]
Laboratory test	[124], [128]
Radiology	[124], [128]
Hospitalization	[124]
Pharmacy	[124], [128], [121]
Transfusion	[124]
Day care	[122], [124]
Outpatient visit or consultation	[124]
Personnel costs	[124], [128]
Home health	[122]

c. Cost results

The cost results of the transplantation cost studies are summarized in **Table 2.10**.

Table 2.10 Cost results for transplantation

Reference No.	Country	Study period	Patients	Type of trans	Costing year	Cost per patient per year	Cost (in 2007 USD)
Agthoven et al.2002 [124]	Netherlands	Pre-transplantation until 2-year follow-up	ALL and AML (97)	BMT PBSCT MUD	1998	BMT: €98,334 PBSCT: €98,977 MUD: €151,754	BMT: $153,227 PBSCT: $154,229 MUD: $236,467
Vicent et al. 2001 [125]	Spain	From admission until discharge	ALL, AML, NHL, HD children(131)	PBPCT BMT	1999	PBPCT: $7,895 BMT: $11,820	BMT: $15,366 PBSCT: $10,264
Cordonnier et al. 2005 [120]	France	1 year	AML (23)	NMA alloSCT MA alloSCT	2001	MA alloSCT: €74900 ±22600 NMA alloSCT: €78700± 37300	MA allSCT: $114,791 NMA allSCT: $120,615
Yu et al. 2006 [107]	Taiwan	Single therapy period	AML adult ≦60 (54)	AlloSCT ASCT	2003	AlloSCT: $29,208 (9,100 – 106,212) ASCT: $10,037 (4,709 – 28,995)	AlloSCT: $24,465 ASCT: $11,644
Esperou et al. 2004 [122]	France	6 months	CML, AML, ALL (85)	AlloSCT	2000	€70,479 (14761-183758)	AlloSCT: $82,136
Chandy et al. 2001 [126]	India	From admission until discharge	AML, CML, THAL children (4)	AlloBMT	1999	AlloBMT: $16,666.75	AlloBMT: $21,666
Mishra et al. 2001 [128]	Norway	From pre-transplantation until 1 year follow-up	CML, ALL, AML,MSD (17)	AlloBMT	1999	AlloBMT: $106,825 ($24,375-$362,492)	AlloBMT: $138,873
Blaise et al. 2000 [121]	France	6 months	AML, ALL, CML adult ≦55 (98)	AlloBMT AlloPBSCT	1998	AlloBMT: €44531±15881 AlloPBSCT: €37410±12109	AlloBMT: $69,389 AlloPBSCT:: $56,293
Barr et al. 1996 [118]	Canada	5 years	AML (2CR) adult 16-45 (7)	AlloBMT	1992	AlloBMT: $CAN 100,600±48380	AlloBMT: $128,347
Uyl-de Groot et al. 1995 [119]	Netherlands	2 years	AML (30)	AutoBMT	1992	AutoBMT: $55,440	AutoBMT: $55,438
Dagher et al. [123]	USA	Unknown	ALL, AML children 9-17 (10)	IP TBI OP TBI	1997	Inpatient TBI save $2,400	Save $3,240
Farah et al.1998 [117]	USA	From admission until discharge	ALL, AML, CML children ≦ 16 (19)	IP TBI OP TBI	1997	Inpatient TBI save $3,250 per patient	Save $4387.5
Schimmer et al. 2002 [127]	Canada	1.5 year	AML (18)	Follow up	2000	$CAN 5,300	$4,500
Stabler et al. 2003 [100]	Germany	3 months	(66)	SCT	2002	€16672 per op contact €45930 per hospital day €80820 per treatment day	

As shown in **Table 2.10**, the transplantation cost results was categorized into three groups: 'BMT and AlloBMT', 'PBSCT and AlloSCT', and 'others'.

- BMT and AlloBMT' group:

  There were seven studies found to be focusing on BMT-related costing [118, 119, 121, 124-126, 128]. Although five of the studies were carried out at a similar time (1998-1999), the cost results varied greatly. This was mainly due to differences in study settings, study populations, study time periods, and involved cost drivers.

- PBSCT and AlloSCT' group:

  There were six studies found to be focusing on BMT-related costing [107, 120-122, 124, 125]. These six studies were carried out at a similar time (1998-2002). However, the cost results also varied greatly in this case for the reasons described previously in the 'BMT and AlloBMT' group.

- Others' group:

  There were three studies related to transplantation costing [117, 123, 127]. However, the authors only reported the amount of the cost saving, and, therefore, the cost results could not be compared with the study results (transplantation cost) of the previously mentioned groups.

2.8.4 Growth factor for AML

As there were controversies regarding whether growth factor can save treatment costs, a number of economic evaluations of growth factors have been conducted. Therefore, despite the fact that growth factor is one of the types of supportive care, it was decided relevant studies to be discussed separately from other supportive care cost studies in the current review. For AML/APML, 11 studies related to growth factor treatment cost were found. The summary of these 11 studies can be found in **Appendix 2.11**.

a. Overview

Most of the relevant studies were published after 2002 [112, 129-138]. This underlined the increasing interest on the topic. The majority of the studies were carried out in the USA [131, 132, 135, 137], and in Europe [112, 129, 133, 134, 138] (one of them in the UK [129]). Elderly AML patients were the main focus study population [131, 132, 134, 135, 137, 138], while no studies related with pediatric AML patients were found. Moreover, five out of the 11 relevant studies cost growth factors 'from start date until ANC (absolute neutrophil count) recover' [112, 129-131, 138], while the remaining studies 'from start date until discharge' [132, 133, 135-137]. Long-term follow-up was taken into consideration in one study [134]. Among all of the relevant studies, 'hospital charges' was the only data source for costing. However, it is worth noting that in two of the studies (from the same study team) [132, 135], charge information was used for costing a limited number of study patients. The obtained information was further converted to relevant unit costs in order to cost whole study patients with the bottom-up method.

b. Cost drivers

The cost drivers that were used in the selected studies for costing growth factors were categorized into two main groups, namely inpatient and outpatient. Most of the studies focused on costing growth factors in inpatient condition. Hospitalization, drug, complication treatment, transfusion, laboratory test, and personnel were the most commonly used cost drivers for this purpose. It is worth noting that three of these cost drivers (hospitalization, drug, and complication treatment) were generally used in all the studies for costing in inpatient condition, while clinic visit (monitoring) was the key cost driver in outpatient condition. Relevant details are listed in **Table 2.11**.

Table 2.11 Cost drivers for costing supportive care (growth factor)

Cost drivers	(Reference No.)
Inpatient condition	
Hospitalization	[112], [129], [130], [131], [132], [134], [135], [136], [137]
CSF (G-CSF or GM-CSF)	[112], [129], [130], [131], [132], [133], [134], [136], [137]
Pharmacy	
Parenteral nutrition	[133], [134]
Other drugs	[112], [129], [131], [132], [134], [135], [137]
complication treatment	
Anti-infection treatment	[112], [129], [130], [131], [133], [135], [136], [137]
Other side-effect treatment	[112]
Transfusion	[112], [129], [131], [132], [133], [134], [135], [136], [137]
Test or evaluation	
Diagnostic test	[129], [132], [133], [134]
Laboratory test	[112], [129], [131], [132], [133], [134], [135], [137]
Radiology	[112], [131], [132], [133], [134], [135], [137]
Respiratory service	[132]
Procedures (ex: surgery)	[134]
Personnel costs	[112], [131], [133], [134], [135], [136], [137]
Overhead and materials	[131], [132], [134], [135], [137]
Outpatient condition	
Monitoring	[131], [134], [135], [137]
Fluid administration	[129]
Long-term follow-up (outpatient visit)	[134]

c. Cost value

The growth factor cost results were converted to the US dollar's value as of 2007 by means of the historical currency exchange rates and the inflation conversion table (please refer to **Appendix 2.6** and **Appendix 2.7**). These cost results are summarized in **Table 2.12** . As shown on the table, two main growth factors were studied, namely G-CSF and GM-CSF.

- **G-CSF group**

There were six studies found to be related to G-CSF costing [112, 129-131, 136, 137]. The cost results of these studies varied significantly from $16,603 to $69,253, due to the inclusion of different chemotherapy costs in the reported results. In terms of cost saving, Bradstock et al. [130], Bennet et al. [131], and Ojeda et al. [133] found that G-CSF increased treatment costs, while Lu's study [136] and Clavio's study [112] showed that G-CSF saved treatment costs.

• **GM-CSF group**

A lower number of studies focused on GM-CSF costs [132, 134, 135, 138]. Similar to G-CSF, the cost results varied (even though the studies were carried out in the same countries with similar study populations, and by the same study team [132, 135]). Uyl-de Groot's study [134] was the only study that took long-term follow-up into account. However, due to different settings, the cost results were lower than those of other relevant studies that only cost the GM-CSF from admission date until patient discharged [132, 135].

Table 2.12 Cost results for growth factors

Reference No.	Country	Study period	Patients	Type of Growth factor	Costing year	Cost per patient per year	Cost (in 2007 USD)
Standaert et al. [129]	UK	24 hours after chemotherapy until ANC recovery	AML adult (82)	G-CSF after chemotherapy	1998	CRF methods: 1st induction: £7531.67 all cycles:£12,726.19 PF method: 1st induction: £9700.69 all cycles: £14,861.09	CRF methods: 1st induction: $16,603 all cycles: $28,057 PF method: 1st induction: $21,385 all cycles: $32,763
Bradstock et al. [130]	Australia	Start date until ANC recovery	AML adult 15-60 (114)	G-CSF after induction chemotherapy	2001	G-CSF increase the cost of A$ 1494	Increase $1,832
Bennet et al. [131]	USA	Start date until ANC recovery	AML elder 55-70 (207)	G-CSF after chemotherapy	1998	Placebo group: $49,693 G-CSF group: $50,593	Placebo group: $66,092 G-CSF group: $67,289
Clavio et al. [112]	Italy	G-CSF: day 11 until neutrophil recovery	AML Adult ≦60 (18)	G-CSF after chemotherapy	1997	CRT 1 (without G-CSF): $12,424 CRT2 (with G-CSF): $9,269	CRT 1 (without G-CSF): $16,772 CRT 2 (with G-CSF): $12,513
Lu et al. [136]	Unknown	Start date until discharge	AML (521)	G-CSF after chemotherapy	1996	Cost saving: $2,230	Save $3,077
Bennett et al. [137]	USA	Start date until discharge	AML elder >55 (207)	G-CSF after chemotherapy	1998	G-CSF group: $52,070	G-CSF group: $69,253
Woronoff-Lemsi et al. [138]	France	Start date until ANC recovery	AML elder 55-75 (83)	GM-CSF after chemotherapy	1997	Overall survival : $97,841 Disease free cost: $53,456	Overall survival: $132,085 Disease free cost: $72,166
Bennett et al. [132]	USA	Start date until discharge	AML elder 55-70 (117)	GM-CSF after chemotherapy	1997	Overall: $38,412 One cycle: $38,617 Two cycle: $37,467	Overall: $51,865 One cycle: $52,133 Two cycle: $50,584
Bennett et al. [135]	USA	Start date until discharge	AML elder 56-70 (117)	GM-CSF after chemotherapy	1997	1 cycle: $66,757 2 cycles: $62,728	1 cycle: $90,122 2 cycles: $84,683
Uyl-de Groot et al. [134]	Netherlands	Start date until 2 year follow-up	AML elder ≧ 60 (103)	GM-CSF after chemotherapy	1992	Treatment cost: GM-CSF: $40,782 Control: $34,465 2 year follow-up cost: GM-CSF: $17,305 Control: $17,402 Total cost: GM-CSF: $58,087 Control: $51,867	Treatment cost: GM-CSF: $40,782 Control: $34,465 2 year follow-up cost: GM-CSF: $17,305 Control: $17,402 Total cost: GM-CSF: $58,087 Control: $51,867
Ojeda et al. [133]	Spain	Transplantation inpatient day	AML, NHL 18-64 (62)	G-CSF after PBSCT	1998	G-CSF: €7,449 ± 645 Control: €6,689 ± 480	G-CSF: $11,607 Control: $10,423

2.8.5 Complication treatment for AML

There were eight studies found to be related to complication treatment costs. A summary of these studies can be found in the following sections.

a. Overview

The relevant studies were published after 2000 [113, 139-144], with the exception of one that was published in 1996 [145]. In relation to treatment cost analysis, studies from the USA were still the main stream. The complication treatment cost studies were carried out in various countries (three in the USA [139, 143, 145], one in the UK [141], one in the Italy [113], one in the Japan [139], one in the Brazil[142], and one in the Turkey [144]), something that underlined a worldwide interest on the topic. It is worth noting that the related studies did not focus specifically on AML/APML patients, but they included AML/APML among various other diseases. The most commonly used study time period was 'treatment time' [140-145], with only one of the study costing complication from admission and until 30 days after discharge [139]. 'Hospital charge' and 'administrative claim payment' were still the main data sources for costing [113, 139, 140, 143-145], and only two studies used the 'reference unit cost for bottom-up costing [141, 142].

b. Cost drivers

The cost drivers that were used for costing complication treatment are listed in **Table 2.13**.

Table 2.13 Cost drivers for complication treatment

Cost drivers	(Reference No.)
Inpatient condition	
Hospitalization	[139], [140], [141], [142], [143], [144], [145]
Pharmacy	[139], [141], [142], [143], [144]
Nutrition	[139]
Anti-infection (antifungal, antibiotics)	[113], [139], [140], [141], [142], [143], [145]
Transfusion	[139], [142]
Test or evaluation	
Diagnostic test	[142]
Laboratory test	[139], [141], [142]
Hemogram	[142]
Procedures (ex: surgery, chemotherapy)	[139]
Personnel costs	[141]
consultation	[141], [142]
Follow-up condition	[140], [142]

As shown in **Table 2.13**, the cost drivers for costing complication treatments were divided into two conditions: inpatient and follow-up conditions.

- Inpatient condition

  Most of the studies focused on costing complication treatment in inpatient conditions. The most commonly used cost drivers for this purpose were hospitalization, anti-infection treatment, drugs for non-infection complication and laboratory test. It is worth noting that anti-infection was a type of complication treatment that was used in all the complication treatment cost studies [113, 139-145].

- Follow-up condition

  Among all the relevant studies, two studies were found to take follow-up costs into account, although the follow-up time periods were not very long (ranging from 20 days to 30 days) [140, 142].

c. Cost results

As shown in **Table 2.14**, the cost results varied significantly (from $60 per day to $147,320 per treatment plus 30 days follow-up). This was due to different study settings, study time periods, study populations, treatment strategies, and result presentations. Since there was no common ground for these studies, it was impossible to compare their costs and, thus, to derive meaningful comparison results. However, it is worth mentioning a number of observations related with the above.

Firstly, the cost results tended to be lower when the study populations were pediatric AML/APML patients. A possible explanation for this was that pediatric patients required lower dosages. Secondly, based on a number of the studies that reported the detailed cost results for each cost drivers, it was found that the drug costs for anti-infection were relatively consistent (range from $870 to $114 per episode) [139, 142, 145].

The cost results of the relevant studies are summarized in **Table 2.14**.

Table 2.14 Cost results for complication treatments

Reference No.	Country	Study period	Patients	Type of treatment	Costing year	Cost per patient or per episode	Cost (in 2007 USD)
Nomura et al.[139]	Japan	Start of chemotherapy to CR or death	AML 40 yrs (30)	3 strategies of antifungal treatment for chemotherapy	2003	Strategy 1 (fluconazole): $25,900 Strategy 2 (empirical amphotericin B): $25,400 Strategy 3 (MCPG): $25,400	Strategy 1: $30,562 Strategy 2: $29,972 Strategy 3: $29,972
Menzin et al. [140]	USA	Inpatient time and 30 days post discharge	AML elder ≧65 (160)	Antifungal treatment	1998	Total charge for hospitalization: $110767 Medicare payment for hospitalization: $34268	Total charge: $147,320 Medicare payment: $45,576
Storti et al. [113]	Italy	Unknown	AML elder 65-80 (17)	Antibiotics	1995	Total cost per month ST: €2900 CC: €1100 LDC: €300	Total cost per month ST: $5,129 CC: $1,945 LDC: $531
Costa et al. [142]	Brazil	Treatment time	AML, ALL, NHL, HL children (22)	Febrile neutropenia	2000	Total cost per episode: $2660($2039) (AML: $2917)	Total cost per episode: $3,675
Rosenman et al. [143]	USA	Treatment time	ALL, AML, CNS children (157 episodes)	Fever and neutropenia	1997	Total charges per episode: $11,967±$16,261 ($40,694±38,831in AML)	Total charges per episode: $54,937
Agaoglu et al. [144]	Turkey	Treatment time	ALL, AML, solid children (87 episodes)	Febrile neutropenia	1999	Daily drug cost: C+N: $53.8 C+A: $46.2 M: $121.4	Daily drug cost C+N: $69.9 C+A: $60.1 M: $157.8
Horowitz et al. [145]	USA	Treatment time	ALL, AML, NHL (10)	Neutropnia	1994	Cost saved: $10,022 per patient (at home)	Saved $14,632
Annemans et al. [141]	Belgium, Netherlands, Spain, UK	Treatment time	ALL, AML, NHL (144)	Complication	Unknown	Incremental cost of prevention Adult: €1752 (1425-1924) Child: €492 (165-664) Incremental cost of treatment Adult: - €426 Child: - €1686	Incremental costs Prevention (adult): $2,340 Treatment (adult): - $567

2.8.6 Examination for AML

There were two studies found to be focusing on examination costs. The summary of these studies can be found in **Appendix 2.13**.

a. Overview

The two studies investigated different examination costs. Gonen et al. [146] studied 'fever investigation cost', while Tonnaire et al. [147] studied 'cytogeneic and molecular test cost'. Moreover, different costing sources and methods were used in these two studies. Gonen et al. [146] used 'hospital charges' for costing fever investigation, while Tonnaire et al. [147] used the 'bottom-up method' for costing laboratory tests.

b. Cost drivers

The cost drivers that were used for costing examination are listed in **Table 2.15**.

Table 2.15 Cost drivers for costing examination

Cost drivers	(Reference No.)
Fever investigation test	Gonen et al. 2005 [146]
1. Blood cultures	
2. Urine cultures	
3. Chest X-ray	
4. Sinus X-rays	
5. Oral smear	
6. Sterile urine examinations	
7. urinalysis	
Cytogenetic and molecular test	Tonnaire et al. 1998 [147]
1. Equipment	
2. Labor	
3. Expenditure on reagents	
4. Other non expendable laboratory supplies	
5. stationery	

Since these two laboratory test cost studies focused on different screening tests and used different costing methods, the cost drivers that were used in both studies were very different. Gonen et al. used several examinations as cost drivers for costing, while Tonnaire et al. used equipments, personnel, and supplies as cost drivers for costing.

c. Cost results

The cost results of these two examination cost studies are summarized in **Table 2.16**.

Table 2.16 Cost results for examination cost studies

Reference No.	Country	Study period	Patients	Type of screening	Costing year	Cost per patient or per episode	Cost (in 2007 USD)
Gonen et al. 2005 [146]	Turkey	Per exam	AML (33 episodes)	Fever investigation	2004	cost of investigation of fever per episode: $64.76	$74.47
Tonnaire et al. 1998 [147]	France	Per exam	ALL, AML 16-91 (107)	Cytogenetic and molecular test	1995	Cytogenetic: $577.4 PCR: $241.2 Additional PCR: $94.8	Cytogenetic: $819.9 PCR: $342.5 Additional PCR: $134.6

Gonen's study [146] showed that the cost of fever investigation test was $74.47 for each given time, while, in Tonnaire's study [147], the costs of cytogenetic test was $819.9 (in 2007 value), and the cost of PCR (molecular biology test) was $342.5 (in 2007 value).

2.8.7 Supportive or palliative care for AML

There were five cost studies that have not been covered in the current review found to be related to non-curative interventions (supportive or palliative cares). Since the number of the studies was low and the study interventions had common character (non-curative), it was decided that they could be discussed as a whole. The summary of these five studies can be found in **Appendix 2.14**, while a related discussion follows in the next sections

a. Overview

As shown on **Appendix 2.14**, three studies focused on 'supportive care' [107, 148, 149], two on 'palliative care' [107, 113], and one on 'home care' [150] for AML/APML.

For these three supportive care cost studies, only one was published after 2000 [107]. All of the studies focused on AML adult patients and used 'hospital charges' for costing. However, great differences were observed among the studies regarding the employed study time periods and the study interventions. Wandt et al. [148] only cost transfusions, with the study time period being unknown. Yu et al. [107] only cost inpatient-base supportive care from admission to discharge. Ruiz-Arguelles's study [149] was the most complete of the three. The authors cost both inpatient-base and outpatient-base supportive care from the care start date and until granulocyte count recovery.

In relation to the two palliative care cost studies, both were published after 2005 [107, 113]. This showed a recently increasing interest on the topic. It is worth noting that both of the aforementioned studies used 'hospital charge' for costing, due to the complexity of the palliative care content.

The single home care cost study [150] was published in 2007 and was carried out in Italy. The authors used the 'bottom-up method' for costing the home care. However, AML/APML was not the only cancer type included in the study, while the study time period was, also, unknown.

b. Cost drivers

The cost drivers used for costing for the three different interventions are listed in **Table 2.17**.

Table 2.17 Cost drivers for costing supportive and palliative cares

Cost drivers	Reference No.
Supportive care	
Hospitalization	[107], [149]
Pharmacy	[107], [149]
Laboratory test	[107]
Transfusion	[107], [148], [149]
Procedure	[107]
Personnel cost	[107], [148], [149]
Out-of-pocket	[107]
Palliative care	
Hospitalization	[107], [113]
Pharmacy	[107]
Laboratory test	[107]
Infection treatment	[113]
Transfusion	[107], [113]
Procedure	[107], [113]
Personnel cost	[107]
Out-of-pocket	[107]
sHome care	
Personnel cost	[150]
Pharmacy and medical supplies	[150]
Transfusion	[150]
Laboratory test	[150]

- Supportive care [107, 148, 149]

  The most commonly used cost drivers were transfusion and personnel costs, followed by hospitalization and relevant drug costs.

- Palliative care [107, 113]

  The most commonly used cost drivers for costing palliative care were hospitalization, transfusion and relevant procedure costs.

- Home care [150]

  Only one study was found to be focusing on costing home care. The authors used personnel, pharmacy and medical supplies, transfusion, and laboratory test costs as cost drivers, to obtain cost of home care in Italy.

c. Cost results

The cost results of the three different intervention cost studies are summarized in **Table 2.18**.

Table 2.18 Cost results for supportive and palliative care cost studies

Reference No.	Country	Study period	Patients	Type of care	Costing year	Cost per patient per year	Cost (in 2007 USD)
Yu et al. [107]	Taiwan	Single therapy period	AML adult ≦60 (54)	Supportive care and palliative care	2003	Supportive care: $3,013 (120 – 25,581) Palliative care: $15,726 (500 – 96,923)	Supportive care: $3,555 Palliative care: $18,557
Cartoni et al. [150]	Italy	Unknown	AML, lymphoma, myeloma (144)	Home care	2005	Total monthly home care cost: Discharge early: €3986.4 (241.2 - 6285.3) Terminal: €4232.5 (437 - 14599) Chronic: €1488.3 (455.9 - 4769.5)	Home care per month Discharge early: $5,511 Terminal: $5,851 Chronic: $2,057
Wandt et al. [148]	Germany	Unknown	AML adult ≦60 (105)	Transfusion Trigger1: 10×10^9/L Trigger2: 20×10^9/L	1996	Transfusion cost per treatment cycle: trigger 1 is cost saved	Lower trigger standard is cost saved
Ruiz-Arguelles et al. [149]	Mexico	Start date until recovery	AML adult 14-63 (24)	Outpatient supportive care Inpatient supportive care	1995	Outpatient setting cost saved by avoiding prolonged hospitalization: $1700 per patient	Outpatient setting saved $2,414
Storti et al. [113]	Italy	Unknown	AML elder 65-80 (17)	Palliative care	2005	Palliative care cost (monthly): €8900 (transfusion include)	$12,303

- Supportive care

  Cost comparison was impossible to be conducted, due to differences in the study coverage for the three relevant studies, while two of the studies, also, did not report the cost results [148, 149].

- Palliative care

  The cost results of the two related studies were generally consistent. Yu's study [107] showed that the average cost of palliative care was $18,557 per treatment cycle, while Storti et al. [113] found that the average palliative care cost was $12,303 per month.

- Home care

  Cartoni et al. [150] measured the home care cost for three different groups of patients. The average home care cost for 'early discharge patients' was $5,511. For patients in 'terminal stage', the home care cost was similar to the cost of patients who discharged early ($5,851), but higher than the home care cost of patient in 'chronic stage' ($2,057).

2.9 Discussion

The current review examined cost drivers and costing methods used in previous relevant studies. Also, cost result comparisons were conducted when possible. The review results extended the methodologies of the previous relevant studies and provided ideas/recommendations of methodologies for future cost studies (as well as for the innovative costing method used at later stages of the current one). These recommendations and related significant findings are summarized as follows.

2.9.1 Bottom-up costing method

Most of the 50 relevant cost studies (42 out of 50 selected studies) made use of hospital charges or payments as costing data sources. The bottom-up costing method was applied only in ten of the studies (one for examination cost, two for complication treatment, four for transplantation, two for adjunctive treatment and one for home care). For countries where national level administrative claim database or hospital accounting system are unavailable (such as UK), the 'bottom-up method' is suggested to be the best alternative for costing.

2.9.2 Overheads costs

Since 40 out of 50 relevant cost studies used hospital charges or payments as costing data sources, overheads cost information was not reported in particular. This was because overheads costs were concealed in charges and payments. However, this was not the case for studies that used the bottom-up method. In order not to overlook overheads costs and not to underestimate overall treatment cost, it is important to take overheads into consideration, while applying the bottom-up method for costing.

2.9.3 Follow-up costs

Follow-up cost was usually overlooked. Among the 50 relevant cost studies, only a few overall treatment cost studies estimated follow-up costs [103-105]. In the remaining studies, follow-up cost was either completely overlooked or cost in a short period of time. In order not to underestimate overall treatment cost, it is suggested that follow-up should be considered as one of the important cost drivers, when costing.

2.9.4. Important cost drivers for costing individual treatments

The current review uncovered a number of key cost drivers for costing individual treatments, including ones that were actually, but not obviously, relevant. For example, complication treatment cost is one of the key cost drivers for costing growth factors,

while infection treatment cost is one of the key cost drivers for costing complications. It is suggested that the aforementioned observations assist in broadening the scope when developing costing methods.

2.9.5 Extrapolation for ‘resource uses’

During the review process, an innovative method for obtaining ‘resource uses’ (quantity) information was observed. Normally, hospital accounting system and administrative claim database are the main data sources for consumed amount of medical resources (quantity). However, Bennett et al employed a new approach for this [132, 135]. The authors firstly used the hospital accounting system to cost chemotherapy and growth factor for a small number of patients. Next, the obtained results were further used for extrapolating the rest of the remaining patients (the majority of the study patient). This provided a new way to obtain resource use information when the latter was unavailable, something important when using the bottom-up method for costing.

The review results (cost drivers and details of costing methods) and related important findings such as the ones mentioned above provided significant amount of information useful for developing costing methods. The information was also adopted in the costing method developed at later stages of the current study.

Chapter 3 Study Databases

Introduction, data handling, preliminary analysis methods

CHAPTER 3 THE STUDY DATABASES

This study was carried out in the UK. Due to the complexity of the current study, three main databases (comprising HMRN) were employed in order to yield robust cost results. The three databases were Haematological Malignancy Research Network (HMRN) database, Palliative Care Database (PCD), and HMDS Integrated Laboratory Information System (HILIS) Database. The relationship between these three study databases is illustrated in **Figure 3.1**.

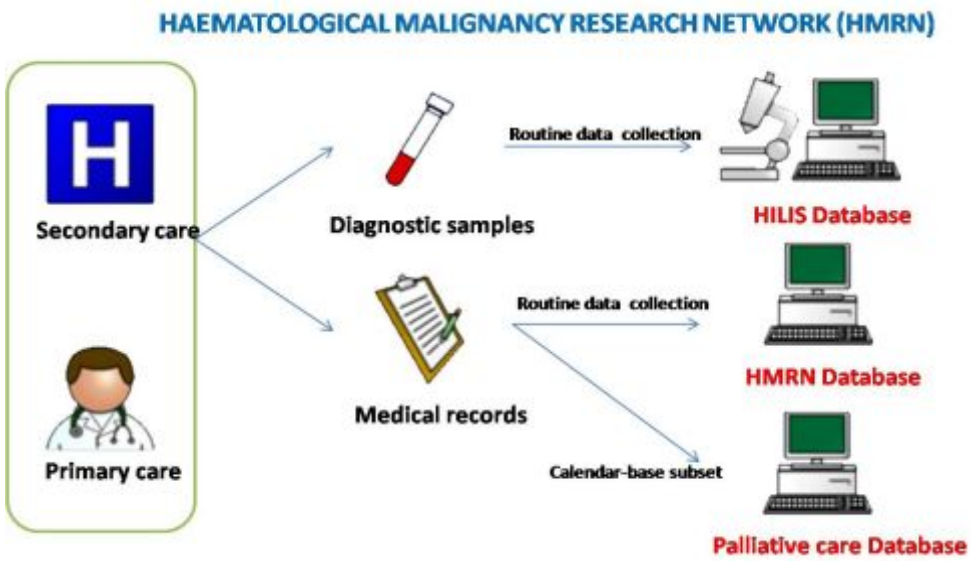


Figure 3.1 Illustration the relationship between three databases in HMRN

As shown in **Figure 3.1**, the HMRN database contained the health care details extracted from medical records. Therefore, it was used as the main data sources for costing. The HILIS database contained all the lab test results, while the PCD database, a subset of the HMRN database, contained detailed health care information in calendar-basis. Due to the information coverage, the PCD databases were used as supplementary data sources for costing.

Although the three databases were all derived from the HMRN, these databases needed to be handled differently, as different databases contained different information, and used different formats. Therefore, in the current chapter, data handling of each study database is described respectively and analyzed preliminarily as follows.

DATABASE 1: HMRN database

3.1Database description

3.1.1 Data collection

The data for treatment pathway building were mainly retrieved from the HMRN database. HMRN is a collaboration between five clinical teams based at 14 hospitals in Yorkshire and Humberside region (**Figure 3.2**) (which covers a population of around 3.6 million), a centralized diagnostic laboratory (Haematological Malignancy Diagnostic Service - HMDS) based in Leeds, and HMRN (Haematological Malignancy Research Network) researchers at the University of York [16, 151]. The clinical teams provide patient care, HMDS provides regional diagnostic service, while HMRN is responsible for collecting the detailed information about all the haematological malignancies diagnosed in the Network. This covers around 2,000 newly diagnosed haematological malignancy patients each year. All of the collected information about diagnosis, treatment and prognosis can be used for further clinical research.

Figure 3.2 The Yorkshire and Humberside Haematology Network Coverage

3.1.2 Study time period

All patients newly diagnosed with a haematological malignancy after 1 September 2004 up to 1 September 2006 were included in the study. All identified patients were tracked from the time of diagnosis onwards until the study close date (30 May 2010). However,

patients were excluded when the disease was a transformation of another Haematological cancer originally diagnosed prior to September 2004 [151]. These decisions were made to allow retrospective tracking of the full course/episode of the disease for study patients.

3.1.3 Data extraction

The clinical data were abstracted from patients' medical records by a group of well trained research nurses, who collected the relevant information on the standard forms from all the new cases in the Network from hospital records. This included hospital notes; however, notes held by private sector institutions were not included because of accessibility and availability constraints. Also, in cases where the patient went out to other cancer networks, notes were not included. All of the extracted data is centralized and stored in HMRN at the University of York, also called 'HMRN database'. This database provides a large volume of clinical information. However, in the context of the current study, only required pieces of information were extracted selectively.

a. Inclusion criteria

The patients who were diagnosed with the following results were considered to be AML or APML patients and, thus, recruited into the study group: AML with adverse cellular features, AML inv(16)(p13;q22), AML arising from transformation of MDS, AML arising from transformation of MPD, AML with multi-lineage dysplasia, AML t(8;21)(q22;q22), AML with MLL (11q23) rearrangement, AML- probable therapy related, and APML t(15;17)(q22;q11-12).

b. Exclusion criteria

- Whenever the treatment episode was not for AML / APML, the episode would be removed from the database in order only the AML/APML-related treatment information to be retained in the database. For instance, the treatment episode would be excluded if it occurred before the patient was diagnosed, as this indicated that the treatment was given for other purposes rather than curing the mentioned disease.
- Patients under 18 years of age were excluded. Given the significant differences in treatment response and prognosis between child and adult patients, it was decided only adult AML/APML patients would be included. The study included patients who were over 18 years old at the time of the diagnosis. The advantage of this was that the results would be more consistent and easy to extrapolate to the whole of the adult patients.

c. Extraction of information items

Although the HMRN database provides a large volume of clinical information, in the current study only the following fields were extracted: patient's age, gender, diagnosis results, date of diagnosis, date of death, date of latest follow-up, name of each treatment, regimen of each treatment, start and end dates of each treatment.

Based on the criteria mentioned above, 243 patients were found to be newly diagnosed with AML/APML.

3.1.4 Remainder

In the HMRN database, the start and end dates of each treatment episode were recorded to justify the delivery of medication. The duration between the start and end dates was defined as the treatment time. It is worth noting that treatment time here does not reflect the actual days of the hospital stay, as patients may stay in hospitals for complication treatment or other purposes after treatment time.

Another thing worth noting is that patients may have more than one cycle of the treatment during the reported treatment time, and, thus, treatment time could include treatment intervals or home leaves. This rendered the treatment time of identical treatments vary significantly. Since information related to actual treatment time was unavailable, 'number of treatment cycles' was required in order to transform the uneven treatment time into a consistent and comparable format. The information related to number of treatment cycle were not routinely recorded into the HMRN database. However, in most of cases, the relevant information can be found manually in the notes of the information extraction form (used by research nurses for extracting data from medical records). In the cases that relevant information could not be derived from data extraction forms, comparisons with similar cases under experts' supervision to yield reliable number of cycles or frequency of usage.

3.2 Database cleaning

Although all the clinical data were extracted by well trained research nurses, human errors/mistakes could have occurred at data input. Therefore, in order to prevent getting distorted results derived from analyzing a corrupted database and to enhance the accuracy of the analyzed results, data cleaning was needed before the database was used for further analyses.

The following errors / mistakes were corrected or excluded from the study analysis for cleaning purposes.

3.2.1 Excluding the problematic cases

All of the study patients were followed up on a regular basis, and their clinical information were extracted by research nurses. However, there were four cases where either the relevant medical notes were unobtainable or the clinical information extraction forms had not been completed yet. These four cases were excluded from the study analysis completely in order not to be mistaken as untreated cases.

3.2.2 Excluding the duplicate treatment records or integrating the treatment records that were likely to be the same

Records duplication does not occur very frequently in the HMRN database. However, in treatment event/episode level, a number of duplicated events were observed. These duplicated cases were integrated into one record, with the wrongly added records being excluded.

'The event records that are likely to be the same' are the records that are not presented in exactly the same way as others in the database but they have very high possibility to be the same events. This was because sometimes research nurses could be misled by the complexity or the purposes of the regimen / drug usage. For example, while cytarabine and daunorubicin could be given as a single agent, they could also be combined and given as a regimen called DA. To prevent this potential misleading information enter the database, this kind of records needed to be integrated into one record and the rest of associated pieces of information to be excluded.

Identifying and integrating possible duplicate records was not an easy task as it could not be done by the use of typical software logic procedures [152]. Therefore, potential duplicated records had to be cleaned up manually, with only the integrated data being kept. The details of the integration can be found in **Appendix 3.1**.

3.2.3 Handling of records including in-equivalent information (observation event)

Observation events were not routinely recorded. In order to ensure that all the patients' records included equivalent amount of information, it was decided that observation should be defined as the outpatient based follow-up visit (during all gaps of treatments with the exception of supportive care).

3.2.4 Ensuring the data is consistently formatted

Correcting the format of the data not only helped the management of the database, but also it made further analysis work much easier, although this process was not as important as initially obtaining the correct data (as mentioned above). For example, since the missing data were recorded differently in the various fields of the HMRN database, blank fields were used for presenting all of the missing data, as a default.

3.2.5 Summary

After database cleaning process, 239 out of 243 patients were found to be eligible for further analysis, as the medical notes of four patients were not obtainable. In terms of event records, overall, 56 treatment events were excluded from the study database due to the duplication and inadequate information. Finally, 763 events remained in the database for further study.

3.3 Missing data imputation

Despite the fact that research nurses tried to extract data from medical notes in as much detail as possible, in some cases the data were impossible to be obtained. In such cases, the missing data were coded separately. In the HMRN database, the missing data were divided into two types: those in the non-interest fields or those in the interest fields. When the missing data appeared in the non-interest fields (the fields that are not related to cost estimation), the most common value was used as a default for imputation. However, the situation was more complicated when the missing data appeared in the interest fields, as the missing data imputation could affect the final result - treatment cost. Therefore, a careful design for handling the missing value was needed.

In the current study, an important field that had many missing data was the 'treatment date' (including 'start date' and 'end date'). 'Treatment date' is considered to be associated with 'treatment time', which is an important parameter for cost measurement. In the HMRN database, among 763 treatment events, 241 events did not have sufficient date data for 'treatment time' calculation (either the treatment start or end date was missing, or both were missing). Therefore, an imputation for the missing dates was urgently needed.

In this section, the imputation of the missing dates is discussed in detail. This includes two parts. First, the missing date of the treatment event was imputed. Second, the treatment events were broken down by treatment cycle. In the end, each treatment event would only have the information (including date and regimen) of one cycle/course of treatment. The benefit of this approach was that it made treatment overlapping easy to be identified, and, thus, made the further cost calculation and analyses easy to be carried out. The details are described in the following paragraphs.

3.3.1 Imputation of missing date data

a. Supplementary data for imputation

In the current study, four sets of information (derived from five different sources) were used to serve the imputation purpose.

- Fragments of actual 'treatment date': The non-missing 'treatment date' that derived from the HMRN database was retained as the main body of the imputation.
- Number of treatment cycles: This information provided a general idea about the supposed length of the treatment, as some of the treatment event records contained more than one cycles of treatment. The 'number of treatment cycles' of each treatment was derived from the notes of the information extraction form.
- Actual hospital stay: the additional information derived from a subset of the HMRN database - medical notes of 30 patients recruited in clinical trial. The 'actual hospital stay' provided the information about the number of bed days that a patient stayed in hospital (even after the delivery of medication). This was particularly useful for imputing when the treatment record contained more than one treatment cycles.
- Standard treatment time: this information was derived from the AML 15 trial protocol and the BCSH treatment guideline. 'Standard treatment time' provided the information related with the general length of the treatment. This was useful when the treatment record contained more than one treatment cycles.

After necessary refinement by clinical experts, all the information for imputation mentioned above was integrated into a table. The details can be found in **Appendix 3.2**. An abstract of the contents of the table is shown below.

Table 3.1 Example of integrated information for imputation

	Cycle 1		Interval	Cycle 2		Imputed treatment time
	Treatment time	Hospital stays		Treatment time	Hospital stays	
ADE	10	30	13	8	25	30+13+8=51
AraC (HD)	5	32	17	5	23	32+17+5=54
DA	10	35	14	8	30	35+14+8=57
FLA	5	28*	17*	5	46*	28+17+5=50
Mylotarg	1	-	6	1	-	One cycle (1)
ATRA	Till remission**	-				Till remission**

* The length was imputed by similar treatment

** The length was imputed by expert opinions

As can be seen in **Table 3.1**, the inpatient chemotherapy of each cycle contained two pieces of information: 'treatment time' and 'hospital stay'. Average treatment interval information for each chemotherapy regimen was also presented. As for the outpatient treatment, such as mylotarg, one cycle was set a default value if the information of numbers of cycle was not obtainable. No hospital stay was applied to outpatient treatment.

b. Imputation methods

After integrating the information for imputation, it was possible for the missing data to be imputed. The integration involved four steps. Details of the four steps can be found below.

Step 1: Grouping treatment events.

The treatments that used similar regimens or followed similar approaches were grouped together in such a way as the missing values to be possible to be imputed together at later stages. This way, not only the complexity of the imputation could be reduced, but also the imputed value could become more robust.

Step 2: Ensuring that each event in the groups has only one date missing.

In order to impute the missing 'treatment date' by means of 'standard / imputed treatment time', at least one of the 'treatment dates' ('start date' and/or 'end date') had to be known. Among 763 study events, eight events were found to have both the 'start-date' and the 'end-date' missing. To deal with this issue, the medical notes of these 8 cases were retrieved and re-extracted with the assistance of research nurses. Based on the above, it could be ensured that each treatment event in the groups had only one date missing.

Step 3: Determining the 'standard / imputed treatment time'

Based on the integrated information (**Appendix 3.2**) and on the 'number of treatment cycles', the 'treatment time' could be imputed in three different ways:

- When the 'number of cycles' was known (cycle=1)
  When the 'number of cycles' was one, then the standard treatment time (derived from guideline or protocol) was used for imputation.

- When the 'number of cycles' was known (cycle>1)
  When the 'number of cycles' was more than one, the imputed treatment time was determined by the lump sum of the hospital stays for cycle 1, interval, and standard treatment time for cycle 2 (the details can be seen in **Table 3.1**)

- When the 'number of cycles' was unknown
  When the 'number of cycles' was unknown, one cycle was set as the default value. The standard treatment time for one cycle (derived from the guideline or the protocol) was used for imputation.

Step 4: Imputing the missing date.

After applying the standard / imputed treatment time to the events that were found to have missing data, the missing date could be calculated by simple addition or subtraction.

The imputation method is illustrated in the following figure (**Figure 3.3**).

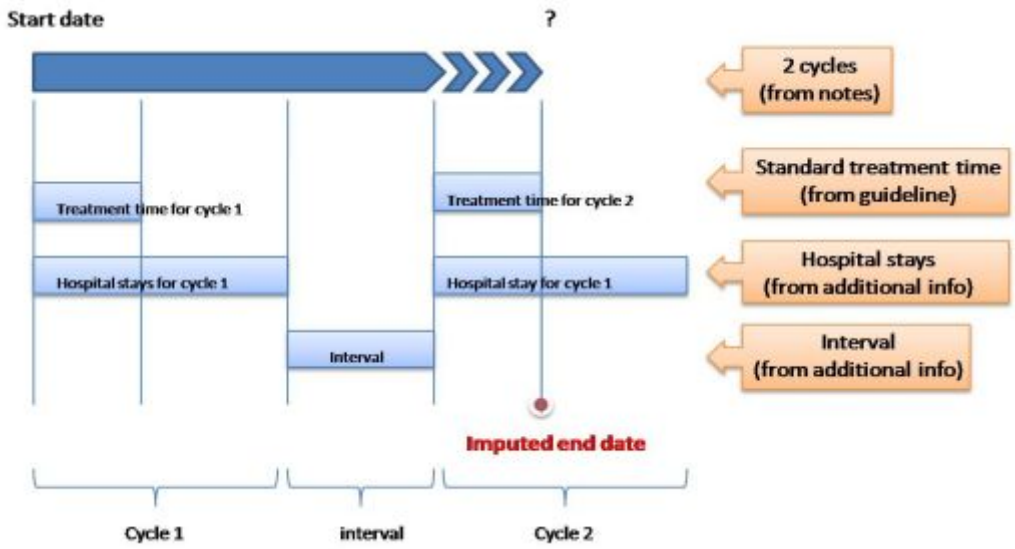


Figure 3.3 The illustration of missing data imputation method

3.3.2 Breaking down the treatment events (by cycles)

Although at this stage each treatment event record had both a 'start date' and an 'end date' (either original or imputed), the treatment event records still could not be used directly for cost calculation. This was because they contained uneven information (some of the records contained 1 cycle of treatment information, while some contained more than 1 cycle). To avoid confusion regarding the information one event record could contain, the treatment events were further broken down into cycles. This way, each cycle of treatment would be registered in one record in the database. This approach was expected to have the following four benefits:

- It could give a better view of the time each treatment cycle was likely to have taken place.
- It could help in avoiding over-counting the treatment cost in cases where the 'treatment time' contained more than one cycle and the 'interval' (also called 'home leave') should not be calculated.
- It made treatment overlapping easy to identify. This made further cost calculation and analyses easier.
- It enhanced the accuracy of the costing method, as the costs of all the cycles could be estimated in detail.

It is worth noting that the 'treatment dates' of each cycle, deriving from the break-down method, were all imputed dates and not the actual occurrence dates. However, this was the closest estimation to the actual occurrence date that could be achieved. The details of the aforementioned break-down process are described below.

a. In-patient treatment events

All the treatment events that contained more than one cycle were further broken down into cycles, according to the 'number of treatment cycles'. As for the events that were found to have missing 'number of treatment cycles', the breaking down number was determined by comparing the treatment length with other cases with known 'number of cycles'. After the above process was completed, only the newly generated event records were retained while all the original records (containing more than one cycle) were removed. The discussed process is illustrated in **Figure 3.4**.

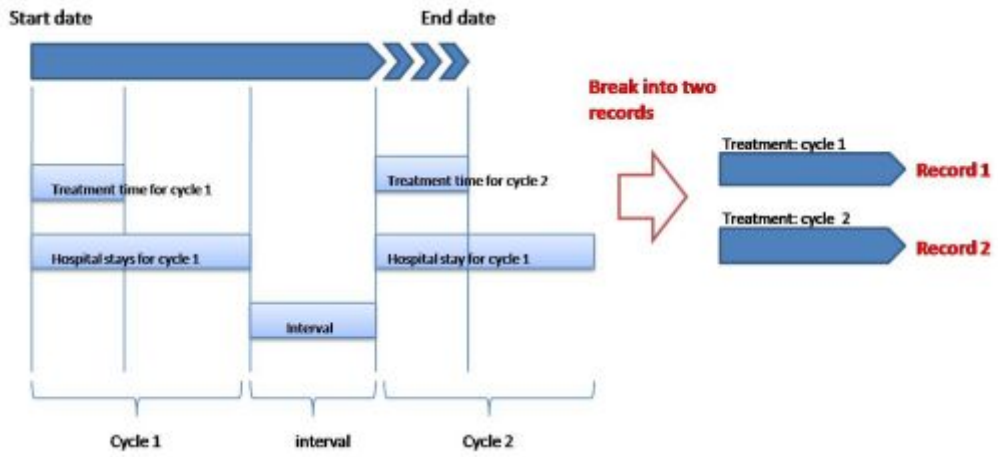


Figure 3.4 The illustration of breaking down event

b. Out-patient treatment events

Unlike the inpatient treatment events, the records of the outpatient treatment event normally do not contain information related with the 'number of cycles'. This is because many of them, such as Hydroxycarbamide, are given either on a daily or on a continuous basis. After careful consideration, it was decided that the outpatient treatment events did not need to be broken down. This was because of two reasons:

Firstly, the pattern of the outpatient treatment delivery was not consistent. This was especially prominent when the outpatient treatment overlapped with the inpatient treatment, in which case the outpatient treatment (such as hydroxycarbamide) was carried out daily by hospital staff during the hospital stay while the delivery style changed after the patient discharged. In the latter case, the patient would only visit the hospital for getting medicine or receiving simple outpatient treatment on a regular basis. The inconsistent delivery pattern made the breaking down of the outpatient event difficult.

Secondly, even in cases where the outpatient treatment did not overlap with the inpatient treatment, the frequency of outpatient visits could be changed when overlapping with other outpatient treatments occurred. This was because the medicines used for the outpatient treatment could be given at the same visit (there was no need for the patient to visit the hospital twice for getting different types of medicine as these could be provided at one visit). The discussed process is illustrated in **Figure 3.5**.

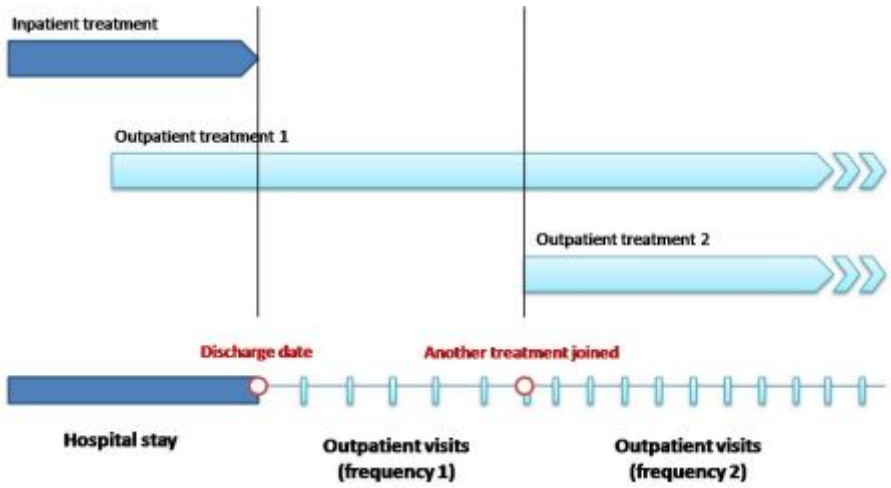


Figure 3.5 The illustration of outpatient treatment overlapping

Based on the figure above, more information was needed in order to break down the outpatient events (such as the overlapping information). Therefore, the outpatient treatment records remained unaffected, at least for this particular phase of the study.

3.3.3 Summary

Overall, 763 events were broken down and, consequently, expanded to 1025 episodes. After the process described above was completed, all the missing treatment date data for each cycle were obtained and ready for cost estimation use.

3.4 Integration with other data sources

3.4.1 Integration with NHS Central Register

For the purposes of current study, additional information was obtained from the National Health Service Central Register (NHSCR) and was linked and integrated into the HMRN database with ethics approval (NHSCR is held by the Office for National Statistics on an agency basis for the Department of Health [153]). NHSCR compiles and maintains computerized records of all NHS registered patients, including information such as cancer and death events [153]. From the NHS Central Register, 'place of death' fields were extracted and added into the study database for study purposes.

The 'place of death' field mainly contained information related with the actual location of the patient's death, for example at home, in hospital, or at nursing home. This information could be later used for calculating the dying cost, and mainly it could help to identify the ward cost for each of the above places. For example, the dying cost was considered to be zero if the patient died at home.

3.4.2 Additional information was available on subset

For a proportion of patients recruited to national clinical trials, additional data were obtained from medical records. The additional data relate to hospital stay and antibiotic use.

a. Actual hospital stay

Since 'treatment time' was not sufficient to provide the required information of the actual medical resource use, the actual hospital stay/bed day had also to be considered for estimating the treatment cost. In the context of the current study, it was initially intended all the actual hospital stays data to be obtained. However, this was not possible because of availability constraints. The only data that were possible to be extracted were those of the clinical trial arms. The aforementioned data were extracted from medical records of 30 patients (including the information of admission date and discharge date). After the data were obtained, they were extrapolated and integrated into the study database.

b. Antibiotic use

Antibiotic is a common supportive care or complication treatment for AML/APML patients. However, this information was not obtainable in the HMRN database. Since it is very expensive, the information of antibiotic use was needed to be additionally extracted in order to enhance the accuracy of the treatment cost estimation. Information related to the number of days the antibiotics were used for each clinical trial arm was extracted from 30 available medical records. This information was extrapolated and added into the study database for further analysis.

3.4.3 Summary

The integration with other data sources enriched the HMRN database. A number of pieces of information became available for costing, namely place of death, index of deprivation, hospital stays, and days of antibiotic use. As the additional information derived from the integration did not alter number of cases, the study population remained the same: overall, 239 patients with 1025 treatment events/episodes.

3.5 Preliminary analysis method

In order to have a better understanding of the type of information contained in the HMRN database, a number of preliminary analyses were conducted. They were descriptive statistics, test of homogeneity, missing data analysis, and treatment pathway. The overview of preliminary analyses is illustrated in **Figure 3.6**, while the detailed analysis methods are discussed in the following sections.

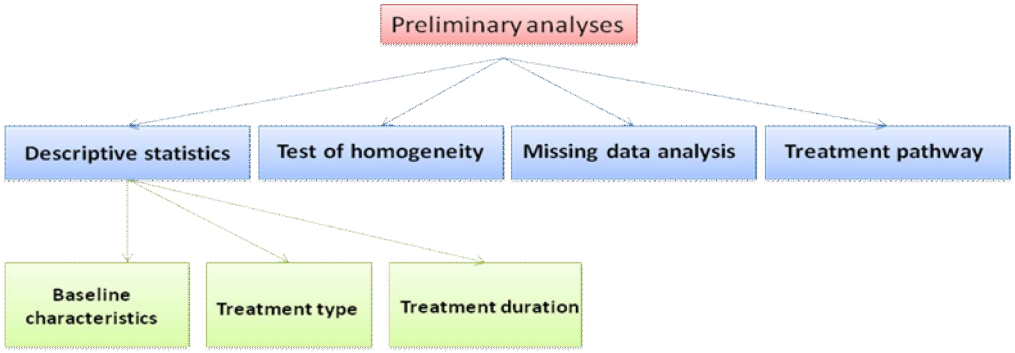


Figure 3.6 Overview of preliminary analyses of HMRN database

3.5.1 Descriptive statistics

All statistical analyses were done by means of SAS/Stats program (SAS software program package, version 8.02, SAS Institute, Cary, NC)

a. Characteristics of study population

According to the information available in the HMRN database, the following demographic variables of the study population were analyzed: gender, age, diagnosis result, disease transformation, index of deprivation, mortality, and place of death. Information such as gender, mortality, place of death, disease transformation, diagnosis and index of deprivation is categorical data. Therefore, the analyses were descriptive in percentages for these variables.

In the case of the 'age' variable, it was decided that the ratio scale should be applied, despite the fact that originally it was continuous data. The reason for this was that the age group was an important determinative factor for clinicians for deciding which was the optimal treatment to patients (Normally, old patients would have poorer response than

younger adult patients [154]). Therefore, the results presented by continuous scale ('average age') would not be helpful enough for portraying the study population. Therefore, the analysis results were presented in age category format. The age data were categorized into three different age groups (based on the AML / APML treatment guideline [155, 156]), namely: less than 59, between 60 and 74, and over 75 year-old. The age of APML patients was divided into two categories: between 18 and 59, and over 60 year-old.

b. Types of treatment

Different patients undertook different treatments, and also most of patients received more than one treatment for AML / APML. To portray the type of treatments that AML / APML patients received, three analyses were conducted.

- Numbers of treatment
- Types of treatment by diagnosis (AML/APML)

  Treatment type was an important piece of information for understanding what kind of treatment AML/APML a patient normally received. To reveal this information, all the treatment episodes that used for treating AML/APML were analyzed and presented in percentage. Since the diagnosis (AML / APML) also plays an important role in treatment decision making [155, 156], the analysis was further broken down into two parts by diagnosis.

- Types of primary induction treatment by diagnosis and age groups

  Type of primary induction treatment has a strong connection with patient's condition on their first diagnosis. Also, the types of primary induction treatment is considered to be related to the prognosis (such as remission rate) and mortality according to the results of many clinical reports [97, 155, 157]. To reveal this connection, the primary induction treatment type was further analyzed with patient's character, including age and diagnosis.

c. The treatment duration

In the HMRN database, there were three different types of treatment duration that were crucial for treatment cost estimation: 1) 'treatment time' which is the duration of the delivery of medication. 2) 'hospital stay' which is the number of bed days a patient stays in the hospital for treatment, including treatment time and other bed days involving

relevant supportive care or complication treatments. 3) 'Antibiotic days': days of receiving antibiotics, which could represent actual expenses of pricey complication treatment. These three different types of treatment duration were presented by types of regimen / arms of clinical trial.

3.5.2 Missing data analysis (patterns of missing values)

Missing data are commonly observed in patient-oriented research and studies [158, 159].The HMRN database is not an exception, although the data were manually extracted by well trained research nurses.

Missing data could produce substantial biases in analysis and reduce the precision of the statistic results, if it is not handled carefully [160, 161]. On this ground, it is very important to test and make sure that these occurrences of missing data are random and not systematical before starting analyzing the data. This was especially important in the context of the current study, as the interest variables (treatment start and end dates) contained significant amount of missing data, and also because these variables were the crucial parameters for treatment cost estimation at later stages. In current study, a two-stage simple missing data analysis was conducted in order to check the pattern of missing data and whether the missing values occurred systematically.

a. Descriptive statistics

In order to describe the distribution of the missing and non-missing values in the interest variables (treatment start-date and end-date), descriptive statistic analysis was conducted and missing and non-missing values were presented in numbers.

b. Missing data analysis

To check whether the missing values occurred randomly or systematically and whether the missing data were influenced by any other variables, a simple logistic regression method was conducted [162, 163].

3.5.3 Treatment pathway

The tree diagram of the treatment pathway was an attempt to present the longitudinal history of main and relevant treatments, which took place not only within one hospital, but also within all the other relevant hospitals that were involved in the HMRN network. It provided a holistic view of the entire patient's treatment pathway. However, the treatment pathway could not be portrayed as straightforward as in other leukemia cases because of rapid progression of the disease that caused complicated treatment processes. To make the tree diagram simple and easy to read, the treatment pathway was sorted and presented according to treatment start date. In order to do so a compromise had to be made, as information regarding treatment overlapping could be lost.

a. Purpose

- Reveal the treatments which AML patients were received in real world
  Treatment pathway for two patients with the same illness could be entirely different depending on patients' situation or physicians' decisions. Therefore, the tree diagram allows the treatment pathway to be highly personalized. This made it a preferable way to calculate the 'actual' treatment cost, compared to the use of the clinical guidelines.
- Transcend the hospital boundaries
  As the data were collected through the network, there were no hospital boundaries in this study. This allowed the collection of information from treatments of individuals in several different hospitals, rather than just form one hospital.
- Display a graphic representation of the pathway in which costs can be later linked to. This is also known as 'clinical process cost analysis'.

b. Method

The 'treatment pathway' was presented as a route that an AML/APML patient took from diagnosis, through treatments, to the completion of the treatments, follow-up or death. In this section, all the clinical information extracted from the database was plotted into a timeline. The events such as chemotherapy, clinical trial, palliative care, and transplantation were mapped to this timeline according to their treatment start date. However, events such as supportive care and observation/follow-up were not included because they were not given with curative intent. To plot the treatment pathway tree, four steps were followed:

Step 1: Identifying patients as AML /APML and dividing them into groups by their age: To plot the AML and APML treatment pathway, the patients were divided into 3 main groups by age, as different age groups of AML / APML patients are suited for different treatment options due to different treatment response rate and treatment tolerance. According to the same definitions of the age groups used to present the descriptive statistics (referred to 3.1.2), AML patients were divided into 3 groups: ≤59, ≥60 and≤74, ≥75, and APML patients were divided into 2 groups: ≥18 and≤59, ≥60

Step 2: Excluding the treatments that were unsuitable to be presented: After the regrouping of treatment types, two treatment types were removed, namely observation/follow-up and supportive care. This was because these two inerventions could make tree diagram plotting problematic as supportive cares were usually given along chemotherapy or other treatments, and observation, and observation were given far too frequently and regularly then any other major treatments.

Step 3: Presenting the main treatment information: Since it was impossible to show all the details in one tree diagram, only the main treatment types were shown in order to portray the whole range of the treatment activities given to a patient without compromising clarity. These treatment types were: chemotherapy, clinical trial, transplantation, palliative care, radiotherapy, and immunosuppressive care.

Step 4: Plot tree diagrams: After identifying and grouping the patients and treatments, all the treatment data were summarized graphically by diagnosis, patient age, and treatment type. Each patient was traced from the diagnosed date onward, to the last follow-up date or death. Patients who died were given a square mark in the end of the branch in the tree diagram. All the sequences of treatments were visualized as a linear timeline according to the chronology of the HMRN records. However, overlapping treatments were not possible to be shown in this pathway tree diagram.

3.6 Overview of the work done on the HMRN database

The HMRN database was used for defining the study population of the current study. In order to obtain the disease-specific information, the HMRN database was handled through several processes (discussed in sections 3.1 to 3.4). These processes were: data extraction, database cleaning, missing data imputation, event breakdown by cycle, and integration with other data sources. The whole process and number of cases are illustrated in **Figure 3.7**.

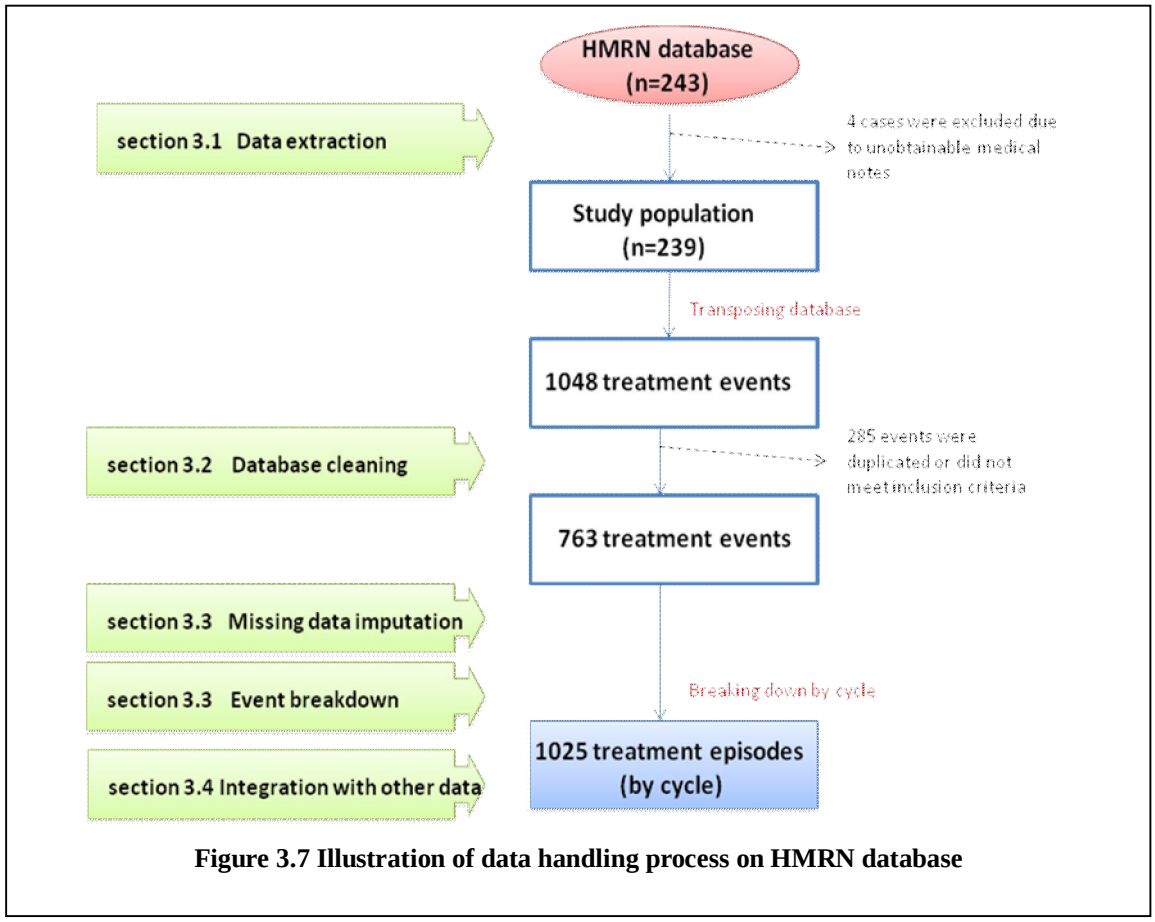


Figure 3.7 Illustration of data handling process on HMRN database

After the study database was set up, a number of preliminary analyses were conducted (please refer to section 3.5). The relevant results are presented and discussed in the next chapter (chapter 4).

DATABASE 2: HILIS database

3.7 Database description

3.7.1 Data collection

Information related with treatment phase distinguishing and laboratory cost estimation was mainly retrieved from the HILIS database, which was maintained by the Haematological Malignancy Diagnostic Service (HMDS), an organization based in Leeds Teaching Hospitals. HMDS, which was the first specialist haematopathology service in the UK, was established in 1993 in order to integrate the diagnostic techniques and experts in the Yorkshire and Humberside areas. Since then, all the regional diagnostic services are centralized and referred to HMDS. The number of tests, which increases annually, reached around 20,000 test requests in 2009. HMDS not only allows the diagnostic resources to be integrated, but also enhances the precision of diagnosis and helps to monitor both patient disease progression and response to treatment. Since this approach has been successfully carried out by HMDS and as the number of test requests increases year by year, a sophisticated and customized web-based laboratory IT system was applied in 2001 within the NHS intranet. The reason for this was to provide better services, better data usage, and a general source of information for potential and/or current users. The IT system is known as 'HMDS Integrated Laboratory Information System (HILIS)', and is used to integrate all the information related with clinical diagnosis, specimen or biopsy tracking, and reports produced in HMDS [164, 165]. In **Figure 3.8**, the reader can find a graphical representation of the data collection process of the HILIS database.

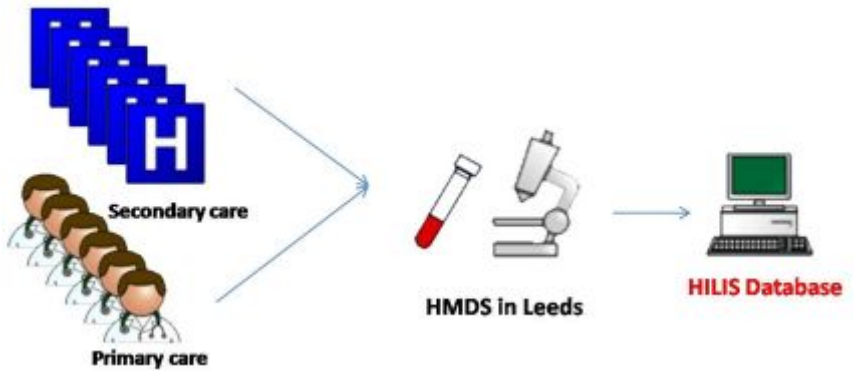


Figure 3.8 Graphical representation of data collection process of the HILIS database

3.7.2 Study time period

All the diagnoses are tracked and relevant reports of the study population (patients who were newly diagnosed with AML or APML between 1 September 2004 to 1 September 2006) in the HILIS database were eligible to be included. However, only the test result information, reported between the diagnosis date and either the death date of the patient or the study close date (30th May 2010) was actually kept. This approach was expected not only to allow retrospective tracking for all the laboratory tests and relevant events, but also to assist in keeping the relevant events that were related to AML/APML treatment.

3.7.3 Missing data

In the HILIS database, no data were found to be missing and all the test results were reported in high detail. Even cases of inappropriate request or unsuitable specimen were recorded, and were continuously audited. Therefore, missing data analysis was not needed for the HILIS database.

3.7.4 Database cleaning

According to the guideline, when specimens or biopsies were referred to HMDS, they were investigated using standardized protocols rather than in response to individual requests for tests from referring clinicians [164]. Briefly, each patient-specific report generated by HMDS was derived from a maximum extent of cross validation information. This contained groups of samples received from clinicians rather than single samples of request for test. This was expected to assist in the investigation of the samples by co-ordinate experts at later stages, as it would allow focusing on specific clinical problems, and also assist in avoiding any duplicated test requests and conflicting reports from different sample types [164].

Despite the fact that this specific approach introduced a number of advantages, a serious issue occurred while analyzing the data. A large amount of requests that were sent during a short period of time to produce one report were all reported and uploaded into the HILIS database. This means bunch of relevant request /sample reports had the same results. The above issue greatly increased the volume of the database rendering it inconvenient for further analysis. In order to have a clean database for analysis and not to double count the laboratory cost, all the duplicated information were summarized into one report according to the ‘report date’ field with all the unnecessary information being excluded. The information that was summarized contained the following fields: report date, test result, and specimen type.

a. Report date

Without considering the screen date, only one patient-specific report was kept for each report date. Effectively, this meant that if the samples were collected on the same date (same screen date) but reported on different dates, these test results could not be combined into one.

b. Test results

Since the test results on the same report date would be consistent, the test results were summarized into one for each report date.

c. Specimen/biopsy types

The summary / combination of specimen of biopsy/specimen types mainly was conducted for laboratory cost estimation purposes, as summarized specimen data are easier to be linked by the unit cost and to be cost. The abbreviations of specimen are list below (**Table 3.2**).

Table 3.2 Abbreviation of specimen test

Full name of the specimen test	Abbreviation
Bone marrow aspirate	BMA
Bone narrow aspirate & Trephine biopsy	BMAT
Cerebral spinal fluid (CSF)	CF
Chimerism, allograft	CHIA
Chimerism, baseline	CHIB
Chimerism, mini-allograft	CHIM
Skin, block	DBL
Skin, fixed	DF
Skin, fixed & unfixed	DFU
Skin, unfixed	DU
Effusion	EF
Haematological slide	HS
Lymph node biopsy, fixed	LF
Lymph node biopsy, unfixed	LU
Peripheral blood	PB
Peripheral blood, stem cell	PBS
Spleen, unfixed	RU
Bone marrow trephine, fixed	TBP
Miscellaneous tissue aspirate	XA
Miscellaneous tissue, block	XBL
Miscellaneous tissue, unfixed	XU

Because of the complexity and variety of specimen/biopsy, the combination of the specimen/biopsy information encompassed three steps:

Step 1: The different sample results that were actually derived from the same specimen were combined. For example, as the LBL (Lymph node biopsy, block), the LF (Lymph node biopsy, fixed) and the LFU (Lymph node biopsy, fixed & unfixed) are similar methods used on the same biopsy (lymph note) they could be combined. In this case, the specimen types were combined into one type, and the rest of the information was removed in order to prevent double counting the lab cost. The specimen types that were combined in this group were:

CHIA, CHIB, CHIM
DBL, DF, DFU, DU
LF, LU
XA, XBL, XU
BMA, BMAT
PB, PBS

Step 2: The duplicated specimen results that were examined for confirmation were combined. For example, 'PB, BMA' and 'BMA, PB' are actually the same methods used on the specimens so they could be combined. In this case, only one of the specimen type sets of information was kept while the rest were removed in order to avoid double-counting the lab cost. The specimen types that were combined in this group were the following:

BMA, TBP / TBP, BMA
BMA / CF / CF, BMA
PB, BMA / BMA, PB
PB, BMAT / BMAT, PB
TBP, HS / HS, TBP
TBP, PB / PB, TBP

Step 3: The remaining specimen type information was summarized into one record for each report date. After completing step 1 and step 2, only one specimen type was kept. However, on the same report date, the specimen type information from different test methods or different specimen still existed in the database and needed to be removed. For example, 'BMA, PB', 'BMA, TBP', and 'CHIM' were all on the same report date, and, therefore, they could be summarized into one record: "BMA, PB, TBP, CHIM". All in all, the main task in step 3 was to summarize and combine all the remaining specimen types into one integrated specimen record. After step 3, each report date would only have one summarized specimen type, while the unnecessary pieces of information were removed from the database.

3.8 Preliminary Analysis Methods for the HILIS database

All statistical analyses and data manipulation tasks, such as summarizing the duplicated data and calculating the lab cost, were done with the SAS/Stats application (SAS software program package, version 8.02, SAS Institute, Cary, NC)

3.8.1 Treatment phase / Length of treatment phase

Treatment phase (for example first remission or first relapse) is an important piece of information for describing the progression of AML treatment, while it is also relevant to the process of deciding the treatment types and calculating treatment costs. To identify the cutting-off date for the treatment phase, test result data from the HILIS database were used.

To identify this cutting-off date, two pieces of information were essential, namely the fields ‘test result’ and ‘date’. More specifically, the ‘report date’ was used as the cutting-off date instead of the screen date. Also, multiple test results were used for identifying the treatment phase. A breakdown of this can be found below:

a. Remission date

When the test result was firstly described as ‘remission bone marrow’ or ‘no evidence of disease’ based on specimen BMAT, then the report date could be defined as the first remission date. After that, all the following remission results could be treated as if the patient stayed in remission until the disease relapsed. If the disease relapsed, and the patient achieved remission again (that is if the patient had remission diagnosis again), then the report date for this remission would be defined as the next successive remission date (for example: second remission, third remission and similar).

b. Relapse date

Relapse is defined as the reappearance of leukemic cells after a patient achieved remission. Therefore, when a patient had previous remission record (achieved remission) and the test results were AML relevant diagnosis, then the first report date could be defined as the first relapse date. It is worth to note that ‘suspicious of malignancy’ was not considered as one of the AML relevant diagnoses. After that, if a patient had achieved

another remission, then the report date of the following first AML diagnosis could be defined as the next successive relapse date (for example: second relapse, third relapse and similar).

It is also worth noting that a patient could have more than one remission and relapse dates depending on the diagnosis results in the HILIS database. All these dates were recorded with ordinal numbers according to the frequency of their appearances in the database (for example: 1st remission date, 2nd remission date, and 3rd remission date).

After the remission dates and relapse dates were identified, the length of treatment phase was calculated in order to present the differences and characters of each treatment phase.

3.8.2 Laboratory costs

To estimate the laboratory costs, two pieces of information were needed, namely: 'quantity' and 'unit cost'. The details of these two elements are described below:

a. Quantity

The laboratory costs were calculated using 1767 test reports from the HILIS database, after the data had been cleaned. Based on the specimen type information (as shown in **Table 3.2**), each report had only one summarized specimen type. This summarized specimen information could be taken as 'quantity' in laboratory cost estimation.

b. Unit cost

For the laboratory cost calculation of each test request the price list was used as unit cost. The price list was derived from the 'Provider-Provider Tariff 2006-7 of the Haematological Malignancy Diagnostic Service at St James's Institute of Oncology, Leeds Teaching Hospital NHS Trust'. The detailed price list is shown in **Table 3.3**.

Table 3.3 Price list of specimen test

Full name of the specimen test	Abbreviation	Price
Bone marrow aspirate	BMA	£148
Bone narrow aspirate & Trephine biopsy	BMAT	£339
Cerebral spinal fluid (CSF)	CF	£29
Chimerism, allograft	CHIA	£265
Chimerism, baseline	CHIB	
Chimerism, mini-allograft	CHIM	
Skin, block	DBL	£218
Skin, fixed	DF	
Skin, fixed & unfixed	DFU	
Skin, unfixed	DU	
Effusion	EF	£90
Haematological slide	HS	£29
Lymph node biopsy, fixed	LF	£90
Lymph node biopsy, unfixed	LU	
Peripheral blood	PB	£148
Peripheral blood, stem cell	PBS	£148
Spleen, unfixed	RU	£200
Bone marrow trephine, fixed	TBP	£218
Miscellaneous tissue aspirate	XA	£148
Miscellaneous tissue, block	XBL	
Miscellaneous tissue, unfixed	XU	

The test cost of each report could be obtained simply through the use of addition, by linking the unit cost to the specimen type information in the HILIS database. The test costs were further summed up by patient level. Finally, each patient would be allocated one total lab cost, and the difference of the lab cost for each patient could then be revealed. In addition to considering the lab cost as a whole, the lab cost could be further divided by the treatment phase. This could provide a whole picture of the lab test usage in each treatment phase.

3.9 Overview of the work done on the HILIS database

The HILIS database was used for identifying treatment phase and for laboratory test cost calculation. In order to obtain the relevant information, the HILIS database was handled through several processes (discussed in sections 3.7). The whole process and number of cases are illustrated in **Figure 3.9**.

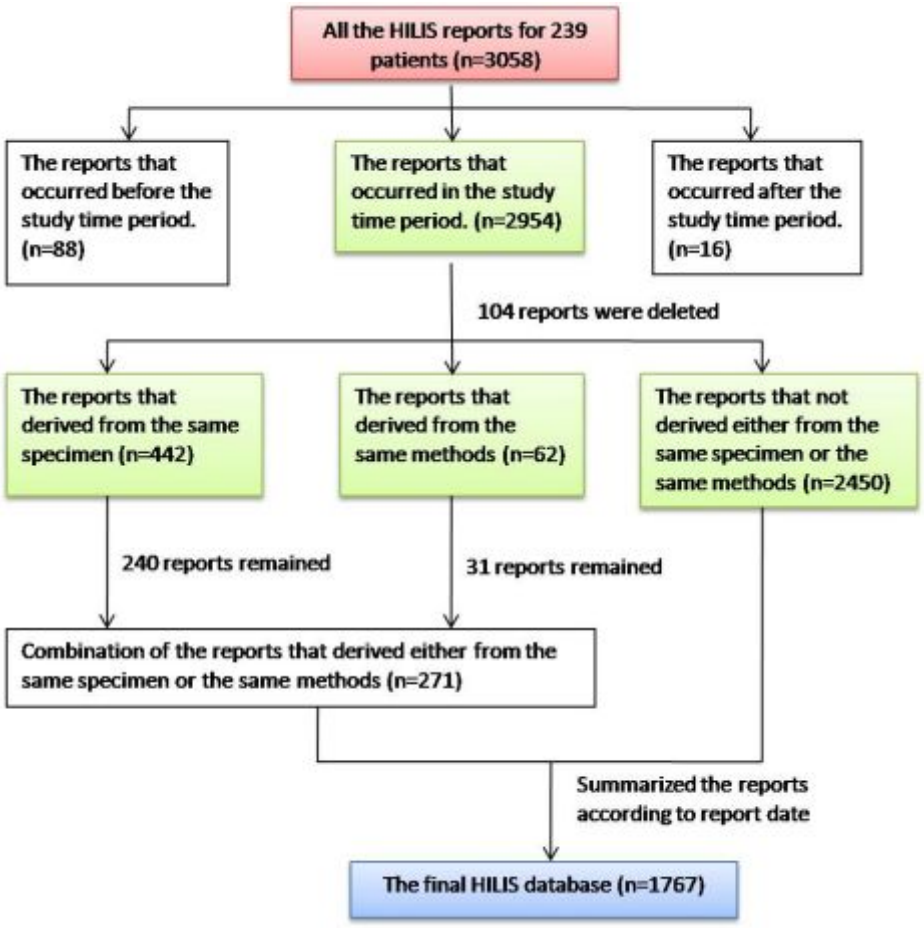


Figure 3.9 Illustration of data handling process on HILIS database

After the study database was set up, a number of preliminary analyses were conducted (please refer to section 3.8). The relevant results are presented and discussed in the next chapter (chapter 4).

Database 3: Palliative care database

3.10 Database Description

3.10.1 Data collection

The HMRN establishes a platform to conduct further researches into patients care. Currently, it is providing the research infrastructure for a portfolio of palliative and end-of-life care projects. This project is directed by the 'HMRN Palliative Care and Haematological Malignancy Steering Group', a group that was established in 2004 and comprises of academics from the University of York (including individuals from the fields of sociology, Health Sciences, and Epidemiology), the clinical director for cancer and clinical support at Castle Hill Hospital, consultant haematologists, specialist haematology nurses, consultants in palliative medicine, specialist palliative care nurses, GPs and patient representatives. The aim of the project is to examine specialist palliative care (SPC) referrals in patients with haematological malignancies. Special attention was given to the investigation of the patient pathway, the palliative care input and the transition to a palliative approach. All the data related with the SPC referrals and with the transition from life prolonging to palliative approaches to care were routinely collected by well-trained research nurses. This was done for all newly diagnosed patients throughout the HMRN area. In total, approximately 350 medical notes of haematology patients who were diagnosed at two of the HMRN hospitals (York and Hull) between 1st April 2005 to 31st March 2008 and had died within the HMRN area by 2009 were examined and transcribed in detail.

Among all the collected data, only 20 patients were found to have been diagnosed with AML / APML. Information such as delivery of medication, admission/discharge dates, units of blood and platelet transfusions, and the names of involving specialist teams were recorded on a day-to-day basis by means of a bespoke calendar approach (which was used extensively and extremely successfully in previous research projects). The above data were put in a database called 'palliative care database (PCD)'. Screenshots and illustrations of the followed calendar approach (mentioned above) are shown in **Figure 3.10** and **Figure 3.11**.

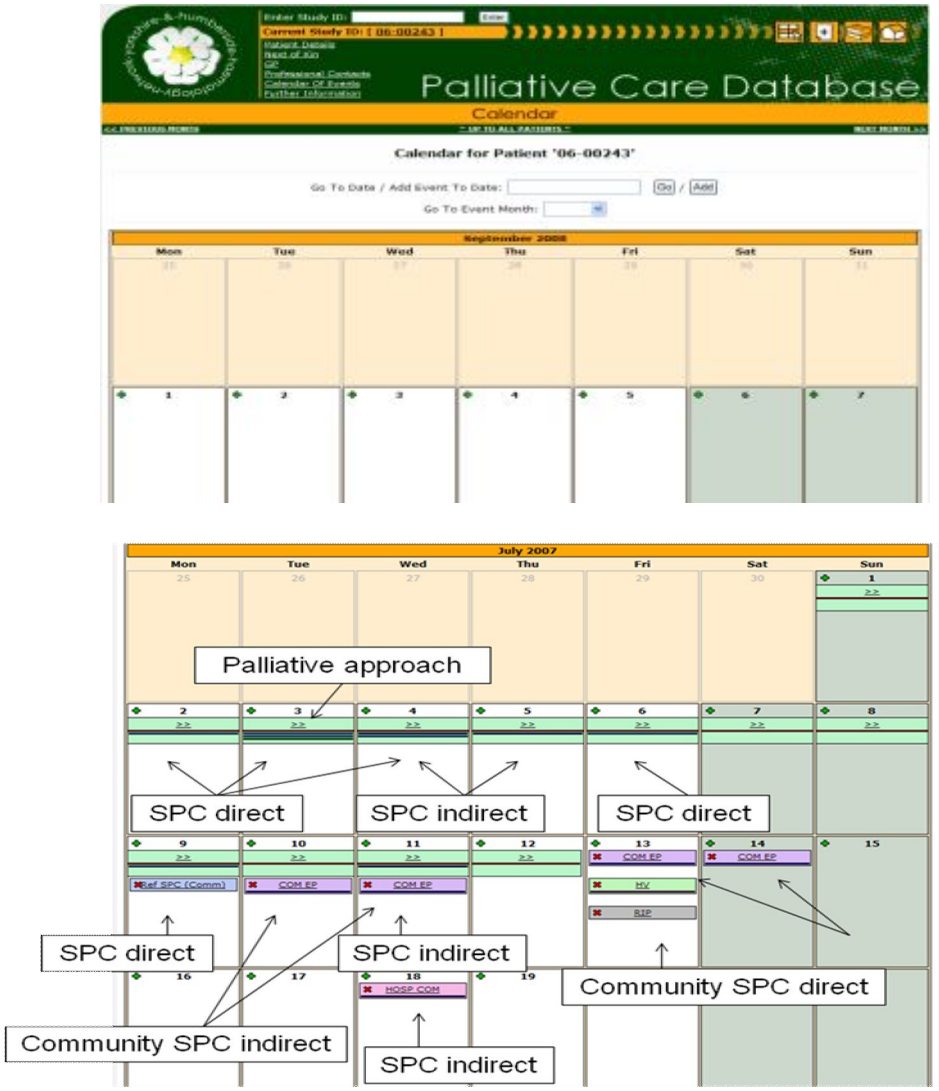


Figure 3.10 Screenshots of bespoke palliative care database created to managed data abstracted using the day-to-day calendar approach

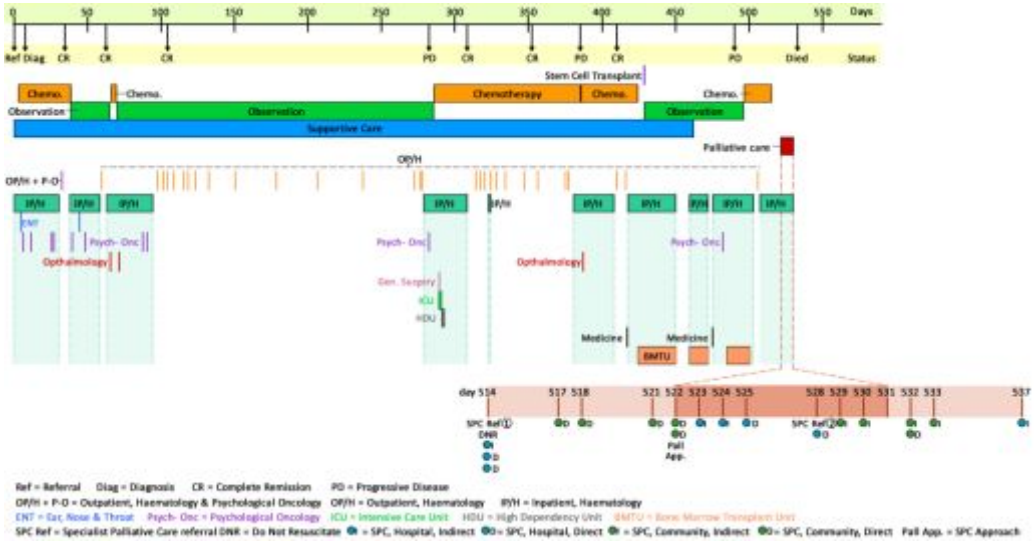


Figure 3.11 Figure 3.10 Analyzed day-to-day data collected using the calendar approach

3.10.2 Data extraction

Although the Palliative Care Database provides a large volume of detailed clinical information on a calendar basis, unfortunately the limited number cases (20 AML / APML cases) restricted the possibility of data use for further analyses. In the current study, only the transfusion relevant details from the records of the aforementioned 20 patients were used for further analysis and for cost estimation at later stages. This includes information related to units of transfusion (blood and platelet) and transfusion frequency. The rest of the clinical information was omitted for two reasons. Firstly, most of the clinical information could also be found in the HMRN database except the transfusion details. Secondly, the case numbers were not high enough to cover all the treatments and conditions of the study population (239 patients from YHHN database). Therefore, it was very difficult to predict the treatment pattern or the patients' conditions, such as the complication rate or the hospital stays for specific treatments, by using the detailed information from palliative care databases.

Moreover, based on the infrastructure of HMRN and with the research nurses' assistance, detailed information of the 20 AML/APML patients were further extracted 'from diagnosed to death'. Therefore, the details of transfusion not only could be completely portrayed during the end-of-life period, which was the study time period of the original project, but also they could cover the whole treatment pathway time period, in such a way as the clear picture of delivery of transfusion could be revealed and analyzed.

3.10.3 Missing data

Since all information was extracted in a very detailed way and was continuously audited, no missing data were found to exist in the Palliative Care Database.

3.10.4 Database cleaning

In the palliative care database all the events are recorded by a day-to-day calendar approach with transfusion details not being an exception to this. All the units that had been transfused to patients were recorded unit by unit and day by day to the palliative care database. Since the transfusion unit and the frequency were the main concerns, three steps of data cleaning were applied to the palliative care database. This was to have an undisturbed database with no duplicated events in order to be use as a base for further analyses.

The first step in the data cleaning process was to keep all the transfusion-related information, such as the transfusion receiving date and transfusion unit. All irrelevant or unnecessary information was then removed from the database.

The second step in data cleaning was to summarize all the transfusion details, including the details of delivered units which were presented separately and hospital stays, into one record per transfusion. This ensured that one transfusion would only have one record. Also, the summarized information provided a clearer view of how each transfusion was given, including the input and time spend.

The third step in data cleaning was to keep the relevant transfusion records. Based on the transfusion time period information from the HMRN database, only records related with transfusion that occurred during the recorded time period were kept. Records of transfusions that occurred outside the given time period were removed, although these transfusions were actually given to patients. The reason for this was to ensure that only the transfusions that were actually delivered in the time period were considered while calculating the transfusion frequency (for later extrapolation use). This was expected to enhance the accuracy of the predictive frequency, although some of the transfusion information could have been lost because of this approach.

After the above 3 steps of data cleaning were carried out, the palliative care database was prepared for transfusion frequency and unit use analysis.

3.11 Preliminary analysis methods for the palliative care database

All statistical analyses and data manipulation, such as the summing of the duplicated data and the calculation of the transfusion frequency, were carried out using the SAS/Stats application (SAS software program package, version 8.02, SAS Institute, Cary, NC)

3.11.1 Unit of transfusion

Unit of transfusion is an important piece of information in order to reflect the input of the transfusion. To summarize how many blood units and platelet units were provided during each transfusion, the average unit was used in the results presentation.

3.11.2 Transfusion Frequency

Transfusion frequency is an important piece of information for cost calculation, especially in cases where the number of transfusions was not available. As research nurses working with the HMRN database tended to record only the first and the last dates of transfusions, the detailed number of transfusion was not obtainable. There was no further information regarding either the actual date for each transfusion or the number of transfusions between the first and last transfusion that could be gained from the HMRN database. Therefore, the frequency information that was extracted from the 20 AML/APML cases in the palliative care database was used as an alternative way to extrapolate the transfusion frequency of the study population (239 patients).

Based on clinical suggestions and considering that the transfusion should only occur during the 'disease time' (which means patients would not receive transfusion when they are in remission), the patients were firstly divided into two groups: patients who had achieved remission and patients who had not done so. Furthermore, each group was further divided into couples of subgroups according to its characters, in order to enhance the prediction power of transfusion frequency. This is further discussed in the following paragraphs.

The group comprised of patients who had achieved remission, was further divided into two sub-groups according to the treatment response time: 'quick response' and 'slow response'. The reason for dividing the group into these sub-groups was that the response time could reflect the disease severity, something that was also relevant to the transfusion frequency. The cut-off time of deciding good or poor response was set to 2 months according to expert suggestions.

The group comprised of patients who had not achieved remission was also further divided into two sub-groups according to the disease severity: those who died quickly and those who did not. The reason for this was that the rapid progress normally leads to more transfusions in a short time. The cut-off time for deciding whether a patient belonged to the rapid progress group or not was set to two months based on expert suggestions.

After classifying patients into four subgroups, the transfusion frequency was calculated and analyzed by each sub-groups.

3.12 Overview of the work done on the PCD database

The PCD database was used for extrapolating transfusion frequency. In order to obtain the relevant information, the PCD database was cleaned in three steps (discussed in sections 3.10). The whole process and number of cases are illustrated in **Figure 3.12**.

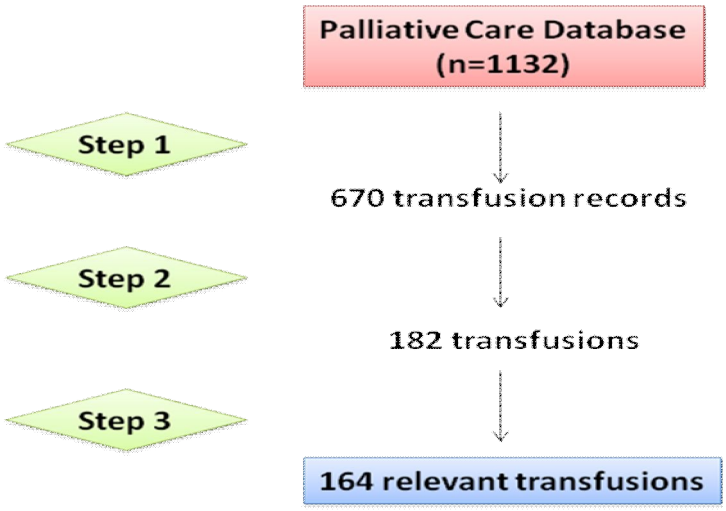


Figure 3.12 Illustration of data handling process on PCD database

After the study database was set up, a number of preliminary analyses were conducted (please refer to section 3.11). The relevant results are presented and discussed in the next chapter (chapter 4).

3.13 Integration of all study databases

3.13.1 Data Merging

Although much of the useful information of each database was extracted, analyzed, and presented earlier (please refer to previous sections of this chapter), it was expected that some extra information could be revealed or extracted if the databases were integrated. This was especially prominent with the clinical evidence that required the treatment phase information (extracted from the HILIS database) in order to be defined. For this reason, database integration was conducted. The integration involved the combination of data from three different datasets (HMRN database, HILIS database, and palliative care database) by matching the patients studies ID, removing the duplicated information, and, finally, keeping the relevant information in the database. After integrating the information from the three databases, the data were ready for advanced analysis.

3.13.2 Advanced Analysis Methods for the integrated database

In order to provide clinical information that is both meaningful and understandable by haematologists/clinical staff, the analyses were divided into two domains. A breakdown of the details of each analysis in each domain follows:

a. Treatment types / options in each treatment phase

In section 3.5.1, the relationship between types of treatment and numbers of treatment was discussed, and details can be seen in next chapter (chapter 4). However, the number of treatments is not clinically meaningful. To make the results significant to haematologists/clinical staff, the type of treatment was further analyzed by each treatment phase, which was derived from supplementary database: HILIS. The frequency of each treatment in each phase was presented in numbers.

b. Treatment response and prognosis

- Complete remission rate

  Complete remission rate (CRR) is one of the indicators that could be used not only to reveal how effective a treatment is, but also to obtain the number of patients who responded to the treatment. In the current work, patient characteristics such as diagnosis, age, and gender, were used in order to test the kind of characteristics that

were more likely to lead patients to achieve remission. As for the primary induction treatment type, it was used to test the kind of treatment that was more effective.

- Relapse

Relapse is the reoccurrence of the disease after remission. It is another indicator that could be used to reveal the effectiveness of a treatment, the patients' response to the treatment, and the severity of a disease. In the context of the current study, this was achieved by comparing the first relapse rates between patient characteristics and the primary induction treatment type. Similarly to the CRR analysis, the diagnosis, age, gender, and primary induction treatment type were used for analysis. Also, regression was conducted in order to determine whether any of these factors were associated with the relapse rate (i.e. what kind of patient or what kind of treatment was more likely to make patient relapse after remission)

3.14 Summary

The current chapter involved the detailed description of data handling for the main study databases. The latter were thoroughly cleaned and all missing data were handled carefully in order to be ready for use for analysis at later stages of the current study. Furthermore, additional data from other sources were integrated into the study databases (place of death, hospital stays, and antibiotic days). The above data manipulation resulted in 1025 relevant treatment events from the HMRN database, 1767 relevant test reports from the HILIS database, and 164 relevant transfusion records from the PCD database, which were analyzed and prepared for further use. The related results are further discussed in the following chapter (chapter 4).

Chapter 4 Analysis Results of Study Databases

HMRN, HILIS, and PCD databases

CHAPTER 4 ANALYSIS RESULTS OF THE STUDY DATABASES

Database 1: HMRN database

243 patients were identified as newly diagnosed with AML and APML between 1st September 2004 and 1st September 2006. However, according to the inclusion and exclusion criteria, only 239 confirmed cases were finally retained for the current study. These cases comprised of 1025 treatment events (from 215 AML patients and 24 APML patients).

4.1 Demographic characteristics of study population

Summaries of the characteristics of the study population (the aforementioned 239 AML/APML patients) are presented in the following paragraphs, while relevant details, such as numbers and percentages, are shown in below.

4.1.1 Diagnosis

As shown on **Table 4.1**, the most common subtype domain of diagnosis was the AML NOS. More specifically, nearly 83% of cases were diagnosed with 'AML NOS', while the rest of the subtypes for AML accounted for 7.53%. In relation to APML patients, 'APML t(15;17)(q22;q11-12)' accounted for approximately 10% of the total cases. The distribution was in line with previous reports both in the UK and worldwide [166-169].

4.1.2 Gender

As shown in **Table 4.1**, 122 female patients (51.05%) and 117 male patients (48.95%) were identified in the current study. AML and APML accounted for 90.16% and 9.84% respectively for female patients, while for male patients 89.74% and 10.26%. This result was slightly inconsistent with the results of other previous studies [167, 168, 170-172]. Generally, AML/APML was more common in men than women, but the difference was not significant [167, 168, 170-172]. It is suggested that two factors contributed to the above. Firstly, four patients that were excluded from the study because of un-obtainable notes, were all male. Secondly, a higher number of male patients was observed among the children (<18 years old) that were excluded from the study. This suggests that no significant gender differences would exist if all the patients were included.

Table 4.1 Demographic characteristics of study population

	Frequency	Percentage
Gender		
Male	**117**	**48.95**
AML	105	89.74
APML	12	10.26
Female	**122**	**51.05**
AML	110	90.16
APML	12	9.84
Diagnosis		
AML	**215**	**89.96**
AML NOS	197	82.43
AML NOS	153	64.02
AML arising from transformation of MDS	10	4.18
AML arising from transformation of MPD	1	0.42
AML with adverse cellular features	32	13.39
AML with multi-lineage dysplasia	1	0.42
AML with core binding factors	10	4.18
AML inv(16)(p13;q22)	5	2.09
AML t(8;21)(q22;q22)	5	2.09
AML - probable therapy related	6	2.51
AML - probable therapy related	6	2.51
AML with MLL (11q23) rearrangement	2	0.84
AML with MLL (11q23) rearrangement	2	0.84
APML	**24**	**10.04**
APML t(15;17)(q22;q11-12)	24	10.04
Age	**Mean: 63.62 (19-97), SD=18.11**	
<60	**86**	**35.98**
AML	67	28.03
APL	19	7.95
60≦y<75	**73**	**30.54**
AML	72	30.13
APL	1	0.42
≧75	**80**	**33.47**
AML	76	31.8
APL	4	1.67
Death (Mortality rate)		
Yes	**189**	**79.08**
At home	22	11.70
At hospice	23	12.23
At hospital	137	72.87
At nursing residential home	6	3.19
No	**50**	**20.92**
History of antecedent haematological disorder		
Yes	17	7.11
No	222	92.89
Total		**239 patients**

4.1.3 Age

Age was an important risk factor for AML. According to the results of the current study, old patients (≥60 years old) were more likely to have AML/APML than young adult patients (<60 years old). However, further examination showed that the age distributions of AML and APML varied significantly. In AML patients, the incidence of AML

increased with age. AML patients over 75 years of age accounted for 31.8% and those between 60 and 75 for 30.13%, while younger AML patients (<60 years old) accounted for 28.03%. Unlike the distribution of AML, most of the APML patients (19 out of 24 APML patients) belonged in the young age group (18-60 years old). APML patients over 60 years of age only accounted for 20.83% of all the APML patients. This result is consistent with the results of other studies [166-169, 171].

4.1.4 Cases of fatality (percentage of death)

The percentage of death of AML/APML was very high. As shown in **Table 4.1**, 79% patients died within a maximum of five years of follow-up (the median number of year of follow-up was 4 years). After cross-analysis, the relationships between the mortality rate and several patient characteristics were identified (**Table 4.2**).

Table 4.2 Mortality rate analysis

	Frequency	Percentage (among groups)	Percentage (within group)
Age			
AML: <60	44	23.28	65.67
60≦y<75	63	33.33	87.50
≧75	75	39.68	98.68
APML: 18≦y<60	4	2.12	21.05
≧60	3	1.59	60.00
Deprivation			
Deprivation group 1 (most affluent)	40	21.16	74.07
Deprivation group 2	34	17.99	77.27
Deprivation group 3	49	25.93	81.67
Deprivation group 4	35	18.52	87.50
Deprivation group 5 (most deprived)	31	16.40	75.61
Diagnosis			
AML NOS	168	88.89	85.28
AML with core binding factors	7	3.70	70
AML - probable therapy related	6	3.17	100
AML with MLL (11q23) rearrangement	1	0.53	50.00
APML t(15;17)(q22;q11-12)	7	3.70	29.17
Primary induction therapy			
Intensive treatment with induction intent	90	47.62	64.75
Intensive treatment without induction intent	39	20.63	97.50
Support or palliative care only	60	31.75	100.00
	189		

As shown in **Table 4.2**, the mortality rate of AML (84.19%) was much higher than this of APML (29.17%). Moreover, older patients appeared to have poorer prognoses, both when they were diagnosed with AML and with APML. It is suggested that this could be because older patients were either less likely to respond well to the treatments or less able to undertake/tolerate the treatments as a whole. This result is also in line with the results of previous studies [166-169, 171]

Table 4.2 also shows the mortality rate results by primary induction therapy and deprivation. In regards to the primary induction therapy, the intensive treatments with induction intent (such as clinical trials or some intensive chemotherapies) provided a better prognosis for patients (lower mortality rate: 64.75%). Patients who only received supportive or palliative care had the worst prognosis (mortality rate was 100%). The results showed that AML/APML could be very fatal if left untreated or treated without induction intent.

As shown in **Table 4.2**, the examination of the relationship between mortality rate and deprivation, uncovered an existing trend: increasing deprivation corresponded to higher mortality rates. The difference ranged from 74.07% for the most affluent group (group 1) to 87.50% for the second most deprived group (group 4). It is worth noting that the most deprived group (group 5) was not consistent with this trend. A possible explanation was that, compared to other groups, the most deprived group contained higher percentages of APML patients with lower mortality rate, compared to AML patients (as mentioned above).

4.1.5 Place of death

"Place of death" information is a useful factor for determining the dying cost, as well as for providing a broad picture of the location AML/APML patients received dying care during the final stages of their life. **Table 4.1** lists the percentages of each possible place. Unsurprisingly, most of the patients died in hospitals (72.87%), a lower number in hospice or nursing residential homes, while only 11.70% of the patients died at home.

4.1.6 Antecedent hematological disorder and therapy related AML

Antecedent hematological disorder (AHD) and therapy related AML has been one of the most important AML/APML prognostic factors for years. In general, patients with a history of antecedent haematological disorder (MDS) or diagnosed with therapy related AML are more likely to have poor prognosis, such as lower CR rate and higher relapse rate after achieving remission [24, 173, 174]. As shown in **Table 4.1**, there were 17 patients (7.11%) with antecedent haematological disorders and 6 patients diagnosed with therapy related AML. Cross-analysis showed that the aforementioned results were in line with the results of previous studies.

4.2 Number and type of treatment

4.2.1 Number of treatments

'Number of treatments' information can reveal the level of complexity and difficulty of the treatment for AML/APML. After the removal of treatments with non-curative or life-prolong intent, the results showed that there were 20.92% of patients receiving either only the observation or no treatment whatsoever. For patients who had received the treatments after being diagnosed, the number of treatments varied significantly. Most of the AML/APML patients received at least one treatment (79.08%), while around half of the patients (46.44%) received two treatments. 24.69% of the patients received three treatments, while the percentage decreased dramatically after this point, with only 3% (4 patients) of the patients having received more than 10 different treatments. The maximum number of treatment was found to be 11. The relevant details can be found in **Table 4.3**.

Table 4.3 Numbers of the treatments

	Number	Percentage (%)	Subtractive number	Subtractive percentage (%)
no treatment (follow-up only)	12	5.02		
Supportive care only	38	15.90		
1	78	32.64	189	79.08
2	52	21.76	111	46.44
3	15	6.28	59	24.69
4	14	5.86	44	18.41
5	7	2.93	30	12.55
6	6	2.51	23	9.62
7	5	2.09	17	7.11
8	5	2.09	12	5.02
9	3	1.26	7	2.93
10	1	0.42	4	1.67
11	3	1.26	3	1.26
Total	**239**	**100**		

4.2.2 Treatments

Treatments information (regimen and drugs) is useful both for understanding the haemotologists' clinical decisions and for costing. The results were presented in 4 different parts: regimens for chemotherapy, regimens for clinical trial, other types of treatment, and primary induction treatments. Relevant details can be found in the following paragraphs.

a. Regimen for chemotherapy

Chemotherapy accounted for 32.50% of a total of 763 treatment episodes. It was the second most commonly used treatment for AML/APML. The variety and the frequency of the regimens are discussed in the following sections. Relevant details can be found in **Table 4.4**, **Appendix 4.1** and **Appendix 4.2**.

Table 4.4 Regimen for chemotherapy

	AML	APML	**Total**	
	No.	No.	**No.**	**Percentage (%)**
Chemotherapy	232	15	**247**	**32.50**
ADE	18	1	19	3.85
AraC(HD)	11	-	11	2.23
AraC(HD) + Mylotarg	2	-	2	0.40
AraC(LD)	37	2	39	7.89
Clofarabine	2	-	2	0.40
DA	38	1	39	7.89
DA + Mylotarg	1	-	1	0.20
FLA	4	-	4	0.81
FLAG	18	-	18	3.64
FLAG-Ida	5	-	5	1.01
FLAG-Ida + Mylotarg	1	-	1	0.20
HAM	1	-	1	0.20
MACE	9	1	10	2.02
MidAC	12	-	12	2.43
Mini-MIDAC	3	-	3	0.61
Amsacrine	1	-	1	0.20
Arsenic trioxide (ATO)	-	2	2	0.40
Campath	1	-	1	0.20
Mylotarg	-	1	1	0.20
Daunorubicin	1	-	1	0.20
Cyclophosphamide	5	1	6	1.21
Cyclophosphamide / MESNA	2	-	2	0.40
ETI	2	-	2	0.40
FC	6	-	6	1.21
Fludarabine	2	-	2	0.40
Vincristine	1	-	1	0.20
Melphalan	3	-	3	0.61
ATRA	-	3	3	0.61
Anagrelide	1	-	1	0.20
Clopidogrel	1	-	1	0.20
Aspirin	2	-	2	0.40
Hydroxycarbamide	39	-	39	7.89
Hydroxycarbamide + Aspirin	1	-	1	0.20
Chelating agent	2	-	2	0.40
MRC like	-	1	1	0.2
Spanish like	-	2	2	0.4

- **Types and frequency**

The 5 most commonly used chemotherapy regimens given to AML patients were (from the highest to the lowest): Hydroxycarbamide (39 episodes), DA (38 episodes), AraC –low dose (37 episodes), FLAG (18 episodes), and ADE (18 episodes). They accounted for 64.66% of the total chemotherapy episodes. It is worth noting that although Hydroxycarbamide and AraC –low dose were found to be the majority, they were mainly used for stabilizing the disease (not for induction intent). This could be an explanation for the exceptionally high frequencies. Another finding worth noting is that some regimens not suggested by the guideline or by the HMRN data manual were identified in the HMRN database. They were either used rarely to treat AML (such as Amsacrine and Clofarabine that are mainly used for ALL), or for treating the complications after AML treatments (such as chelating agent for overflow of iron, and Anagrelide for rash). Also, a new, but rare, way to treat AML in the UK was identified: HAM (cytarabine 0.5 g/m2/12 h i.v., days 1–3; mitoxantrone 10 mg/m2 i.v., days 2 and 3). In total, these regimens accounted for 4.74% (**Table 4.4**).

Most of APML patients were treated in clinical trials not chemotherapy outside trial conditions. The most commonly used chemotherapy regimens (outside clinical trial) were ATRA, Arsenic trioxide (ATO), MRC approach like regimen, and Spanish approach like regimen. The regimen name ‘like’ was given when a patient was not eligible for entering clinical trial (usually because patients were too old), but received the same regimens as in clinical trial. These regimens accounted for 66.67% of total chemotherapy regimens. However, as shown in **Table 4.4**, a number of regimens that were normally used on AML patients were also used on APML patients, such as ADE, DA, and MACE. Although this was unusual, but the frequency of usage was very low (usually each of the regimens appeared only once). Therefore, it was decided these treatment episodes to be kept in this study.

- **Number of occurrence on the timeline**

Appendix 4.1illustrates the regimen usage on a timeline. Most of the chemotherapy regimens were used for the first-five-time treatment episodes, and especially for the first-time treatment (34%). For the first-time chemotherapy, AraC (LD), DA and Hydroxyurea were the most commonly used regimens, with each of them accounting for more than 25% in the first-time treatment group. After the first-5-time treatments, the usage of chemotherapy decreased significantly, and none of the regimens appeared more than 4 times in such late stages. It is worth noting that Hydroxyurea was the only regimen

that appeared in all phases on the timeline, as it was used for stabilizing the disease.

Similarly to the chemotherapy usage for AML patients, in the case of APML patients, chemotherapy was only used for the first-five-time treatment episodes. The highest usage was for first-time treatment (40% of total chemotherapy episodes) and the used regimens were ATRA, MRC approach like and Spanish approach like. The rest of the regimens only appeared once or twice between 2nd and 5th treatments (**Appendix 4.2**).

b. Regimen for clinical trial

Clinical trial was the third most commonly used treatment for AML/APML patients. In total, clinical trials accounted for 23.56% of the total treatment episodes, and they were mainly used as induction treatment. The regimen options of clinical trials were limited. Basically, they could be divided into two main groups: AML 14 and AML15, the trials open for newly diagnosed patients between 2004-2006. The variety and the frequency of regimens are discussed in the following paragraphs, while all the relevant details are presented in **Table 4.5**, **Appendix 4.1**, and **Appendix 4.2**.

Table 4.5 Regimen for chemotherapy

	AML	APML	**Total**	
	No.	No.	**No.**	**Percentage (%)**
Clinical trial	155	25	**180**	**23.56**
AML 14 AraC	4	-	4	0.81
AML 14 AraC + Mylotarg	1	-	1	0.20
AML 14 D35 C200	3	-	3	0.61
AML 14 D35 C400	1	-	1	0.20
AML 14 D50 C200	4	-	4	0.81
AML 15 ADE	15	-	15	3.04
AML 15 ADE + Mylotarg	9	-	9	1.82
AML 15 AraC	20	-	20	4.05
AML 15 AraC + Mylotarg	7	-	7	1.42
AML 15 DA	16	-	16	3.24
AML 15 DA + Mylotarg	6	-	6	1.21
AML 15 FLAG-Ida	23	-	23	4.66
AML 15 FLAG-Ida + Mylotarg	13	-	13	2.63
AML 15 MACE	10	-	10	2.02
AML 15 MACE + Mylotarg	9	-	9	1.82
AML 15 MidAC	14	-	14	2.83
AML 15 MRC approach	-	12	12	2.43
AML 15 Spanish approach	-	12	12	2.43
AML 15 Spanish Maintenance	-	1	1	0.2

- **Types and frequency**

As shown in **Table 4.5**, most of the patients who agreed to join clinical trial were assigned to AML 15 trial (91.61%), while only 8.39% of the cases were assigned to AML 14 trial. In the HMRN database, the most common trial arms for AML 15 trial were: FALG-Ida, AraC, and ADE. FLAG-Ida arm (with and without mylotarg) accounted for 23.23%, and AraC and ADE arms accounted for 17.42 and 15.48% respectively.

Table 4.5 shows that all of the APML patients who agreed to join clinical trial were assigned to AML 15 trial. Furthermore, only two trial arms were given to APML patients: AML 15 APL (MRC) and AML 15 APL (Spanish). The percentage of the AML 15 APL (MRC) arm was 47.83%, while for AML 15 APL (Spanish) arm it was 52.17%.

- **Numbers of occurrence on the timeline**

Most of the clinical trial arms (74.19%) took place in the first-two-time treatment. Only AML 15 AraC, MACE, and MidAC took place after the 2nd treatment, as they were the second-line arms of the clinical trial. The results were consistent with the clinical guideline (**Appendix 4.1**).

Similarly to clinical trial arms for AML patients, the trial arms for APML patients were also given during the first occurrences of the treatments. 17 out of 28 arms took place in the first-time treatment, while the rest occurred between the 2nd to the 4th time of treatments. No trial arms were found to have occurred later than the 4th time (**Appendix 4.2**).

c. Other treatments

Treatments other than chemotherapy and clinical trial accounted for 39.30% of the total treatment episodes (refer to **Table 4.6**).

Table 4.6 Other treatments

	AML	APML	Total	
	No.	No.	No.	Percentage (%)
Supportive care	225	28	253	33.29
Erythropoietin	3	-	3	0.39
G-CSF	43	5	48	15.70
Transfusion	172	18	190	24.87
Steroids	9	5	14	1.83
Immunosuppressive	6	-	6	0.79
Palliative care	31	2	33	4.45
Radiotherapy	14	-	14	1.83
Transplantation	13	-	13	1.70
Splenectomy	2	-	2	0.26
Venesection	3	-	3	0.39
No treatment	10	-	10	1.31
Refused treatment	2	-	2	0.26
Total	693	70	764	%

Supportive care was the most commonly used treatment for AML patients (especially transfusion and G-CSF), among all types of treatments. It accounted for 58.50% (transfusion) and 14.63% (G-CSF). Palliative care followed with 10.55%, while the percentage for the rest of the treatments in this group was not very high. It is worth to note that, in this group, 12 patients were found to be either receiving no treatment or refusing treatment altogether.

In relation to the APML patients group, it was observed that only a small number of treatments were given. In this group, similarly to the case of AML patients, transfusion was the most commonly used treatment (60%), followed by steroids and G-CSF with 33.33%. No APML patients were found to receive no treatment or to refuse treatment.

Most of the treatments in this group occurred in the later phases of the timeline, as they were not carried out with curative intent. Details related with the occurrence of treatment on the timeline could be found in **Appendix 4.1** and **Appendix 4.2**.

d. Types of primary induction treatment

Primary induction treatment has been considered to be relevant to patient prognosis for years. Primary induction treatment was manually identified for each patient, and the related analysis results are shown on **Table 4.7**. Relevant details are also discussed in the following paragraphs.

Table 4.7 Primary induction treatments

	AML				APML				Total	
	18-60 yr	60-75 yr	>75 yr		18-60 yrs	60-75 yr	>75 yr		Number	Percentage
Intensive treatment with induction intent									**139**	**58.16**
Chemotherapy	17	22	3	42	2	-	4	6	48	20.08
ADE	2	1	-	3	-	-	-	-	3	1.26
ATRA	-	-	-	-	-	-	3	3	3	1.26
DA	13	18	2	33	1	-	-	1	34	14.32
ETI	-	1	-	1	-	-	-	-	1	0.42
Etoposide	-	1	-	1	-	-	-	-	1	0.42
FC	1	-	-	1	-	-	-	-	1	0.42
FLAG	1	1	-	2	-	-	-	-	2	0.84
MRC like	-	-	-	-	1	-	-	1	1	0.42
Spanish like	-	-	-	-	-	-	1	1	1	0.42
Vincristine	-	-	1	1	-	-	-	-	1	0.42
Clinical trial	47	22	5	74	16	1	-	17	91	38.08
AML 14 AraC	-	1	4	5	-	-	-	-	5	2.09
AML14 DA	-	8	1	9	-	-	-	-	9	3.77
AML 15 AraC	1	-	-	1	-	-	-	-	1	0.42
AML 15 ADE	15	1	-	16	-	-	-	-	16	6.70
AML 15 DA	12	3	-	15	-	-	-	-	15	6.28
AML 15 FLAG-Ida	19	9	-	28	-	-	-	-	28	11.72
AML 15 MRC	-	-	-	-	9	0	0	9	9	3.77
AML 15 Spanish	-	-	-	-	7	1	-	8	8	3.35
Intensive treatment without induction intent	**1**	**9**	**30**	**40**	**-**	**-**	**-**	**-**	**40**	**16.74**
AraC (LD)	1	7	19	27	-	-	-	-	27	11.30
Hydroxycarbamide	-	2	11	13	-	-	-	-	13	5.44
Supportive or palliative care only	**2**	**19**	**38**	**57**	**1**	**-**	**-**	**-**	**60**	**25.10**
Observation	2	4	4	10	-	-	-	-	10	4.18
Supportive care	-	14	25	39	-	-	-	-	39	16.32
Palliative care	-	1	9	10	1	-	-	-	11	4.60
Total	**67**	**72**	**76**	**215**	**19**	**1**	**4**	**24**	**239**	**100**

As shown in **Table 4.7**, treatment with induction intent was the most common treatment for AML patients, especially for the young adult patients (18-60 year-old). Among all the regimens and trial arms, chemotherapy DA and clinical trial arm FLAG-Ida were the most common. They accounted for 78.57% and 37.84% respectively. Treatment with non-induction intent was commonly used as well, but less often than supportive care and palliative care. Both treatment with non-inductoin intent and supportive/palliative care were mainly given to older patients, especially patients older than 75 years of age. This might be because older patients showed poor response and decreased tolerance to the intensive curative treatment. Thus, treatment with non-induction intent and supportive/palliative care were given as alternatives

In **Table 4.7**, it was observed that intensive treatment with induction intent was the only induction treatment option given to APML patients, with the exception of one patient who received palliative care. Among all the induction intent treatments, clinical trial was the most commonly used (70.83%), especially in the young adult patient group (18-60 years old). MRC approach arm and Spanish approach arm were also common, while chemotherapies (outside trial) only accounted for 25% of the induction treatment, and were mainly used for old patients (>60 years old) who were unable to enter the clinical trial.

4.3 Treatment duration

For various purposes, the treatment duration related information was recorded in different forms and stored in different locations. In order to classify information from different sources, the treatment duration was categorized into 3 main groups: treatment time (duration of medication delivery derived from the HMRN database), hospital stays (actual hospital stays derived from subset of HMRN database), and antibiotics days (days for complication treatment derived from subset of HMRN database).

4.3.1 Treatment time

Treatment time is information related with the duration of medication delivery. Since the treatment time did not necessarily contain one cycle/course of treatment, the possible number of courses was determined according to the treatment time, on the basis of known cases (**Table 4.8**). For example, as shown in **Table 4.8**, 23 treatment episodes that ranged from 1 to 12 days contained one course of ADE, while in 12 treatment episodes that ranged from 37 to 74 days contained 2 complete cycles of ADE. This summary provided a broad view of how the treatment time was recorded. Also, it was expected to be useful for imputation of missing treatment dates.

Table 4.8 Summarized treatment time derived from the HMRN database

Type of treatment	Treatment time			
	Number of course	Number of episode for calculation	Treatment time (Days)	Means
Chemotherapy and clinical trial				
ADE	1	23	1-12	9
AML 15 ADE	2	12	37-74	
AML 15 ADE + Mylotarg	missing	8		
AraC (HD)	1	30	4-29	8
AML 15 AraC	2	6	36-72	
AML 15 AraC + Mylotarg	4	1	221	
	missing	3		
AraC (LD)	1	24	1-38	10
AML 14 AraC	2	4	43-49	
	3	4	59-77	
	4	3	92-116	
	5	2	124-125	
	6	1	147	
	10	1	182	
	missing	5		
Clofarabine	1	1	5	5
	2	1	38	

DA	1	39	2-41	11
AML 14 D35 C200	2	14	42-74	
AML 14 D50 C200	3	4	88-112	
AML 14 D35 C400	4	1	152	
AML 15 DA	missing	12		
AML 15 DA + Mylotarg				
FLA	1	1	5	5
	2	2	42-48	
	missing	1		
FLAG	1	11	4-11	6
	2	3	41-55	
	3	2	76-118	
	missing	2		
FLAG-Ida	1	18	5-11	6
FLAG-Ida + Mylotarg	2	11	31-101	
AML 15 FLAG-Ida	Missing	13		
AML 15 FLAG-Ida + Mylotarg				
HAM	missing	1		
MACE	1	17	3-9	6
AML 15 MACE	2	1	38	
AML 15 MACE + Mylotarg	Missing	11		
MidAC	1	24	1-10	5
Mini MidAC	2	2	47-58	
	missing	3		
MRC approach	1	5	4-11	8
	2	-	-	
	3	2	69-79	
	4	5	105-141	
Spanish approach	1	3	3-15	9
	2	2	33-99	
	3	2	148-189	
	4	5	216-917	
	Maintenance	1	732	
	missing	2		
Amsacrine	-	1	1	1
Arsenic trioxide	-	2	32-33	33
Campath	-	1	6	6
Mylotarg	missing	1		
Daunorubicin	-	1	38	38
Cyclophosphamide	-	5	1-2	2
	missing	1		
Cyclophosphamide / MESNA	-	2	2	2
ETI	-	2	67-206	137
FC	-	4	1-29	10
	missing	2		
Fludarabine	-	1	2	2
	missing	1		
Vincristine	-	1	4	4
Melphalan	-	3	14-53	30
ATRA	-	3	3-40	16
Anagrelide	-	1	5	5
Clopidogrel	-	1	7	7

Aspirin	-	1	35	35
	missing	1		
Hydroxycarbamide	-	23	1-757	67
Hydroxycarbamide / Aspirin	missing	17		
Chelating agent	-	1	593	593
	missing	1		
Supportive care				
Erythropoietin	-	2	15-274	145
Steroids	-	7	4-783	213
	missing	6		
Transfusion	-	101	1-1424	184
	missing	89		
G-CSF	-	26	1-805	86
	missing	21		
Immunosuppressive treatment	-	3	1-1310	610
	missing	3		
Radiotherapy	-	12	1-22	4
	missing	2		
Stem cell transplantation	once	9	1	1
	missing	4		
Splenectomy	once	2	1	1
Palliative care	-	16	2-34	12
	missing	17		
Venesection	-	3	99-888	479
No treatment	-	10		
Refused treatment	-	2		
Total		776		

4.3.2 Hospital stays and antibiotic days

Actual hospital stays (also known as 'bed days') information is very important for cost calculation. Unfortunately, this information was not required to record in the HMRN database, and, thus, 30 additionally available subset medical notes were used to obtain hospital stays and antibiotics day information. This information is summarized in **Table 4.9** below.

As an example of the above, from 11 episodes of AML 15 ADE clinical trail arms, 1st cycle took an average of 30 days of stay in the hospital (please refer to **Table 4.9**). Among these 30 days, antibiotics were given for 14 days in total. In the 2nd cycle, the average hospital stays duration was 5 days shorter (25 days in total). Antibiotics were given in 7 out of 25 days, while the average interval between 1st and 2nd cycle was 13 days. This summary was also very useful for the imputation of missing treatment dates that was carried out at later stages of the current work. However, it must be stressed here that part of the actual hospital stays information of the trial arms was derived from a limited

number of treatment episodes, due to data availability constraints. For example, AraC (HD), AraC(LD), MRC and Spanish approach were all derived from only 2 treatment episodes. Therefore, it could be useful that the reliability of these results to be further checked by experts or haematologists.

Table 4.9 Hospital stays and antibiotic days derived from additional information of 30 medical notes

	Cycle 1			Interval		Cycle 2			Interval	
	No. of event	Average hospital stays (day)	Average antibiotic days (day)	No. of event	Average interval days (day)	No. of event	Average hospital stays (day)	Average antibiotic days (day)	No. of event	Average interval days (day)
AML 15 ADE	11	30	14	10	13	10	25	7		
AML 15 AraC (HD)	2	32	10	3	17	3	23	8		
AML 15 AraC (LD)	2	30	11	1	25	1	30	7		
AML 15 DA	8	35	16	5	14	7	30	12		
FLAG	1	33	21	1	19	1	45	26		
AML 15 FLAG-Ida	11	28	15	7	17	7	46	29		
AML 15 MACE	13	25	12							
AML 15 MidAC	9	30	10							
AML 15 MRC	Cycle 1			Interval		Cycle 2			Interval	
	2	32	13	2	11	2	25	23	2	15
	Cycle 3			Interval		Cycle 4				
	2	27	7	2	17	2	28	6	2	
AML 15 Spanish	Cycle 1			Interval		Cycle 2			Interval	
	2	31	14	1	0	1	23	14	1	0
	Cycle 3			Interval		Cycle 4				
	1	32	14	-	-	-	-	-		

4.4 Missing data analysis

Since treatment date information was crucial for cost estimation purposes, it was decided a missing data analysis to be conducted. This was in order to inspect whether the missing values occurred systematically or randomly. The analysis was separated into two parts. Firstly, 'descriptive statistics' was employed for portraying the picture of the distribution of the missing value, as a whole. Secondly, in order to determine whether the missing values occurred randomly, or were affected by specific factors, logistic regression was conducted. The results are shown on **Table 4.10**and **Table 4.11**.

Table 4.10 Descriptive statistics of missing data

	Total Events	Treatment start date		Treatment end date		Total	
		No. of missing data	(%)	No. of missing data	(%)	No. of missing data	(%)
Chemotherapy	247	1	0.40	50	20.24	50	20.24
Clinical trial	180	1	0.56	36	20.00	37	20.56
Immunosuppressive therapy	6	1	16.67	2	33.33	3	50.00
Radiotherapy	14	0	0	2	14.29	2	14.29
Stem cell transplantation	13	0	0	4	30.77	4	30.77
Supportive care	253	17	6.72	107	42.29	116	45.85
G-CSF	46	1	2.17	20	43.48	21	45.65
Erythropoietin	3	0	0	0	0	0	0
Steroids	14	0	0	6	42.86	6	42.86
Transfusion	190	16	8.42	81	42.63	89	46.84
Venesection	3	0	0	0	0	0	0
Splenectomy	2	0	0	0	0	0	0
Palliative care	33	6	18.18	17	51.52	17	51.52
No treatment / refused treatment	12	12	100	12	100	12	100
Total	763	37	4.85	230	30.14	241	31.59

4.4.1 Descriptive statistics of missing data

As shown in **Table 4.10**, supportive care had the largest amount of missing date data, among a total of 763 treatment episodes. More specifically, it accounted for 45.85% of a total of 253 supportive care episodes, and for 48.18% of a total of 763 treatment episodes. For chemotherapy and clinical trial, the number of missing data was lower than 50, and accounted for 36.1% (763 treatment episodes). The rest of the treatments only accounted for 15.72% of the total treatment episodes. It is worth noting that most of the missing date data occurred in the treatment end date rather than the start date. It accounted for 95.44% of the total missing data episodes.

4.4.2 Logistic regression

Logistic regression was conducted in order to investigate the reason for the missing. After putting all the important interest variables in the model, the regression result is shown in **Table 4.11**.

Table 4.11 Logistic regression result

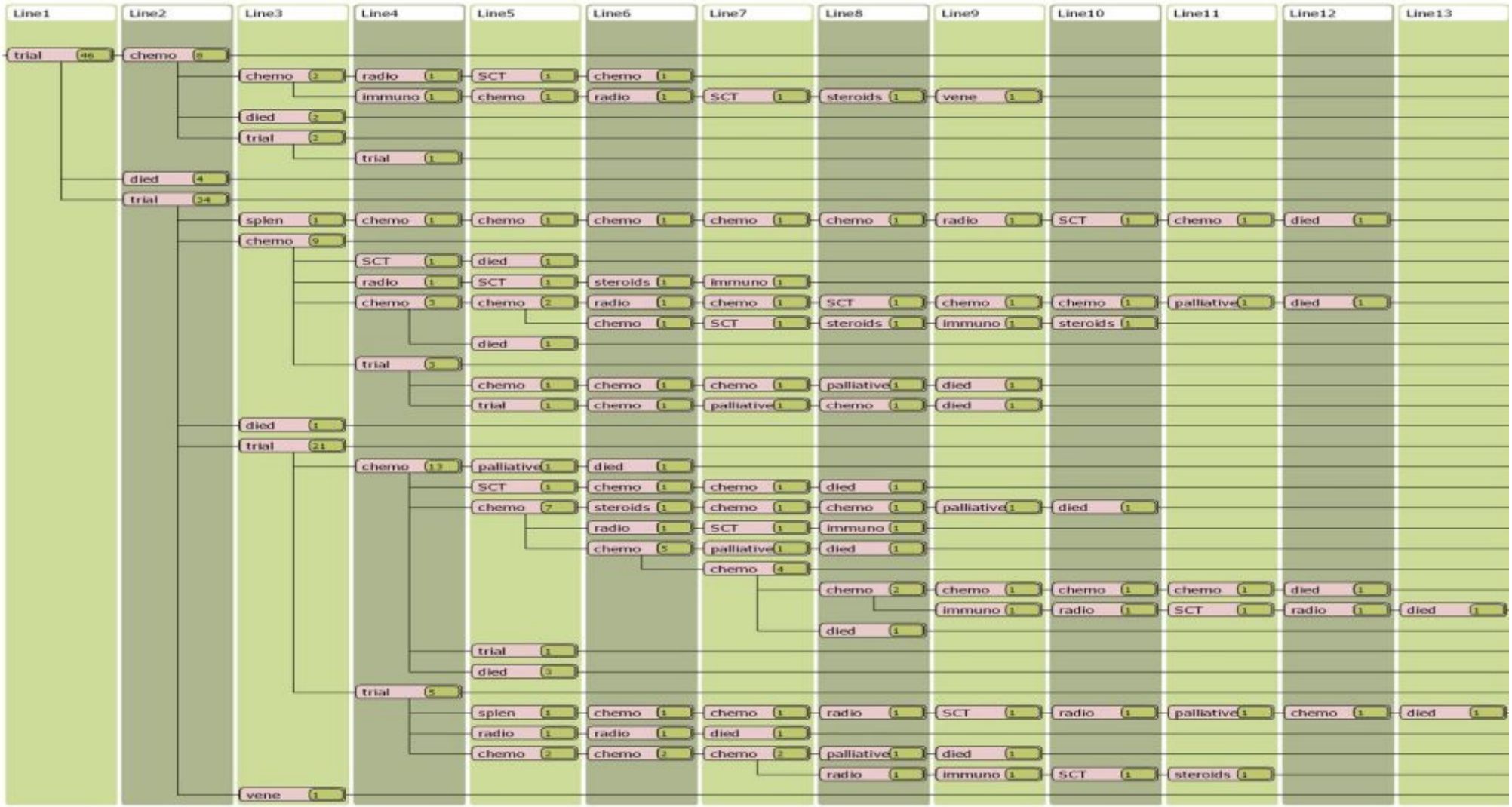
Parameters		Estimates	P	Odds ratio
Intercept		-1.0904	<.0001	
Age group	18-60 yr	0.0324	0.7945	0.956
	60-75 yr	-0.1100	0.4193	0.829
	>75 yr (reference group)	-	-	-
Gender	Female	-0.1724	0.0434	0.708
	Male (reference group)	-	-	-
Diagnosis	AML	0.1776	0.2906	1.427
	APML (reference group)	-	-	-
Death or not	Alive	-0.3490	0.0020	0.498
	Dead (reference group)	-	-	-
Treatment type	Immunosuppressive	1.0590	0.1507	4.644
	Radiotherapy	-1.1270	0.0981	0.522
	Stem cell transplant	-0.0533	0.9234	1.527
	Palliative care	0.6977	0.0608	3.236
	Chemotherapy	-0.7069	0.0037	0.794
	Supportive care	0.6071	0.0082	2.955
	Clinical trial (reference group)	-	-	-

It is illustrated on the table that most of the variables were not associated with missing data (P value > 0.05). This indicated that no identifiable patterns existed in the missing data, with the exception of 'death or not'. 'Death or not' was the only variable that had a significant effect (P=0.002). The results (**Table 4.11**) implied that patients who were still alive were less likely to have missing date data in the treatment episode record. A possible explanation for this is that the missing data of alive patients had more chances to be corrected, as the records were continuously audited by research nurses. In contrast, auditing stopped for dead case records, after patients died. This resulted in missing data to remain unknown. Overall, the results of the logistic regression suggested that the date data were missing at random.

4.5 Pathway tree diagram

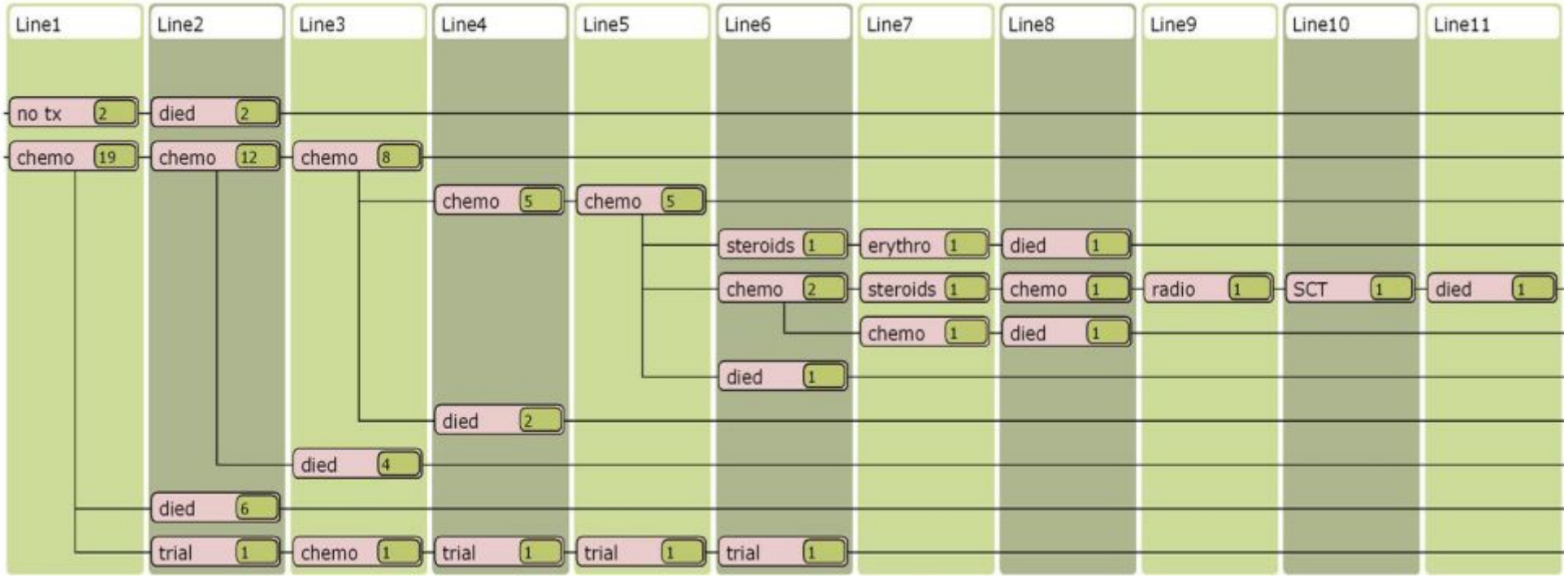
Treatment pathway tree diagram provided the means to graphically represent the treatment pathway, to which the unit costs could be linked at later stages of the current work. After removing the 'supportive care' treatment episodes (the reasons are discussed in section 3.5.4), 510 treatment episodes remained. The latter were used for building the tree diagrams. Because of the large volume of the information, the tree diagram was divided into the following 4 parts (grouped by diagnosis and age group): 1) AML (18-59 years old), 2) AML (60-74 years old), 3) AML (≧75 years old), and 4) APML. The four diagrams are presented in below **Figure 4.1**, **Figure 4.2**, **Figure 4.3**, **Figure 4.4**, and **Figure 4.5**.

Taking the AML (60-74 years old) group as an example, the treatment pathway was plotted into a tree diagram that can be found in. As shown in **Figure 4.3**, a total of 72 patients belonged in this group. Of these patients, 30 had chemotherapies and 21 had clinical trial as induction treatment. All patients who received either no treatment, or supportive/palliative care as first line treatment, eventually died. As expected the use of non-aggressive treatment did not lead to a better prognosis. Half of the patient who received chemotherapies as induction treatment died after the treatment, while the other half survived and had a second chemotherapy. Most of the patients who initially survived kept receiving chemotherapy until their death. Overall, only two patients were still alive at the time of the current work. Of the patients who received clinical trials as induction treatment, only one third died after the trial, with the surviving patients (2/3 of the overall number of patients) receiving further chemotherapy or clinical trial. After one to three cycles of clinical trials, all the patients started receiving chemotherapy until their death. In this group, 4 out of 21 patients were still alive at the time of the current work.



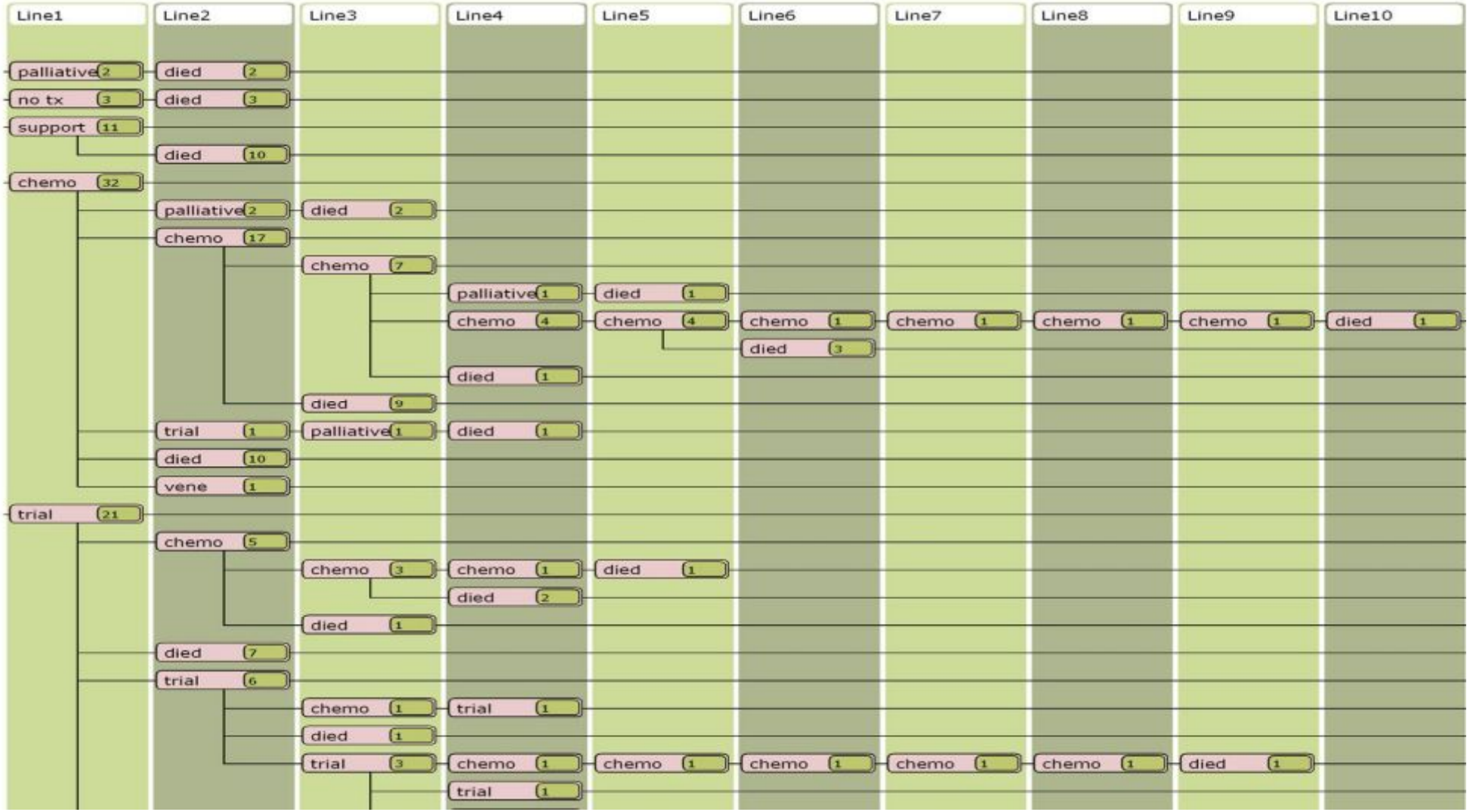
*chemo: chemotherapy; trial: clinical trial; radio: radiotherapy; immune: immunosupression; vene: venesection; erythro: erythropoietin; splen: splenectomy; no tx: no treatment; support: supportive care

Figure 4.1 Treatment Pathway tree diagram-1 (AML 18-59 years old: part 1)



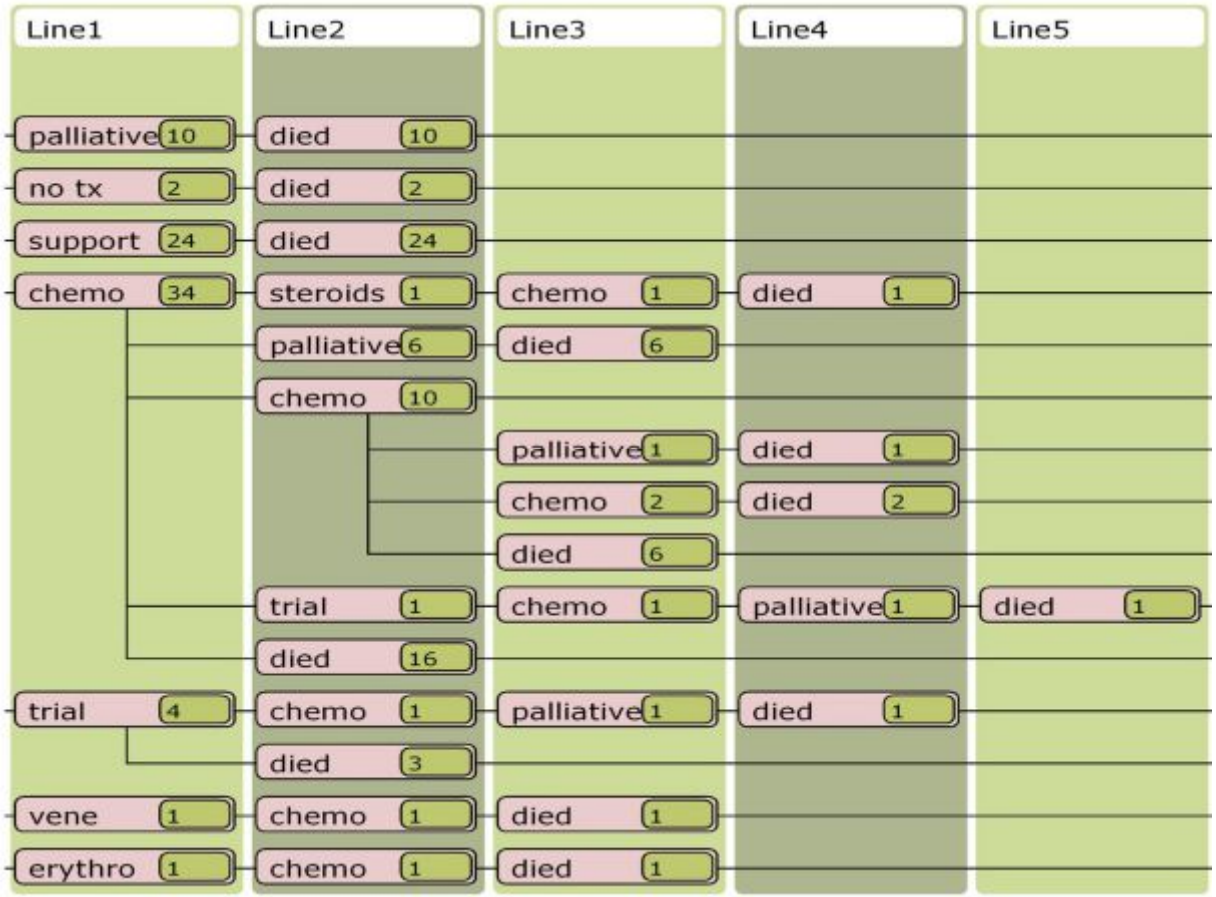
*chemo: chemotherapy; trial: clinical trial; radio: radiotherapy; immune: immunosupression; vene: venesection; erythro: erythropoietin; splen: splenectomy; no tx: no treatment; support: supportive care

Figure 4.2 Treatment Pathway tree diagram-1 (AML 18-59 years old: part 2)



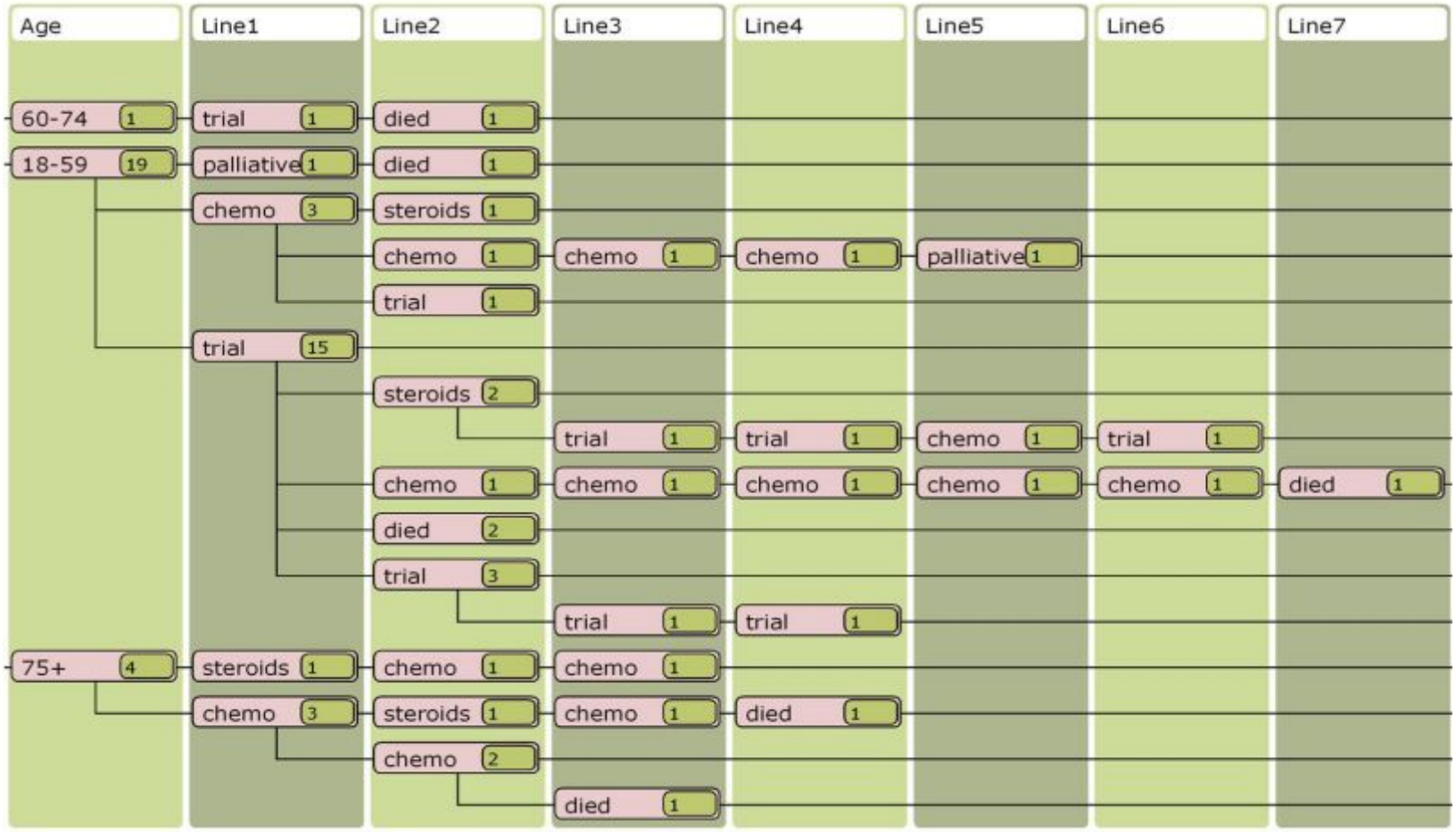
*chemo: chemotherapy; trial: clinical trial; radio: radiotherapy; immune: immunosupression; vene: venesection; erythro: erythropoietin; splen: splenectomy; no tx: no treatment; support: supportive care

Figure 4.3 Treatment Pathway tree diagram-2 (AML 60-74 years old)



*chemo: chemotherapy; trial: clinical trial; radio: radiotherapy; immune: immunosupression; vene: venesection; erythro: erythropoietin; splen: splenectomy; no tx: no treatment; support: supportive care

Figure 4.4 Treatment Pathway tree diagram-3 (AML≧75 years old)



*chemo: chemotherapy; trial: clinical trial; radio: radiotherapy; immune: immunosupression; vene: venesection; erythro: erythropoietin; splen: splenectomy; no tx: no treatment; support: supportive care

Figure 4.5 Treatment Pathway tree diagram-4 (APML)

Database 2: HILIS database

The HILIS database was used for identifying treatment phase and for laboratory test cost calculation.

4.6 Descriptive statistics (HILIS)

After mapping the study population (derived from the HMRN database) to the patient ID in the HILIS database, a total of 3058 reports were matched. After database cleaning and reported results integration, 1767 laboratory reports were obtained. The summarized specimen types of the 1767 reports can be found in **Table 4.12**.

Table 4.12 Summary of specimen types and numberss

Summarized test results	Frequency	Percentage
BMA	192	10.87
BMA, BMAT, HS, PN, TBP	47	2.66
BMA, BMAT, PB	149	8.43
BMA, CF	6	0.34
BMA, HS, PB, TBP	24	1.36
BMA, HS, TBP	15	0.85
BMA, PB	76	4.30
BMA, PB, TBP	3	0.17
BMA, TBP	11	0.62
BMAT	575	32.54
BMAT, PB	13	0.74
CF	95	5.38
CHI group	177	10.02
DF group	46	2.60
EF	13	0.74
HS	39	2.21
HS, PB, TBP	3	0.17
LF group	10	0.57
PB	213	12.05
PB, TBP	1	0.06
PBS	25	1.42
RU	25	1.41
TBP	1	0.06
TBP, HS	1	0.06
XA group	7	0.40
Total	**1767**	

As illustrated in **Table 4.12**, the most common specimen/biopsy test types were the specimen test: BMAT test alone (32.54%), BMA test alone (10.87%), and PB test alone (12.05%). The multi-specimen test types were found to be uncommon (less than 1%). Only four of the above accounted for more than 1%, with the two most common test types in this group being “BMAT, BMA, PB” and “BMA, PB”, accounting for 8.43% and 4.30% respectively.

4.7 Length of treatment phases (HILIS)

In order to provide a visual representation of the length of each treatment phase, the results had to be presented in a time axis format as shown in **Table 4.13**. As shown in **Table 4.13**, it took shorter time to achieve the 1st remission rather than the 2nd remission. Also, the patient stayed in the disease absence stage longer in 1st remission time rather than in 2nd remission time. This implied that the relapse not only could make the remission more difficult to achieve, but also it could make the disease easier to relapse again. However, the above trends were only observed for the first and the second treatment phases, as the mentioned patterns did not appear during the third and fourth treatment phases. This change of pattern could be related with the fact that only few cases were found to have reached the third and fourth treatment phases, something that could make the available information insufficient for extracting consistent results.

Table 4.13 The length of treatment phase

From diagnosed to 1st relapse		**1st relapse to 2nd relapse**		**2nd relapse to 3rd relapse**		**3rd relapse to 4th relapse**	
Average length: 479 days (n=49)		Average length: 204 days (n=6)		Average length: 356 days (n=1)		Average length: - days (n=.)	
Diagnosed to 1st remission (induction)	**1st remission to 1st relapse (consolidation)**	**1st relapse to 2nd remission**	**2nd remission to 2nd relapse**	**2nd relapse to 3rd remission**	**3rd remission to 3rd relapse**	**3rd relapse to 4th remission**	**4th remission to 4th relapse**
Average length: 66 days (n=107)	Average length: 420 days (n=49)	Average length: 88 days (n=23)	Average length: 154 days (n=6)	Average length: 38 days (n=3)	Average length: 300 days (n=1)	Average length: 50 days (n=1)	Average length: - days (n=.)

4.8 Laboratory test cost (HILIS)

The total and the individual lab costs for each treatment phase (at patient level) are presented in **Table 4.14**. Since the costs of transplantation-related tests (such as CHIA and CHIM) and the 'stem cell harvest cost' (derived from reference cost for calculating the transplantation cost at later stages of the study) are actually the same, the transplantation-related test cost was removed from the database and the total treatment cost estimation. This was in order not to double count the harvest cost. However, in the context of the current work, information related with transplantation-related test cost was kept and presented separately in **Table 4.14**.

Table 4.14 Laboratory test cost

Including the cost of transplantation-related tests			**Excluding the cost of transplantation-related tests**		
Phase	Number of patient	Average cost per patient	Phase	Number of patient	Average cost per patient
First-line treatment	239	£1406.40	First-line treatment	239	£1385.89
1st relapse	49	£2683.54	1st relapse	49	£2167.88
2nd relapse	6	£2105.50	2nd relapse	6	£1780.17
3rd relapse	1	£3706	3rd relapse	1	£2256.00
Total	239	£2003.95	Total	239	£1867.35
Average cost per report: £275.59 (n=1767)					

As shown in **Table 4.14**, irrespectively of whether the stem cell harvest cost was included or not, the lab cost increased gradually from phase to phase, with the exception of the 2nd relapse phase. It is suggested that this could be because of the significantly low numbers of cases for the 2nd relapse (n=6). However, the general trend indicated that increased relapse occurrences corresponded to increased lab costs (including the disease time and remission time).

Database 3: PCD database

In the current study, the PCD database was used for extrapolating transfusion frequency. The latest update of the palliative care database used for analysis was made on January 2010. In this database, there were 20 AML / APML patients, 14 of whom appeared to have had received once or more transfusions during the recorded transfusion time. Data summarizing and cleaning was carried out on 670 detailed records of transfusion, related to these 14 patients. In total, there were 164 summarized transfusion events that were ready for further analysis.

4.9 Transfusion cost

4.9.1 Unit of transfusion

Based on the 164 summarized transfusion events, 1.87 blood units and 0.66 platelet units were assigned on each transfusion, on average. After rounding these values, about 2 blood units and 1 platelet unit were found to have been given during each transfusion.

4.9.2 Transfusion frequency

The 164 summarized transfusion events were divided into 4 subgroups. Next, the transfusion frequency was calculated for each of these groups (defined in the previous section). Further analysis of the above can be found in the following paragraphs.

Within a group comprising of patients who had achieved remission, 2 patients were found to have good treatment response (had achieved remission in less than 2 months), with the average transfusion frequency being once every 4 days (in round numbers) during the disease time, while 3 patients were found to belong to the poor response subgroup. In this subgroup, the average transfusion frequency was once every 14 days during the disease time.

In the group comprising of patients who had not achieved remission, there were 6 patients who died quickly (within 2 months), with the average transfusion frequency being once every 4 days (in round numbers) during the disease time. In the group comprising of patients who had achieved remission, 3 patients were found not to have rapid progress (survived more than 2 months), with the average transfusion frequency being once every 14 days during the disease time.

As the above results were highly consistent, it was possible the transfusion frequency to be summarized to the following statement: Transfusions would take place once every 4 days when the disease time lasted less than 2 months, and once every 14 days when the disease time lasted longer than 2 months. The summary can be found in **Table 4.15**.

Table 4.15 Summary of transfusion frequency extrapolation

	Number of cases	Transfusion frequency
Had achieved remission		
Quick response to treatment (2 months)	2	Once every 4 days
Slow response to treatment (2 months)	3	Once every 14 days
Died before achieving remission		
Die soon (2 months)	6	Once every 4 days
Die slowly (2 months)	3	Once every 14 days

Integrated database

4.10 Preliminary analysis results of integrated database

4.10.1 Types of treatment

Treatment types in each treatment phase provided an indication of what type of treatment was normally given in specific treatment phases. Without considering the supportive care, most of regimens of chemotherapy or arms of clinical trial were used for first-line treatment (**Table 4.16**). Especially regimens or arms like ADE, FLAG-Ida, MRC, and Spanish approach normally were used as induction treatment, while AraC(HD), MACE, and MidAC were mainly used as consolidation treatment. Other treatments, like radiotherapy, stem cell transplantation, and immunosuppressive therapy, were commonly used for treating relapse, but sometimes were also used as consolidation treatment. In relation to palliative care, it could be used at any treatment phase because of its nature of care. Overall, the timing of each treatment type use was in line with the guidelines [97, 151, 155, 156] and with previous review studies[24], which suggested that the treatment information in the study database was fairly reliable.

Table 4.16 Treatment types by treatment phase

	First-line		**2nd relapse**	**3rd relapse**	**After 3rd relapse**	**Total**
	Induction	Consolidation				
Inpatient treatment	**222**	**109**	**73**	**10**	**2**	**416**
ADE	28	4	11	-	-	43
AraC(HD)	6	22	11	1	-	40
AraC (LD)	38	1	3	1	1	44
DA	59	7	2	2	-	70
Clofarabine	-	-	2	-	-	2
FLA	1	2	1	-	-	4
FLAG	6	6	6	-	-	18
FLAG-Ida	32	5	5	-	-	42
HAM	-	-	1	-	-	1
MACE	3	24	2	-	-	29
MidAC	5	22	2	-	-	29
MRC	11	2	-	-	-	13
Spanish	10	4	-	-	-	14
Amsacrine	-	-	-	1	-	1
Arsenic trioxide	-	-	2	-	-	2
Campath	-	-	1	-	-	1
Daunorubicin	-	-	1	-	-	1
Palliative care	23	2	6	1	1	33
Radiotherapy	-	2	10	2	-	14
Stem cell transplant	-	4	7	2	-	13
Splenectomy	-	2	-	-	-	2
Outpatient treatment						**84 (82)**
ATRA	3	-	-	-	-	3

Cyclophosphamid	-	4	2	-	-	6
Cyclophosphamid / MESNA	-	-	2	-	-	2
ETI	1	-	1	-	-	2
FC	1	-	4	1	-	6
Fludarabine	1	-	-	1	-	2
Melphalan	2	-	1	-	-	3
Mylotarg	-	-	1	-	-	1
Spanish maintenance	-	1	-	-	-	1
Vincristine	1	-	-	-	-	1
Aspirin	-	2	-	-	-	2
Hydroxycarbamide	30	4	4	1	1	40
Hydroxycarbamide / Aspirin	1	1	-	-	-	2
Chelating agents	1	-	1	-	-	2
Anagrelide	-	1	-	-	-	1
Clopidogrel	-	1	-	-	-	1
Immunosuppressive	-	2	3	1	-	6
Venesection	-	3	-	-	-	3
No treatment						**12**
Total	**275**	**128**	**92**	**14**	**3**	**512**

4.10.2 Treatment response and prognosis

a. Complete remission rate

CR rate is always one of the indexes of treatment effect. Based on information extracted from the HILIS database, the CR rate was further analyzed in the current study with the following prognostic factors: age, gender, diagnosis, and primary induction treatment. The results are shown in **Table 4.17** and **Table 4.18**.

Table 4.17 CR rate by gender, age, diagnosis, and primary induction treatment

	CR cases	CR rate (%)
Gender		
Female	52	42.62
Male	53	45.30
Age group		
18-60	67	77.91
60-75	33	45.21
> 75	5	6.25
Diagnosis		
AML NOS	76	38.58
AML with core binding factors	8	80.00
AML - probable therapy related	2	33.33
AML with MLL (11q23) rearrangement	1	50.00
APML t(15;17)(q22;q11-12)	18	75.00
Primary induction treatment		
Intensive treatment with induction intent	102	73.38
Intensive treatment without induction intent	1	2.50
Support or palliative care only	2	3.33
Total	105	43.9

As illustrated in **Table 4.17**, gender did not introduce any differences in CR rate. However, the rest of the factors did. According to the analysis results, older patients had worse outcome (lower CR rate). Also, in terms of diagnosis, 'APML' and 'AML with core binding factors' had better prognosis (higher CR rate). In relation to the primary induction treatment, treatments with induction intent resulted in much better CR rate. These results were consistent with the results of previous related studies [24, 157, 167, 173].

Furthermore, in order to determine the effectiveness of each prognostic factor, a simple logistic regression was conducted. The regression result showed that both age and primary induction treatment had a significant effect to the CR rate ($P<0.05$), while 'diagnosis' did not. There was no significant difference of the CR rate between AML and APML patients. The relevant details can be found in **Table 4.18**.

Table 4.18 CR rate and relapse rate analysis

		CR			Relapse		
		Estimate	**P value**	**Odd ratio**	**Estimate**	**P value**	**Odd ratio**
Intercept		-1.7005	0.0006		-1.0147	0.9973	
Age group	18-60	0.9115	0.0014	8.832	0.3941	0.4023	1.658
	60-75	0.3554	0.2298	5.065	-0.2827	0.5724	0.843
	>75	-	-	-	-	-	-
Gender	Female	0.0720	0.7078	1.155	-0.2034	0.3435	0.666
	Male	-	-	-	-	-	-
Diagnosis	AML	-0.2145	0.4778	0.651	1.1975	0.0030	10.969
	APML	-	-	-			-
Primary induction treatment	With induction intent	2.3832	<0.0001	35.503	-0.2224	0.9994	>999
	With non-induction intent	-1.1968	0.1034	0.990	13.3540	0.9197	>999
	Palliative or supportive care only	-	-	-	-	-	-
Case number				**239**			**105**

b. Relapse

Based on the 104 patients who had achieved remission, the factors that had effect on relapse were tested by means of a simple logistic regression. As shown in **Table 4.18**, only diagnosis had significant effect. AML patients were more likely to relapse than APML patients, after achieving remission. The rest of factors did not have significant effects, even analyzed separately by AML and APML.

4.11 Summary

The current chapter involved the analysis of the main study databases. Information from the HMRN, the HILIS, and the PCD databases, such as geographic characteristics of patients, types of treatments, treatment duration, treatment pathway, laboratory test, diagnosis, and transfusion frequency were discussed and summarized. The above formed the basis for costing, which is discussed in the following chapters (chapters 6, 7, 8).

Chapter 5 Costing Methodology

Costing structure, data sources

CHAPTER 5 STUDY METHODOLOGY

The aim of this thesis is to explore how to obtain detailed costs of care per patient over the patient pathway from diagnosis to cure or death. Based on the review results discussed previously (chapter2) and Drummond et al. [175] suggest that costing care requires three stages: identification of items to cost, measurement of the amount of resource used for each item and thirdly valuation of each resource, an innovative five-step costing approach that contained three-phase costing method was designed.

Information about the population on which the study was conducted has been described in the previous two chapters. In the current chapter, the overview of the costing methods and its data sources are discussed. The further details of the above three-phase costing method are described in the later chapters (respectively chapter 6, chapter 7, and chapter 8).

5.1 Overview of the costing structure

To calculate the overall/lifetime treatment costs of individuals, a five-step approach (adopted to cost the care the patients received) was applied

Step 1. Cost items that were required to be calculated were identified.
Step 2. Information for estimating the required cost items was collected.
Step 3. Cost for each treatment episode/event was calculated.
Step 4. Cost of each treatment episode was linked to the patient treatment pathway.
Step 5. Overall treatment cost was estimated individually

In the following sections, the preparation procedures employed before performing the actual costing (step 1) and the structure of the cost estimation methods (steps 2, 3, 4, 5) are presented and briefly discussed.

5.2 Defined and determine the cost drivers (three-level classification)

Based on the review results of the relevant cost studies discussed in chapter 2, several key cost drivers were identified (such as drug cost and personnel cost). To ensure that all the resources were thoroughly considered, the cost drivers/items that should be estimated were further checked and identified by focus group meetings (composed by haematologists, research nurses, and the managers of financial department in hospital) with the application of three-level classification, according to three different and distinct characteristics. In each classification level, only one characteristic was used. This was done mainly in order to avoid problems in categorizing some resources, as it is easy to count the same resource twice or forget to count the resource altogether [176]. The details of the three-level classification and the cost items identified are described below:

5.2.1 First level of cost classification by treatments/services

Although there are many ways to classify the resource input (such as activity, level at which resources are used, currency and others), it was decided that the 'classification by treatments/services (activity)' should be used for the purposes of the current study. This decision was made for two reasons. Firstly, classifying or identifying the resource inputs by treatment/services is a relatively straight-forward process [44]. Secondly, classifying resources by treatment matches the main purpose of the study, which was to estimate the individual overall cost from the patient treatment pathway by summing up all the treatment event costs. Under the treatments/services classification, the costs were divided into 12 categories according to the types of treatment/service given to the AML/APML patients:

a. Treatment costs identified from the HMRN database

Ten treatment costs were identified from the HMRN database: costs of chemotherapy (including treatment given a part of a clinical trial), clinical trail, supportive care (including erythropoietin, steroids, G-CSF, and transfusion), venesection, splenectomy, palliative care, transplantation, radiotherapy, immunosuppressive therapy, and follow-up. These treatment costs occurred when they are given to patients.

b. Service cost identified from the HILIS database

Only one service cost item was identified from the HILIS database, namely the Laboratory test cost. Test costs can be defined as the costs that occur when patients

receive the lab testing service. Normally, the lab test is used for confirming the diagnosis, monitoring the effectiveness of treatment, and monitoring the progress of the disease.

c. Care cost derived from the central register

Only one care cost was identified from the central register: the end-of-life care. The care cost (dying cost) is the cost that occurs when a patient dies at healthcare institutes, such as hospitals and nursing homes, without receiving any aggressive treatment. The end-of-life care normally only involves basic daily care and emotional / psychological support.

5.2.2 Second level of cost classification by information availability

According to the availability of the detailed treatment information, the treatment costs were further divided into two types: the cost can be estimated by bottom-up costing and the cost that can not.

a. cost type 1: cost that can be estimated by bottom-up costing method

The costs can be estimated by bottom-up costing method when the treatment details are available. For example, chemotherapy treatment cost falls into this category as the regimen details are available in the HMRN database.

b. cost type 2: cost that can not be estimated by bottom-up costing method

The cost can not be estimated by bottom-up costing method when the treatment details are not obtainable. For example, transplantation cost falls into this category as the treatment details of transplantation are not available from any of the databases used in the current study.

Based on the cost type, the treatment costs that can not be obtained by bottom-up costing method were estimated by substituting their values with the national average cost (from 'Reference Cost Schedule'). As for the treatment costs that can be estimated by bottom-up costing method, they were further identified with the third level classification.

5.2.3 Third level of cost classification by functions

According to the cost functions (derived from practical experience, expert opinions, literature mentioned in Chapter 2, and relevant publications [44, 176, 177]), the cost drivers/items that had to be estimated for all the treatments were listed below.

a. Drug costs (product costs): the costs for the delivered medicine/products of the treatment, such as the drug costs, regimen costs, and cost of blood products.

b. Personnel costs: the costs of human resources used for the treatment, but not for care or support duties/purposes.

c. Overheads and capital overheads costs: overheads costs are the resources serving different departments or treatments for supporting purposes (for example, administration, management, utility, central laundry, porter, outsource cleaning, and even infectious medical waste treatment expenditure or similar [44]). Capital overheads costs are the resources that are used to purchase the capital assets required by the treatment, such as equipment, buildings, vehicles, and land.

d. Ward/clinic costs: the resources that are used in ward or outpatient clinic for care duties, such as changing beddings, providing medicine and meals and space cost.

e. Complication treatment costs: the resources that are used to treat the side effects caused by treatments.

This three-level cost classification ensures that all the relevant activities are captured and reported. Once all the costs were identified, different types of costs for each treatment were able to be calculated through different methodologies. The structure of cost measurement methods is discussed below.

5.3 Structure of three-phase costing method

– microcosmic to macrocosmic

5.3.1 Item cost measurement

After the range of the cost items had been identified, the values of individual cost items for each treatment were measured. The general item cost measurement encompassed two parts: assignment of unit cost/price and measurement of quantities of the used resources.

For the purposes of the current study, consumed amount was set as the quantity unit. In general, quantity measurement was estimated by means of the data sources: database, medical notes, expert or staff survey, and literature review. To reflect the costs in the real world, information of 'patient actual resource consumption' (such as the information derived from database and medical notes) was mainly used as the quantity unit. Staff / expert surveys and literature review were only used whenever the actual patient data were not available.

For the assignment of unit cost, tariffs and publications of national average prices and costs were used as information sources (official price lists such as BNF) in order to make the estimation methods coherent and the estimates close to actual unit costs.

5.3.2 Treatment cost measurement

Assuming that the treatment cost is the bridge between the item cost and the patient total pathway cost (as treatment cost is the sum up of the item costs while it is also a chunk of the patient total pathway cost), then the bridge between the item cost and the treatment cost is 'number of uses (frequency)'. To estimate the treatment cost, all the item costs under each treatment were summed up according to the 'frequency' information. For example, the transfusion cost (treatment cost) was calculated from a multiplication of a lump sum of the item costs (such as blood product s and personnel) of each transfusion and the delivery frequency (once every four days when the disease time is less than two months) during the treatment (episode) time.

In the current study, a number of data sources were used to obtain the adequate frequency information for each treatment. Generally, patient treatment pathway databases were the main and most reliable sources for frequency. If the frequency information was not available in the relevant databases, then guidelines and expert opinions were taken into account.

For the treatment cost that was unobtainable by bottom-up costing (item costs were not available or frequency information were insufficient), the national average cost (derived from 'Reference Cost') was used instead. For example, in the case of transplantations (13 treatment episodes were found in the HMRN database), the 'Reference Cost' of transplantation was used as a substitute for treatment cost because the treatment details (cost drivers) were not obtainable. This approach was expected not only to be more time-efficient, but also to provide better human resources management.

5.3.3 Overall treatment cost measurement

After each treatment cost had been identified, the final step to the total cost was to link all the treatment costs to the patient treatment pathway (derived from the HMRN database), and then sum them up in order to reflect the individual total cost in the real world. The illustration of the relationship between cost identification and measurement is shown in **Figure 5.1**, while the relationship between three-phase cost measurement and five-step costing approach is illustrated in **Figure 5.2**.

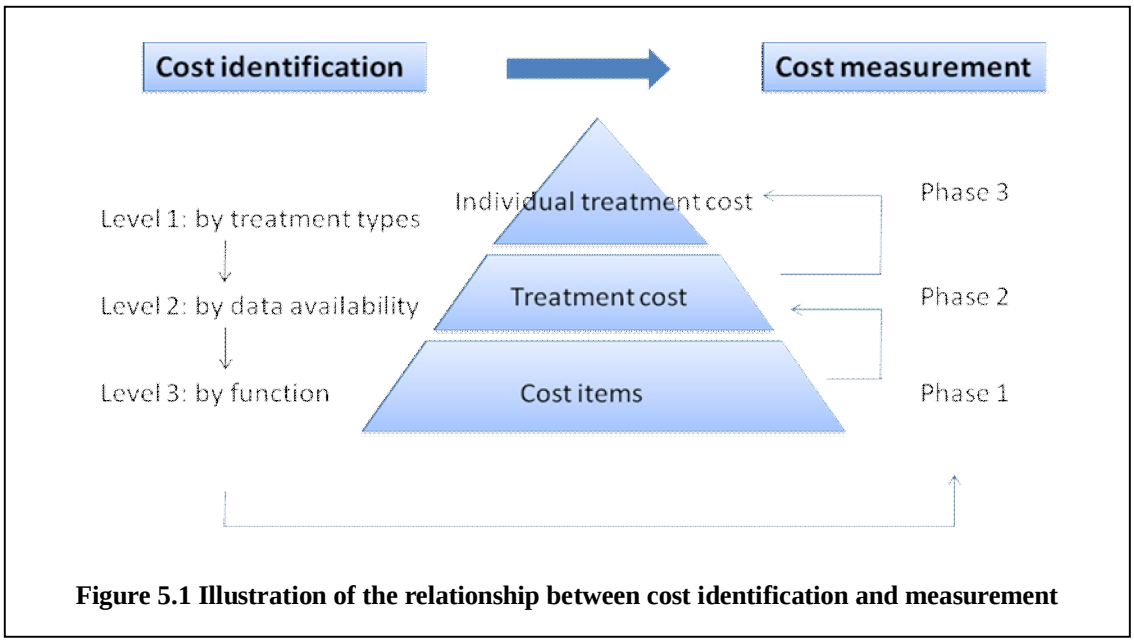


Figure 5.1 Illustration of the relationship between cost identification and measurement

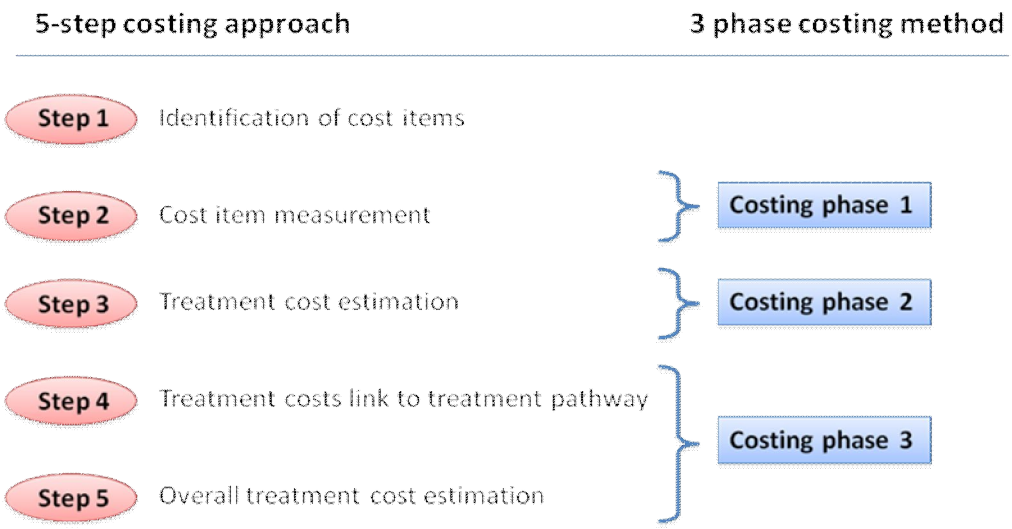


Figure 5.2 The illustration of the relationship between five-step costing approach and three-phase costing method

5.4 Relevant data sources for valuation

A number of different sources were used to obtain the value information for costing. The valuation methods were chosen depending on the availability of information.

- If the quantity information could be derived from the study databases, the national sources of unit costs (such as the BNF price list) provided the representative information that could be used for bottom-up costing.

- If the quantity information for bottom-up costing could not be retrieved from the study databases, the national cost data (such as the 'Reference Cost') were considered, as they were an alternative but reliable source of information.

In order to be consistent with the time in which the majority of events occurred in the HMRN database, the relevant data sources that were used for valuation were the ones published in 2006/07. The main relevant sources were used in the current study as detailed below.

5.4.1 British National Formulary (BNF) [178]

The BNF provides UK authoritative and practical information (including medical directions and drug price) on the selection and clinical use of medicines. In the current study, the BNF was used as a reliable 'unit cost' source for drugs and regimens.

5.4.2 PSSRU Unit Cost [179]

Unit Cost derived from the Personal Social Services Research Unit (PSSRU) provides detailed and comprehensive unit cost estimates in heath and social care in the UK. Thus, the unit costs of the staff and the overheads for cost estimations were derived from this document.

5.4.3 NHS Reference Cost Schedules 2006/07 [180]

'NHS Reference Cost Schedules' provides the national average cost data of different health groups in the UK. In cases where the treatment event failed to be calculated by means of bottom-up costing, the 'Reference Cost Schedule' was used as an alternative way to represent the cost. In the current study, it was decided data from the 'NHS trust Reference Cost Index' group to be used instead of data from 'Primary Care (GP) Trust

Reference Cost Index' group. This was because most of AML/APML patients were treated in a secondary care settings, and also the participating hospitals of the HMRN are all NHS trust.

5.4.4 Other sources

Except the national data sources mentioned above, other value sources, such as price list or tariff, were also used as 'unit cost' for cost calculation. For example, the 'National blood and blood components price list' from the National Blood Service[181] was used as 'unit cost' for transfusion cost calculation, while the 'Provider Tariff 2006-7 of the Haematological Malignancy Diagnostic Service' [182] was used for laboratory test cost calculation.

5.5 Relevant data sources for quantification

HMRN was the main data source for qualification. However, in some cases, detailed information was not possible to be retrieved from the HMRN database, and, thus, a number of alternative available sources were used instead. The details regarding aforementioned data sources are presented in the following paragraphs.

5.5.1 Database

As mentioned previously (chapter 3 and 4), three main databases compromising HMRN were used, namely the HMRN, the HILIS, and the PCD databases. The HMRN database was the main data source of the current study. It provided the information related with patients' baseline characteristics, which were used for defining the study population. The associated treatment details in the HMRN database were also used for treatment cost estimation at later stages. As for the HILIS and the PCD databases, they were used as supplement databases. The HILIS database provided the information related with the treatment progress, the diagnoses, and the details of laboratory resource use. The PCD database was used for predicting the transfusion frequency as this information could only be obtained from this particular database (please refer to chapter 3 for detailed reasons and methods of predicting).

5.5.2 Medical notes

As information gaps were found in the databases, additional information (such as antibiotic days, actual hospital stay) was alternatively extracted from available medical notes, with the assistance of research nurses.

5.5.3 Clinical guideline for AML/APML treatment [183, 184]

The clinical guidelines issued by the British Committee for Standards in Haematology (BCSH guideline) are widely used in the UK. It provides haematologists with up to date advice on the diagnosis and treatment of haematological disease [183]. Generally, the AML/APML treatments in the HMRN network followed the BCSH guideline. The AML 15 clinical trial protocol [185] was also used to retrieve more details regarding the chemotherapy regimens administered to patients on this trial. AML 15 trial is a clinical trial held by The Medical Research Council with the aim of improving the AML/APML treatment. The protocol contains all the dosage and delivery details of the regimens that are used in the trial arms. These regimens of the trial arms cover the, well-established,

mainstream treatments in the UK at present (such as ADE and FLAG-Ida) and the latest developed treatments (such as the treatment combination with Mylotarg). In the current study, the BCSH guideline and the AML 15 protocol were used as supplement for obtaining the 'quantity' and the 'frequency' information for the calculation of chemotherapy and clinical trial costs. For example, the numbers of days the specific drugs were delivered for each cycle of the clinical trial (frequency) was derived from the AML 15 trial guideline.

5.5.4 Experts and clinical staff survey

Expert opinion survey and staff survey were conducted when it failed to obtain information either from database or guidelines. This included the staff working time for each treatment delivery and some information for missing value imputation.

5.5.5 Literature review

Literature review was the last in order source option used for quantification in the current study. It was only used when data was impossible to be obtained from all the other data source options. Mainly, this data source (literature review) served as 'quantity' information for complication treatment cost calculation, as the complication (adverse event) incidence rate of each treatment for specific disease was difficult to be obtained from other sources.

5.5.6 Summary

The summary of the function that was served by each data source is listed below (**Table 5.1**).

Table 5.1 Summary of the data sources

1. Treatment cost that could be derived by bottom-up costing			
	Quantity	**Unit cost**	**Frequency**
Data sources	Database (5.5.1) Medical notes (5.5.2) Clinical guideline (5.5.3) Expert survey (5.5.4) Literature review (5.5.5)	National data (5.4) Tariff (5.4.4)	Database (5.5.1) Expert survey (5.5.4) Clinical guideline (5.5.3)
2. Treatment cost that failed to be derived by bottom-up costing			
Data sources	National data (5.4)		

5.6 Conclusion

The connections between the costing methods and data sources that are discussed above are visually illustrated in **Figure 5.3**.

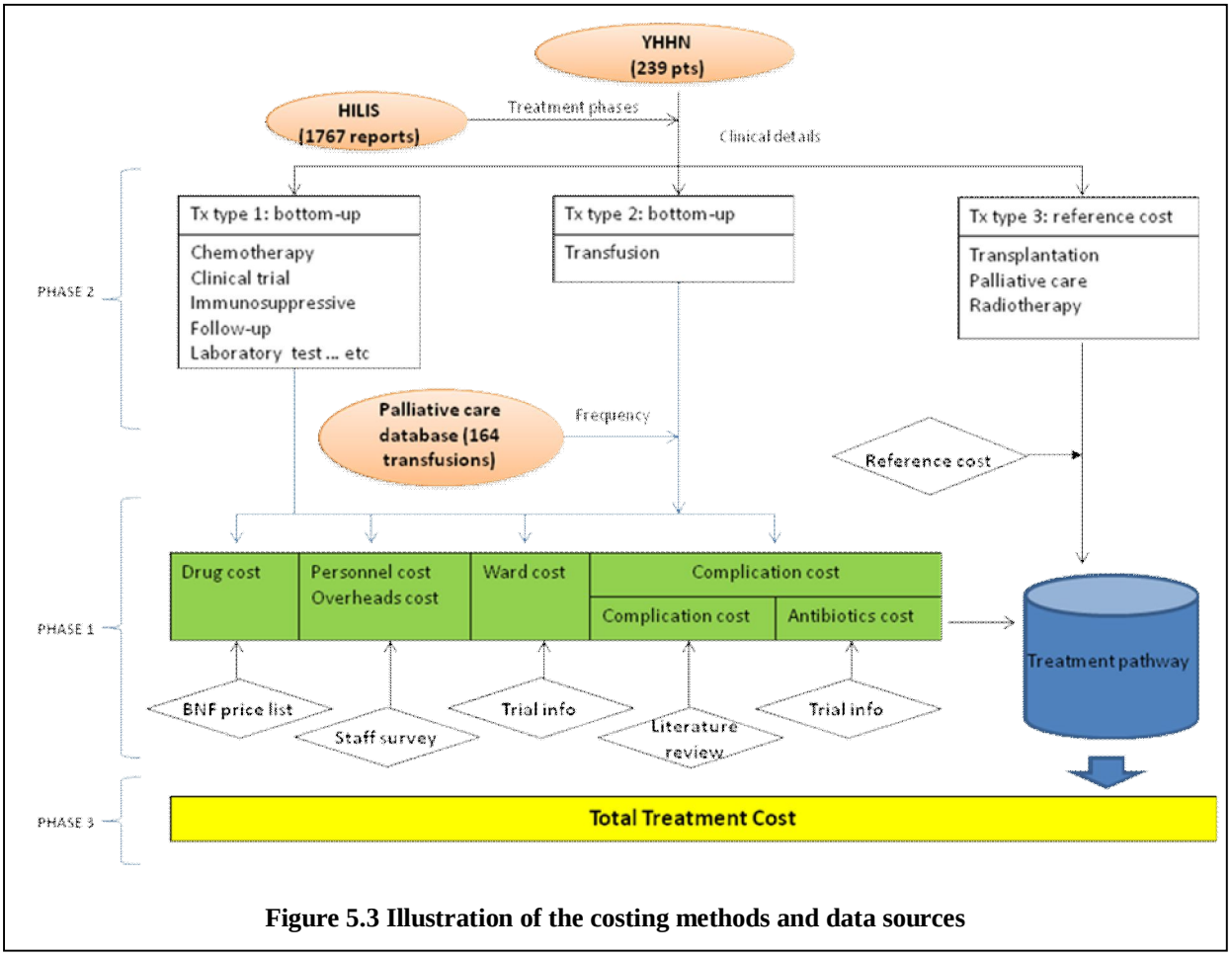


Figure 5.3 Illustration of the costing methods and data sources

As it can be seen in **Figure 5.3**, the three databases used in the current study provided the information about treatment details, lab test details, and transfusion frequency respectively (marked in red). Based on the information availability, treatment type can be divided into two categories: estimated by bottom-up method or not. The treatment costs that could be estimated by the use of the bottom-up method were further divided into a number of cost items, such as drug cost and personnel cost. These cost items/drivers are marked in green in **Figure 5.3**. Also, all the data sources that provided the relevant information for cost item estimations are presented in rhombus shapes. As for the treatment costs that were impossible to be estimated by means of the bottom-up costing method, the 'Reference Cost' was used to represent the treatment cost. Finally, **Figure 5.3** shows that all the treatment costs were linked to the treatment pathway, and the total treatment cost for each individual was generated by summing up these treatment costs.

Chapter 6 Costing method phase 1

Costing items/drivers estimation

CHAPTER 6 COSTING METHOD PHASE 1

Based on the study design presented in the previous chapter (chapter 5), 12 types of treatment/intervention were defined and the costs of these 12 treatments/interventions have to be calculated in order to obtain the lifetime/overall treatment cost of individuals. These 12 treatment costs were: chemotherapy, clinical trial, supportive care (erythropoietin, steroids, G-CSF, and transfusion), radiotherapy, transplantation, immunosuppressive therapy, splenectomy, venesection, palliative care, observation (follow-up), end-of-life care, and laboratory test.

Given data availability, it was possible to calculate eight out of 12 treatments/interventions by summing up five different cost items/drivers using a bottom-up costing method. These are, namely: drug cost (product cost), personnel cost, overheads cost (overheads, and capital overheads), ward cost (inpatient ward and place of outpatient visit), and complication cost. As for other 4 treatments (splenectomy, radiotherapy, transplantation, and palliative care), the 'Reference Cost' was used to represent the treatment cost.

According to the study design (section 5.3.2), cost measurement could be divided into three phases (illustrated below). In the current chapter, costing phase 1 for the eight treatments that can be estimated by bottom-up method is discussed. The general costing details of each of the five cost items/drivers are described in the following sections. Also, the specific details of the cost items/drivers for costing each treatment/intervention are discussed in next chapter (chapter 7)

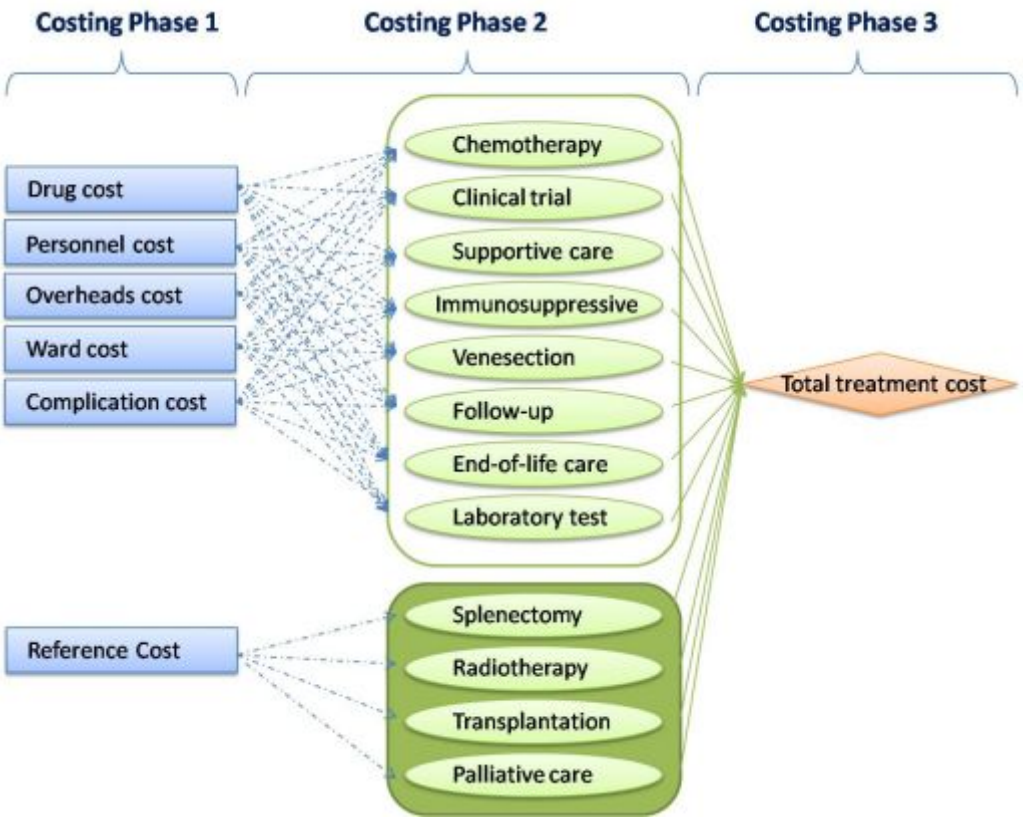


Figure 6.1 The illustration of costing phases

6.1 Drug / product cost

For the treatments/interventions that could be cost by means of the bottom-up method, drug costs were calculated based on the price lists (derived from published sources) and the quantity (derived from the HMRN database). Overall, 3 price list sources were used in the current study. These lists are discussed in the following paragraphs:

6.1.1 BNF price list [178]

Except transfusions and laboratory tests, all the drug /regimen prices included in the current study were based on the BNF price list (UK manufacturers price)[178]. These official prices may vary from (and generally be higher than) the real cost that hospitals actually spend on patients, depending on the contract between each given hospital and the manufacturers. Also, BNF prices include the VAT, given that hospitals are required to pay VAT on medicines.

6.1.2 National blood and blood components price list [181]

In order to obtain the unit cost of the blood products that were used for transfusion, the 'National blood and blood components price list' from the National Blood Service[181]of the UK was used. The full version of the price list can be found in **Appendix 6.1**. Based on the above, the blood product cost of the transfusion was calculated by the multiplication of the unit cost and the quantity (derived from the HMRN database).

6.1.3 Provider Tariff of the Haematological Malignancy Diagnostic Service[182]

In order to obtain the unit cost of the laboratory test services, the 'Provider Tariff 2006-7 of the Haematological Malignancy Diagnostic Service (HMDS) [182]' (derived from the Leeds teaching hospital NHS trust) was used. The reason for using the HMDS tariff instead of the national price list was that all the regional laboratory test requests were not only centralized, but also referred to HMDS. Therefore, the application of the HMDS tariff provided closer estimates to the actual laboratory test cost. The detailed price list of the laboratory tests for haematological malignancy diagnosis that was used in the current study can be found below (**Table 6.1**) . Based on the above information, the laboratory test cost was calculated by the multiplication of the unit cost and the quantity (derived from the HILIS database, the subset of the HMRN database).

Table 6.1 Provider Tariff 2006-7 of the HMDS

Full name of the specimen test	Abbreviation	Price
Bone marrow aspirate	BMA	£148
Bone narrow aspirate & Trephine biopsy	BMAT	£339
Cerebral spinal fluid (CSF)	CF	£29
Chimerism, allograft	CHIA	£265
Chimerism, baseline	CHIB	
Chimerism, mini-allograft	CHIM	
Skin, block	DBL	£218
Skin, fixed	DF	
Skin, fixed & unfixed	DFU	
Skin, unfixed	DU	
Effusion	EF	£90
Haematological slide	HS	£29
Lymph node biopsy, fixed	LF	£90
Lymph node biopsy, unfixed	LU	
Peripheral blood	PB	£148
Peripheral blood, stem cell	PBS	£148
Spleen, unfixed	RU	£200
Bone marrow trephine, fixed	TBP	£218
Miscellaneous tissue aspirate	XA	£148
Miscellaneous tissue, block	XBL	
Miscellaneous tissue, unfixed	XU	

Regarding the follow-up and the end-of-life care, no drug/product cost was applied, as these two interventions do not involve any treatments with curative intent.

Overall, the drug/product/service cost can be simply summarized as the multiplication of the unit cost and the quantity. The summary of the drug/product costing method for each treatment is shown in **Table 6.2**.

Table 6.2 The summary of the drug/product costing method

Drug/product cost of each treatment/intervention	Unit cost	Quantity
Chemotherapy Clinical trial Supportive care Erythropoietin Steroids G-CSF Immunosuppressive therapy	BNF price list	HMRN database
Supportive care Transfusion	National blood and blood components price list	HMRN database
Laboratory test	Provider Tariff from the Leeds teaching hospital NHS trust	HILIS database
Follow-up / observation		
End-of-life care		

6.2 Personnel cost

Hospital personnel could be divided in two distinct categories: staff directly involved with the treatment (such as doctors and nurses) and other support staff (such as managers, cleaners, and porters). In the current context, personnel cost was specifically defined as the cost related with the staff directly involved in the 'treatment' (such as delivery the medicine or injection), and not that involved with 'care duty' (like change beddings) or any other 'supportive services'.

In order not to overlook the cost of human resources in the hospital, the human resources were separated into three categories. The 'cost of human resource for the supportive service' was counted in overheads cost, and the 'cost of human resource for care duty' was counted in the ward/clinic costs at later stages. The only cost that was calculated separately was the one related with the human resource that was devoted to the treatment delivery. This was for two reasons. Firstly, it was difficult to separate the human resource costs from the overheads cost and the ward cost. Secondly, it was not possible to obtain information regarding the usual amount of working time spent on supportive services and care duty from the clinical staff during the staff survey. Therefore, only the cost of working time for treatment was considered as personnel cost. Also, the personnel cost was calculated by multiplying the unit cost with the quantity. The details of the costing method for the personnel cost are described in the following paragraphs.

6.2.1 Assumptions

Regarding the required calculation, a number of assumptions were needed. In particular the following two assumptions were made:

a. It was assumed that under the same chemotherapy regimen, the working time of each member of staff was constant every day.
b. It was assumed that during the working time, the member of staff involved in the treatment activity was not on any other care or supportive duty.

Under the above assumptions, the personnel cost was calculated by multiplying the unit cost with the working time. The unit cost was derived from the government founds the publication: 'PSSRU: Unit Costs of Health and Social Care [186]', and the staff working time was derived from staff working time survey. The details can be found as follows.

6.2.2 Unit cost

In order to obtain the personnel unit cost, the salary grade was used instead of the actual salary. This decision was made for three reasons. Firstly, the actual salary was unavailable because most individuals tended not to reveal their real income when asked. Additionally, since income has many different probable definitions, it could be claimed that some individuals could not fully understand the exact meaning of the term 'gross (net) earnings' in the current context, something that could lead to inaccurate answers. Secondly, the actual individual salary varied, so it could not be used to interpret or reflect the salary of other members of staff that were involved in the same treatment activity. Thirdly, the information of the national average salary amount for each salary grade could usually be obtained from the publications, something that rendered the staff unit cost estimates more robust, reliable and interpretable.

For the above reasons, the salary grade and the government founds the publication: 'PSSRU: Unit Costs of Health and Social Care [186]' were used for the estimation of the personnel unit cost. Furthermore, in order to bring the personnel unit cost estimates closer to the actual cost and to avoid overlooking any relevant costs, costs, such as allowances, bonuses and qualification were all taken into account (total salary). The salary unit cost list is shown on **Table 6.3**.

Table 6.3 The unit cost list of personnel cost

	Category	Working time per year	Total Working mins	Wages	
				Total	Unit cost
Nurse	Band 2	42 weeks / year 37.5 hours / week	94500 minutes	£16,332	**£0.17 / min**
	Band 5	42 weeks / year 37.5 hours / week	94500 minutes	£30,366	**£0.32 / min**
	Band 6	42 weeks / year 37.5 hours / week	94500 minutes	£36,633	**£0.39 / min**
	Band 7	42 weeks / year 37.5 hours / week	94500 minutes	£43017	**£0.46 / min**
Doctor	Specialist registrar	41 weeks / year 39.9 hours / week	88578 minutes	£93,617	**£1.06 / min**
	Consultant: medical	41 weeks / year 48.2 hours / week	118572 minutes	£178,360	**£1.50 / min**
Pharmacist		42 weeks / year 37.5 hours / week	94500 minutes	£38,912	**£0.41 / min**

6.2.3 Quantity

To obtain the information related with the staff working time for each treatment and each regimen, a scenario form was built (the example of this form can be found in **Appendix 6.2**). In this form, staff was divided into three main groups: doctors, nurses, and pharmacists. Based on the salary band set in the current study and the clinical grading system, each group was further divided into the following sub-groups:

a. Doctors: Foundation House Officer 1, Foundation House Officer 2, Specialty Registrar (StR), Clinical Practitioner, and Consultant.
b. Nurses: Band 1, Band 2 (Clinical support worker), Band 3, Band 4, Band 5 (24-hour ward nurse), Band 6 (Nurse team leader), Band 7 (Nurse team manager), Band 8, and Band 9.
c. Pharmacists: Pharmacist and pharmacy technician.

After the scenario form for each regimen and treatment was completed (in line with expert opinions), it was further simplified by grouping together regimens and treatments containing similar medicines or processes. For example, all the mild outpatient-based chemotherapies were grouped into one. After simplifying the form, a staff survey was performed. For each simplified treatment group, the involved staffs were asked to state their position on a salary scale (or the clinical grade) and the time spent on the treatment for one patient per day (working time per patient on a daily basis). This included direct and indirect working time. The result of the survey was later checked by experts resulting in a final table (containing the personnel cost per day/visit per patient for each treatment.)The resulting table can be found on **Appendix 6.2**. An abstract of the complete table is also shown below (**Table 6.4**).

Table 6.4 The abstraction of the staff working time survey result

			ADE								
			In-patient period								
			Indirect contact				Direct contact				
			No	Min	wages	overheads	capital	No	Min	wages	overheads	capital
Doctor (Modernising Medical Careers)												
Foundation House Officer 1												
Foundation House Officer 2												
Specialty Registrar (StR)								1	15	£15.9	£0.5	£0.5
Clinical Practitioner												
Consultant												
Nurse (Agenda for Change)												
Band 1												
Band 2	A	Clinical support worker	2	30	£10.2	£1.8	£0.9	2	30	£10.2	£1.8	£0.9
Band 3	B											
Band 4	C											
Band 5	D	24-hour ward nurse	2	20	£17.8	£1.2	£0.6	2	90	£51.6	£5.4	£2.7
Band 5	D	Day ward nurse										
Band 6	E	Nurse team leader	2	10	£7.8	£0.6	£0.5	2	10	£7.8	£0.6	£0.5
Band 7	F,G	Nurse team manager	1	10	£4.6	£0.3	£0.3	1	10	£4.6	£0.3	£0.3
Band 8	H, I											
Band 9	H, I											
Pharmacist												
Pharmacist			1	10	£4.3	£0.3	£1.5					
Pharmacist technician												

It is worth noting that the personnel cost was not applied to end-of-life care, as the latter did not involve any treatment process but only care, which, in the current study, was covered by ward cost.

Overall, the personnel cost can be simply summarized as the multiplication of the 'unit cost of staff working time' and their 'actual working time for treatment purposes' (quantity). The summary of the personnel costing method for each treatment is shown on **Table 6.5**.

Table 6.5 The summary of the personnel costing method

Personnel cost of each treatment/intervention	Unit cost	Quantity
Chemotherapy	PSSRU unit cost	Staff survey
Clinical trial		
Supportive care		
Erythropoietin		
Steroids		
G-CSF		
Transfusion		
Immunosuppressive therapy		
Laboratory test		
Follow-up / observation		
End-of-life care		

6.3 Overheads cost

Overheads (such as utility, management, or administrative personnel) and capital overheads (such as space, building or general equipment) were very important cost items/drivers for treatment cost estimation. However, it was impossible to itemize the above costs and reallocate them to each treatment separately. Therefore, another alternative reasonable way to estimate these costs had to be found. Considering the needs of the current work, it was decided that the use of the national average cost from the publication: 'PSSRU: Unit Costs of Health and Social Care 2006-07 [186]' provided the optimal alternative solution.

In the 'Unit Costs of Health and Social Care', the overheads costs were allocated to staff working time. Therefore, overheads costs were estimated by multiplying the staff working time survey results with the unit cost. The unit cost list of overheads and capital overheads for each member of staff is shown on **Table 6.6**. Also, the table of the staff working time survey can be found on **Appendix 6.2**.

Table 6.6 The unit cost list of overheads and capital overheads costs

Category		Working time per year	Total Working mins	Overheads		Capital overheads	
				Total cost	Unit cost (per min)	Total cost	Unit cost (per min)
Nurse	Band 2	42 weeks / year 37.5 hours / week	94500	£2,904	**£0.03**	£1,394	**£0.015**
	Band 5	42 weeks / year 37.5 hours / week	94500	£2,904	**£0.03**	£1,394	**£0.015**
	Band 6	42 weeks / year 37.5 hours / week	94500	£2,904	**£0.03**	£2,479	**£0.026**
	Band 7	42 weeks / year 37.5 hours / week	94500	£2,904	**£0.03**	£2,479	**£0.026**
Doctor	Specialist registrar	41 weeks / year 39.9 hours / week	88578	£2,904	**£0.03**	£3,084	**£0.03**
	Consultant: medical	41 weeks / year 48.2 hours / week	118572	£35,167	**£0.30**	£4,610	**£0.04**
Pharmacist		42 weeks / year 37.5 hours / week	94500	£2,904	**£0.03**	£4,486	**£0.05**

It is worth to note that overheads cost was not applied to end-of-life care, as end-of-life care does not involve any treatment processes. Therefore, no overheads cost could be allocated to the relevant staff working time information, as the latter was non-existent.

Overall, the overheads cost was calculated with the assistance of the staff working time survey results (quantity) and the PSSRU unit cost (unit cost). The summary of the overheads costing method for each treatment is shown on **Table 6.7**.

Table 6.7 The summary of overheads costing method

Overheads cost of each treatment/intervention	Unit cost	Quantity
Chemotherapy	PSSRU unit cost	Staff survey
Clinical trial		
Supportive care		
Erythropoietin		
Steroids		
G-CSF		
Transfusion		
Immunosuppressive therapy		
Laboratory test		
Follow-up / observation		
End-of-life care		

6.4 Ward/outpatient clinic cost

Except the actual treatment activities, all the other activity costs that occurred in the 'place of treatment' (including care, beddings change, meals, space and similar) were defined as the ward /clinic costs. For inpatients, the ward costs occurred in the ward. For outpatients, the ward costs occurred in the outpatient clinic.

The ward cost was a key to the treatment cost calculation, as it encompassed two important parts missing from both the personnel costs and the overheads costs. Firstly, it contained all the care costs, including the human resources costs, which were excluded from the "personnel costs (for treatment purpose only)". Secondly, it contained the cost of treatment space, which was not included in capital overheads in the 'PSSRU Unit cost of Health and Social Care 2006-07 [179]' (the source used in the current study to estimate the overheads costs).

For similar reasons to the ones described in the overheads costs section (difficult to itemize the ward cost, and to re-allocate all the activities separately), the national price list was used as the unit cost for ward/outpatient clinic. The relevant details are described in the following paragraphs.

6.4.1 Assumptions

For the required calculation, a number of assumptions had to be made:

a. It was assumed that no "single / multi people" or "standard / specialist" wards differences existed, as this information was not available in the study databases.
b. It was assumed that each inpatient used the same amount of care resources in ward for every inpatient day, and also the same with each outpatient in the outpatient treatment place for every outpatient visit.
c. It was assumed that under different inpatient-based treatments, all the inpatients used the same amount of care resources both with one another, and also with all the outpatients.
d. It was assumed that all the outpatient visits occurred in the hospital.

6.4.2 Unit cost

A number of different publications were used in order to obtain robust and reliable estimations of the ward unit cost for the inpatient stay and of the clinic unit cost for outpatient visit.

a. Inpatient

According to the 'Nursing care for older people' from the Personal Social Services Expenditure and Unit Costs England, 2006-07 [187], the cost of hospital stay was found to be £467 per week (£67 per day in round numbers). The reason for using this information as ward cost was that the cost of nursing care for older people could reflect the cost of simple care duty in the ward (which matches the study design of the current study). Regarding the other information sources, such as the reference cost or the national tariff, it was decided that they could not provide the precise cost of simple care duty in ward, as all the costs provided contained the care duty and the relevant treatment costs.

b. Outpatient

According to the "outpatient specialty code 324: Anticoagulant Service Total Attendances" from the 'Reference Cost Index', the cost of an outpatient visit was found to be £19 per visit (based on Consultant Led Follow up Attendance Outpatient Face to Face for Adult Attendance). The reason for choosing this information as the outpatient clinic cost was that the anticoagulant service was the closest estimate to all the non-treatment costs that occurred in outpatient clinics. This was because the anticoagulant service involved the least treatments and examinations (compared to other outpatient visits mentioned in the 'Reference Cost Index').

c. Sampling

According to the 'Pathology Services' from the 'Reference Cost', the cost of the blood sampling was £3 per sampling (Haematology - code: DAP823), while the cost of the tissue sampling (such as bone marrow sampling) was £26 per sampling (Histology / Histopathology– code: DAP824).

6.4.3 Quantity

The quantity for the ward/outpatient clinic cost calculation was based on 'the number of use'.

a. Inpatient

For the inpatient treatments, the quantity for the ward cost calculation was defined as the 'hospital stays'. Because of information insufficiency reasons (as mentioned in Chapter 5), the' number of hospital stays' for each cycle of treatment was derived from the relevant imputations (imputed by the assistance of 'treatment time' derived from the HMRN database, additional information from medical notes, and clinical guidelines/protocol).

b. Outpatient

For the outpatient treatments, the quantity for outpatient clinic cost calculation was defined as the 'number of outpatient visits'. Since the exact visit dates were not obtainable from the HMRN database, the outpatient visit frequency was set to once per month during the 'treatment time' (according to expert opinions). Therefore, the number of outpatient visits was possible to be obtained by simple division.

c. Sampling

For the sampling, the quantity for the sampling place cost calculation was defined as the 'number of sampling'. This information could be easily obtained by simple addition, as the exact sampling/screen dates could be derived from the HILIS database (the subset database of HMRN database).

Overall, the ward/space cost could be calculated by the multiplication of the unit cost (from three different information sources) and the quantity (number of uses). The summary of the ward costing method for each treatment is shown on **Table 6.8**.

Table 6.8 The summary of ward costing method

Ward/space cost of each treatment/intervention	Unit cost	Quantity
Inpatient treatments Chemotherapy Clinical trial End-of-life care	Nursing care for older people (£67)	Hospital stays
Outpatient treatments Supportive care Immunosuppressive therapy Follow-up / observation	Reference Cost Index (£19)	Numbers of visits
Laboratory test	Reference Cost Index	Numbers of sampling

6.5 Complication treatment cost

Apart from the drug, personnel, overheads, and ward costs, complication treatment cost was also an important cost item/driver which had a significant effect on the total treatment cost (based on the review results discussed in chapter 2). To be consistent with the cost estimation method discussed in the previous sections (section 6.1 to section 6.4), the complication treatment cost was estimated by the complication rate (quantity) and the unit cost of complication treatment (unit cost). It is worth to note that haematological complication (such as haemorrhage and similar) was not taken into consideration, as the treatment (transfusion) had already been considered.

According to expert opinions, the infection treatment (antibiotics use) was also calculated separately, as it was an important and costly complication treatment. The calculation process is illustrated in **Figure 6.2**.

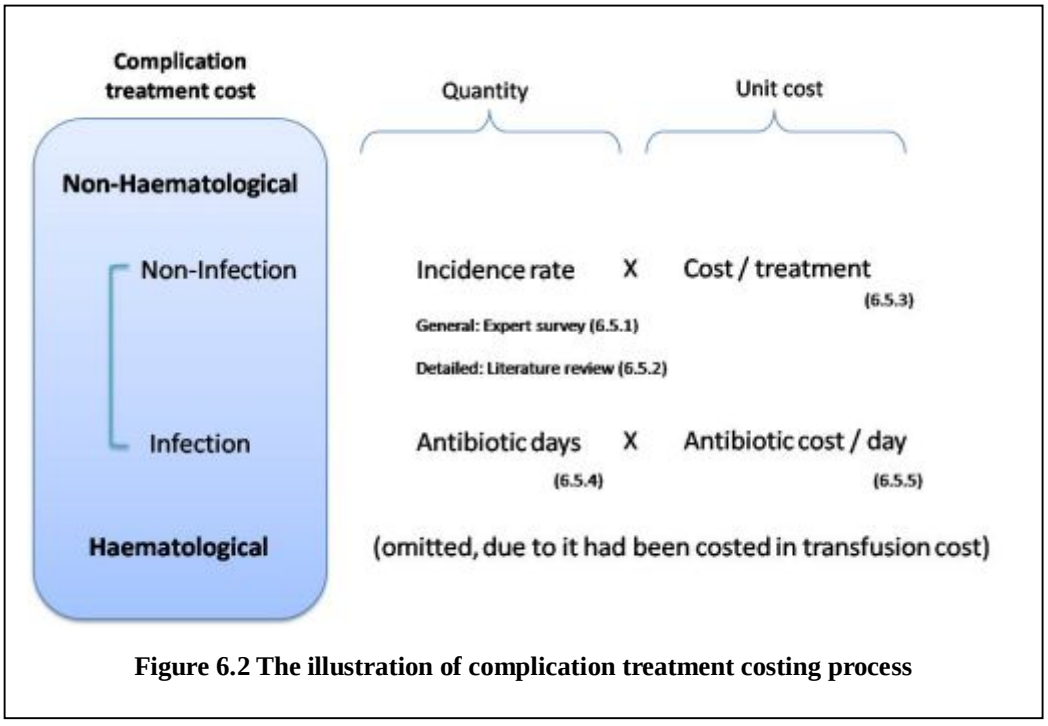


Figure 6.2 The illustration of complication treatment costing process

The two different approaches for complication incidence rate and all of the details for the complication treatment cost calculation are discussed in the following section.

6.5.1 Non-infection complication rate derived from expert survey

Based on the detailed information in the Palliative care database, the complications were classified into the following 10 categories: Digestion disorder, ENT disorder, renal disorder, respiratory disorder, cardiac disorder, ophthalmological disorder, Neurological disorder, Rheumatic disorders, and pain. After the complication categories had been identified, an expert survey was performed in order to obtain the incidence rate of each complication category for the treatments that did not include the complication cost into the treatment cost. The result is shown below (**Table 6.9**).

Table 6.9 The expert survey results of the complication incidence rate

	chemotherapy	Clinical trial	Transfusion	Venesection Supportive care Immunosuppressive End-of-life care Follow-up
ENT disorder	1%	1%	-	-
Renal disorder	2%	2%	-	-
Cardiac disorder	5%	5%	-	-
Respiratory disorder	10%	10%	-	-
Skin disorder	-	-	-	-
Ophthalmological disorder	5%	5%	-	-
Pain	10%	10%	10%	-
Digestion disorder	5%	5%	-	-
Neurological disorder	2.5%	2.5%	-	-
Rheumatic disorders	2.5%	2.5%	-	-

6.5.2 Non-infection complication rate derived from literature review

Expert survey provided a general idea of the complication incidence rate of each treatment as detailed information for each regimen was not available. To obtain detailed complication rates for each treatment and each regimen, both a comprehensive system review and a meta-analysis of all reported complication rates in AML / APML patients were carried out, without language restriction. The details are described below.

a. Literature search strategy

Three sources were used for searching for relevant literature: electronic databases, conference proceedings, and hand-searching relevant articles. A systematic review was firstly performed by searching the following electronic databases and conference proceedings (from 1990 to 2009): Medline, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials. The standard search strategy recommended by the Cochrane Collaboration was used for different databases after being modified. As for the references from the included papers and relevant journals were hand searched. There was no language restriction used in the search process. Subject headings and keywords used included the following:

- Adult AML / APML: The definitions and keywords of AML / APML used in Chapter 2 (literature review) were applied to this search process.
- AML / APML treatment: All the relevant treatment names and regimen names mentioned in previous sections were used, such as AraC, ADE, G-CSF and similar.
- Complication: complication, side effect, adverse effect, toxicity, and all the relevant complication terms (such as vomit, infection or similar) were used.

In total, 193 relevant studies were found.

b. Inclusion and exclusion criteria

- Inclusion criteria

  Eligible studies were defined as those that could provide the detailed numbers or percentages about the complication incidence cases, even if the complication report was not their main study purpose/subject.

  To maximize the amount of review study sources, studies in which the AML / APML patients received relevant treatment or regimen only in one arm (either the study arm or the control arm) were also permitted.

- Exclusion criteria

  Studies that failed to provide the detailed numbers and percentages of the complication cases were excluded. Moreover, studies were excluded if they

included more than one treatment or one regimen in one research arm. This was in order to keep the complication rate simple and to avoid using the numbers that were affected by more than one treatment or regimen. However, this exclusion criterion could not be applied to the supportive care regimen (G-CSF). Previous studies and guidelines concluded that G-CSF is usually used as a subside regimen. Therefore, studies were eligible if the regimen G-CSF was combined with other treatments or regimens in any trial arms, in the perspective study design. However, the extracted complication rates for G-CSF had to be further analyzed and sorted by the regimens that were subsided by G-CSF before summarizing the results.

Also, the studies were excluded if they only provided the "haematological complication rate". This is because the haematological complication treatment cost had already been calculated in 'transfusion', and, therefore, it would be double counted if this cost was considered again here.

In addition, pediatric studies were also excluded because the main study population in the current research consisted of adults, rendering pediatric information unsuitable for our purposes. However, studies were permitted / included if they included patients under 18 years old as part of their study population (but not only patients under 18 years old).

Overall, 77 studies were found to be suitable for analysis. 116 studies were excluded because they failed to provide the details of complication rate or because all the study arms were applied with more than one treatment or regimen. The details of the searching process are illustrated in **Figure 6.3**.

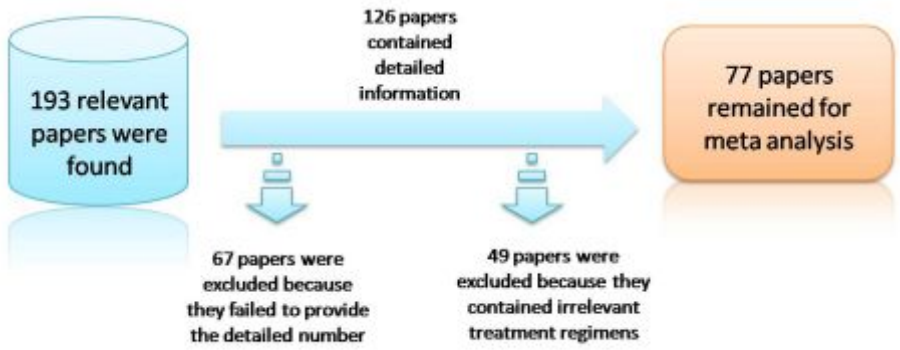


Figure 6.3 The illustration of relevant paper searching process

c. Data extraction

The following data were extracted from each of the included studies: general information, participants, intervention, and complication rates.

- General information
  Title, authors, source (year / volume / pages / journal or conference), country, and study design (RCTs or not) information was collected.
- Participants
  Number of study population (‘initial sample size’ or ‘number of AML or APML patients’ if AML / APML is not the only study population), setting of target population /patients’ baseline characteristics (age and cancer treatment stage), and study period.
- Intervention
  The following information was included: treatment or regimen type (such as regimen AraC, transplantation, and similar) and the dosage used in the study arm.
- Complication:
  Details related with all the reported complications were collected. This included main domains of complications, the grade of complication, numbers or percentages of complications.

Since the authors of the related literature presented/reported the rates in various formats, it is worth to note that two rules were applied in order to extract and report the complication rates systematically:

- Categorizing the reported complications into 11 domains
  According to the WHO Common Toxicity Criteria [188] and the National Cancer Institution (NCI) Common Terminology Criteria for Adverse Events v3.0 [189], the reported complications were divided into 11 domains: cardiovascular disorder, dermatological (skin) disorder, gastrointestinal disorder, hepatic disorder, Renal / genitourinary disorder, pulmonary disorder, neurological disorder, edema, local, pain, and infection.

- Grading the severity of each reported complication
  According to the WHO Common Toxicity Criteria [188] which grades complications into 5 levels (grade 0 to 4) and the National Cancer Institution (NCI) Common Terminology Criteria for Adverse Events v3.0 [189], each reported complication was further divided into three levels: unspecified, mild, severe. If the reported

complication was graded between 0 and 2 in the WHO Common Toxicity Criteria or graded between 1 and 3 in the NCI toxicity criteria, then the complication was classified as ‘mild’. If the reported complication was graded between 3 and 4 in the WHO Common Toxicity Criteria or graded between 4 and 5 in the NCI toxicity criteria, then the complication was classified as ‘severe’ All the remaining situations (including the ones labeled as ‘not specified’) were classified as ‘unspecified’.

- Ensuring the reported result is consistently formatted
  To ensure that the formats of each of the reported results were consistent, the ‘exact number of patients’ was set as the only representation format for this review (although ‘numbers’ and ‘percentages’ are both common formats for complication reports). Therefore, all the percentages extracted from the reviewed studies were converted to numbers, according to their study sizes.

After all the required information had been extracted from the respective studies, it was sorted by treatment type, regimen, domains of complications, and grades of complications. The systematic review result is shown on **Appendix 6.3**.

d. Meta analysis

After the systematic review had been performed, the results from multiple studies needed to be summarized into a single estimate in order to be used later for cost calculation. According to Glasziou P [110] and to the opinions of other leading figures in the meta-analysis field, the result synthesis for the complication rate was simply pooling the results altogether if the complication incidence rate was considered to arise from a single common population (fixed effect model). Therefore, it was assumed that all the study results found arose from a common group of population, and that the synthesis of complication rate was calculated as the total cases in the total population. The relevant summary is shown on **Appendix 6.3**, while an abstract of the summary table is shown below (**Table 6.10**).

As it can be observed in **Table 6.10**, the complication incidence rates for regimen ADE (chemotherapy) were derived from 12 previous clinical studies. After data extraction and systematic report, a total of 18 different types of complications were found and reported. With the application of the meta-analysis method, all the complication rates were summarized into a single estimate. For example, nausea was found to be the adverse event of ADE from 4 study arms in 3 studies. After the results were summarized, the nausea incidence rate for ADE treatment was found to be 34.5%.

Table 6.10 The abstract of the summarized literature review for complication rates

		ADE											
		Heil 1995 [223]	Bishop 1996 [224]	Lee 1999 [225]	Heil 1995 [223]	Hann 1997 [226]	Heil 1997 [227]	Heil 1997 [227]	Heil 1997 [227]	Heil 1997 [227]	Heil 1997 [227]	Bishop 1996 [224]	
Number of Patient		30	152	41	39	770	262	67	157	58	26	149	
Age		15-75 yr	15-60 yr	≥60 yr	15-75 yr	All age	≥16 yr	≥16 yr	≥16 yr	≥16 yr	≥16 yr	15-60 yr	
Randomised trial		Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
Controlled trail		Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	
Phrase		-	In	In	-	In	In 1	In 2	Con 1	Con 2	Con 2	In	
Regimens													
AraC	mg/m2	100	100	100	100	100	200	200	200	200	3000	3000	
	Days (dose)	7	7	7	8	10	7	5	5	5	6	4 (8)	
Daunorubicin	mg/m2	45	50	30	60	50	45	45	45	45	30	50	
	Days	2	3	3	3	3	3	2	2	2	2	3	
Etoposide	mg/m2	100	75	100	100	100	100	100	100	100	-	75	
	Days	5	7	3	5	5	5	5	5	5		7	
Complications													
Fever							241	50	99	33	24		78%
Severe		5			2								10%
Infection			96				252	47	85	30	24	128	76%
Severe		2			2	46							6%
Pneumonia													
Severe		2			2								6%
Pain													
Severe		-			1								3%
Nausea / vomiting									144			137	91.8%
Severe (grade 3-4)		0.5			1				49			79	34.5%
Diarrhea									25			34	19.3%
Severe (grade 3-4)		-			1				13			25	11.3%
Severe Stomatitis										4			7%
Severe Cardiac disorder (failure)		0.5			2	8							1.3%
Severe Hepatic disorder		3			4								10.1%
Sever Bilirubin										16			27%
Cerebellum disorder									6	10		10	10.8%
Severe (grade 3-4)							0					3	0.7%
Neurologic disorder								15					22%

6.5.3 Unit cost of complication treatment

In order to obtain the unit cost of the complication treatment and to be consistent with the cost estimation methods mentioned in previous sections, the national average cost (NHI Reference Cost Index [180]) was used. The 4-step procedure is discussed in detail in the following paragraphs.

Step 1: Selecting relevant adverse events from Common Toxicity Criteria

Although all the adverse events were listed in the WHO or NCI Common Toxicity Criteria tables, not all of them could be related to the AML / APML treatment. In the current study, only the adverse events that were caused by AML/APML treatments were taken into consideration. Therefore, the adverse events listed in the Common Toxicity Criteria were re-selected by experts, with only the relevant adverse events being kept.

Step 2: Translating all the selected adverse events into HRG 4 codes

To obtain the unit cost, the HRG 4.0 code for each selected adverse event was needed. Since ICD-10 code is the linkage between disease and HRG 4.0, 'matching ICD-10 to each selected adverse event' was performed. After ICD-10 for each adverse event had been identified, the codes were further translated into HRG 4 codes with the use of HRG 4 Chapter Listing [190]. The details are shown in **Appendix 6.4**.

Step 3: Linking the national average cost to each adverse event

After the HRG 4 code for each adverse event were identified, the final step for obtaining the unit cost was linking these HRG4 codes to the National average cost index (NHS Reference Cost Index 2006/07 [180]). However, before obtaining the unit cost estimation (by applying the NHS reference cost directly to each adverse event), some assumptions and adjustments had to be made. The relevant details are discussed below.

- Using the 'lower quartile' data

  The 'lower quartile cost' (from 'Reference Cost Index [180]') was decided to be used as the unit cost, instead of the average cost. This was because the adverse events / complications were not the main reason that patients seek

care in hospitals. Therefore, it was assumed that the "lower quartile cost" was the cost that was closer to the actual complication treatment cost rather than the average cost.

- Cost adjustment

  As the complication treatment usually took place during the main AML/APML treatment, some medical resources/cost drivers (such as the ward cost and the overheads cost) were shared between these two simultaneous treatments. In order not to double count these costs, it was assumed that the shared cost was 30% of the complication treatment cost, and also this shared cost was already included in the AML / APML treatment cost discussed in previous sections. Therefore, the adjusted complication treatment cost was set to 70% of the associated lower quartile NHS Reference Cost.

The unit cost list for each selected adverse event can be found in **Appendix 6.4**.

Step 4: Grouping and merging the cost by adverse event domains

As mentioned earlier, the unit cost for each adverse event was identified as described in previous 3 steps. However, the grouping complication treatment cost was still needed. This was because, in many included studies, the authors only reported the complication rate in the main domain (such as cardiovascular disorder and hepatic disorder) instead of reporting it in detail (such as vomit and nausea).

For grouping or merging the cost, the 'weighted cost' was used instead of averaging the adverse event costs belonging to the same domain. The domain cost was weighted by the 'reported numbers of cases' of each adverse event in the 'NHS Reference Cost Index [180]'. The results can be found in **Appendix 6.4**, and an abstract of the table is shown below (**Table 6.11**).

Table 6.11 The abstract of the summary of the unit cost list for complication

	Adverse event	ICD-10	HRG 4.0	No of cases	Lower quartile	× 70%
Oedema	Oedema, not elsewhere classified	R60	WA18Y	299	£403	£282
	Cerebral oedema	G93.6	AA25Z	2684	£649	£454
	Gestational oedema	O12.0	NZ04A	629	£336	£235
			NZ07A	382	£500	£350
	Pulmonary oedema	J81	DZ20Z	76	£815	£571
	Pulmonary oedema due to heart disease	I50.1	EB03I	904	£916	£641
					£634	£444

Taking ‘oedema’ as an example (please refer to **Table 6.11** above), when the reported complication was ‘pulmonary oedema’, the unit cost of the complication was £641. However, when the reported complication was ‘oedema (unspecified)’, then the weighted estimation (£444) was used as its unit cost.

6.5.4 Infection complication: Antibiotic days

Except the treatments for non-infection complication, another important complication treatment was the antibiotic use for treating infections. Since it is a widely used but very costly treatment, the costing is discussed separately. In order to be consistent with the costing methods discussed in previous sections, the bottom-up method was used for costing the ‘antibiotic use’. The number of antibiotic days (quantity) is discussed in the current section, while the cost of antibiotic day (unit cost) is discussed in section 6.5.5.

The ‘number of antibiotic days’ was derived from additional information from a subset of the HMRN database (please refer to chapter 3 for details). However, information was not available for all the treatments/interventions due to data source unavailability. To overcome this issue, an expert survey was carried out as a supplement for the treatments/interventions that were found to have missing ‘number of antibiotic days’ information. Relevant details can be found in Appendix 6.7.

6.5.5 Infection complication: Unit cost of antibiotic day

To ensure consistency when calculating treatment cost, the bottom-up costing method was also used for estimating the unit cost of antibiotic day. The aforementioned unit cost contained three different cost drivers, namely drug cost, personnel cost, and overheads cost. Ward cost was not included, as it is a cost shared with the AML/APML treatment (mentioned in 6.5.4) and, thus, it had been already calculated in the treatment cost (mentioned in 6.4). Details of the three cost drivers are described below.

1. Drug cost

According to expert survey, 2 drugs are commonly given for antibiotic treatment, namely gentamicin (i.v.) and Tazocin (i.v). Based on the BNF price list [178], the unit cost for the former is £8.45 and for the latter £60.68 per day. Therefore, the sum of these two drug costs was set as the drug cost for each antibiotic day (£69.13). It is worth noting that the

estimate was close to the 'Band 2 anti-fugal drug cost (£67)' from the 'Reference Cost Index[180]'. Therefore, it is safe to claimthat the estimate was reliable.

2. Personnel cost and overheads cost

According to expert survey, the 'extra staff time' for delivering these two drugs as antibiotic treatment was 10 minutes for one Band 2 nurse, 5 minutes for two Band 5 nurses, 10 minutes for one Band 6 nurse, and 5 minutes for one pharmacist. Based on the 'PSSRU unit cost'[179], the calculated amount of the personnel cost for antibiotic treatment was found to be £10.85, while the overheads cost was found to be £1.86.

Overall, the unit cost of antibiotic day was found to be £81.84 per day.

6.5.6 Integration of the complication cost

After the unit costs and the quantities for 'non-infection complication' and for 'infection complication' had been identified, the non-infection and infection complication treatment costs were calculated by multiplying the quantity (complication rate / antibiotic days) with the unit cost of complication. The total complication cost was the sum of these two types of complication costs. The integration process is illustrated in **Figure 6.4**, and the details are described in the following paragraphs.

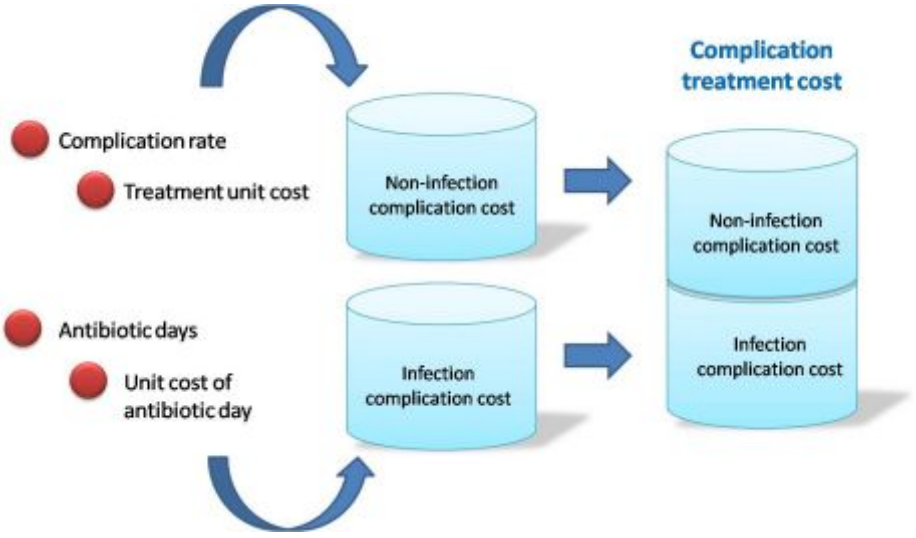


Figure 6.4 The illustration of the complication cost integration process

1. Non-Infection complication cost (approach one: based on expert survey)

According to the complication rate derived from the relevant expert survey (please refer to **Table 6.9**), the non-infection complication treatment costs were calculated by multiplying the rates by the unit cost calculated earlier (please refer to section 6.5.3). However, there were three types of complication that could not be matched to any adverse event on the unit costs list. Therefore, the 'NHS Reference Cost Index' [180] was used to represent the cost. These three complications and their unit costs (after adjustment) were: ENT disorder £103, Ophthalmological disorder £101, and Rheumatic disorders £183. The cost list is shown below (**Table 6.12**).

As it can be observed (**Table 6.12**), the non-infection complication cost of chemotherapy and clinical trial was £115.1, while the non-infection complication cost of transfusion was £32.4, without considering the regimen.

Table 6.12 The complication cost list (based on expert survey)

	chemotherapy	Clinical trial	Transfusion	Venesection Supportive care Immunosuppressive End-of-life care Follow-up
ENT disorder	£1.0	£1.0	-	-
Renal disorder	£1.9	£1.9	-	-
Cardiac disorder	£18.2	£18.2	-	-
Respiratory disorder	£30.1	£30.1	-	-
Skin disorder	-	-	-	-
Ophthalmological disorder	£5.1	£5.1	-	-
Pain	£32.4	£32.4	£32.4	-
Digestion disorder	£15	£15	-	-
Neurological disorder	£6.8	£6.8	-	-
Rheumatic disorders	£4.6	£4.6	-	-
	£115.1	£115.1	£32.4	£0

2. Non-Infection complication cost (approach two: based on literatures)

In relation to the non-infection complication treatment costs (based on the literature review), the costs were also calculated by multiplying the summarized complication rates with the unit cost. However, only the 'severe' complication rates were taken into account and used in the cost calculation. This was because of two reasons. Firstly, most

patients recovered from the mild complications without any treatment. Therefore, there was no need to take the cost of mild complication treatment into account. Secondly, when the complication rate was reported in an abstract way with no sufficient details (for instance 2% of patients had headache including mild and severe cases) it was impossible to distinguish the percentage of mild and severe complications. Therefore, only the "severe" complication rate was used for cost calculation.

Furthermore, when both the domain cost and its detailed adverse event costs of the severe complication treatment were available, the detailed severe adverse event cost belonging to the domain was not counted. This was in order to prevent double counting. The result can be found on **Appendix 6.6**, while an abstract of the appendix is shown below (**Table 6.13**).

Table 6.13 The abstract cost list for non-infection complication (based on literatures)

	Incidence rate	Unit Cost	Cost	Total cost
ADE				£188
Severe fever	10%	£273	£27	
Severe pain	3%	£324	£10	
Severe Nausea / vomiting	34.5%	£120	£41	
Severe Diarrhea	11.3%	£130	£15	
Severe Stomatitis	7%	£97	£7	
Severe Cardiac disorder	1.3%	£364	£5	
Severe Hepatic disorder	10.1%	£224	£23	
Neurologic disorder (Severe)	22%	£272	£60	
Severe Cerebellum disorder	0.7%	£393		

As it can be observed (**Table 6.13**), only the severe complication cost was calculated. Also, when the unspecified complication domain details were available, the subset adverse event cost was not calculated. After simple multiplication and addition, the non-infection complication of regimen ADE (chemotherapy) was found to be £188.

3. Infection complication cost (antibiotic use)

In relation to the infection complication treatment, the cost was calculated by multiplying the 'number of antibiotic days' with the 'unit cost of antibiotic day'. The calculated amount was £81.84' (please refer to 6.5.5 for details). The infection complication treatment cost for each treatment/intervention can be seen in **Appendix 6.7**.

4. Integrated complication cost

After the non-infection and the infection complication costs were obtained, the complication treatment cost was calculated by simple addition of the aforementioned two costs. The integrated complication costs for each treatment/intervention are listed in **Appendix 6.7**, and an abstract of them can be seen below (**Table 6.14**).

It is worth to note that complication rates were not provided for some of the treatment, such as chemotherapy regimen Aspirin and supportive care. This was because no relevant information (complication rates) could be found in the examined AML/APML studies. Therefore, it was assumed that no severe complication occurred due to these treatments. The integrated complication cost and the integration details for each treatment/intervention are listed in **Appendix 6.7**. An abstract of the **Appendix 6.7** is shown below (**Table 6.14**).

Table 6.14 An abstract of the cost list of complication treatment

	Non-Infection Complication cost		Infection complication cost (Antibiotics Cost)			Total complication cost	
	Type 1 (derived from literatures)	Type 2 (derived from expert survey)	Antibiotics days	Day cost	Antibiotics cost	Type 1	Type 2
ADE	£188	£115.1	12 / course	×81.8	£981	£1169	£1096
Course 1	£94	£57.6	14	×81.8	£1145	£1239	£1203
Course 2	£94	£57.6	7	×81.8	£573	£667	£631
ADE + Mylotarg	£188	£115.1	12 / course	×81.8	£981	£1169	£1096
Course 1	£94	£57.6	14	×81.8	£1145	£1239	£1203
Course 2	£94	£57.6	7	×81.8	£573	£667	£631

As it can be seen in **Table 6.14**, two approaches were used in order to derive the non-infection complication cost. Based on expert opinions, the cost was further broken down evenly into courses/cycles. Also, according to expert suggestions, it was decided that the cost of regimens was the same with or without the inclusion of Mylotarg. Overall, the total cost was the sum of the non-infection complication cost and the infection complication cost. As it can be observed in **Table 6.14**, the complication cost of regimen ADE course 1 was found to be £1239 based on literature review, while it was found to be £1203 based on expert survey. It is worth to note that the complication

costs between the two different approaches (of non-infection complication cost calculation) were not significantly different (£36). Therefore, it is quite safe to claim that the estimates derived by using the two aforementioned approaches were highly consistent.

6.6 Reference cost

In relation to the 4 treatments that were impossible to be cost using the bottom-up method, the 'Reference Cost [180]' was used for cost representation the cost. Further details related to the above can be found in the following chapter.

6.7 Summary

The current chapter dealt with the calculation of cost drivers. More specifically, the related calculation methodologies, data sources, and results were presented and briefly discussed. The work presented here formed the basis for the next phase of the study, which involved treatment/intervention costing (chapter 7).

Chapter 7 Costing Method Phase 2

Treatment/intervention cost estimation

CHAPTER 7 COSTING METHOD PHASE 2

According to the study design (section 5.3.2), the cost measurement was divided into three phases (illustrated below). The current chapter covers costing phase 2, which is related to treatment/intervention cost estimation.

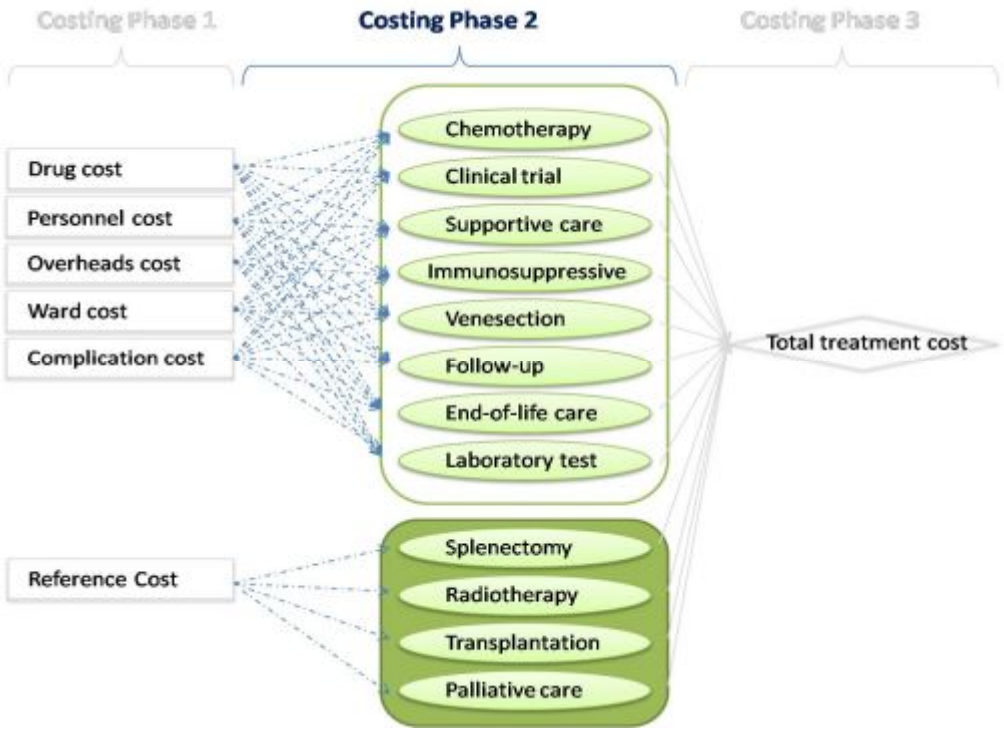


Figure 7.1 The illustration of costing phase 2

Based on the study design (discussed in chapter 5), it was decided that 12 types of treatment/intervention costs would be calculated in costing phase 2. These treatment costs were chemotherapy, clinical trial, supportive care (erythropoietin, steroids, G-CSF, and transfusion), radiotherapy, transplantation, immunosuppressive therapy, splenectomy, venesection, palliative care, observation (follow-up), end-of life care, and laboratory test. Each of the treatment/intervention is discussed in detail in the following sections. In the current chapter, the emphasis on the role of the 'number of uses' (usage frequency) as a means to calculate the treatment/intervention costs (by multiplying it with the obtained values of the five cost divers as discussed in chapter 5).

7.1 Chemotherapy

In the HMRN database, twenty eight different chemotherapy regimens were found to have been used on AML/APML patients. According to expert opinions, these twenty eight regimens could be divided into the following four groups: intensive inpatient chemotherapy, mild inpatient chemotherapy, intensive outpatient chemotherapy and mild outpatient chemotherapy.

- Intensive inpatient chemotherapy includes regimens such as ADE, AraC, Clofarabine, DA, FLA, FLAG, FLAG-Ida, HAM, MACE, and MidAC.
- Mild inpatient chemotherapy includes regimens such as Amsacrine, Arsenic trioxide, and campath.
- Intensive outpatient chemotherapy includes regimens such as Daunorubicin, Cyclophosphamid, ETI, FC, Fludarabine, Etoposide, Melphalan, Mylotarg, Vincristine, ATRA, Anagrelide, and Clopidogrel.
- Mild outpatient chemotherapy includes regimens such as Aspirin, Hydroxycarbamide and Chelating agent.

The cost calculation methods used in each of the above groups varied. Details about the five cost drivers used for costing the chemotherapy can be found in the following sections.

7.1.1 Drug/Regimen cost

As there a large number of chemotherapy regimens was involved, it was decided the process of costing each regimen to be described separately in 3.

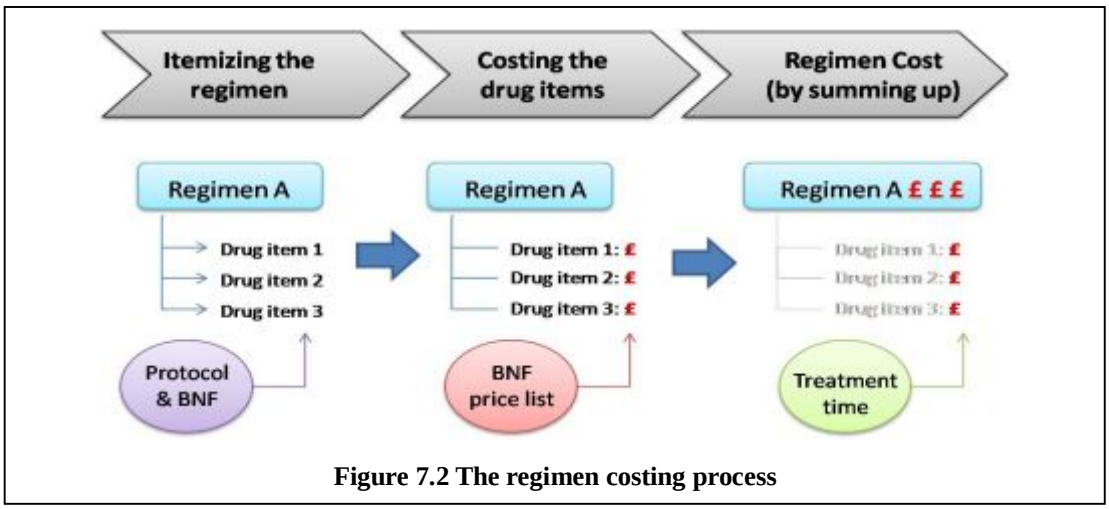


Figure 7.2 The regimen costing process

These three distinctive parts were: itemizing each regimen, costing drug items for each regimen, and costing each regimen. The costing process is illustrated above (**Figure 7.2**).

a. Assumptions

For the required calculation, a number of assumptions had to be made.

- The average patient body surface area required for the calculation of the dose and the actual cost was assumed to be $1.8m^2$ (based on 70 kg of body weight). This was because no relevant information about the patient body weight or body surface was available in the HMRN database. Therefore, the assumption was made based on the experts' suggestions.
- It was assumed that the regimen used for chemotherapy followed the clinical trial protocol. If the chemotherapy was not possible to be related to any clinical trial, then the regimen usage was assumed to follow the BNF suggestions or expert opinions.
- It was assumed that the full doses were given when the treatment time reached or exceeded the standard treatment time by the guideline/protocol.
- It was assumed that regimen Mini-MidAC used the same kind of drugs and the same amount of dosage as MidAC

b. Itemizing the regimen

According to the relevant information sources, the regimens of chemotherapy were divided into two categories in order to itemize the drugs used in each regimen. The categorization criteria were whether the regimen can be connected to the AML 15 trial protocol [184] / guideline [191] or not.

When the regimen could be connected to the clinical trial, the AML 15 trial protocol / guideline was used for itemizing the drugs that were used in each regimen. This included the dosage and the length of usage of the drugs. The regimens that fell into this category were ADE, AraC, DA, FLAG, MACE, MidAC and similar. In our context, taking regimen ADE as an example (and according to the AML 15 trial protocol suggestions), the chemotherapy regimen ADE was decided to contain the following drugs: 100mg/m2 Cytarabine twice per day from day 1 to 10, 50mg/m2 Daunorubicin once per day on day 1, 3, 5, 100mg/m2 Etoposide once per day from day 1 to 5, and some subside drugs, like 300g Allopurinol, 8mg Dexamethasone 5 doses, 1mg Granisetron 5 doses, and 10mg Metoclopramide).

When the regimen could not be connected to the clinical trial, the BNF [178] as well as relevant published studies, and expert opinions were used for itemizing the drugs and dosages of each regimen. The regimens that fell into this category included HAM, Amsacrine, Clofarabine, Anagrelide, Chelating agent and similar. Taking regimen HAM as an example (and according to Buchner's study [192], Schlenk's study [193] and expert agreements), regimen HAM was assumed to contain the following drugs for our purposes: 3g/m2 Cytarabine once per day for three days and 10mg/m2 Mitoxantrone once per day for 2 days for the current study. The same situation also applied to 'amsacrine' [183, 194].

c. Costing each drug item

After the drug items of each regimen had been identified and confirmed by experts, the relevant BNF price (official market price) was applied to each drug item.

Here, it is worth pointing out the costing method followed for regimen 'Mylotarg'. Mylotarg is a common supplementary regimen in AML / APML chemotherapy treatment in the UK. Although it is particularly expensive, its efficiency cannot be easily argued. However, the UK price for Mylotarg was not obtainable because it was still under trial and, thus, it was paid from the pharmaceutical company while the current study was carried out. Therefore, for our purposes, Mylotarg cost was considered to be the shadow cost (term used when a resource has been subsidized or an input is paid partly from some other national source of funds or organization). Because Mylotarg is a significant cost that would inevitably affect the final total cost, it was decided that for our purposes the Mylotarg cost had to be counted in order to avoid the regimen cost appearing significantly lower than its actual value.

To obtain the cost information for Mylotarg, worldwide prices were checked. However, this was not easy because this particular drug was still under trial in many countries and, thus, the prices were not available. For example, according to the official document, all the EU countries still refused Mylotarg's marketing authorization application [195] while the current work was carried out. Also, even in countries that allowed Mylotarg to be up for sale, in most occasions only relevant local health professionals could access the official website and obtain the price. With the kind assistance of various individuals, the Mylotarg international price and source list was obtained (shown on **Appendix 7.1**). In the frame of the current work, Mylotarg international average price was set as the Mylotarg unit cost (£1619).

The detailed drug item costs for each chemotherapy regimen are listed in **Appendix 7.2**, while the summarized list of the chemotherapy regimen cost and source is shown below (**Table 7.1**).

Table 7.1 The summarized list of the regimen cost and sources

		Dose reference	Cost reference
Intensive Inpatient Treatment			
ADE 10+3+5	£1159	AML 15 trial protocol	BNF
ADE + Mylotarg	£2780	AML 15 trial protocol	BNF
AraC (HD)	£1700	AML 15 trial protocol	BNF
AraC (LD)	£92	AML 15 trial protocol	BNF
Clofarabine	£17071	AML 16 trial protocol	BNF
DA 10+3	£1016	AML 15 trial protocol	BNF
DA + Mylotarg	£2637	AML 15 trial protocol	BNF
FLA	£1979	AML 15 trial protocol	BNF
FLAG	£2558	AML 15 trial protocol	BNF
FLAG-Ida	£3790	AML 15 trial protocol	BNF
FLAG-Ida + Mylotarg	£5411	AML 15 trial protocol	BNF
HAM	£2831	Buchner T and Schlenk RF	BNF
MACE	£1181	AML 15 trial protocol	BNF
MidAC	£1204	AML 15 trial protocol	BNF
Mini MidAC	£1204	As full dose of MidAC	BNF
Mild Inpatient Treatment			
Amsacrine	£156/day	BNF & Robert A	BNF
Arsenic trioxide	£470/day	Guideline	BNF
Campath	£991/week	BNF	BNF
Intensive Outpatient Treatment			
Cyclophosphamid	£70/week	Guideline: FC (remove F)	BNF
Cyclophosphamid/MESNA	£132	Guideline: Cyclo (HD)	BNF
Daunorubicin	£316/day	Guideline	BNF
Mylotarg	£1619	AML 15 trial protocol	**Appendix 7.1**
ETI	£41/day	Guideline	BNF
FC	£157/day	Guideline: F & C	BNF
Fludarabine	£153/day	Guideline	BNF
Etoposide	£13/day	BNF & expert opinion	BNF
Melphalan	£5/day	Guideline	BNF
Vincristine	£25/week	BNF & Expert opinion	BNF
ATRA	£16/day	Guideline	BNF
Anagrelide	£14/day	BNF & expert opinion	BNF
Clopidogrel	£1/day	BNF & expert opinion	BNF
Mild Outpatient Treatment			
Aspirin	£0.1/day	BNF & expert opinion	BNF
Hydroxycarbamide	£0.7/day	AML 15 trial protocol	BNF
Hydroxycarbamide + Aspirin	£0.8/day	AML 15 trial protocol	BNF
Chelating agent	£31/week	BNF & expert opinion	BNF

d. Costing each regimen

After the regimen cost per cycle were obtained, the regimen costs were calculated by multiplying the unit cost with the 'treatment time' (number of uses).

For inpatient chemotherapies, the unit cost list of each regimen was further broken down into daily cost before multiplication in order to cost the incomplete chemotherapy. Incomplete chemotherapy was defined as the one that had a 'treatment time' shorter than standard treatment time suggested by the AML 15 trail protocol. This was because in this case the full dose of chemotherapy was not delivered. It is also worth mentioning here that incomplete chemotherapy was associated with factors related to patient tolerence, treatment complications, and similar. The cost details for regimen that were broken down by day can be found in **Appendix 7.3**. After the breakdown cost lists were built up, the inpatient chemotherapies were simply obtained by matching the 'treatment time' to the comparative breakdown cost lists. The matching process is illustrated in **Figure 7.3**.

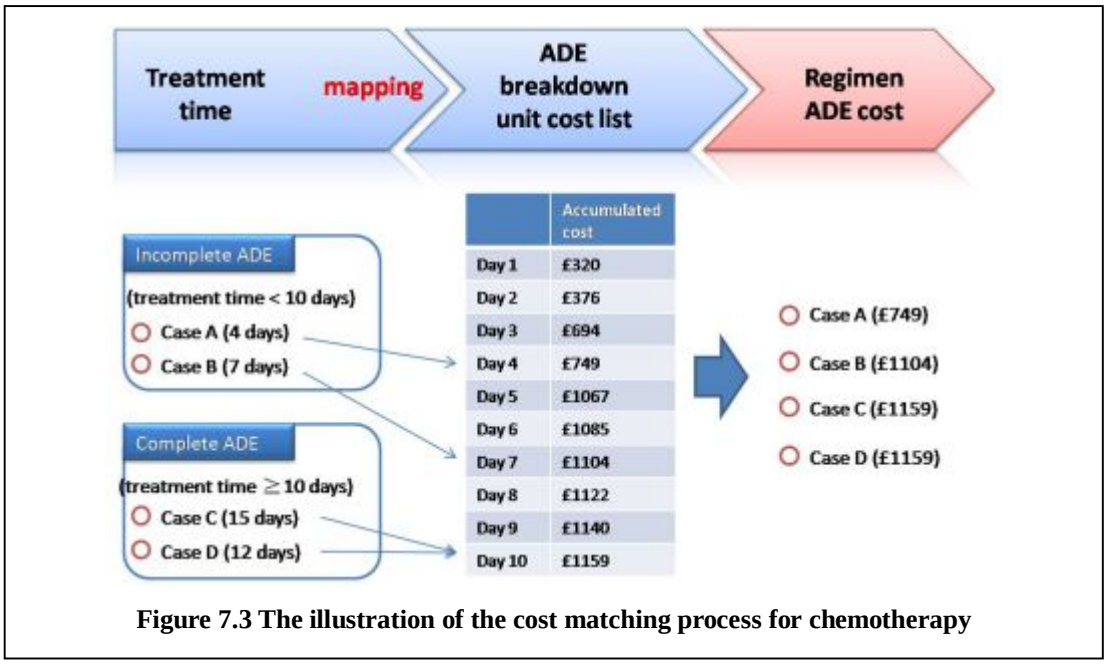


Figure 7.3 The illustration of the cost matching process for chemotherapy

For outpatient chemotherapies, the regimen cost was calculated simply by multiplying the unit cost with the 'treatment time' (number of uses), as the regimens were given either daily or regularly with no difference between the ones that were complete and those were not.

7.1.2 Personnel cost

To estimate the personnel cost for each chemotherapy regimen, the costing method was divided into two parts according to the types of the treatment delivery, namely for inpatient or for outpatient chemotherapy.

For inpatient chemotherapies, the personnel costs were calculated by multiplying the unit cost with the number of uses. The personnel cost per day for each regimen is discussed in earlier chapter (please refer to section 6.2 for descriptions and to Appendix 6.2 for details). Regarding the number of uses, the 'treatment time' was used in order to obtain robust cost estimations.

For outpatient chemotherapies, the personnel costs were also calculated by multiplying the unit cost with the number of uses. The personnel cost per day for each regimen is discussed in earlier chapters (please refer to section 6.2 for descriptions and to Appendix 6.2 for details). However, instead of the 'treatment time', the 'number of outpatient visits' was set as 'number of uses'. This is because the outpatient regimens did not need to be delivered by clinical staff on daily basis. Therefore, the personnel cost only occurred when the patient re-visited hospital. To calculate the 'number of outpatient visits', the following assumption was made: outpatients returned to hospital to get the medicine, consultation and have simple treatments once per month, as no detailed information could be obtained from the HMRN database. On this ground, the 'number of uses' (number of outpatient visits) was calculated by dividing the 'treatment time' by 28 days (equivalent to 1 month / 4 weeks).

The costing process for personnel cost calculation is illustrated in **Figure 7.4**.

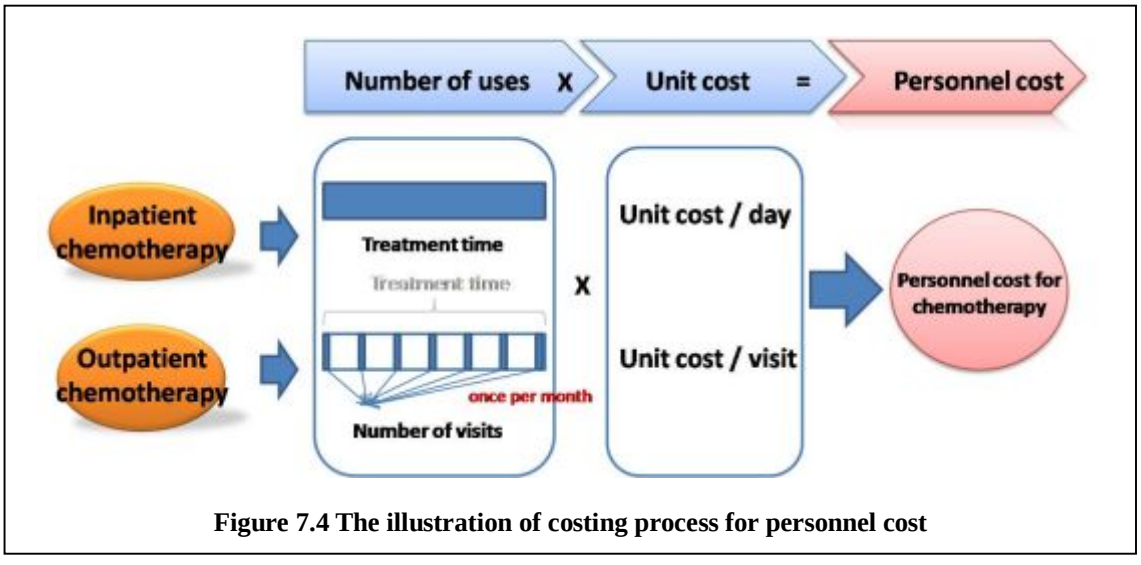


Figure 7.4 The illustration of costing process for personnel cost

7.1.3 Overheads cost

Based on the study design (refer to chapter 5) and on data availability, the overheads and capital overheads costs were calculated by allocating the national average overheads cost to staff working time, as it was impossible to itemize the overhead costs and reallocate them (please refer to section 6.3 for details). On this ground, the overheads and capital overheads costs only occurred when clinical staff delivered the treatments, similar to the personnel cost. For inpatient chemotherapies, the overheads costs occurred during the 'treatment time'. For outpatient chemotherapies, the overheads cost occurred when the outpatient visit took place.

Therefore, the overheads cost was calculated by 'unit cost' and 'number of uses' ('treatment time' or 'number of visits' depending on whether the chemotherapy was inpatient-based or not). The overheads cost per day for each regimen was obtained by multiplying the staff working time (from the staff survey) with the staff unit cost of the overheads (from 'PSSRU Unit Cost' [179]). For more details please refer to section 6.2, section 6.3, and in Appendix 6.2. The details regarding the 'number of uses' ('treatment time' and 'number of visits') can be found in the previous section (section 7.1.2). The costing process for overheads cost is illustrated below (**Figure 7.5**).

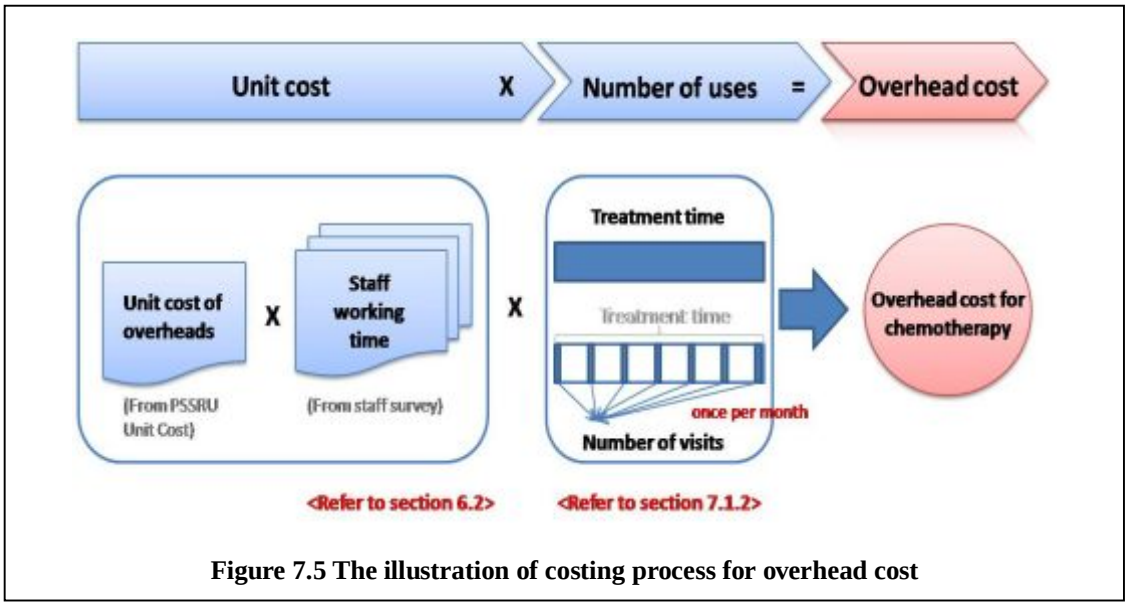


Figure 7.5 The illustration of costing process for overhead cost

7.1.4 Ward and outpatient clinic cost

According to the study design (chapter 5), ward cost and outpatient clinic costs were considered to be the costs that occurred in inpatient ward / outpatient clinic for care service and for other related supportive services. In this context, the inpatient ward and outpatient clinic costs were calculated by multiplying the 'unit cost' with the 'number of uses'.

The ward cost per day and the outpatient clinic cost per visit for each regimen have been obtained at earlier stages (details can be found in section 6.4). Regarding the 'number of uses', the calculation method was similar to the method used earlier (section 7.1.2 and 7.1.3). The 'number of outpatient visits' was set as the 'number of uses'. However, the 'number of uses' was calculated differently for the inpatient chemotherapies. Instead of 'treatment time', the 'hospital stay' was set as the 'number of uses' in order to reflect the actual resource consumption,

7.1.5 Complication cost

The 'complication costs' of each chemotherapy regimen were obtained at earlier stages (details can be found in section 6.5). It is worth to note that, the 'non-infection complication cost' based on literature review was used for treatment/intervention cost calculation. This was because, the complication cost list based on literature review provided more detailed information for each chemotherapy regimen (although both cost results were consistent with each other) comparing to the one based on the expert survey. Therefore, it was expected that, by employing this approach, the subtle complication cost differences between chemotherapy regimens could be captured at the later stage of the current work.

Also, in order to calculate the complication costs for each chemotherapy cycle, the complication cost needed to be further broken down into cycles. Regarding the 'infection complication cost', the detailed cost information for each cycle was available from the subset of the HMRN database (please refer to Appendix 6.3 for details). However, this was not the case for 'non-infection complication cost', for which it was assumed that the non-infection complication cost shares of each chemotherapy cycle were the same. Therefore, the non-infection complication cost of each cycle was obtained by dividing the total non-infection complication cost evenly. For example, as demonstrated in Appendix 6.3, the non-infection complication cost of regimen ADE was £188. Therefore, the non-infection complication cost of each cycle was calculated as £94, as the complete

chemotherapy of regimen ADE contained two cycles (£188/2=£94). The costing process is illustrated below (**Figure 7.6**).

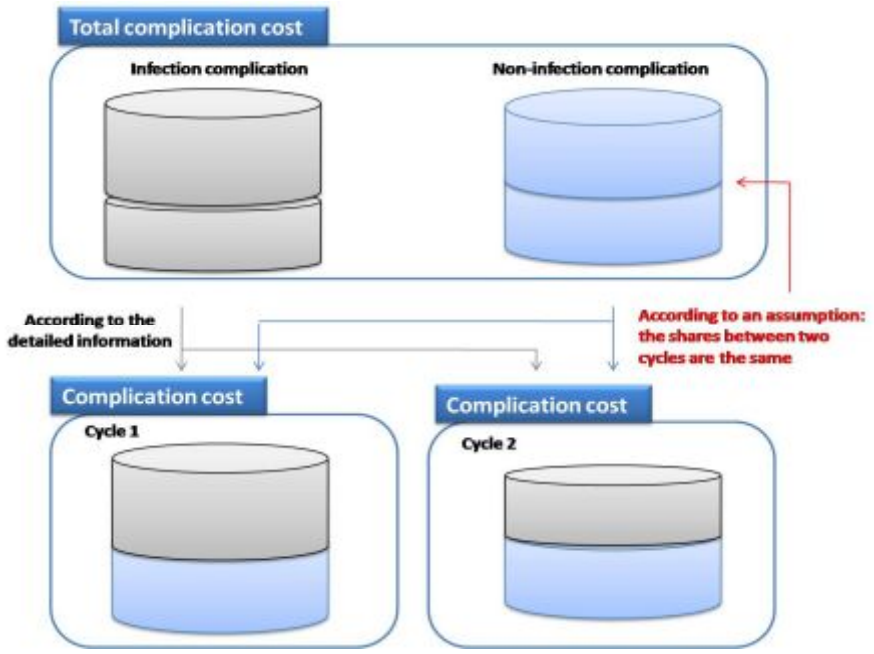


Figure 7.6 The illustration of costing process for complication cost

7.1.6 Summary

Considering the 5 cost drivers mentioned above, chemotherapy cost was considered to be the lump sum of drug/regimen cost (section 7.1.1), personnel cost (section 7.1.2), overheads/capital overheads cost (section 7.1.3), ward/clinic cost (section 7.1.4), and complication treatment cost (section 7.1.5). The summary of chemotherapy cost for each regimen is shown on **Appendix 7.4**, while an example is shown on **Table 7.2**.

Table 7.2 Example of the summary of chemotherapy cost

	Treatment cost								
	Drug cost		Personnel cost		Overheads cost		Ward/clinic cost		Complication (incl. antibiotic cost)
	Per Day	Quantity	Per Day	Quantity	Per Day	Quantity	Per Day	Quantity	
ADE									
10+3+5	£1158.46 (full course)		£135.6	× treatment time	£20.5	× treatment time	£67	× hospital stay	£1239
8+3+5	£1121.90 (full course)		£135.6	× treatment time	£20.5	× treatment time	£67	× hospital stay	£667
ADE + Mylotarg									
Course 1	£2779.87 (full course)		£135.6	× treatment time	£20.5	× treatment time	£67	× hospital stay	£1239
Course 2	£1121.90 (full course)		£135.6	× treatment time	£20.5	× treatment time	£67	× hospital stay	£667

7.2 Clinical trial

In the HMRN database, ten different clinical trial arms were found to have been used on AML/APML patients. The details about the five cost drivers and their number of uses that were used for calculating the clinical trial cost are described in the following sections. It is worth to note that the costing methods used for calculating the clinical trial cost was very similar to the method used for costing the intensive inpatient chemotherapies. This was because the costing methods for calculating the costs of intensive inpatient chemotherapies were all based on the 'AML 15 trial protocol [184]' and 'AML 14 trial protocol [196].

7.2.1 Drug/Regimen cost

Following the costing method and the assumptions made for intensive inpatient chemotherapy (discussed in section 7.1), the regimen cost of clinical trial was calculated by multiplying the 'unit costs of clnical trial regimens' with their 'number of uses'. The 'unit costs of clinical trial regimens' were derived from the following sources: the 'AML 15 trial protocol [184]' , the 'AML 14 trail protocol [196]' and the 'BNF price list [178]' (please refer to section 7.1.1 and section 6.1 for details). In relation to the 'number of uses', the calculation method was divided into two parts according to the completness of the treatment (please refer to section 7.1.1 for details and reasons):

- Treatment completed: When the 'treatment time' derived from the HMRN database was longer than the 'standard treatment time' derived from the AML 15 trial protocol, the 'standard treatment time' was set as 'number of uses'.
- Treatment incompleted: When the 'treatment time' was shorter than the 'standard treatment time', the 'treatment time' was set as 'number of uses'.

The detailed unit costs, usage frequencies and total regimen cost for each clinical trial regimen are shown on **Appendix 7.2**.

7.2.2 Personnel cost

Following the costing method and the assumptions made for intensive inpatient chemotherapy (discussed in section 7.1), the personnel cost was calculated by multiplying the 'personnel cost per day' with the 'number of uses'. The 'personnel cost

per day' was derived from the calculation based on the 'PSSRU Unit cost' and the 'staff working time' (derived from the staff survey). For more details regarding this please refer to section 6.2. In relation to the 'number of uses', the 'treatment time' or the 'standard treatment time' (derived from protocols [184, 196]) was set as 'number of uses' depending on the completeness of the clinical trial (please refer to section 7.1.2 for details and reasons):

- Treatment completed: the 'standard treatment time' was used as 'number of uses'.
- Treatment incompleted: the 'treatment time' was used as 'number of uses'.

The detailed unit costs, usage frequencies and total regimen cost for each clinical trial regimen are shown on **Appendix 7.4**

7.2.3 Overheads cost

Following the methodology discussed in the chemotherapy section (section 7.1.3), the overheads and capital overheads costs were caulculated by multiplying the 'overheads cost per day' with the 'number of uses'. The 'overheads cost per day' is discussed in section 6.3. In relation to 'number of uses', it was identical with 'number of uses' that was used for the personnel cost calculation, as the amount of the overheads cost was related to the 'staff working time' (relevant calculation details can be found in sections 7.1.3 and 7.2.1). The 'overheads cost per day' and the 'number of uses' for each clinical trial arm can be found in **Appendix 7.4**.

7.2.4 Ward cost

Following the costing method and the assumptions made for intensive inpatient chemotherapy (discussed in section 7.1.4), the ward cost was calculated by multiplying the 'ward cost per day' with the 'number of uses'. According to the calculations in section 6.4.2, the 'ward cost per day' was found to be £67 per day. Also, in order to reflect the actual resource consumption, the 'hospital stay' was set as 'number of uses', instead of 'treatment time'. The 'ward cost per day' and the 'number of uses' for each clinical trial arm can be found in **Appendix 7.4**.

7.2.5 Complication cost

The 'complication costs' of each chemotherapy regimen were obtained earlier (for related details please refer to section 6.5). The method that was followed for breaking down the complication cost into cycles was in line with the one used for chemotherapy (please refer to section 7.1.5). The cost details for each clinical trial arm can be found in **Appendix 7.4**.

7.2.6 Summary

According to the 5 cost drivers discussed earlier, clinical trail cost was considered to be the lump sum of drug/regimen cost (section 7.2.1), personnel cost (section 7.2.2), overheads/capital overheads cost (section 7.2.3), ward cost (section 7.2.4), and complication treatment cost (section 7.2.5). The summary of clinical trial cost for each regimen is shown in **Appendix 7.4**, while an example is shown on **Table 7.3**.

Table 7.3 Example of the summary of clinical trial cost

	Treatment cost								
	Drug cost		Personnel cost		Overheads cost		Ward/clinic cost		Complication (incl. antibiotic cost)
	Per Day	Quantity	Per Day	Quantity	Per Day	Quantity	Per Day	Quantity	
AML 15 ADE									
10+3+5	£1158.46 (full course)		£135.6	× treatment time	£20.5	× treatment time	£67	× hospital stay	£1239
8+3+5	£1121.90 (full course)		£135.6	× treatment time	£20.5	× treatment time	£67	× hospital stay	£667
AML 15 ADE + Mylotarg									
Course 1	£2779.87 (full course)		£135.6	× treatment time	£20.5	× treatment time	£67	× hospital stay	£1239
Course 2	£1121.90 (full course)		£135.6	× treatment time	£20.5	× treatment time	£67	× hospital stay	£667

7.3 Supportive care - Transfusion

Supportive care/therapy can be defined as a therapy that is given in addition to the primary therapy [197], or as a part of the main treatment [198]. Based on three sources (experts' opinions, information from Macmillan Cancer Support [198], and the treatments used on AML/APML), supportive therapy was definded as a therapy that contained five different sub-type treatments for AML/APML. These five treatments were transfusion (including blood and platelet transfusion), erythropoietin, haematopoietic grown factors (G-CSF), and steroids, the first of which (transfusion) is discussed in the current chapter.

7.3.1 Introduction

Transfusions in AML/APML treatment can be grouped into two types depending on the blood products transfused, namely whole blood and platelet transfusions. The whole blood transfusion mainly is given for correcting anaemia and other similar side effects (haematological complications) caused by AML/APML treatments (such as chemotherapy), while the platelet transfusion mainly is given for haemorrhage and other similar side effects (haematological complications) again caused by AML/APML treatments. Therefore, costing the transfusion can be seen as costing the haematological complication, which was excluded from the complication cost (please refer to section 6.5 for more details). The details about the five cost drivers and their usage frequencies used for calculating the transfusion cost are described below.

7.3.2 Blood product cost

Based on the relevant study design (discussed in chapter 5), the transfusion was calculated by multiplying the 'blood product unit cost' with the 'number of transfusions'. The calculation details are described as follows.

a. Blood product unit cost

The transfusion unit cost was calculated by multiplying the'unit cost' with the 'quantity'. The unit costs of the blood products were derived from the 'National blood and blood components price list' from the National Blood Service [181] (please refer to section 6.1 for details). Based on the analysis result of the 'Palliative Care Database', the 'quantity' that was given for each transfusion was found to be two blood units and one platelet unit in round numbers (please refer to chapter 4 for details). Therefore, the unit cost of each

transfusion was the lump sum of each blood product cost, which in turn was found to be £512 in total for each transfusion.

b. Transfusion frequency

The actual 'number of transfusions' or actual 'transfusion frequency' was not obtainable, as the transfusion date was not routinely recorded by the research nurses. In order to overcome this issue, an extrapolated 'transfusion frequency' was needed. For our purposes, the detailed treatment records of 20 patients from 'Palliative Care Database' were used for extrapolating the 'transfusion frequency'. The details of the extrapolation can be found in chapter 4. Based on the results of the extrapolation, it was observed that patients received transfusion once every four days when the disease time was less than two months, or once every 14 days when the disease time was longer than 2 months.

After the extrapolated 'transfusion frequency' was obtained, the extrapolated 'number of transfusions' was calculated by dividing the 'treatment time' (derived from HMRN database) by the extrapolated 'transfusion frequency'.

c. Summary

Overall, the blood product cost of transfusion was calculated based on the blood product unit cost and the extrapolated 'number of transfusions'. The calculation process is illustrated below (**Figure 7.7**), while the detailed unit costs, frequencies and total blood product cost for transfusion are shown on **Appendix 7.4**.

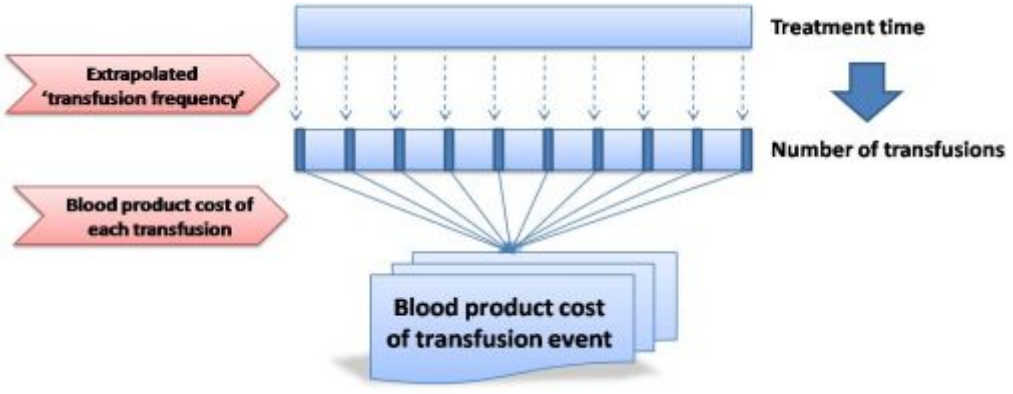


Figure 7.7 The illustration of blood product costing process for transfusion

7.3.3 Personnel cost

Following the same definitions and assumptions made for the personnel cost for the chemotherapy treatment (discussed in section 7.1), the personnel cost was also specifically defined as the cost of the 'staff working time' for the staff who involved directly and exclusively in the 'treatment activities'. To be consistent with the costing method in pervious sections (sections 7.1.2 and 7.2.2), the personnel cost for transfusion event was calculated based on the 'personnel cost for the transfusion' and the 'number of transfusions'. The 'personnel cost for each transfusion' was derived from the 'staff working time survey' (please refer to section 6.3). The 'number of transfusions' was derived from the extrapolated 'transfusion frequency'. The calculation process can be found in section 7.3.2. Overall, the detailed unit costs (£42 per transfusion), number of transfusions and the total personnel cost for transfusion can be found in **Appendix 7.4**.

7.3.4 Overheads cost

To estimate the overheads cost with the bottom-up costing method, the 'overheads cost per transfusion' and the 'number of transfusions' were needed. The 'overheads cost per transfusion' was obtained earlier and is discussed in section 6.3. For the 'number of transfusions', the extrapolated 'number of transfusions' was used in order to be consistent with the method used for blood products and personnel costs estimation (sections 7.3.2 and 7.3.3). In summary, overheads cost was estimated by the unit cost (£6 per transfusion) and the 'number of transfusions' (per transfusion event). The summarized details can be found in **Appendix 7.4**.

7.3.5 Ward cost

To be in line with the costing method used in previous sections (sections 7.1.4 and 7.2.4), the ward cost of transfusion event was also based on the 'unit cost' and the 'number of transfusions'. Based on the analysis result of the 'Palliative Care Database', it was observed that most of the transfusions took place in inpatient setting and lasted for one day only (please refer to chapter 4). Therefore, according to the inpatient ward cost (discussed in section 6.4.2), the ward cost for each transfusion was found to be £67. With the assistance of the extrapolated 'number of transfusions' (discussed in section 7.3.1), the ward cost for transfusion event was obtained. The summarized details are shown in **Appendix 7.4**.

7.3.6 Complication cost

Since the transfusion mainly was given for treating the haematological complications caused by the AML/APML treatments, it was not possible to calculate the costs of treating further complications caused by the transfusion due to time and human resources constraints. Therefore, the complication cost of transfusion was decided not to be included in the transfusion cost.

7.3.7 Summary

According to the five cost drivers discussed above, transfusion cost was considered to be the lump sum of the blood product cost (section 7.3.2), the personnel cost (section 7.3.3), the overheads and capital overheads cost (section 7.3.4), and the ward cost (section 7.3.5). The total cost of each transfusion event was found to be £628. The summarized costing details for the transfusion event can be found in **Appendix 7.4**, while the costing process is illustrated below (**Figure 7.8**).

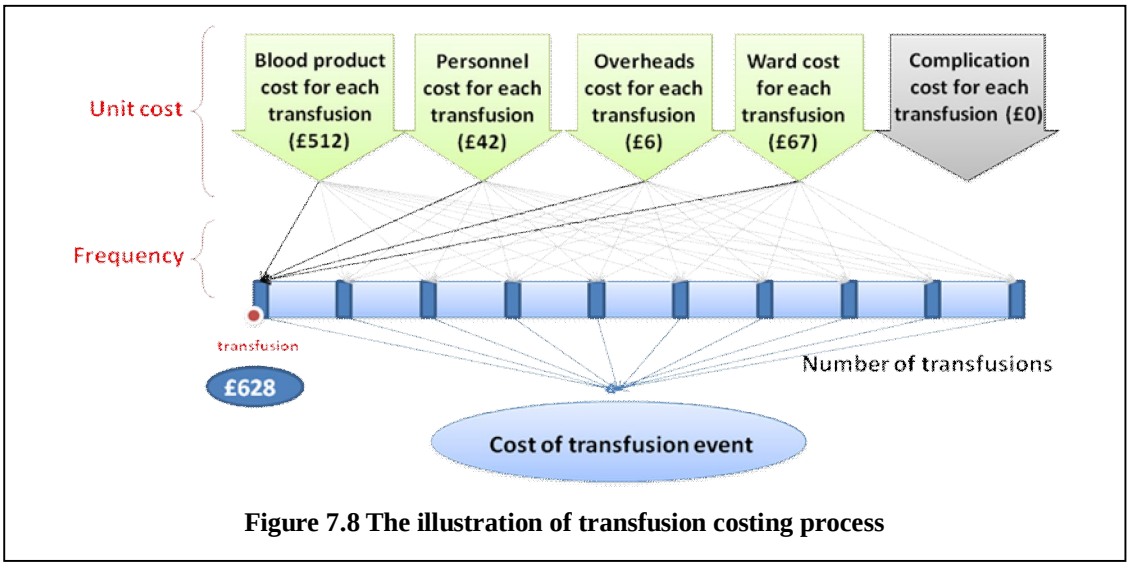


Figure 7.8 The illustration of transfusion costing process

7.4 Supportive care - Erythropoietin

Erythropoietin (or EPO) is a red blood cell growth factor for cancer treatment. It encourages the bone marrow to make more red blood cells. Therefore, it can help patients confront tiredness, beathlessness, dizziness, headaches and other side effects associated with cancer treatment-induced anemia [198, 199]. According to National Institute for Health and Clinical Excellence (NICE) recommendations, only people who could not have blood transfusions should have Erythropoietin, as an injection under the skin (subcutaneous injection) [199]. On the ground of the above information, the details of the cost estimation method and the information sources are discussed as follows.

7.4.1 Drug cost

The drug cost of erythropoietin was estimated based on the 'drug cost for each erythropoietin' and the 'number of uses'.

a. Drug cost for each erythropoietin injection

Based on information from the HMRN database, it was found that the 'Aranesp' was the only erythropoietin drug used on AML/APML patients in the HMRN network. Based on expert opinions and BNF suggestions [178], the dosage of the 'Aranesp' was decided to be 300mg/ml injections once a week (assuming that the average body weight was 70Kg). On this ground, the drug cost of 300mg/ml 'Aranesp' for each erythropoietin treatment was found to be £467.55 (based on the BNF price list [178]).

b. Number of uses

The 'number of the erythropoietin injections' was used in order to calculate the drug cost of the erythropoietin. Based on the information discussed above (that the erythropoietin was decided to be given once a week), the 'number of erythropoietin injections' was calculated by divinding the 'treatment time' by the 'usage frequency' (once a week).

The summarized details can be found in **Appendix 7.4**.

7.4.2 Personnel cost

In accordance to the definitions and assumptions related with the personnel cost in chemotherapy treatment (section 7.1.2), the 'personnel cost for each eyrthropoietin' and the 'number of uses' were used for estimating the personnel costs of the erythropoietin treatment. Based on the results of the staff working time survey and the staff unit cost list from the 'PSSRU Unit Cost' [179], the 'personnel cost for each erythropoietin' was found to be £45.3 (please refer to section 6.2 for further details). Also, in line with the 'number of uses' used in drug cost calculation mentioned earlier (section 7.4.1), the 'number of the erythropoietin injections' was used for personnel cost calculation. The summarized details can be found in **Appendix 7.4**.

7.4.3 Overheads cost

Based on the results of the staff working time survey and on the unit cost of the overheads from the 'PSSRU Unit Cost' [179], the 'overheads cost for each erythropoietin treatment' was found to be £9.95. With the assistance of the 'number of erythropoietin injections', the overheads cost for erythropoietin was calculated by multiplying the 'overheads cost for each erythropoietin treatment' with the 'number of erythropoietin injections'. The details can be found in **Appendix 7.4**.

7.4.4 Outpatient clinic cost

According to the BNF suggestions and expert opinions, the erythropoietin treatment usually takes place in outpatient clinics. Therefore, the outpatient clinic cost was needed to be calculated. To cost the outpatient clinic cost for erythropoietin, the 'outpatient clinic cost for each erythropoietin' and the 'number of erythropoietin injections' were used. The former was found to be £19 (please refer to section 6.4 for details), and the latter was in line with the 'number of erythropoietin injections' used in previous sections (sections 7.4.1, 7.4.2, and 7.4.3). The details can be found in **Appendix 7.4**.

7.4.5 Complication cost

The erythropoietin was given mainly for treating the anaemia caused by the AML/APML treatments or the disease itself. In the current study it was not possible to calculate the costs of treating further complication caused by erythropoietin due to time and human resources constraints. Therefore, the complication cost of erythropoietin was decided not to be included in the erythropoietin cost.

7.4.6 Summary

According to the five cost drivers discussed above, erythropoietin treatment cost was considered to be the lump sum of the drug cost (section 7.4.1), the personnel cost (section 7.4.2), the overheads and capital overheads cost (section 7.4.3), and the outpatient clinic cost (section 7.4.4). The total cost of each injection was found to be £542 in round numbers, and the summarized costing details for erythropoietin event can be found in **Appendix 7.4**. The costing process is illustrated in **Figure 7.9**.

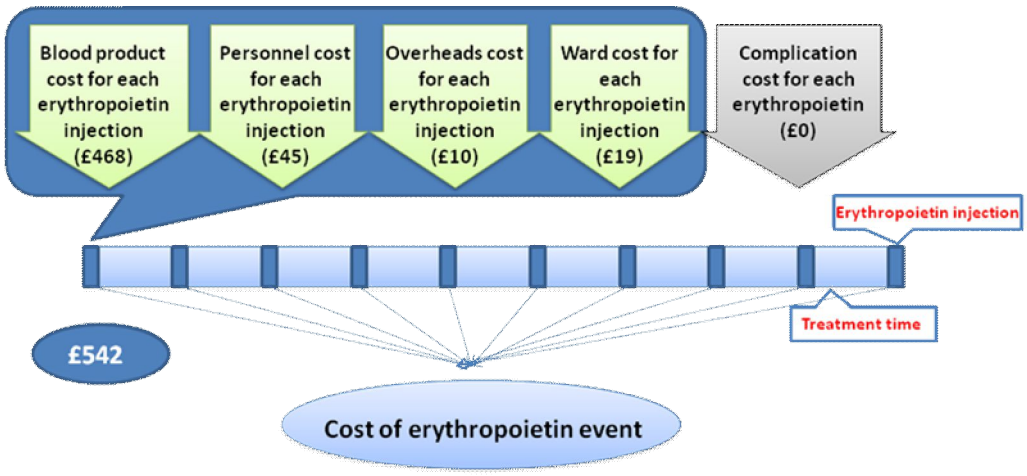


Figure 7.9 The illustration of erythropoietin costing process

7.5 Supportive care - Steroids

It is widely accepted that steroids is one of the most widely used drugs in cancer treatment. Steroids can be used as part of the cancer treatment to help destroy cancer cells. Apart from treating cancer, it can be also used as a suppletment treatment in chemotherapy for reducing sickness and allergic reaction caused by the latter. Additionally, it helps in reducing inflammation and response of immunity after a transplantation, while it also increases appetite [198, 200]. Based on information from the HMRN database, the common types of steroids that were used as a single agent on AML/APML patients were the following three: Dexamethasone, Prednisolone, and Hydrocortisone. The details of the cost estimation for each of these drugs are described below.

7.5.1 Drug cost

According to BNF suggestions and expert opinions, the dosage of Dexamethasone was set to 40mg twice per day, while the dosage of Prednisolone to 20mg once per day, and the dosage of Hydrocortisone to 20mg per day. Based on the BNF price list, the cost of a 40mg Dexamethasone tablet was £0.29, the cost of a 20mg Prednisolone tablet was £0.14, and the cost of a 20mg Hydrocortisone tablet was £1.4. Since the steroids are normally given for continuous periods of time, it was decided that the 'treatment time' was used as 'number of uses'. The summarized costing details are listed in **Appendix 7.4**.

7.5.2 Personnel cost

When estimating the personnel cost for steroids, the 'number of uses' was a key factor. The steroids were considered to be the outpatient-based treatment, as they can be administered by patients at home (something that indicated that it is a treatment that required patients to go to hospitals to get medicines on a regular basis). Based on expert opinions, it was assumed that the outpatient visit frequency was once per month. Therefore, the 'number of uses' for personnel cost calculation was possible to be calculated by dividing the 'treatment time' by the outpatient visit frequency. After the 'number of uses' was obtained, the personnel cost was calculated with the assistance of the 'personnel cost for each outpatient visit for steroids treatment' (£26.6, please refer to section 6.2 for details). The summarized costing details can be found in **Appendix 7.4**.

7.5.3 Overheads cost

The 'overheads cost for each outpatient visit for steroids treatment' was found to be £6.05 (refer to section 6.3). The overheads cost was calculated by multiplying the 'number of uses' (also used for personnel cost calculation for steroids treatment discussed in section 7.5.2) with the 'overheads cost for each outpatient visit for steroids treatment'. The summarized costing details are presented in **Appendix 7.4**.

7.5.4 Outpatient clinic cost

Similarly to the costing method mentioned above (sections 7.5.2 and 7.5.3), the outpatient clinic cost was estimated based on the 'number of uses' and the 'clinic cost for each outpatient visit' (£19, please refer to section 6.4 for details). The summarized costing details can be found in **Appendix 7.4**.

7.5.5 Complication cost

The steriods were mainly given for treating the side effects caused by chemotherapy or transplantation. In the current study it was not possible to calculate any costs for further complications caused by the steroids due to time and human resources constraints. Also, when steroids were used as a supplement treatment, they were usually given only for short periods of time, thus no side effects usually would occur [198]. Therefore, it was decided that the complication cost of steroids should not be included in the steroids cost.

7.5.6 Summary

According to the five cost drivers discussed above, steroids treatment cost was considered to be the lump sum of the drug cost (section 7.5.1), the personnel cost (£26.6, section 7.5.2), the overheads and capital overheads cost (£6.05, section 7.5.3), and the outpatient clinic cost (£19, section 7.5.4). The summary of steroids treatment is shown in **Appendix 7.4**, while an example is shown on **Table 7.4**.

Table 7.4 Example of the summary of steroid cost

	Treatment cost								
	Drug cost		Personnel cost		Overheads cost		Ward/clinic cost		Complication
	Per Day	Quantity	Per Day	Qauntity	Per Day	Quantity	Per Day	Quantity	
Dexamethasone	£0.58	× treatment time	£26.6	× treatment time /28d	£6.05	× treatment time /28d	£19	× treatment time /28d	-
Prednisdone	£0.14	× treatment time	£26.6	× treatment time /28d	£6.05	× treatment time /28d	£19	× treatment time /28d	-
Hydrocortisone	£1.4	× treatment time	£26.6	× treatment time /28d	£6.05	× treatment time /28d	£19	× treatment time /28d	-

7.6 Supportive care – G-CSF

G-CSF (granulocyte-colony stimulating factor) is a growth factor that can simulate the bone marrow to produce white blood cell quickly. Mainly, it is used to treat the chemotherapy-induced neutropenia [198]. G-CSF can be given either before or after the chemotherapy. Also, it can be administered by hospital nurses, GP practice nurses, and even patients themselves [198].

Due to the complexity of the administration mentioned above and lack of relevant details in the HMRN database, some assumptions had to be made in order to calculate the G-CSF cost. Considering expert opinions, it was assumed that the G-CSF injection was given once per day, four days continuously after chemotherapy. Also, it was assumed that all the G-CSF injections took place in hospital only.

Details about the five cost drivers and their usage frequency for costing the G-CSF treatment are described below.

7.6.1 Drug cost

Based on the treatment guidelines [183, 184], the dosage of the G-CSF was found to be 300 microgram once per day. According to the BNF price list [178], the 'drug cost for each G-CSF injection' was found to be £80.38 per day and £321.52 for four days. In relation to the 'number of uses', the 'number of chemotherapies' that took place during the G-CSF 'treatment time' was used as the 'number of uses' for calculating the drug cost. The count of the 'number of chemotherapies' was carried out manully, as the G-CSF was only given after certain types of chemotherapy (such as intensive inpatient chemotherapies). After the 'drug cost for each G-CSF cycle' and the 'number of chemotherapies' were obtained, the drug cost for the G-CSF treatment was calculated by a multiplication. The summary can be found in **Appendix 7.4**.

7.6.2 Personnel cost

Employing the method also used in previous sections for personnel cost (section 7.1.2, 7.3.2, and similar), the personnel cost was estimated based on the 'personnel cost per cycle for the G-CSF treatment' and the 'number of uses'. The 'personnel cost per cycle for the G-CSF treatment' was found to be £40.8 (please refer to section 6.2), and the 'number of chemotherapies' (mentioned above) was set as the 'number of uses' for personnel cost calculation. A relevant summary can be found in **Appendix 7.4**

7.6.3 Overheads cost

The 'overheads cost per cycle for the G-CSF treament' (£8.9, please refer to section 6.3 for details) and the 'number of the uses' were used for estimating the overheads cost for the G-CSF treatment event. Using the same method as for personnel cost (section 7.6.2), the 'number of chemotherapies' was set as the 'number of uses'. The related summary can be found in **Appendix 7.4**.

7.6.4 Ward cost

Based on assumptions mentioned earlier (section 7.6), the inpatient ward cost was applied to the G-CSF cost, as in most of the cases patients still stayed in hospital four days after the chemotherapies. The ward cost per day was found to be £67 (refer to section 6.4), and the 'number of chemotherapies' was used as 'number of uses' for the ward cost calculation. The related summary is shown in **Appendix 7.4**.

7.6.5 Complication cost

Similarly to the decisions made for other types of the supportive therapy, it was decided the complication cost not to be counted in the G-CSF cost (refer to sections 7.3, 7.4, and 7.5).

7.6.6 Summary

According to the cost drivers mentioned above, the G-CSF treatment cost was considered to be the lump sum of the drug cost (section 7.6.1), the personnel cost (section 7.6.2), the overheads and capital overheads cost (section 7.6.3), and the ward cost (section 7.6.4). The summary of the G-CSF treatment can be found on **Appendix 7.4** (£640 for four days), while the costing process is illustrated below.

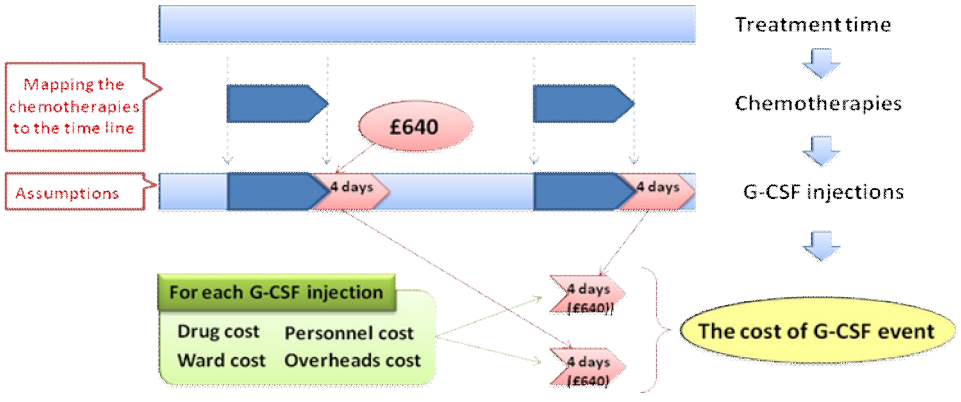


Figure 7.10 The illustration of the G-CSF costing process

7.7 Immunosuppressive therapy

Immunosuppressive therapy is a treatment that is used after the transplantation. It employs drugs to suppress (weaken) the immune system in order to prevent the immune system attacking the transplanted cells. It is also used for preventing or treating the graft-versus-host disease [178]. In the HMRN database, only six cases were found to make use of the immunosuppressive therapy.

7.7.1 Drug cost

In the HMRN database, it was observed that the 'cyclosporin' was the only drug that was used on AML/APML patients in the network. Because of the complexity of the administration of each 'cyclosporin' sub-type, some assumptions had to be made in order to calculate the drug cost for immunosuppressive therapy. Based on BNF suggestions [178] and expert opinions, it was assumed that the 'Neoral' was the drug that was used for immunosuppressive therapy. Also, it was assumed that the dosage was 12.5mg/kg on a daily basis (by mouth) from day before transplantation onward. Moreover, it was assumed that the 'Prednisolone' was used as an adjunct therapy with a dosage of 10 mg daily (by mouth). Therefore, based on the BNF price list [178], the 'drug cost for immunosuppressive therapy per day' was found to be £23.5. In relation to 'number of uses', the 'treatment time' was set as 'number of uses', as the immunosuppressive therapy was given continuously. The relevant summary can be found in **Appendix 7.4**.

7.7.2 Personnel cost

Since the drugs of the immunosuppressive therapy can be administered by patients at home, the immunosuppessive therapy was considered to be an outpatient-based treatment (same as steroids discussed in section 7.5.2). Based on expert opinions, it was assumed that patients went back to hospital for medicine once per month. Therefore, the 'number of outpatient visits' was set as 'number of uses' for the personnel cost calculation. Since the 'personnel cost for each outpatient visit for immunosuppressive therapy' was found to be £32.1 (refer to section 6.2), the personnel cost was possible to be calculated by a simple multiplication. The summary of the costing details can be found in **Appendix 7.4**.

7.7.3 Overheads cost

The 'overheads cost for each outpatient visit for immunosuppressive therapy' was found to be £6.95 (refer to section 6.3). By using the 'number of outpatient visits' that was used earlier for personnel cost calculation (section 7.7.2), the overheads cost were calculated by a simple multiplication.The summary of the costing details can be found in **Appendix 7.4**

7.7.4 Clinic cost

Using the same method as for costing the steroids (section 7.5.4), the clinic cost was also calculated by multiplying the 'outpatient clinic cost for each visit' with the 'number of outpatient visits'. The 'outpatient clinic cost for each visit' was found to be £19 (please refer to section 6.4). The summary of the costing details is shown in **Appendix 7.4**.

7.7.5 Complication cost

The immunosuppressive therapy was given mainly for treating the complications caused by the transplantation. In the current study it was not possible to calculate any costs for further complications caused by the immunosuppressive therapy due to time and human resources constraints. Therefore, the complication cost of immunosuppressive therapy was decided not to be included in the immunosuppressive therapy cost.

7.7.6 Summary

According to the five cost drivers mention above, the immunosuppressive therapy cost was considered to be the lump sum of the drug cost (section 7.7.1), the personnel cost (section 7.7.2), the overheads and capital overheads cost (section 7.7.3), the ward cost (section 7.7.4), and the complication cost (section 7.7.5). Take one-month immunosuppressive care as an example (with outpatient visit once per month), the immunosuppressive care cost was found to be £763 per month. The summary of the immunosuppressive therapy costing method can be found in **Appendix 7.4**.

7.8 Venesection

Venesection is a surgical incision process during which a vein is directly opened for giving an intravenous therapy. In the HMRN database, three cases were found to involve venesection treatment. Based on expert opinions, the venesection was considered to follow the same procedure as the transfusion, with the exception of transfused blood products. Therefore, the costing method was in accordance with the method used for costing the transfusion. The relevant details are described below.

7.8.1 Drug cost

No drug was given during the venesection, as it is a simple outpatient procedure.

7.8.2 Personnel cost

In line with the personnel cost of the transfusion (section 7.4.2), the personnel cost was calculated by multiplying the 'personnel cost for each venesection' (£41.8, please refer to section 6.2 for details) with the 'number of venesections' (section 7.4.2).

7.8.3 Overheads cost

Similarly to the transfusion (section 7.4.3), the overheads cost was calculated by multiplying the 'overheads cost for each venesection' (£9.4, please refer to section 6.3 for details) with the 'number of venesections'.

7.8.4 Outpatient clinic cost

To be in line with the transfusion, the clinic cost was estimated based on the 'clinic cost per visit' (£19, refer to section 6.4 for details) and the 'number of venesections'.

7.8.5 Complication cost

In line with the transfusion, no complication cost was applied to the venesection cost.

7.8.6 Summary

According to the five cost drivers mention above, the venesection cost was considered to be the lump sum of the personnel cost (section 7.8.2), the overheads cost (section 7.8.3), and the clinic cost (section 7.8.4). The summary of the venesection cost is shown on **Appendix 7.4** (£70 per venesection).

7.9 Follow-up / observation

Follow-up is a regular checking activity that monitors a patient's health over time, after treatment. Since there was no sufficient information related to the actual follow-up date in the HMRN database, an assumption was made in order to cost the follow-up. Based on expert opinions, it was assumed that the follow-up was carried out once per month between any gaps between treatments. Also, it was assumed that the patient who didn't receive any treatments after diagnosed or refused to be treated still had observation interventions before they died. The costing details are described below.

7.9.1 Drug cost

Since follow-up is a simple consultation process, no drug cost was given.

7.9.2 Personnel cost

Based on the results shown in section 6.2, the 'personnel cost for each follow-up visit' was found to be £28. The 'number of follow-up visits' was calculated by dividing the 'treatment time' by 28 days. Therefore, the personnel cost for follow-up was calculated by multiplying the two pieces information mentioned above.

7.9.3 Overheads cost

To calculate the overheads cost, the 'overheads cost for each follow-up visit' (£6.2, refer to section 6.3) and the 'number of follow-up visits' (mentioned in section 7.9.2) were used. The summary can be found in **Appendix 7.4**.

7.9.4 Outpatient clinic cost

The outpatient clinic cost was calculated by multiplying the 'clinic cost for each visit' (£19, refer to section 6.4) with the 'number of follow-up visits' (mentioned above).

7.9.5 Complication cost

No complication cost was applied to the follow-up cost, as there was no treatment took place.

7.9.6 Summary

According to the five cost drivers mentioned above, the follow-up cost (£53 per visit) was considered to be the lump sum of the personnel cost (section 7.9.2), the overheads cost (section 7.9.3), and the clinic cost (section 7.9.4). The summary of the follow-up cost is shown on **Appendix 7.4**.

7.10 End-of-life care

In the HMRN database, end-of-life care was defined as the care that took place when a patient died at the hospital or nursing home, with no palliative care or other relevant treatment being carried out. In order to cost the end-of-life care, it was assumed that it was carried out 14 days before death. The assumption was made based on expert opinions. The costing details are described below.

7.10.1 Drug cost

Since end-of-life does not involve any treatments, no drug cost was applied to the end-of-life care.

7.10.2 Personnel cost

Since end-of-life does not involve any treatments, no personnel cost existed.

7.10.3 Overheads cost

Since no treatment was given, no overheads cost could be allocated to the relevant staff working time information, as the latter was non-existent.

7.10.4 Ward cost

Based on the results presented in section 6.4, the ward cost per day was found to be £67. Since it was assumed that patients received 14 days of end-of-life care before death, the calculated ward cost was found to be £938 in total.

7.10.5 Complication

No complication cost was applied to the end-of-life care cost.

7.10.6 Summary

According to the five cost drivers mentioned above, the end-of-life cost was considered to be the ward cost only (£938 for 14 days). The summary can be found in **Appendix 7.4**.

7.11 Laboratory test

The Laboratory test cost can be divided into two parts: the cost of the test itself, and the sampling cost (including personnel, overheads, and clinic costs). The relevant costing details are described below.

7.11.1 Test cost

Based on the 'Tariff of the Haematological Malignancy Diagnostic Service' [182], the test cost was calculated by multiplying the 'tariff cost' with the 'number of tests' from the the HILIS database (please refer to chapters 3 and 4 for details about the calculation method and results).

7.11.2 Personnel cost

According to the sampling recources, the laboratory tests can be divided into two groups: blood sampling and bone-marrow sampling. Based on the results in section 6.2, the personnel cost for blood sampling was £7 and for bone-marrow was £20 each time. By using the 'number of tests' derived from the HILIS database, the personnel cost was possible to be calculated by a simple multiplication.

7.11.3 Overheads cost

Similarly to the personnel cost mentioned above, the overheads cost was calculated based on the 'number of tests' and the 'overheads cost per test' (Base on the results in section 6.3: £1 for blood sampling and £3 for bone-marrow sampling).

7.11.4 Clinic cost

Similarly to the costing method used for personnel cost mentioned above, the clinic cost was calculated by multiplying the 'number of tests' with the 'clinic cost per test' (based on the results in section 6.4: £3 for blood sampling and £26 for bone-marrow sampling).

7.11.5 Complication cost

No complication cost was applied to the laboratory test cost.

7.11.6 Summary

According to the five cost drivers mentioned above, the lab cost was considered to be the lump sum of the test cost (section 7.11.1), the personnel cost (section 7.11.2), the overheads cost (section 7.11.3), and the ward cost (section 7.11.4).

7.12 Splenectomy

Splenectomy is a surgical procedure involving the partial or complete removal of the spleen. The reasons for removing the spleen can be various and the procedure can be performed either for diagnostic or for therapeutic reasons. In haematological malignancy, the spleen is commonly enlarged as a result of lymphatic cancer, such as lymphomas or leukemia. When the spleen becomes significantly large, it can be destructive to platelets/red cells. Therefore, a splenectomy is needed [201-203].

In the HMRN database, only two cases were found to involve the splenectomy treatment. Since the splenectomy was one of the four treatments that can not be cost with the bottom-up method (due to lack of detailed information, please refer to chapter 6), the 'Reference Cost Index' was used as an alternative method.

7.12.1 Code translation

To identify the splenectomy cost from the "Reference Cost Index", the HRG4 code (Healthcare Resource Group Code) of splenectomy was needed. According to the known ICD-9 code of splenectomy (41.43: partial splenectomy and 41.5: total splenectomy), it was matched to the 'OPCS classification of interventions and procedures' [204]. The matching showed that the corresponding OPCS codes was J69: partial splenectomy and J70: total splenectomy. Next, by using the "HRG4 Definitions" [205] , it was found that the corresponding HRG4 code was GA07 (Hepatobiliary Procedure Category 3).

7.12.2 Treatment cost

After the HRG4 code of the splenectomy was identified (GA07), the corresponding splenectomy treatment cost was obtained by using the 'Reference Cost Index'. It was found that the treatment cost of the splenectomy was £4,010, including the complication cost. The reported cost included the same cost information (five cost drivers) as the other treatment costs derived from the bottom-up method. Therefore, the reference cost (£4,010) was used to represent the splenectomy treatment cost. The costing process is illustrated below.

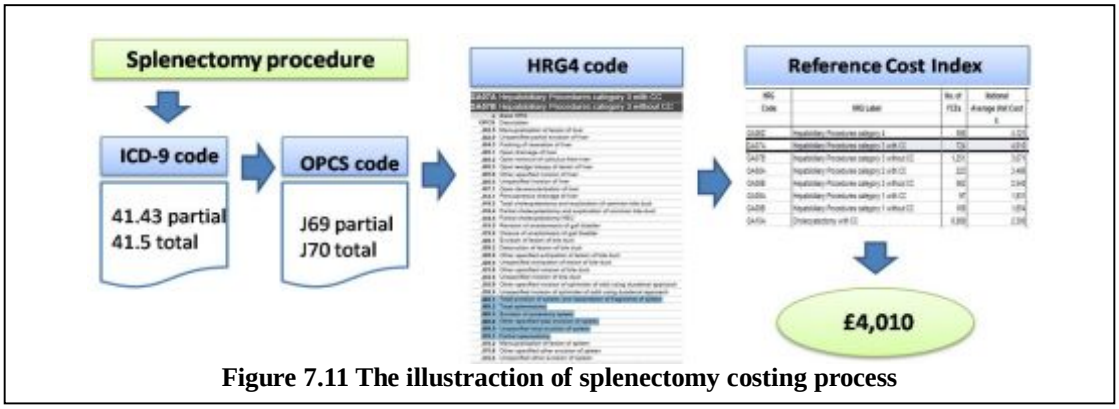


Figure 7.11 The illustration of splenectomy costing process

7.13 Radiotherapy

Radiotherapy is a treatment of blood cancers and it involvessupplying high but measured doses of radiation. Radiotherapy can damage the DNA of the cancer cells (stops cancer cells from growing/reproducing/dividing), improve the results of chemotherapy, and prepare the body for transplant. Total body irradiation (TBI) and non-TBI are the two main types of the curative radiotherapy [201].

In the HMRN database, 14 cases were found to involve radiotherapy treatment. Similarly to splenectomy (section 7.12), the radiotherapy was also one of the four treatments that could not be costed with the bottom-up method. Therefore, the 'Reference Cost Index' was used to represent the radiotherapy. The costing details are described below.

7.13.1 Assumptions

To decide the treatment cost of the radiotherapy, two assumptions were made:

a. Since TBI was used primarily as part of the preparative regimen for stem cell transplantation, it was assumed that only radiotherapy used before the stem cell transplantation would be considered as the TBI. Rest of the unspecified radiotherapies considered to be non-TBI.

b. It was assumed that radiotherapy planning was always carried out before the radiotherapy. This was because the treatment planning before the radiotherapy is a necessary procedure, as it helps in controlling the damage of the healthy cells near the cancer cells during the radiotherapy.

7.13.2 Costing process

Based on the assumptions and on expert suggestions, it was decided that the radiotherapy cost contained two parts: the pre-radiotherapy treatment planning and the radiotherapy itself.

a. Pre-radiotherapy treatment planning

Based on expert opinions, two medical services were found to be needed for the treatment planning before the radiotherapy, namely the 'radiotherapy planning outpatient visit' and the 'preparation for the radiotherapy'.

- 'Radiotherapy planning outpatient visit' : here the purpose is to measure the proper dose and control the radiation damage to the body. Therefore, based on the

'Reference Cost Index' and the expert opinions, 'HRG SC05Z: Define volume for Radiation Therapy with imaging, Dosimetry and technical support' (£117) was used to represent the planning visit cost.

- 'Preparation for the radiotherapy': According to the types of radiotherapy, the 'HRG SC08Z: Prepare for intracavitary radiotherapy' (£284) was used to represent the cost of non-TBI preparation, and the 'HRG SC07Z: Prepare for Total Body Irradiation' (£334) was used to represent the cost of TBI preparation.

Overall, the pre-radiotherapy treatment planning cost was found to be £401 for non-TBI radiotherapy and £451 for TBI radiotherapy.

b. Radiotherapy

According to expert opinions, the 'HRG SC26Z: Deliver a fraction of intracavitary radiotherapy without general anaesthetic' (£250) was set as the cost of the non-TBI radiotherapy, and the 'HRG SC25Z: Deliver a fraction of Total Body Irradiation (£184)' was set as the cost of the TBI radiotherapy.

7.13.3 Summary

Overall, the radiotherapy treatment cost was the lump sum of the pre-radiotherapy planning cost and the radiotherapy cost. The treatment cost of non-TBI radiotherapy was found to be £651, and the treatment cost of TBI radiotherapy £635. The costing process is illustrated below (**Figure 7.12**).

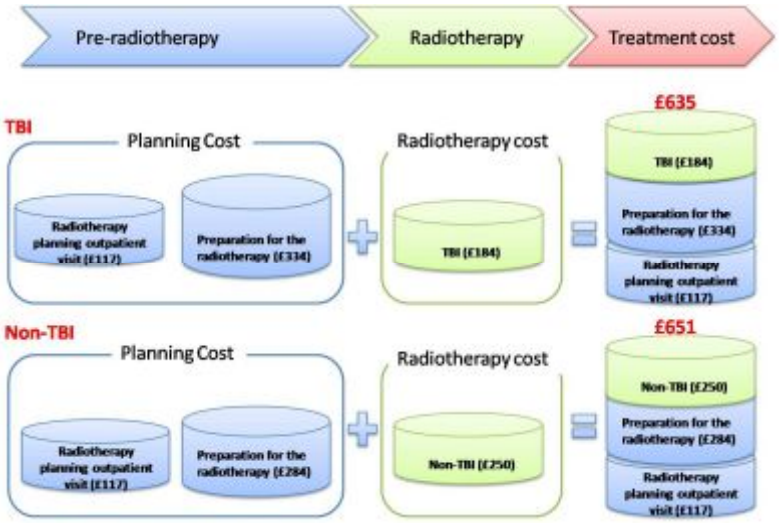


Figure 7.12 The illustration of the radiotherapy costing process

7.14 Stem cell transplantation

Stem cell transplant is a treatment that infuses healthy stem cells into the patient's body aiming to produce enough healthy blood cells in order to prevent life threatening infection or anemia. Two different approaches can be employed for the transplantation depending on the ways of harvest. One is the bone marrow transplantation (BMT), in which stem cells are drawn out of pelvic bone or, less frequently, from the sternum. Another approach is peripheral blood stem cell transplantation (PBSCT), in which the numbers of stem cells are drawn out from bloodstream. These two stem cell transplantation approaches are very similar. In addition, stem cell transplantation can use the stem cells from patient's own body (autologous stem cell transplantation) or stem cells from donors (allogenic stem cell transplantation) [201].

In the HMRN database, 13 cases were found to involve transplantions. All of them were the allogenic BMT. Since the stem cell transplantation was one of the four treatments that can not be costed with the bottom-up method (refer to chapter 6), the 'Reference Cost Index' was used to represent the treatment cost. The costing details and the relevant information are presented below.

7.14.1 Assumptions

To decide the treatment cost of the radiotherapy, two assumptions were made.

a. It was assumed that the patients who received the stem cell transplantation had to have three pre-transplant outpatient visits beforehand (based on expert opinions).
b. It was assumed that the costs of the mini-BMT and BMT were the same.

7.14.2 Costing process

Based on the assumption a, the stem cell transplantation cost was divided into two parts: pre-transplantation cost and the transplantation cost. The post-transplantation follow-up cost was not taken into consideration, as the follow-up costs discussed in section 7.9 covered all kinds of the follow-up event costs.

a. Pre-transplantation cost

According to assumption a, three outpatient consulting visits were found to be needed before the stem cell transplantation. Therefore, based on the outpatient clinic cost (£19, refer to section 6.4), the three outpatient visits were found to be £57. It is worth to note that all the exam/test/typing costs occurred during this period of time have been included

in the 'Laboratory cost' (discussed in section 7.11). Therefore, the exam cost was not taken into account here in order not to double count the cost.

b. Transplantation cost

To calculate the allogeneic stem cell transplantation, two types of costs were taken into consideration: the cost of the stem cell harvest and the cost of the stem cell transplantation itself.

- The cost of the stem cell harvest
  Based on the 'Reference Cost Index', 'HRG SA18Z: Bone Marrow or Stem cell Harvest' (£7845) was used to represent the harvest cost.

- Stem Cell transplantation cost
  Depending on the stem cell sources, allogenic transplantation can be further divided into two types. They are 1) allogeneic graft from sibling and 2) allogeneic graft from volunteer unrelated donor. After reviewing the extraction forms manually, it was found that the stem cell sources of the 13 allogenic transplantations were all from siblings. Therefore, based on the 'Reference Cost Index', 'HRG SD05A: Allogeneic Graft (sibling) 19 years and over' (£36297) was used to represent the cost of the allogenic stem cell transplantation.

7.14.3 Summary

Overall, the stem cell transplantation cost was the lump sum of the pre-transplantation visit cost and the cost of the allogeneic stem cell transplantation (sibling). Therefore, the treatment cost of transfusion was found to be £44199. The costing process is illustrated below (**Figure 7.13**).

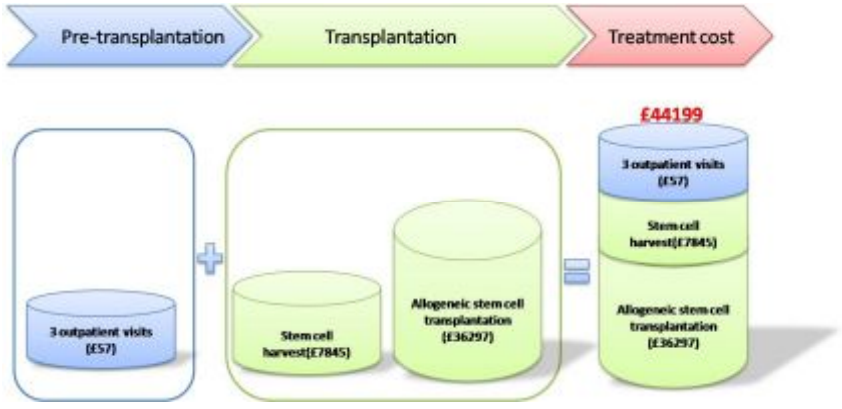


Figure 7.13 The illustration of the transplantation costing process

7.15 Palliative care

Palliative care is a non-curative treatment for patients whose disease is not responsive to curative treatment. The goal of palliative care is to control symptoms and improve patient's quality of life. In practice, palliative care involves many different approaches, including physical and psychological cares [201]. Unlike the 'end-of-life care', the palliative care involves the substantial interventions rather than simply care.

In the HMRN database, 31 patients received the palliative care before death. To obtain the palliative care cost, the 'Reference Cost Index' was used, as the palliative care was one of the four treatments that can not be costed with the bottom-up method (refer to chapter 6). The costing details are described below.

7.15.1 Assumptions

a. It was assumed that all the palliative care episodes were inpatient treatments.
b. It was assumed that the patients received the palliative care intervention three times per week during the palliative care period (based on the expert suggestions). As for the rest of the week, only the simple care was given (similar to the end-of-life care).
c. It was assumed that the treatment content of the palliative care for each time was the same.

7.15.2 Costing process

a. Unit cost

According to assumption b, the palliative care cost was divided into two parts: the cost of the palliative care day and the cost of no palliative care day.

- The cost of no palliative care day
  Since only simple care was given on the no palliative care days during the palliative care period, the ward cost (£67 per day, refer to section 6.4) was used to represent the cost of no palliative care day.
- The cost of the palliative care day
  Based on the 'Reference Cost Index', the 'HRG 4 code in reference cost: SD01A: Inpatient Specialist Palliative Care 19 years and over' (£336) was used to present the cost of the palliative care day

b. Number of uses

The ‘treatment time’ derived from the HMRN database was set as the ‘number of uses’ for palliative care cost calculation.

7.15.3 Summary

Overall, the palliative care cost was estimated based on the unit cost and the number of uses. Take one-week palliative care as an example (three days under the palliative care and four days were not), the palliative care cost was found to be £1276 per week. The costing process is illustrated below.

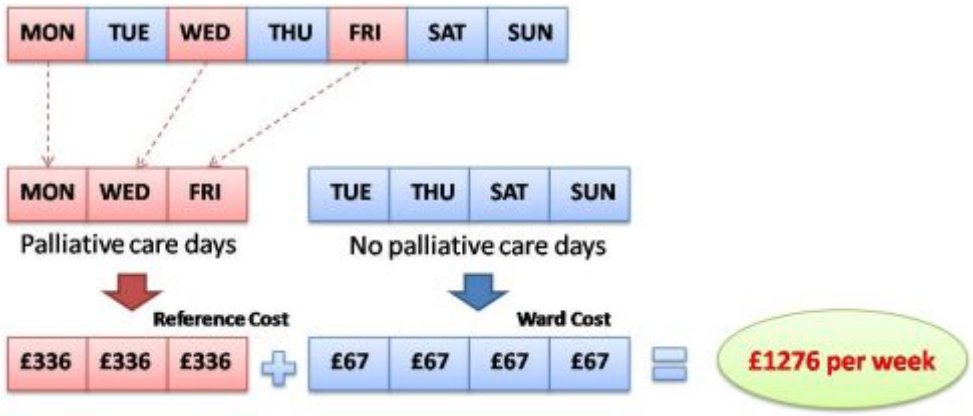


Figure 7.14 The illustration of palliative care costing process

7.16 Summary

In this chapter, the detailed costing methods for 12 types of treatments/interventions were described. Each method contained the previously obtained five cost drivers (please refer to chapter 6), with an exception of four treatments (splenectomy, radiotherapy, stem cell transplantation, and palliative care). The Reference Cost was used to represent the costs of these four treatments. Finally, all of the treatment events were cost and the cost results were ready for individual overall/lifetime cost calculation, which is discussed in the following chapter (chapter 8).

Chapter 8 Costing Method Phase 3

Total treatment cost and cost predictors

CHAPTER 8 COSTING METHOD PHASE 3

According to the study design (please refer to section 5.3.2), the total treatment costing process was divided into three phases, of which costing phase 3 is discussed in the current chapter. The costing process is illustrated below (**Figure 8.1**).

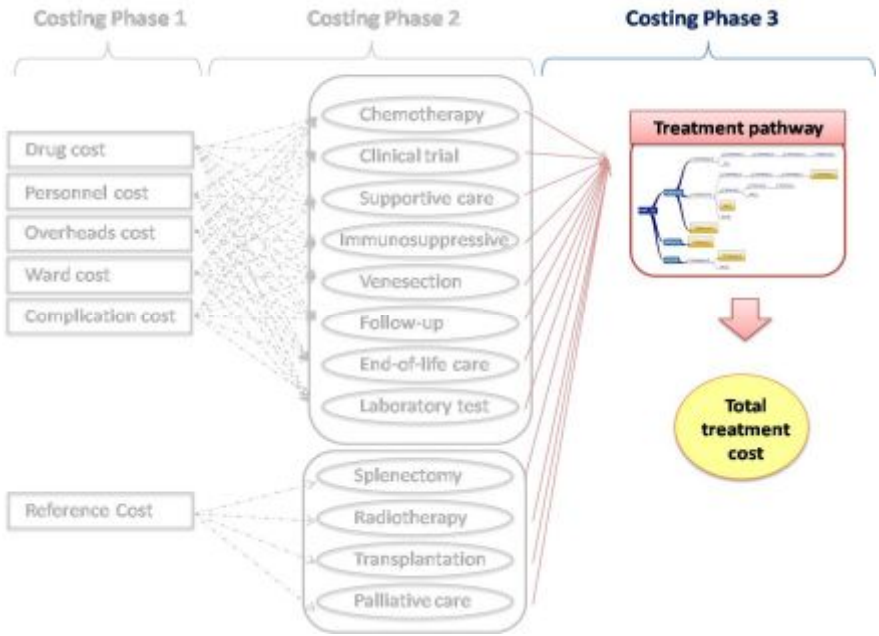


Figure 8.1 The illustration of the costing phase 3

The costing phase 3 contained two important processes, namely total treatment calculation (for each patient) and predictive factors analysis. The details of each process (including the ones related with the treatment overlapping) are described in the following sections.

8.1 Total cost calculation (non-treatment overlapping)

To capture the subtle cost differences between patients, the 'patient treatment pathway' (summarized the data in the HMRN database as described in chapters 3 and 4) was employed to render the total treatment cost results for each patient.

The treatment events in the pathway were sorted by chronological order, then cost, and, finally, summed up to a single number, namely the 'total treatment cost' (without considering the treatment overlapping). To cost each event, the treatment/intervention costs discussed in chapter 7 were linked to the corresponding events in the pathway, making use of the 'treatment time' or the 'number of uses' of each event. After all of the event costs were obtained, the total treatment cost was calculated as the lump sum of the treatment costs that occurred on the patients' treatment pathway.

It is worth noting that, in order to make the cost result comparable, the total treatment cost was further broken down into parts depending on the 'treatment phase' (chapter 3) it belonged to. The costing process is illustrated below (**Figure 8.2**).

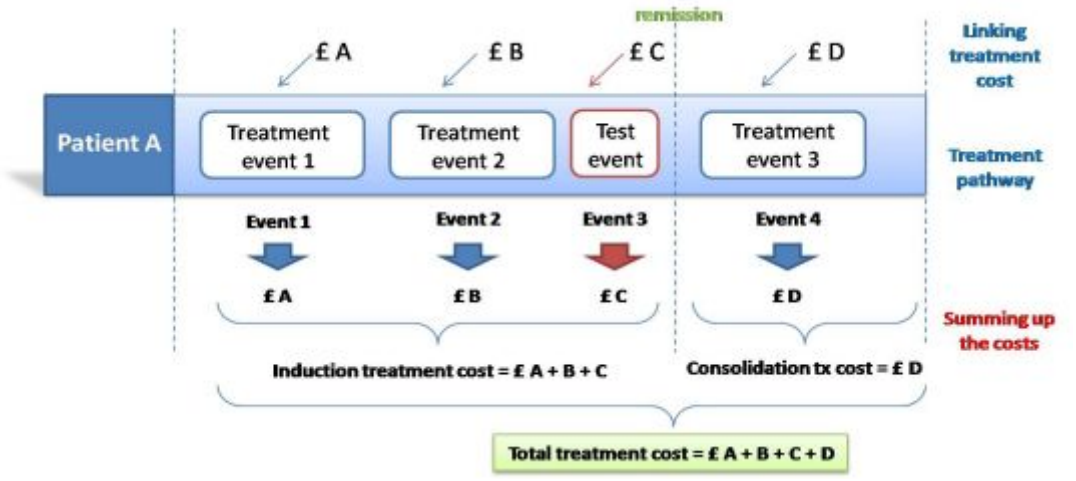


Figure 8.2 The illustration of the costing process for total treatment cost

8.2 Total cost calculation (treatment overlapping)

The total treatment cost can be simply calculated by the required addition (please refer to section 8.1). However, it is suggested that the calculated result could not reflect the actual medical resource consumption accurately. This is because, practically, treatments frequently overlap with each other, and, thus, it is not always possible to sum up directly. The studied AML/APML treatments were not an exception to this as more than 100 treatment events were found to be overlapping with other treatments in the HMRN database (763 events in total),.

The overlapping issue had to be handled with caution for two reasons. Firstly, medical resources were shared between treatments when more than one treatment was performed simultaneously. Therefore, it was easy to overestimate the total treatment cost if these overlapping treatments were summed up directly without any deduction. Secondly, the hospital stays or the outpatient visit frequency (discussed in section 5.4.2) could change as the treatment overlapped with others. Since the actual medical resource consumption pattern changed, the costing method should change correspondingly in order to avoid the total treatment cost to be overestimated or underestimated.

The issues discussed above can be difficult to uncovered if the individual events are cost separately and once at a time. Therefore, a macro costing method that took the overlapping issue into consideration was needed in order to yield more reasonable and accurate cost results. Details on how the overlapping issue and the relevant costing method were handled can be found in following sections.

8.2.1 Identifying the overlapping events

To identify the overlapping events, a number of definitions and assumptions were needed. Relevant details can be found below.

a. Definitions

- Disjointed events: two treatments that did not overlap with each other.
- Touching events: two events that shared one end date (the end date of the first event).

c. Overlapping events: two events that overlapped over a period of time.

d. Subset event: one event is a subset of another event.
e. Interval less than 3 days: the period/gap between two events is less than 3 days
f. Interval more than 3 days: the gap between two events is more than 3 days

b. Assumptions

Based on expert suggestions and on the aforementioned definitions, it was decided that the following situations had to be considered as overlapping events, and, thus, more caution was needed when costing these treatment events.

- If two inpatient treatments were touched, it was assumed that these treatments overlapped.
- If two treatments were overlapping events, it was assumed that these two treatments overlapped and had effects on each other (including hospital stays or outpatient visit frequency).
- If one treatment was a subset event, it was assumed that it overlapped with another treatment and had effects on each other.
- If the interval between two inpatient treatments was less than three days, it was assumed that the two events actually overlapped, and the hospital stays continued without stopping.

The definitions and assumptions are illustrated below (**Figure 8.3**).

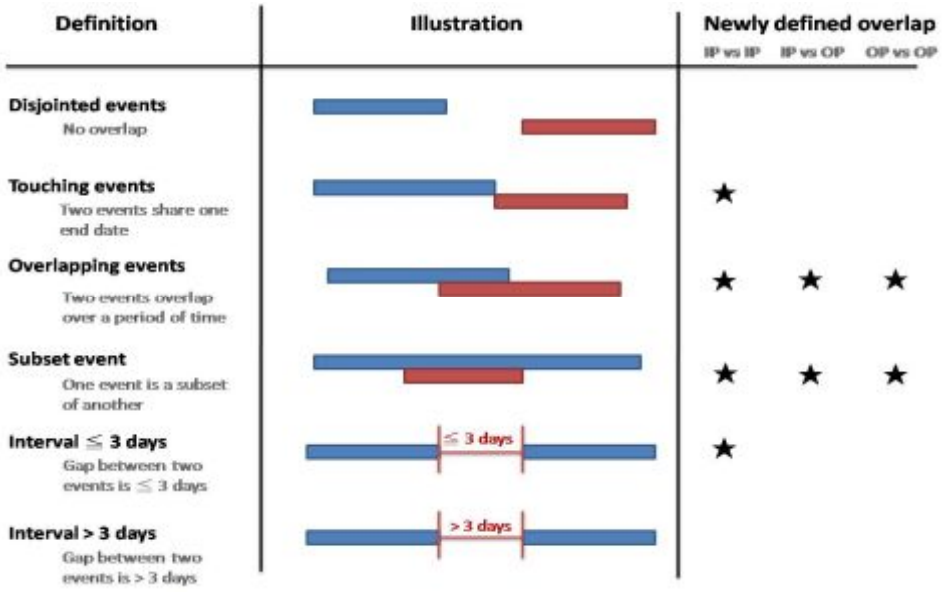


Figure 8.3 The illustration of the overlapping types

8.2.2 Handling the overlapping treatments

In order to overcome above issue, the concept of 'span' was introduced. 'span' was set as a unique treatment length record that engulfed all the relevant overlapping treatment events. The details of the 'span' calculation are described in the following paragraphs.

a. Inpatient span

The length of hospital stay determined the medical resources utilization and cost. Therefore, as the length of hospital stay changed when inpatient treatments overlapped, an inpatient span that engulfed the overlapping inpatient treatments was needed. To obtain the 'span' of a batch of relevant overlapping inpatient treatments, two steps were involved. This was in order to yield an inpatient span that was expected to reflect the actual hospital stays more accurately.

- Grouping the relevant overlapping inpatient treatments

  Based on the extrapolated treatment admission and on the discharge dates (discussed in section 5.4.2), the inpatient treatments fell into the same group when they overlapped or when intervals between each other were less than 3 days. It is worth to note that the transfusion and the laboratory test were not included, as they did not affect the hospital stays. Also, treatment events that did not overlap with others formed one span by themselves.
- Determining the 'span'

  Based on the batch of relevant overlapping inpatient treatments (defined above), the start date of the 'span' was determined by the earliest point of the grouped inpatient treatments. Similarly, the end-date of the 'span' was determined by the latest point of the grouped inpatient treatments. An illustrated example can be found below (**Figure 8.4**).

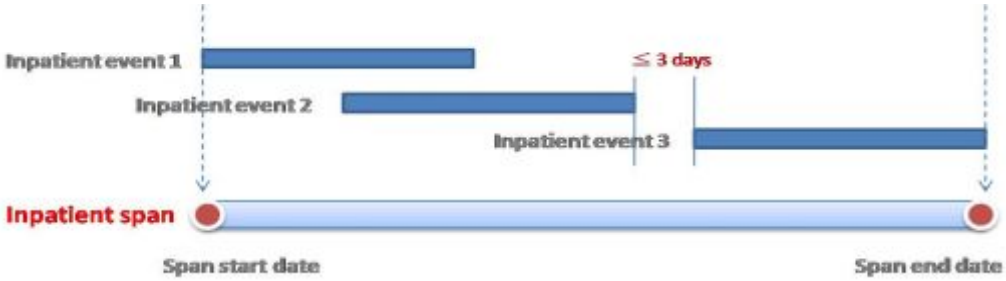


Figure 8.4 An illustrated example of determining the inpatient span

b. Outpatient span

Similarly to the hospital stays, the number of outpatient visits determined the medical resources utilization and cost. Therefore, an outpatient span that could divide different visit frequencies was needed, as the outpatient visit frequency changed when outpatient treatment overlapped. To obtain the outpatient 'span', two steps were involved. This was in order to yield an outpatient span that could both separate different visit frequencies and render the number of outpatient visits more accurate in relation to the actual number.

- Grouping the relevant overlapping outpatient treatments

  Based on the 'treatment time' (derived directly from the HMRN database), the outpatient treatments fell into the same group when they overlapped with each other. It is worth to note that the transfusion and the laboratory test were not included, as they did not affect the outpatient visit frequency. Also, treatment events that did not overlap with others formed one span by themselves.
- Determining the 'span'

  Based on the batch of relevant overlapping outpatient treatments (defined above), the cut-off points of each span were determined by the dates that overlapping started or ended. A relevant illustrated example can be found below (**Figure 8.5**).

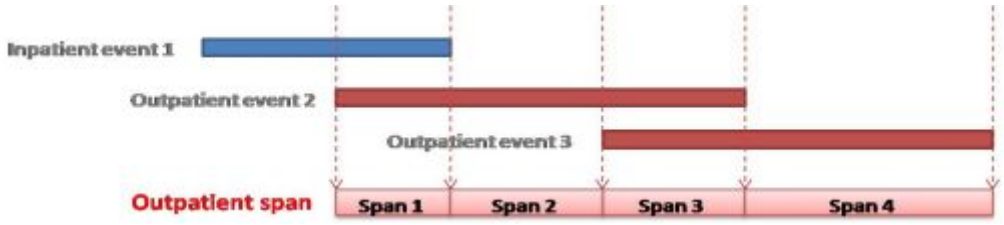


Figure 8.5 The illustrated example of determining the outpatient spans

c. Follow-up span

Any gaps found between the spans (considering all the inpatient and outpatient spans) were defined as the follow-up spans. It is worth to note that the transfusion and the laboratory test were not taken into consideration for reason mentioned previously.

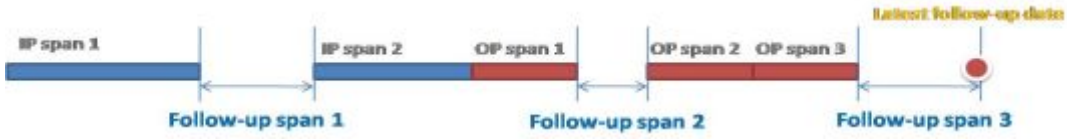


Figure 8.6 The illustrated example of determining the follow-up spans

8.2.3 Costing method for overlapping treatment

After all the spans were identified (involving stood along and overlapping treatment event), the treatments within the same spans were ready to be cost. Details related to the costing method and the principles of cost sharing are described below.

a. Inpatient spans

- If the treatment events in the 'spans' were disjointed or touching events, the treatment cost was calculated normally, without considering the cost sharing.
- If the treatment events in the 'spans' were overlapping events, the ward cost was considered to be the shared cost, and it was calculated only once. The rest of the cost drivers were considered to be non-shared cost, as they were all directly related to the treatments themselves.
- If the inpatient treatment overlapped with any of the 4 treatments that their costs were directly derived from the 'Reference Cost Index', the overlapping ward cost was not counted for two reasons. Firstly, ward cost had already included in the reference cost. Secondly, it was impossible to separate the shared ward cost from the reference cost. Therefore, instead of calculating the shared ward cost separately, the overlapping reference cost was fully kept without considering other ward cost. This was in order not to over-count the ward cost.

The costing process is illustrated below (**Figure 8.7**).

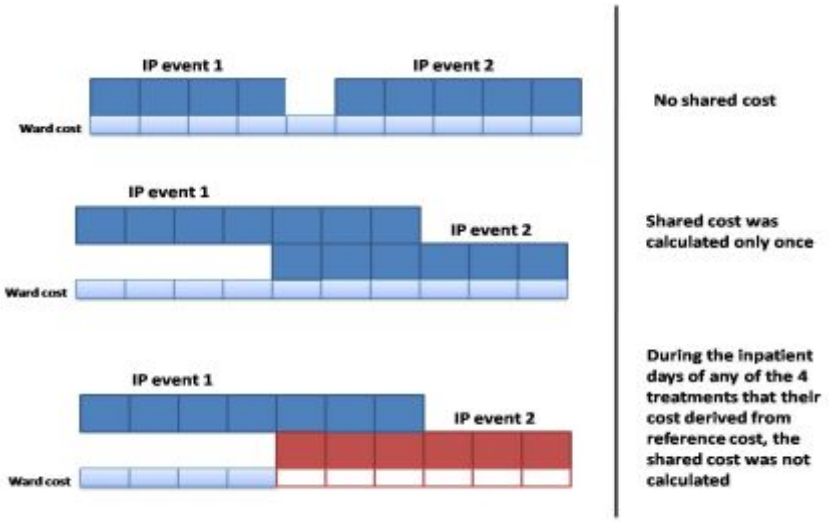


Figure 8.7 The illustration of the shared cost calculation for overlapping IP treatments

b. Outpatient spans

- If the treatment events in the 'spans' were disjointed or touching events, the treatment cost was calculated normally without considering the cost sharing.
- If the treatment events in the 'spans' were overlapping events, the one with the highest outpatient visit frequency was set as the visit frequency for the span.
- If the outpatient events overlapped with the inpatient event/span, different costing methods were used, depending on the type of the outpatient events.

Type 1: If the outpatient treatment involved only drugs, then only the drug and the complication costs were calculated, as the rest of the costs (personnel, overheads, and other costs) were covered by the hospital staff responsible for the inpatient treatment event/span. It is worth to note that the complication cost that was taken into consideration was the evenly divided complication cost (according to the numbers of the spans the treatment covered) and not the total complication cost.

Type 2: If the outpatient treatment involved surgical or other medical procedures (such as Mylotarg and immunosuppressive therapy), then all costs except the outpatient clinic cost were calculated. This was because these costs (drug, personnel, and other costs) could not be covered by the hospital staff responsible for the inpatient treatment event/span.

The costing process is illustrated below.

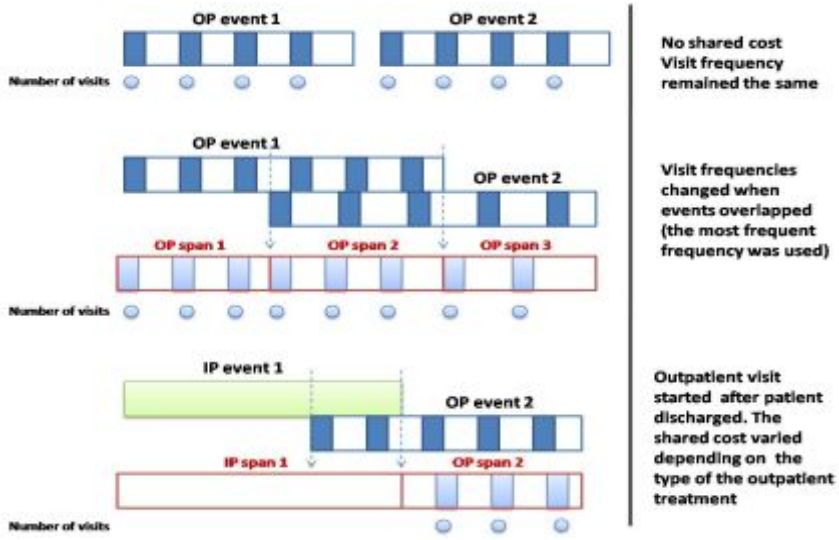


Figure 8.8 The illustration of the change of visit frequency for overlapping OP treatments

c. Follow-up spans

Follow-up span was defined as the gaps between any treatment spans, without considering the transfusion and the laboratory test event (the reasons for this are discussed in section 8.2.3). Meanwhile, the follow-up frequency was defined as once every month (please refer to chapter 3 for more details). Therefore, the number of follow-up visits was simply calculated by dividing the length of the follow-up span by 28 days (1 month, 4 weeks).

After the number of follow-up visits was obtained, the follow-up cost was calculated by multiplying the number of follow-up visits with follow-up cost per visit (£53.2, please refer to section 7.9 for details). The relevant costing details are illustrated below.

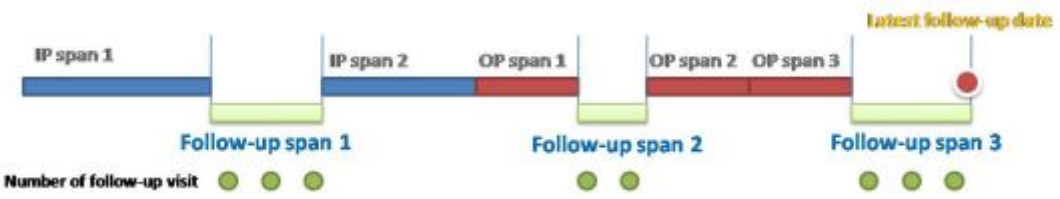


Figure 8.9 The illustration of follow-up span costing process

8.2.3 Overall/lifetime treatment cost calculation

After the costs for all the treatment spans were obtained, the total treatment cost of each patient was calculated by summing up these costs. To render the cost results more comparable and clinically meaningful, the total treatment cost was further broken down into ‘treatment phase’ (please refer to chapter 3).

Chapter 9 Results

Cost results and cost predictors

CHAPTER 9 RESULTS

The current chapter aims at presenting the cost results and comparing them with previous study results. This includes the results of estimated treatment and overall treatment costs. Furthermore, the result of the cost predictor analysis is also included in this chapter.

After the three costing phases of the calculation process discussed in chapters 6, 7, and 8, the cost results for each treatment and the estimated total cost for each patient were obtained.

In costing phase 1, the unit costs of five cost drivers for each treatment were calculated. Several important procedures were carried out in order to obtain robust values. This included staff working time survey for personnel cost and meta-analysis for complication treatment cost (please refer to chapter 6 for details).

In costing phase 2, the costs for each treatment were calculated by summing up the five cost drivers mentioned above. To resolve the issues caused by the complexity of different drug delivery types and patient conditions, several assumptions for the treatment use frequency were made under experts' guidance (please refer to chapter 7 for details).

Finally, in costing phase 3, the total treatment costs for each patient were calculated by linking the treatment costs (mentioned above) to the patient treatment pathway (discussed in chapter 4). Costing the overlapping treatments can be challenging, as the AML/APML treatment combinations varied and no sufficient detailed information was possible to be obtained regarding the way each treatment was carried out. Overall, two different types of total cost results were generated: the total cost for non-treatment overlapping, and the total cost for treatment overlapping (please refer to chapter 8 for costing details).

Before proceeding to the cost results, a summary of the data handling is presented in order to provide an overview of the costing process (section 9.1). Next, the estimated costs for each treatment, the total cost results for both the non-treatment and for the treatment overlapping costing are presented in the subsequent sections. Finally, the possible cost predictive factors are discussed in section 9.5.

9.1 Summary of the data handling

For purposes of the current study, a total of 239 patients who were newly diagnosed with AML/APML from September 2004 to September 2006 in the HMRN network were recruited and studied. This included 215 patients with AML and 24 patients with APML. All the patients were followed from the diagnosis onward, and until mortality or the latest follow-up date. By the close date of the study (05/31/2010), 763 treatment records had been obtained from the HMRN database (please refer to chapter 4 for details).

After imputing all the missing data, the 763 obtained treatment records were further broken down into 1025 treatment cycle records for calculation reasons (please refer to chapter 4 for details and reasons). Up to that stage, the 1025 treatment cycle records were ready for the 3-phase cost calculation (described in chapters 6, 7, and 8).

9.1.1 Study material in costing phase 1

In costing phase 1 (chapter 6), the number of treatment cycle records remained the same, as the aim of the costing phase 1 was to obtain the unit cost of the five cost drivers for each treatment record.

9.1.2 Study material in costing phase 2

In costing phase 2 (chapter 7), the number of treatment cycle records increased to 2731, as the two intervention costs (the end-of-life care cost and the laboratory test costs derived from the HILIS database) were added or integrated into the study database. The end-of-life care (a care that patients received at terminal stage of life) was taken into consideration as it was an important cost driver, but, unlike palliative care, it has not been recorded on a regular basis In order to avoid underestimating the total treatment cost, the intervention was cost based on experts' opinions as described in chapter 7. For convenience reasons, since the laboratory test events were collected from HILIS and stored in the HMRN database, the laboratory test events were firstly integrated into the study database and then cost. Based on the treatment cost definitions described in chapter 7, 66 patients were found to have received the end-of-life care and 1640 laboratory test records were found to be related (please refer to chapter 4 for details). Overall, 2731 treatment event records were cost for further analysis.

9.1.3 Study material in costing phase 3

In costing phase 3, the number of treatment cycle records changed again as the treatment overlapping was taken into consideration. To resolve the treatment overlapping issue, the concept of the 'span' was introduced (please refer to chapter 8). Firstly, the inpatient spans were defined by considering the overlapping treatments. Based on the durations of each treatment, the 675 inpatient treatment cycle records were merged into 529 inpatient spans. Secondly, the outpatient treatment cycle events were taken into consideration. By composing different outpatient spans when the outpatient treatment overlapped with inpatient spans or other outpatient treatments, the 460 outpatient treatment cycle records were further cut into 884 outpatient spans. Finally, based on the definition described in section 7.9 and the method described in section 8.2.2, the follow-up spans were defined as the gaps between any treatment spans and 269 follow-up spans (out of 588 treatment gaps) were found on the 123 patients. It is worth to note that the laboratory test did not take part in the span calculation for reasons mentioned in section 8.2. Therefore, the intervention records remained the same and they were not merged into any other treatment spans. After a complicated calculation, 2731 treatment event records expended to 3322 treatment span records. These treatment spans were further cost and the results were summed up as the final estimated total treatment cost for each patient.

The process of handling the study material is illustrated below. (**Figure 9.1**)

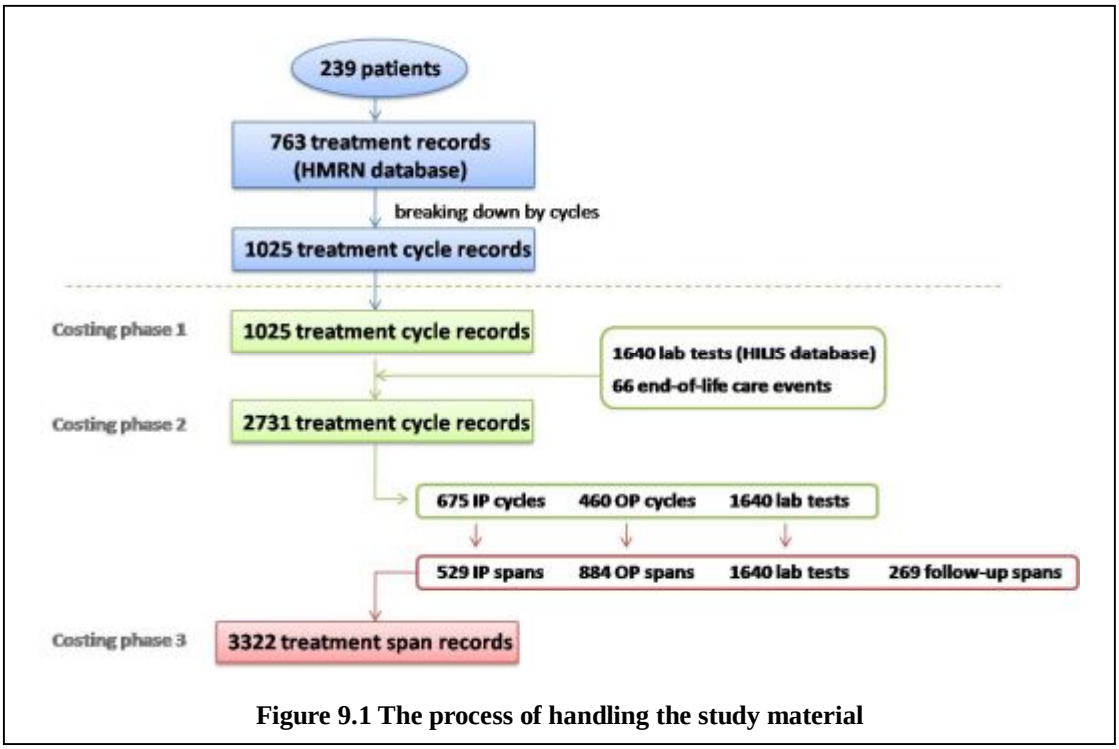


Figure 9.1 The process of handling the study material

9.2 Cost results of each treatment

In the current section, the cost results of each treatment are presented. According to the costing method described in chapter 7, the treatment/intervention costs were calculated based on the patient conditions (completed treatment or not) and the different types of drug delivery.

In order to make the result section concise and easy to follow, only the costs for the most commonly used or the most important treatments are discussed. This includes chemotherapy, clinical trial, supportive care, radiotherapy, stem cell transplantation, immunosuppressive care, palliative care, and follow-up intervention. Analyses of each treatment cost can be found in the following sections. For the rest of the treatments, the calculated cost values can be found in **Appendix 9.1**.

9.2.1 Chemotherapy and clinical trial

Since the regimen used in the clinical trial arms were also used in chemotherapies, the regimen costs for the clinical trial and the chemotherapy were discussed together. Regarding the patient conditions and the differences of each drug/regimen delivery, all the regimen costs were calculated separately and the main cost results are discussed in the following sections. This includes nine inpatient chemotherapy regimen costs and four outpatient chemotherapy regimen costs.

a. ADE

ADE was one of the most commonly used regimens in the HMRN network. In total, 47 cycles of ADE and ten cycles of ADE + Mylotarg were used on the study patients. The cost results for the ADE regimen are illustrated in **Figure 9.2**.

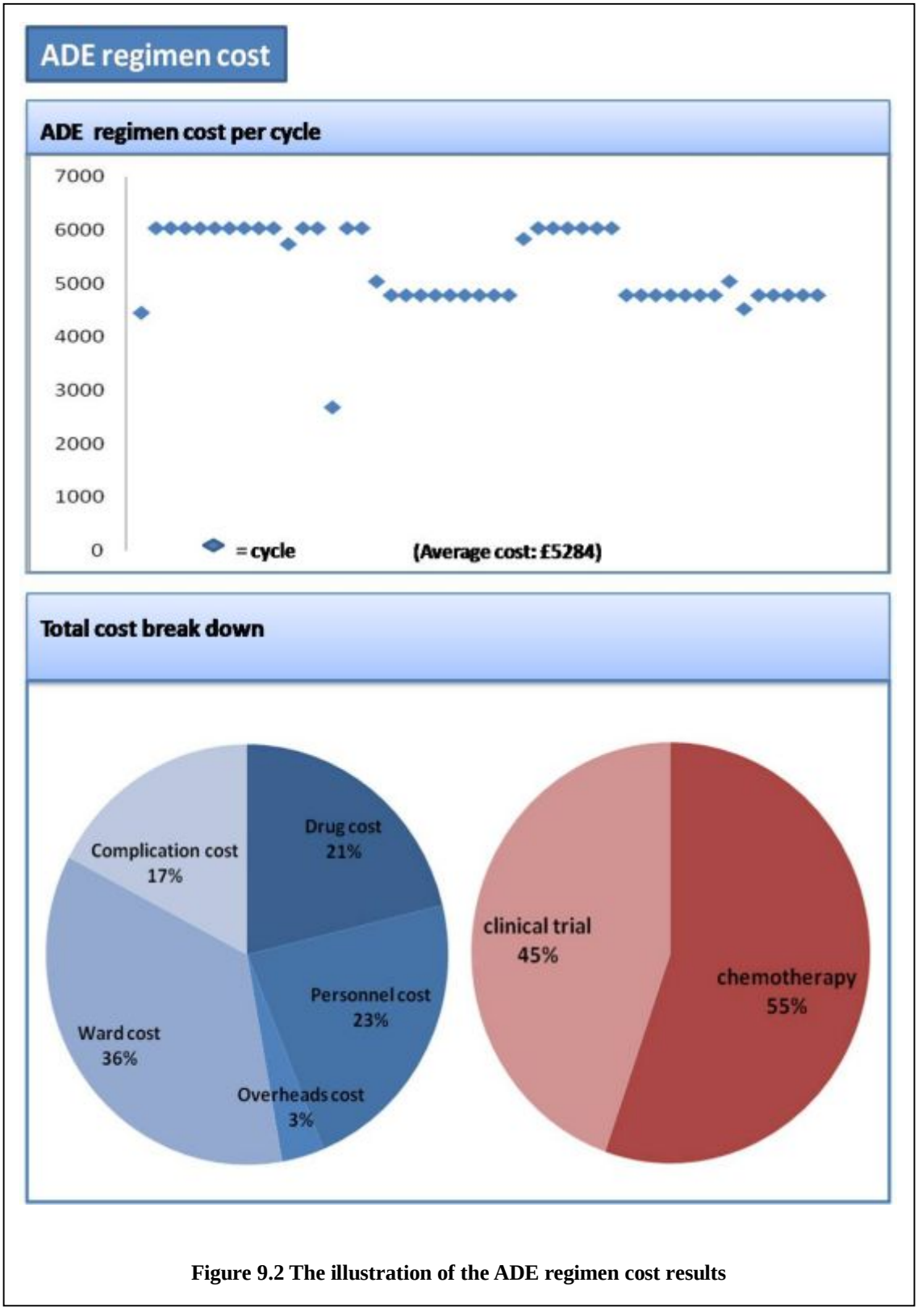


Figure 9.2 The illustration of the ADE regimen cost results

As it can be observed in the relevant plot, the ADE regimen costs mainly fell into two groups. This was because ADE regimen contained two cycles. The cost of cycle one was slightly higher than the cost of cycle two, as the full course of cycle one was longer than the one of cycle two. The proportion of the five cost drivers that were used for costing and the proportion of the regimens used in the chemotherapy or in the clinical trial are also illustrated in the related pie charts. As indicated in **Figure 9.2**, the ward cost accounted for the highest percentage (36%), which was much higher than drug cost (21%) or personnel cost (23%).

As shown in the detailed cost result table (**Table 9.1**), the average ADE regimen cost per cycle was £5284 (including the complication treatment cost). Specifically, the average cost for ADE cycle one was found to be £5799 and £4790 for cycle two.

Table 9.1 The detailed cost results of the ADE regimen

	Events No	Cost 1 (exclude complication cost)			Cost 2 (include complication cost)		
		Mean	Min	Max	Mean	Min	Max
ADE	47 courses	£4367	£2553	£4797	£5284	£2677	£6036
Course 1	23 courses	£4625	£2553	£4797	£5799	£2677	£6036
Course 2	24 courses	£4120	£3938	£4287	£4790	£4522	£5037
Chemotherapy	26 courses	£4395	£2553	£4797	£5361	£2677	£6036
Course 1	16 courses	£4562	£2553	£4797	£5708	£2677	£6036
Course 2	10 courses	£4310	£4113	£4287	£4805	£4779	£5037
AML 15	21 courses	£4331	£3938	£4797	£5189	£4522	£6036
Course 1	7 courses	£4768	£4596	£4797	£6007	£5835	£6036
Course 2	14 courses	£4113	£3938	£4287	£4779	£4522	£5037
ADE + Mylotarg	10 courses	£6132	£4113	£6418	£7290	£4779	£7657
Chemotherapy	-	-	-	-	-	-	-
AML 15	10 courses	£6132	£4113	£6418	£7290	£4779	£7657
Course 1	9 courses	£6357	£6069	£6418	£7568	£7060	£7657
Course 2	1 course	£4113	-	-	£4779	-	-

b. AraC (High Dose)

AraC (HD) is the fifth most commonly used chemotherapy regimen in the network. The related cost results are illustrated in **Figure 9.3**.

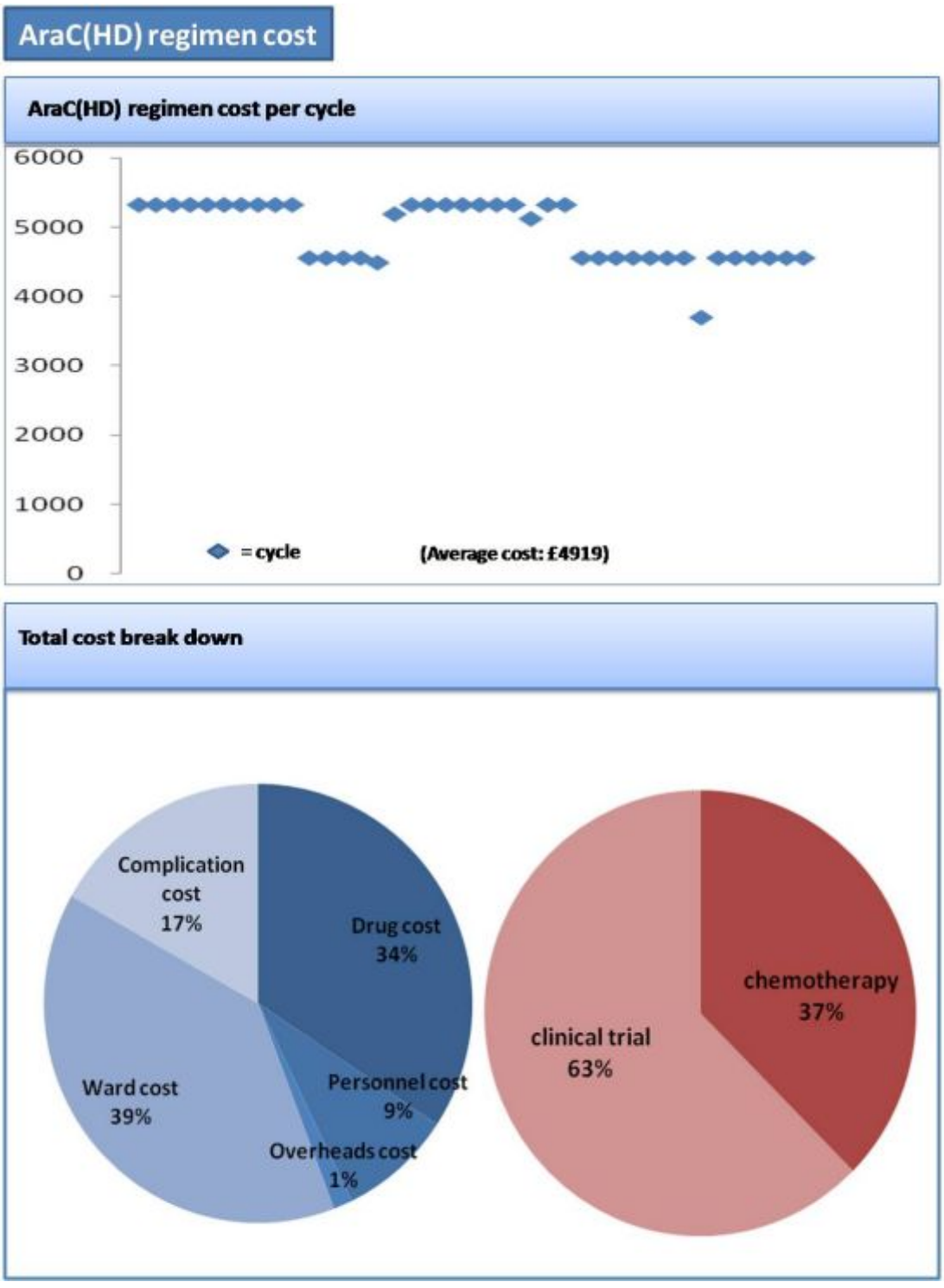


Figure 9.3 The illustration of the AraC (HD) regimen cost results

As it can be observed in the relevant plot, AraC (HD) costs were divided into two groups. This was because the AraC (HD) regimen contained two cycles, and the hospital stays of cycle one were longer than the ones of cycle two (please refer to section 5 for details). Also, as shown on the relevant pie chart, the ward cost still accounted for the highest percentage (39%) similar to the ADE regimen. Compared to other regimens, the drug cost of AraC (HD) accounted for relatively high percentage (34%), while the personnel cost accounted for relatively low percentage (9%). It is also worth noting that the AraC (HD) regimen was used more frequently in clinical trial (63%) rather than in non-clinical trial (37%).

Table 9.2 The detailed cost results of the AraC (HD) regimen

	Events No	Cost 1 (exclude complication cost)			Cost 2 (include complication cost)		
		Mean	Min	Max	Mean	Min	Max
AraC (HD)	40 courses	£4091	£3092	£4405	£4919	£3689	£5315
Course 1	21 courses	£4389	£4204	£4405	£5299	£5114	£5315
Course 2	19 courses	£3761	£3092	£3802	£4499	£3689	£4548
Chemotherapy	15 courses	£4199	£3735	£4405	£5055	£4481	£5315
Course 1	10 courses	£4405	£4405	£4405	£5315	£5315	£5315
Course 2 +	5 courses	£3788	£3735	£3802	£4535	£4481	£4548
AML 15	25 courses	£4025	£3092	£4405	£4838	£3689	£5315
Course 1	11 courses	£4374	£4204	£4405	£5284	£5114	£5315
Course 2	14 courses	£3751	£3092	£3802	£4487	£3689	£4548
AraC(HD) + Mylotarg	7 courses	£5926	£5316	£6028	£6810	£6044	£6938
Chemotherapy	-	-	-	-	-	-	-
AML 15	7 courses	£5926	£5316	£6028	£6810	£6044	£6938
Course 1	7 courses	£5926	£5316	£6028	£6810	£6044	£6938
Course 2	-	-	-	-	-	-	-

The detailed cost results are shown in **Table 9.2**. As it can be observed, the average AraC (HD) regimen cost per cycle was £4919 (including the complication treatment cost). More specifically, the average cost for AraC (HD) cycle one was found to be £5299 and £4499 for cycle two.

c. AraC (Low Dose)

AraC (LD) was the second most commonly used regimen. The cost results are illustrated in **Figure 9.4** below.

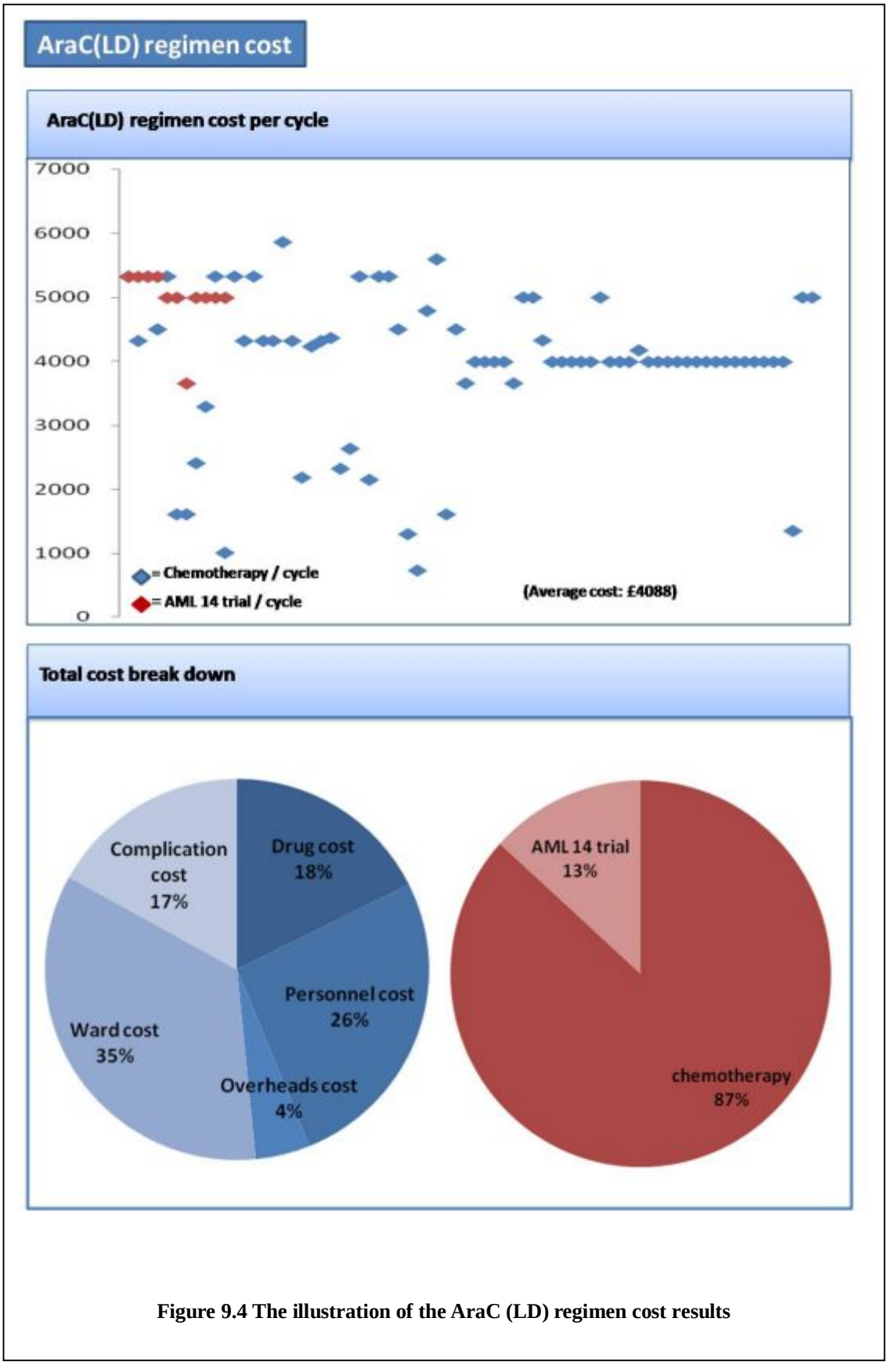


Figure 9.4 The illustration of the AraC (LD) regimen cost results

As shown on the plot, the Arac (LD) costs varied. A possible reason for this could be that the full course was not given when the AraC (LD) was used for prolonging life rather than using for an intensive induction treatment. However, when the full dose was given, cost patterns could be found in the plot. As it can be seen in the relevant plot, the costs could be categorized into two groups. The AraC (LD) cost used for clinical trial was slightly higher than the one used for standard chemotherapy, as the hospital stays of the clinical trial were higher than the one of the standard chemotherapy (please refer to section 4.3.2 for details). As it can be observed in the relevant pie chart, the ward cost accounted for the highest percentage (35%). The rest percentages of the cost drivers were consistent with the percentages of the ADE regimen. It is worth noting that AraC (LD) was used mainly as the standard chemotherapy (87%). The AraC(LD) was used in clinical trial only in a few cases.

The cost results are shown in **Table 9.3** below. It can be observed that the average AraC (LD) regimen cost per cycle was £4088 (including the complication treatment cost). Thus, it was slightly cheaper than AraC (HD). Specifically, the average cost for AraC (LD) cycle one was found to be £4022 and £4164 for cycle two.

It is worth noting that it was assumed that all the patients received AraC(LD) in inpatient setting in the current study, although, clinically, AraC(LD) can be delivered in inpatient setting and outpatient setting. This assumption was made due to lack of the relevant information about where the patient received the treatment. Therefore, the AraC(LD) cost results here were considered to be overestimated, compared to the actual treatment cost.

Table 9.3 The detailed cost results of the AraC (LD) regimen

	Events No	Cost 1 (exclude complication cost)			Cost 2 (include complication cost)		
		Mean	Min	Max	Mean	Min	Max
AraC (LD)	83 courses	£3396	£638	£4895	£4088	£729	£5852
Course 1	39 courses	£3226	£638	£4895	£4002	£729	£5852
Course 2	44 courses	£3547	£1285	£4359	£4164	£1348	£4989
Chemotherapy	72 courses	£3267	£638	£4895	£3951	£729	£5852
Course 1	35 courses	£3096	£638	£4895	£3851	£729	£5852
Course 2+	37 courses	£3430	£1285	£4359	£4045	£1348	£4989
AML 14	11 course	£4237	£3019	£4359	£4986	£3649	£5316
Course 1	4 courses	£4359	£4359	£4359	£5316	£5316	£5316
Course 2+	7 courses	£4168	£3019	£4359	£4798	£3649	£4989
AraC (LD) + Mylotarg	2 courses	£5170	£4359	£5980	£5963	£4989	£6938
Chemotherapy	-	-	-	-	-	-	-
AML 14	2 courses	£5170	£4359	£5980	£5963	£4989	£6938
Course 1	1 course	£5980	-	-	£6938	-	-
Course 2	1 course	£4359	-	-	£4989	-	-

d. DA

DA was the most commonly used regimen among all the chemotherapy regimens. In total, 91 cycles of DA and eight cycles of DA + Mylotarg were used on the study patients. The cost results are illustrated below (**Figure 9.5**).

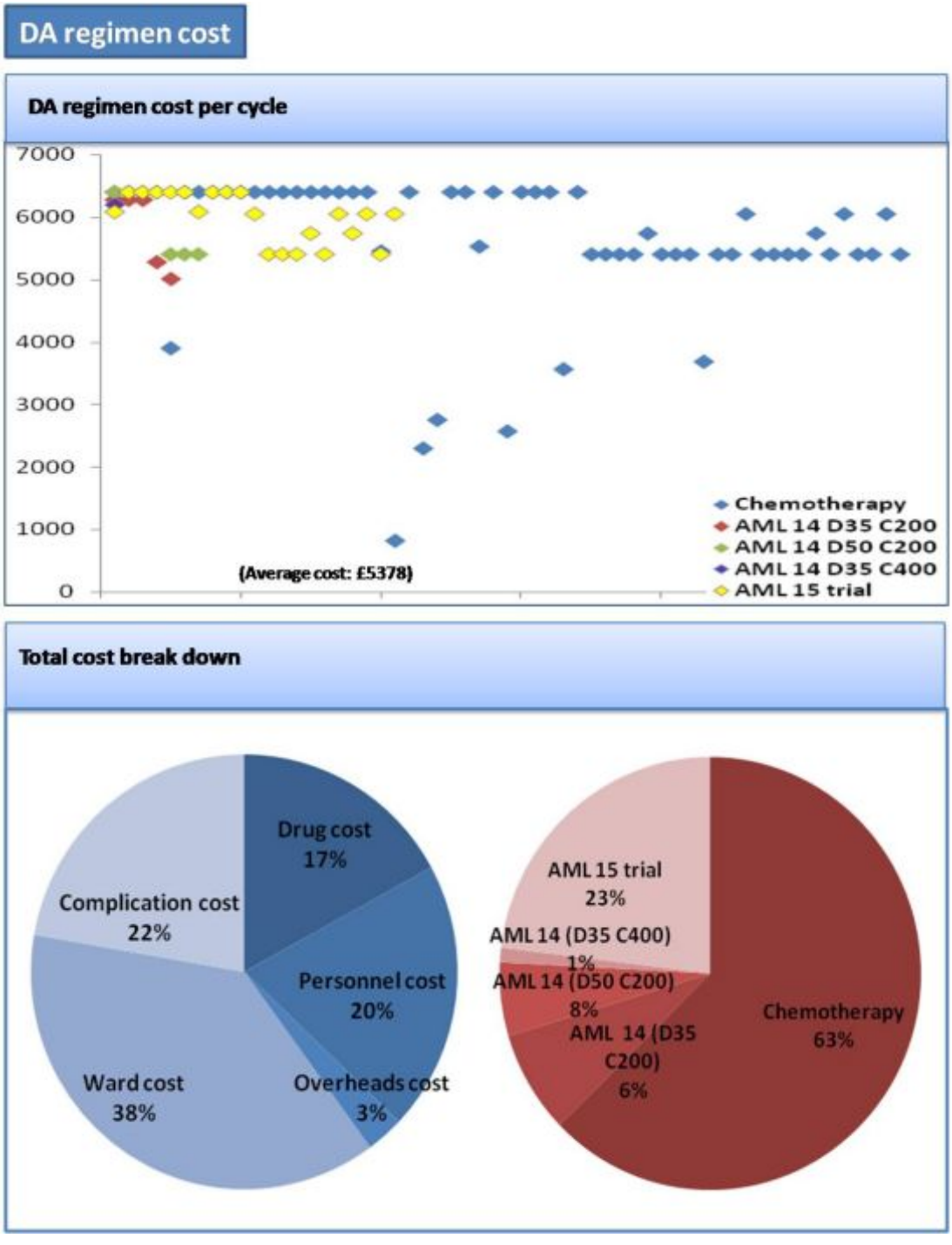


Figure 9.5 The illustration of the DA regimen cost results

As shown in the plot, the costs were divided into two groups. Similarly to the ADE regimen, the cost of cycle one was slightly higher than the one of the cycle two, as the full course of the cycle one was longer. Also, it was observed that the dosage differences did not have significant effect on the cost results. As illustrated in the relevant pie chart, the ward cost still accounted for the highest percentage (38%). However, the personnel cost (20%) accounted for relatively higher percentage, while the drug cost (17%) accounted for relatively low percentage. The low percentage drug cost provided a possible explanation for the little effect that the dosage differences had on the regimen cost.

Table 9.4 The detailed cost results of the DA regimen

	Events No	Cost 1 (exclude complication cost)			Cost 2 (include complication cost)		
		Mean	Min	Max	Mean	Min	Max
DA	91 courses	£4458	£750	£4918	£5738	£819	£6405
Course 1	52 courses	£4559	£750	£4918	£5913	£819	£6405
Course 2	39 courses	£4322	£2774	£4751	£5501	£3688	£6055
DA (D50 C200)	85 courses	£4454	£750	£4918	£5726	£819	£6405
Course 1	48 courses	£4542	£750	£4918	£5885	£819	£6405
Course 2	37 courses	£4340	£2774	£4751	£5520	£3688	£6055
Chemotherapy	57 courses	£4349	£750	£4918	£5591	£819	£6405
Course 1	34 courses	£4397	£750	£4918	£5689	£819	£6405
Course 2 +	23 courses	£4279	£2774	£4751	£5447	£3688	£6055
AML 14	7 courses	£4631	£4248	£4918	£5977	£5408	£6405
Course 1	4 courses	£4918	£4918	£4918	£6405	£6405	£6405
Course 2	3 courses	£4248	£4248	£4248	£5408	£5408	£5408
AML 15	21 courses	£4679	£4248	£4918	£6008	£5408	£6405
Course 1	10 courses	£4884	£4751	£4918	£6341	£6089	£6405
Course 2	11 courses	£4492	£4248	£4751	£5704	£5408	£6055
DA (D35 C200)	5 courses	£4470	£3854	£4792	£5826	£5014	£6278
AML 14	5 courses	£4470	£3854	£4792	£5826	£5014	£6278
Course 1	3 courses	£4792	£4792	£4792	£6278	£6278	£6278
Course 2	2 courses	£3988	£3854	£4122	£5148	£5014	£5282
DA (D35 C400)	1 course	£4707	-	-	£6194	-	-
AML 14	1 course	£4707	-	-	£6194	-	-
Course 1	1 course	£4707	-	-	£6194	-	-
Course 2	-	-	-	-	-	-	-
DA+Mylotarg	8 courses	£6253	£4248	£6539	£7699	£5408	£8026
Chemotherapy	1 course	£6539	-	-	£8026	-	-
Course 1	1 course	£6539	-	-	£8026	-	-
Course 2 +	-	-	-	-	-	-	-
AML 15	7 courses	£6212	£4248	£6539	£7652	£5408	£8026
Course 1	6 courses	£6539	£6539	£6539	£8025	£8025	£8025
Course 2	1 course	£4248	-	-	£5408	-	-

The detailed cost results are shown in **Table 9.4**. As listed, the average DA regimen cost per cycle was £5738 (including the complication treatment cost). More specifically, the average cost for cycle one was found to be £5913 and £5501 for cycle two. The costs of different dosages were similar. However, it is worth noting that the costs of DA used in the clinical trials were higher than the cost of DA used in the non-clinical trail. Also,

among the clinical trial arms, the costs of DA in the AML 14 trial were higher than the costs of DA in the AML 15 trial.

e. FLAG-Ida

FLAG-Ida regimen was the third most commonly used chemotherapy regimen. The cost results are illustrated in **Figure 9.6**.

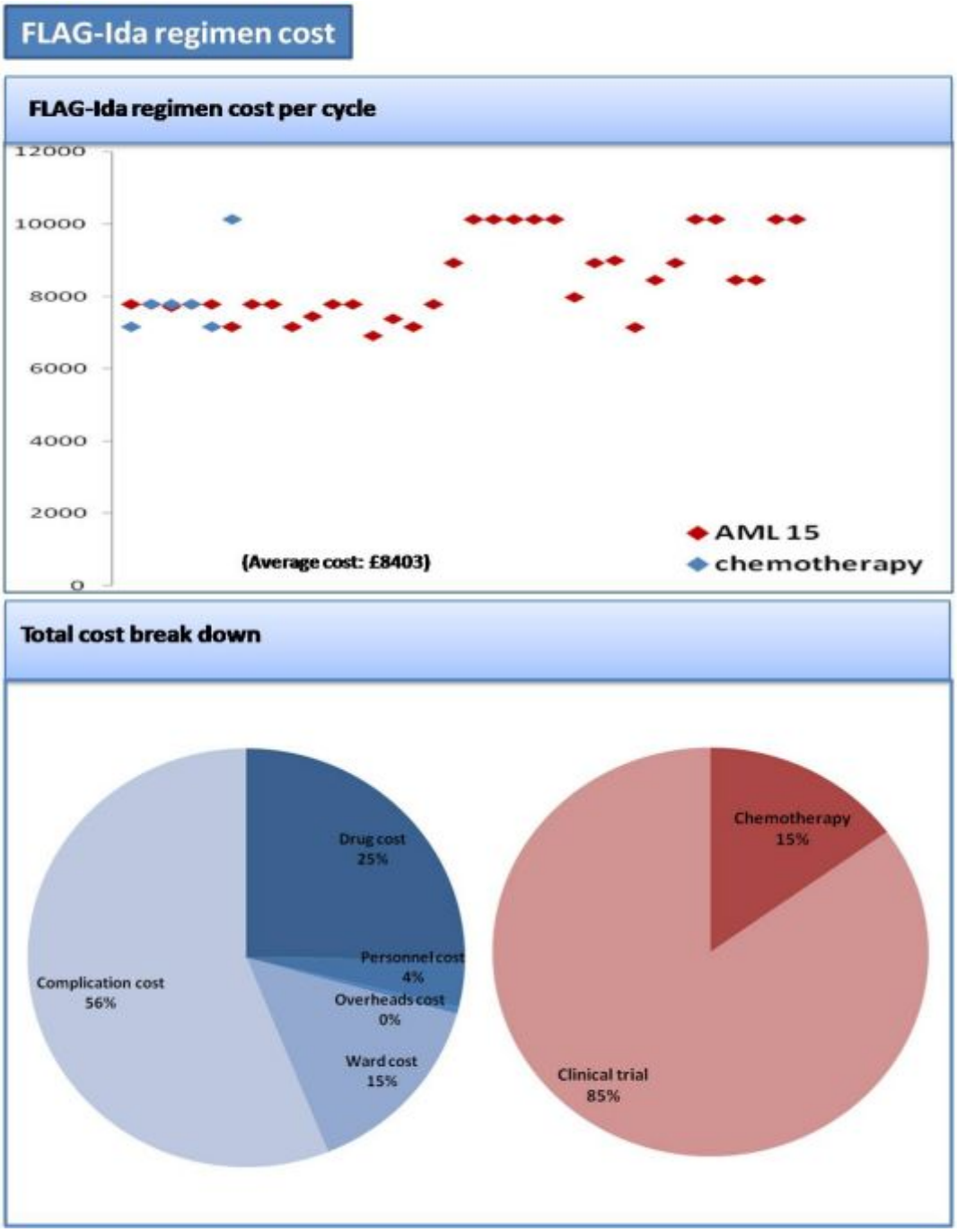


Figure 9.6 The illustration of the FLAG-Ida regimen cost results

As illustrated, the FLAG-Ida was used mainly in clinical trial (85%). As shown on the plot, the costs were divided into two groups. Cycle two was more costly than cycle one, as the hospital stays of cycle two were much longer (please refer to chapter 5). It is worth noting that, compared to other regimen cost drivers, the FLAG-Ida complication treatment cost was the only complication treatment cost that accounted for such high percentage (56%). A possible reason for this was that more antibiotic days were prescribed during the FLAG-Ida treatment (refer to section 4.3.2 for details).

Table 9.5 The detailed cost results of the FLAG-Ida regimen

	Events No	Cost 1 (exclude complication cost)			Cost 2 (include complication cost)		
		Mean	Min	Max	Mean	Min	Max
FLAG-Ida	40 courses	£6575	£5505	£7582	£8403	£6909	£10131
Course 1	21 courses	£6243	£5505	£6376	£7551	£6909	£7780
Course 2	19 courses	£6943	£5572	£7582	£9344	£7139	£10131
Chemotherapy	6 courses	£6503	£6153	£7582	£7963	£7155	£10131
Course 1	5 courses	£6287	£6153	£6376	£7530	£7155	£7780
Course 2 +	1 course	£7582	-	-	£10131	-	-
AML 15	34 courses	£6588	£5505	£7582	£8480	£6909	£10131
Course 1	16 courses	£6230	£5505	£6376	£7558	£6909	£7780
Course 2	18 courses	£6907	£5572	£7582	£9300	£7139	£10131
FLAG-Ida + Mylotarg	19 courses	£7807	£7037	£7998	£9449	£8040	£10131
Chemotherapy	1 course	£7774	-	-	£8777	-	-
Course 1	1 course	£7774	-	-	£8777	-	-
Course 2 +	-	-	-	-	-	-	-
AML 15	18 courses	£7809	£7037	£7997	£9486	£8040	£10131
Course 1	13 courses	£7896	£7037	£7997	£9238	£8040	£9401
Course 2	5 courses	£7582	£7582	£7582	£10131	£10131	£10131

The detailed cost results are shown in **Table 9.5**. As listed, that the average FLAG-Ida regimen cost per cycle was £8403 (including the complication treatment cost). More specifically, the average cost for cycle one was found to be £7551 and £9344 for cycle two.

f. MACE

MACE was the one of the most commonly used consolidation chemotherapies for AML. The related cost results are illustrated below (**Figure 9.7**).

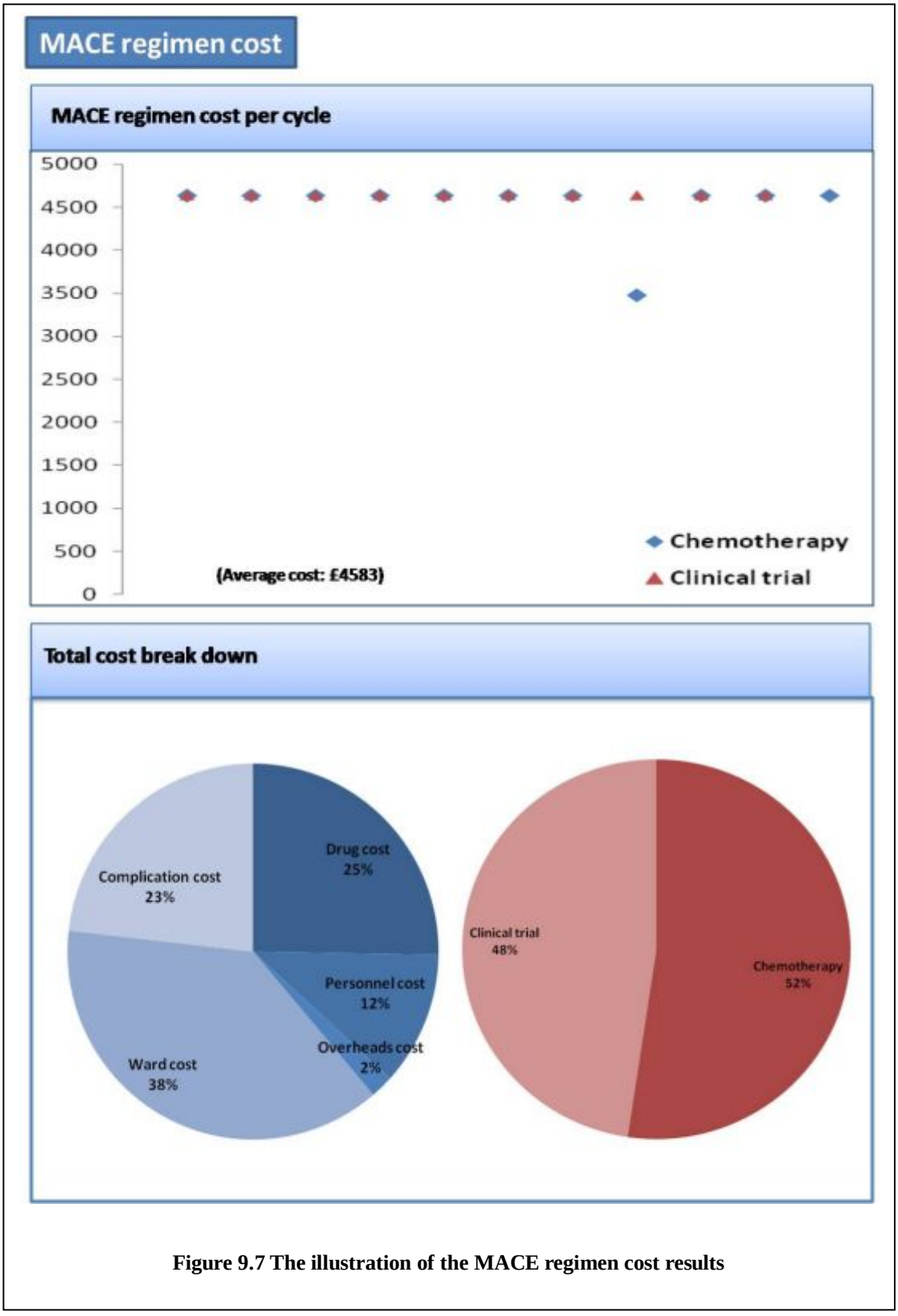


Figure 9.7 The illustration of the MACE regimen cost results

As shown in the plot, the MACE cost was quite consistent, as most of the patients were given one full dose cycle of MACE. As shown in the pie chart, the ward cost still account for the highest percentage (38%), while the drug cost was next (25%). The detailed cost results are shown in **Table 9.6** below. As shown on the table, the average MACE regimen cost per cycle was found to be £4583 (including the complication treatment cost).

Table 9.6 The detailed cost results of the MACE regimen

	Events No	Cost 1 (exclude complication cost)			Cost 2 (include complication cost)		
		Mean	Min	Max	Mean	Min	Max
MACE	21 courses	£3519	£2829	£3553	£4583	£3480	£4638
Chemotherapy	11 courses	£3488	£2829	£3553	£4533	£3480	£4638
Course 1	10 courses	£3481	£2829	£3553	£4522	£3480	£4638
Course 2 +	1 course	£3553	-	-	£4638	-	-
AML 15	10 courses	£3553	£3553	£3553	£4638	£4638	£4638
Course 1	10 courses	£3553	£3553	£3553	£4638	£4638	£4638
Course 2	-	-	-	-	-	-	-
MACE + Mylotarg	9 courses	£5175	£5175	£5175	£6259	£6259	£6259
AML 15	9 courses	£5175	£5175	£5175	£6259	£6259	£6259
Course 1	9 courses	£5175	£5175	£5175	£6259	£6259	£6259
Course 2	-	-	-	-	-	-	-

g. MidAC

MidAC was another commonly used consolidation chemotherapy for AML normally used after MACE. The cost results are illustrated in **Figure 9.8**.

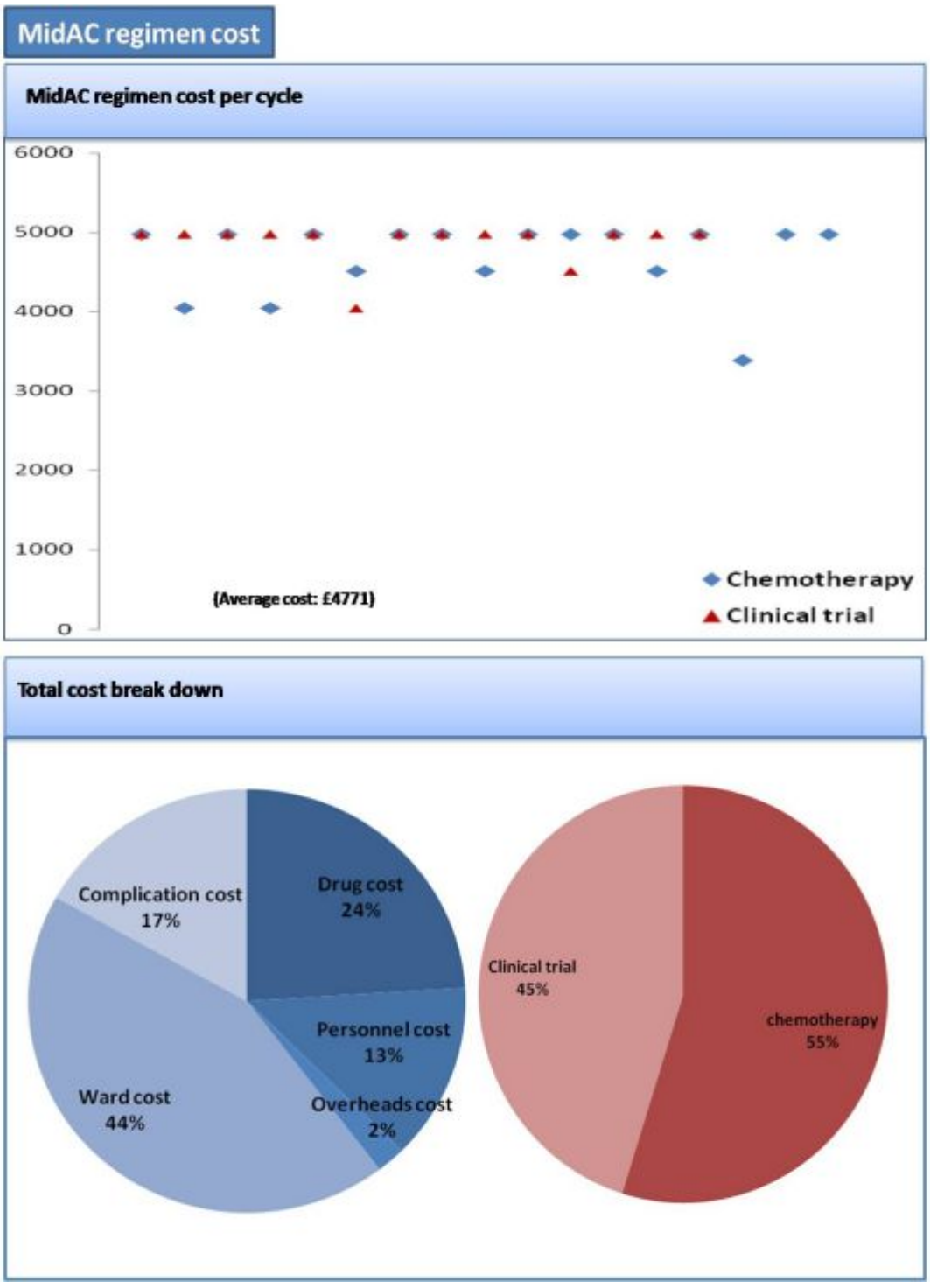


Figure 9.8 The illustration of the MidAC regimen cost results

As it can be observed in the relevant plot, the MidAC cost was generally consistent when the full dose was given. As illustrated in the pie chart, the ward cost accounted for the highest percentage (44%) and the drug cost was next (24%). The ward cost percentage was also the highest percentage among all the chemotherapy regimens.

The detailed cost results are shown in **Table 9.7** below. As illustrated, the average MidAC regimen cost per cycle was found to be £4771 (including the complication treatment cost).

Table 9.7 The detailed cost results of the MidAC regimen

	Events No	Cost 1 (exclude complication cost)			Cost 2 (include complication cost)		
		Mean	Min	Max	Mean	Min	Max
MidAC	31 courses	£3967	£3038	£4094	£4771	£3389	£4971
Chemotherapy	17 courses	£3913	£3038	£4094	£4687	£3389	£4971
Course 1	15 courses	£3889	£3038	£4094	£4649	£3389	£4971
Course 2 +	2 courses	£4094	£4094	£4094	£4971	£4971	£4971
AML 15	14 courses	£4032	£3518	£4094	£4872	£4044	£4971
Course 1	14 courses	£4032	£3518	£4094	£4872	£4044	£4971
Course 2	-	-	-	-	-	-	-

h. Spanish Approach

The Spanish approach was one of the most commonly used regimens for APML. The cost results are illustrated in **Figure 9.9**.

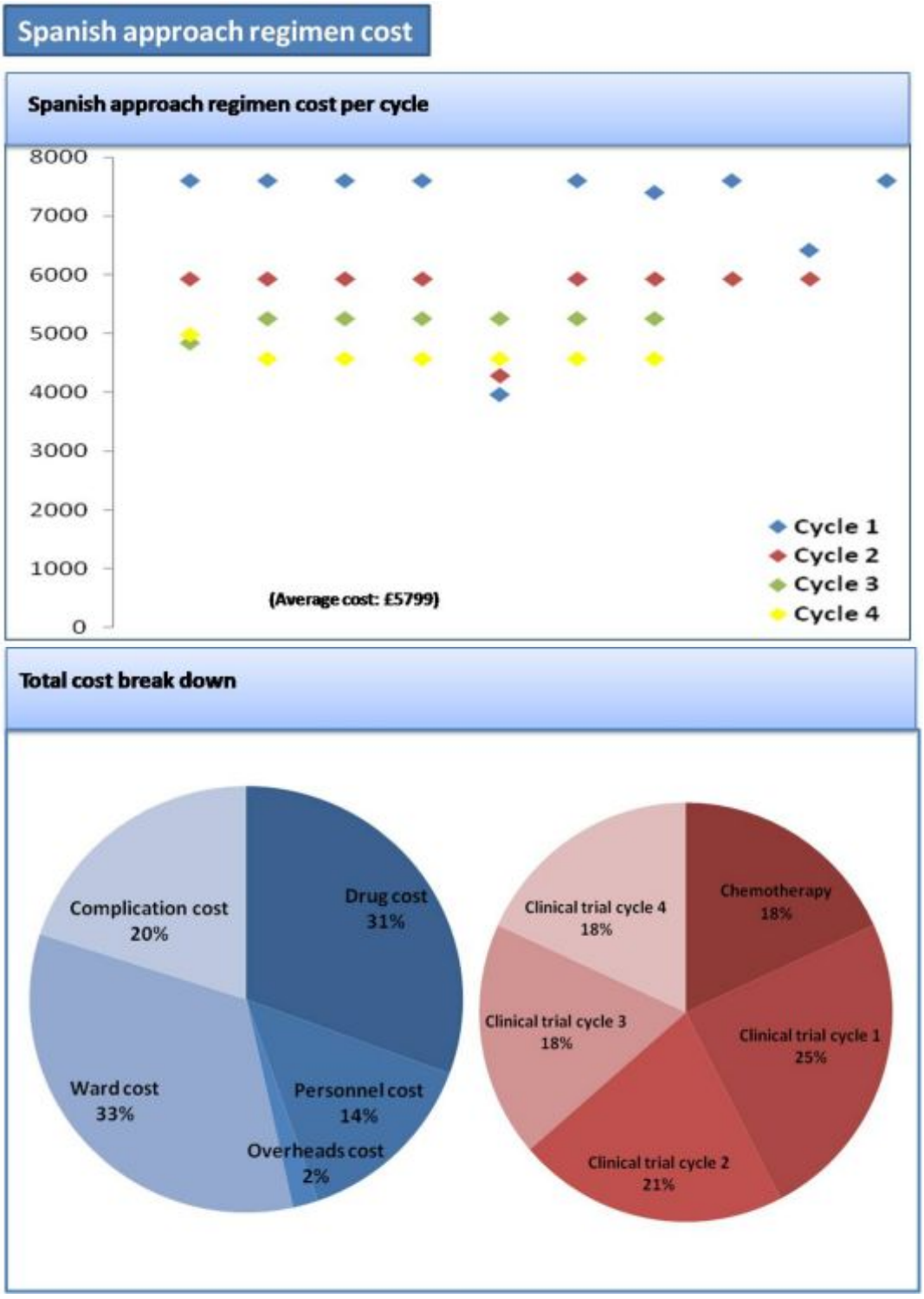


Figure 9.9 The illustration of the Spanish approach regimen cost results

The Spanish approach costs contained four cycles. Generally, cycle one cost was the highest followed by cycle two, while the cycle four cost was the lowest. As it can be observed in the pie chart, the ward cost still accounted for the highest percentage (33%) followed by the drug cost. It is worth noting that the Spanish approach was used mainly in clinical trial (82%) for patients who met the required criteria. For patients who did not meet the criteria, only few cases were found to have received the Spanish approach.

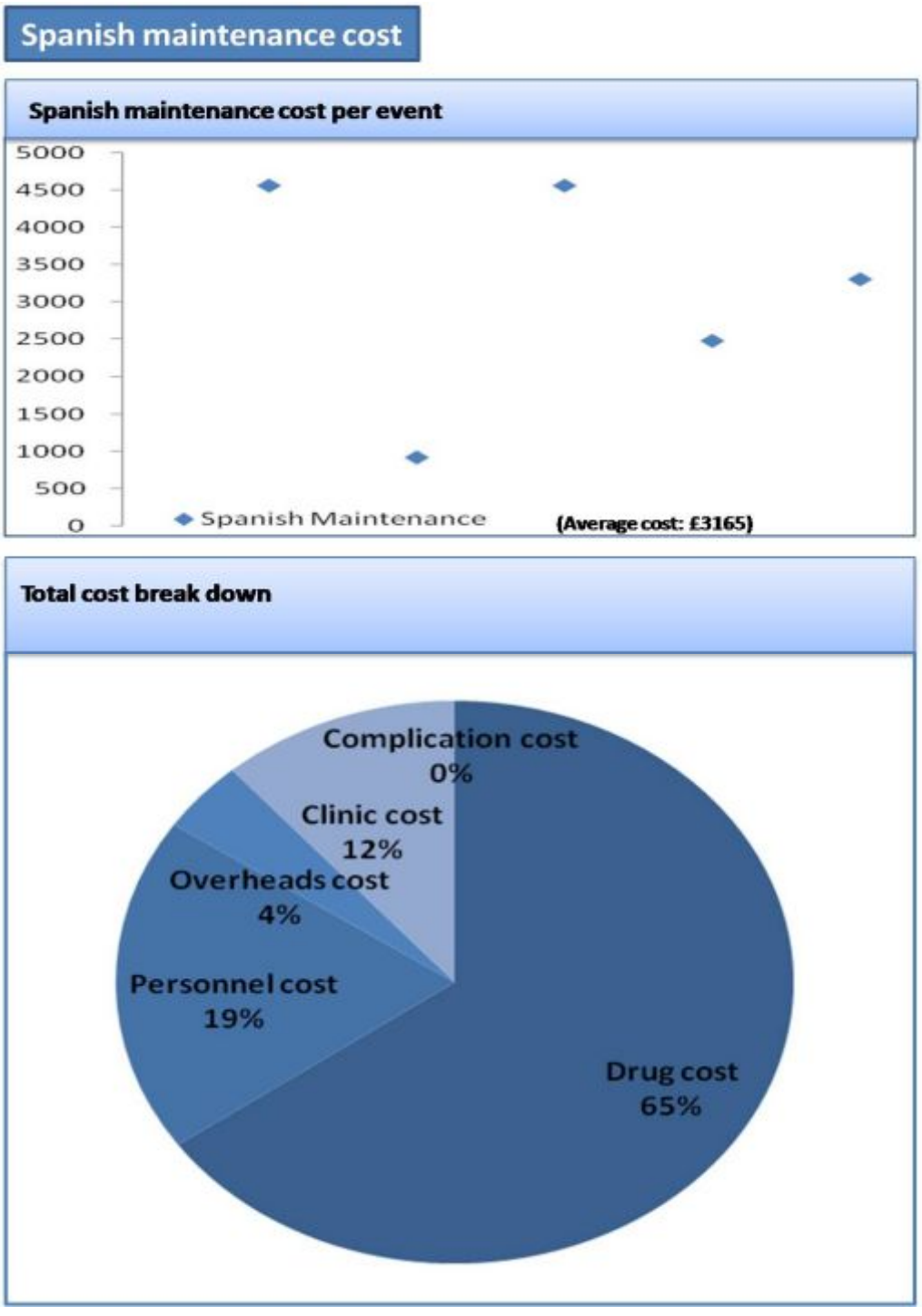


Figure 9.10 The illustration of the Spanish maintenance cost results

Except the intensive four-cycle inpatient treatment, the Spanish approach also contained long term outpatient maintenance. The cost results are illustrated **Figure 9.10**. As it can be observed in the plot, the costs varied depending on the maintenance time. Also, since the maintenance was outpatient based, the drug cost accounted for the highest percentage (65%)

The detailed cost results are shown in **Table 9.8**. As it can be seen in the table, the average Spanish regimen cost per cycle was found to be £5799 (including the complication treatment cost). More specifically, a rise in the number of treatment cycles resulted in a progressive decrease in average costs. The average costs for cycle one to cycle four were found to be £7094, £5743, £5211, and £4608 respectively. For the maintenance cost, only five patients were found to receive the Spanish maintenance treatment, and the average maintenance cost was found to be £3165.

Table 9.8 The detailed cost results of the Spanish approach / maintenance regimen

	Events No	Cost 1 (exclude complication cost)			Cost 2 (include complication cost)		
		Mean	Min	Max	Mean	Min	Max
Spanish	33 courses	£4636	£3339	£6403	£5799	£3964	£7595
Course 1	10 courses	£5975	£3508	£6403	£7094	£3964	£7595
Course 2	9 courses	£4579	£3339	£4734	£5743	£4285	£5926
Course 3	7 courses	£4019	£3789	£4057	£5211	£4981	£5249
Course 4	7 courses	£3416	£3377	£3645	£4608	£4569	£4837
Spanish-like	6 courses	£4951	£3645	£6403	£6143	£4837	£7595
Course 1	2 courses	£6403	£6403	£6403	£7595	£7595	£7595
Course 2	2 course	£4734	£4734	£4734	£5926	£5926	£5926
Course 3	1 course	£3789	-	-	£4981	-	-
Course 4	1 course	£3645	-	-	£4837	-	-
AML 15	27 courses	£4566	£3339	£6403	£5722	£3964	£7595
Course 1	8 courses	£5868	£3508	£6403	£6968	£3964	£7595
Course 2	7 courses	£4534	£3339	£4734	£5691	£4285	£5926
Course 3	6 courses	£4057	£4057	£4057	£5249	£5249	£5249
Course 4	6 courses	£3377	£3377	£3377	£4569	£4569	£4569
Spanish maintenance	5 patients	£3165	£914	£4563	£3165	£914	£4563

i. MRC approach

The MRC approach was another commonly used regimens for APML. The cost results are illustrated in **Figure 9.11**. As illustrated in the relevant plot, unlike the Spanish approach, the costs did not decrease progressively. In general, the cost of cycle one was the highest, followed by the one of cycles two and four, while the cycle three was the

lowest. Similarly to the Spanish approach, the MRC approach was also used mainly in clinical trial (89%). As it can be observed in the pie chart, the ward cost still accounted for the highest percentage (33%) followed by the drug cost (23%).

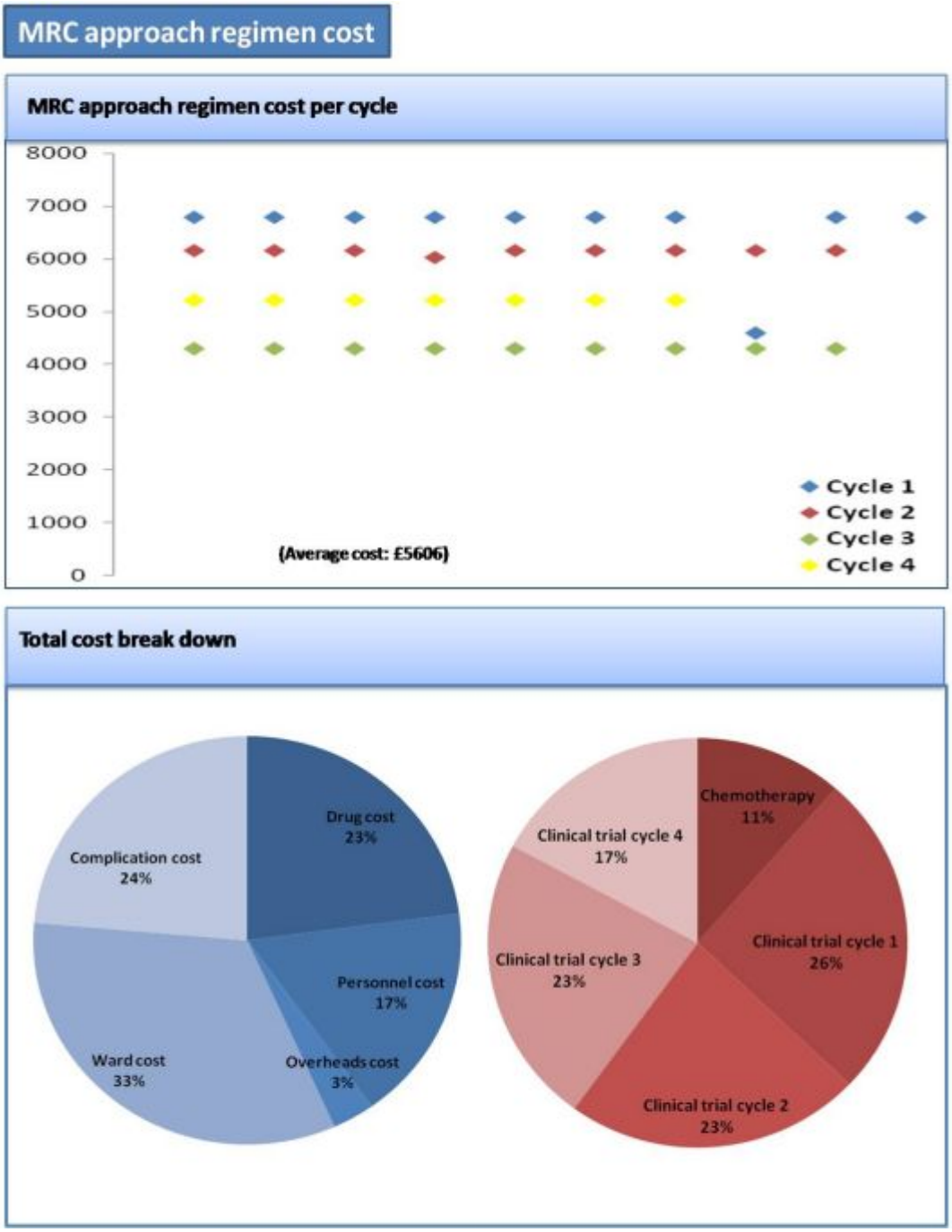


Figure 9.11 The illustration of the MRC approach cost results

The detailed cost results are shown in **Table 9.9**. As it can be seen in the table, the average MRC approach regimen cost per cycle was found to be £5606 (including the complication treatment cost). Consisted with the plot result, the costs did not decrease progressively. The average costs were £6575, £6143, £4300, and £5216 respectively for cycles one to four.

Table 9.9 The detailed cost results of the MRC approach regimen

	Events No	Cost 1 (exclude complication cost)			Cost 2 (include complication cost)		
		Mean	Min	Max	Mean	Min	Max
MRC	35 courses	£4283	£3511	£5500	£5606	£4300	£6795
Course 1	10 courses	£5301	£3511	£5500	£6575	£4594	£6795
Course 2	9 courses	£4160	£4041	£4175	£6143	£6024	£6158
Course 3	9 courses	£3617	£3617	£3617	£4300	£4300	£4300
Course 4	7 courses	£3841	£3841	£3841	£5216	£5216	£5216
AML 15	31 courses	£4283	£3511	£5500	£5606	£4300	£6795
Course 1	9 courses	£5279	£3511	£5500	£6550	£4594	£6795
Course 2	8 courses	£4159	£4041	£4175	£6141	£6024	£6158
Course 3	8 courses	£3617	£3617	£3617	£4300	£4300	£4300
Course 3	6 courses	£3841	£3841	£3841	£5216	£5216	£5216
MRC like	4 courses	£4283	£3617	£5500	£5617	£4300	£6795
Course 1	1 course	£5500	-	-	£6795	-	-
Course 2	1 course	£4175	-	-	£6158		
Course 3	1 course	£3617	-	-	£4300	-	-
Course 4	1 course	£3841	-	-	£5216	-	-

j. Hydroxycarbamide

The hydroxycarbamide was the most commonly used outpatient based regimen. In total, 39 events of using hydroxycarbamide were used. The cost results are illustrated in **Figure 9.12**.

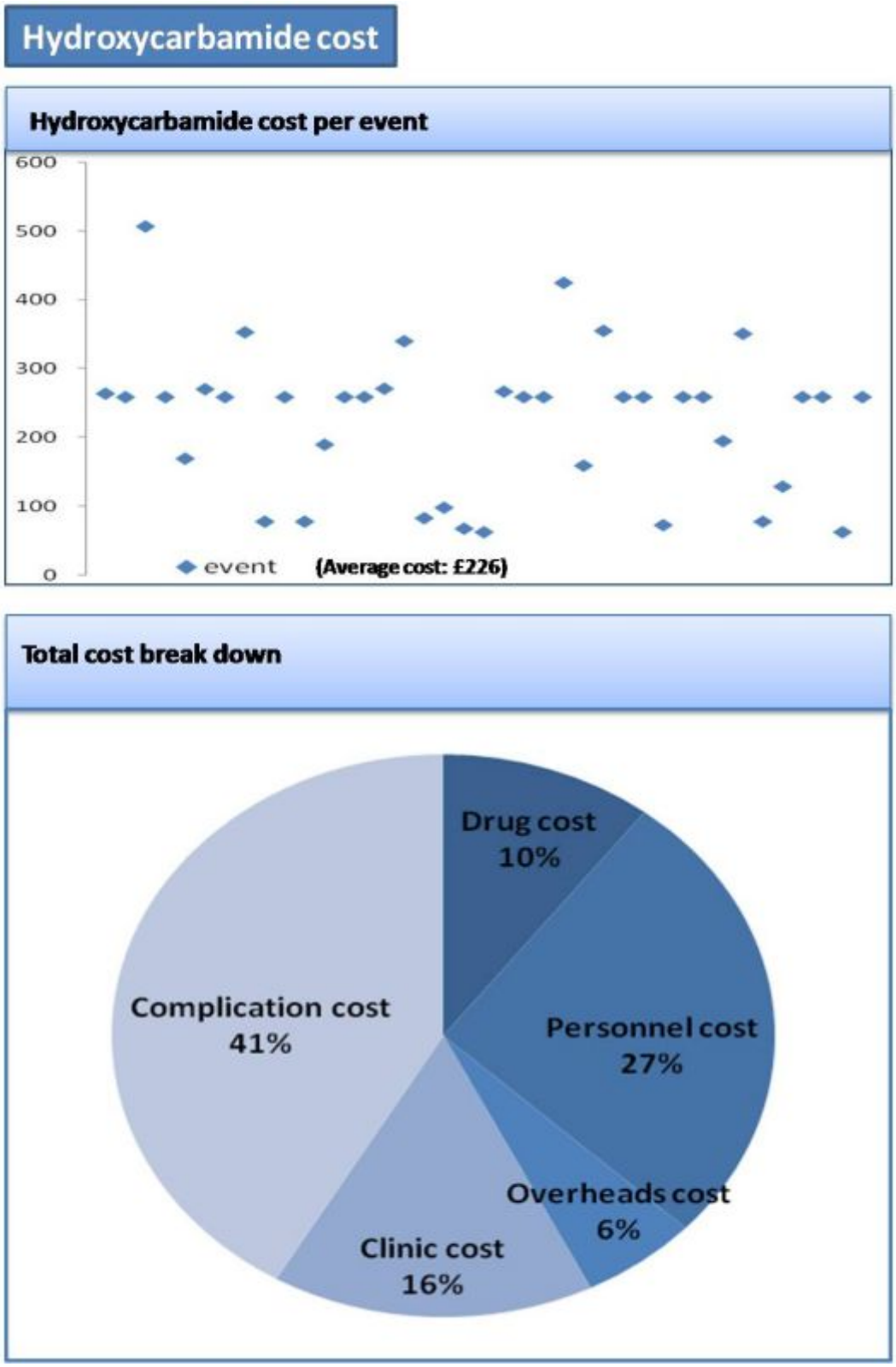


Figure 9.12 The illustration of the Hydroxycarbamide cost results

As illustrated in the plot, the hydroxycarbamide cost varied depending on the treatment time. Also, as shown in the pie chart, the composition of the hydroxycarbamide cost was very different from the inpatient-based regimens. The drug cost only accounted for a very low percentage (10%), with the complication treatment cost and the personnel costs dominating the percentage shares (41% and 27% respectively).

The detailed cost results are shown in **Table 9.10** below. As it can be seen in the table, the average hydroxycarbamide regimen cost per event was found to be £226 (including the complication treatment cost). No hydroxycarbamide was used in clinical trial.

Table 9.10 The detailed cost results of the hydroxycarbaminde regimen

	Events No	Cost 1 (exclude complication cost)			Cost 2 (include complication cost)		
		Mean	Min	Max	Mean	Min	Max
Hydroxycarbamide	39 events	£132	£59	£384	£226	£63	£506

k. FC related regimens

The FC related regimens were the second commonly used outpatient based regimen. The drugs of the FC regimen can be used separately as a single agent or combined. The cost results are illustrated in **Figure 9.13**.

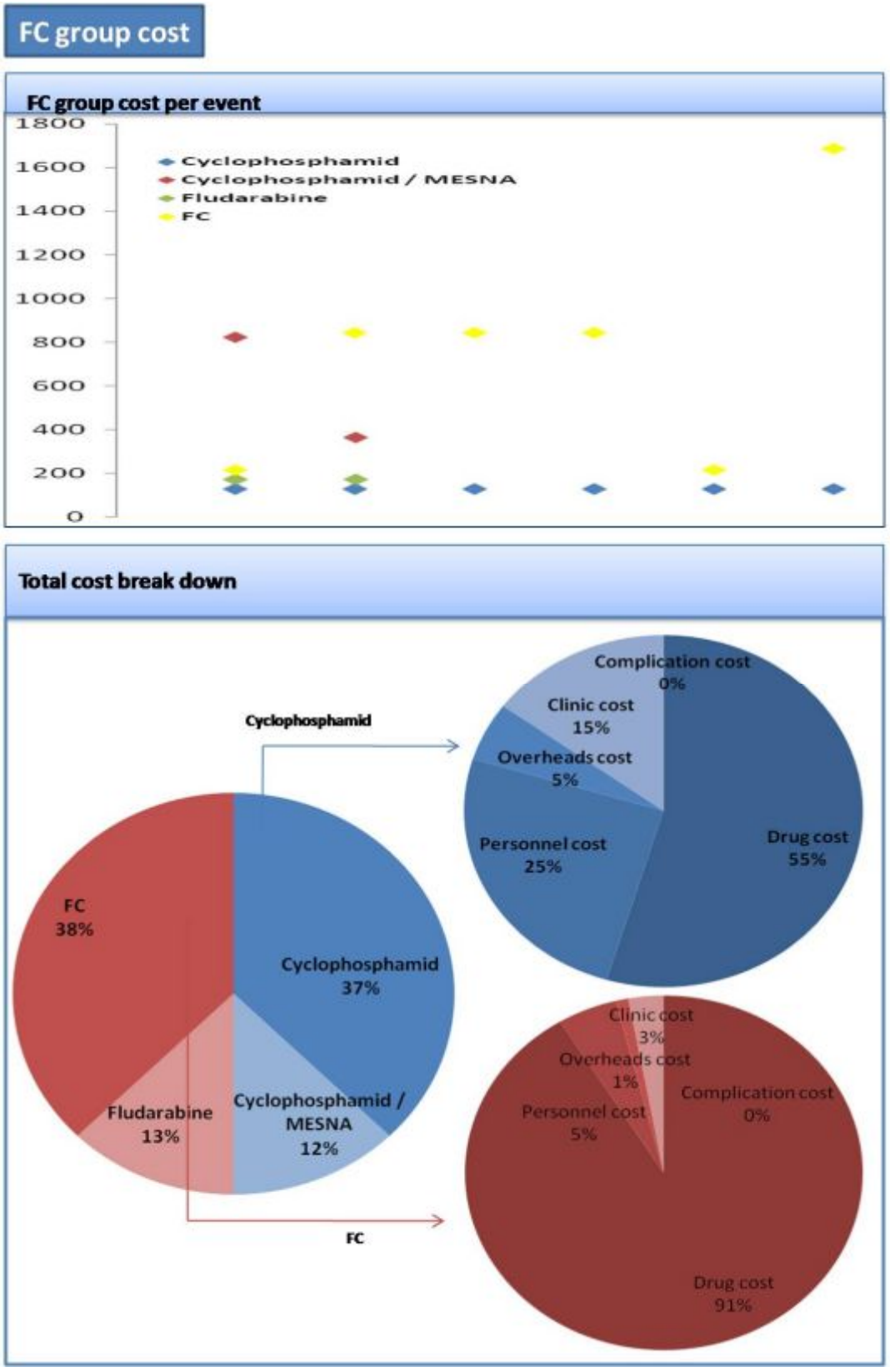


Figure 9.13 The illustration of the FC related regimen cost results

As illustrated in the plot, the cost of the combination of Fludarabine and Cyclophosphomide was the highest, followed by the cost of Fludarabine (used alone), while the cost of cyclophosphomide (used alone) was the lowest. As shown in the pie chart, it was observed that cyclophosphamide (37%) and FC occupied the largest percentage share (38%). After further breaking down, it was found that drug costs were the most important cost drivers for cyclophosphamide (55%) and for FC (91%)

The cost results are shown in **Table 9.11**. As shown in the table, the average FC regimen cost per event was found to be £775. For the single agent, the average costs for Fludarabine and Cyclophosphamide were found to be £594 and £128 respectively.

Table 9.11 The detailed cost results of the FC related regimens

	Events No	Cost 1 (exclude complication cost)			Cost 2 (include complication cost)		
		Mean	Min	Max	Mean	Min	Max
FC	6	£775	£215	£1687	£775	£215	£1687
Fludarabine	2	£594	£364	£823	£594	£364	£823
Cyclophosphamide	6	£128	£128	£128	£128	£128	£128
Cyclophosphamide + MESNA	1	£173	-	-	£173	-	-

l. Summary

The costs of chemotherapies and clinical trial arms varied depending on several factors. From the results discussed in previous sections, it was observed that, among all the chemotherapy regimens, the cost of clinical trial was slightly higher than the cost of non-clinical trial (chemotherapy), except ADE, AraC (HD), and the Spanish approach. The possible reason for this could be that the patients who entered the clinical trial were selected with specific criteria. Therefore, they had higher possibility to tolerate full course of treatment compared to other patients, something that caused the average cost of the clinical trial to be increased.

Furthermore, taking the clinical trial arms and chemotherapies as a whole, regimen costs were driven by the five cost drivers. For inpatient chemotherapies, it was found that the ward cost was the largest fraction (from 33% to 44%) and followed by the drug cost (from 18% to 34%), and then all the others. The FLAG-Ida was the only exception to the above. Possible reason for this might be that the relatively high level of the antibiotic needs (refer to chapter 6) compressed the percentages of other cost drivers. For the cost distribution of

the outpatient chemotherapies, the composition percentages of cost drivers varied. This was because the drug costs of outpatient chemotherapies varied extremely from very low (i.e. Hydroxycabarmide at £0.72 per day) to very expensive (i.e. Daunorubicin at £316 per day). Therefore, the composition percentage patterns of outpatient chemotherapies were not as consistent as the inpatient based chemotherapies.

Based on the whole of the regimen cost results, it is worth noting that the cost results of the regimens along with Mylotarg equated to the costs of the regimen alone plus the Mylotarg cost. Taking ADE + Mylotarg as an example, the average cost for cycle one was found to be £7290. This value was close to the summation of the ADE cycle one cost (£5799) with the Mylotarg cost (£1619).

Overall, the average cost per inpatient chemotherapy cycle was found to be £5829 and the cost per outpatient chemotherapy event £640. The summary of the costs of all the regimens used on the study patients (including regimen costs that are not covered in detail in section 9.1) can be found in the **Table 9.12** below, while the relevant details can be found in **Appendix 9.1**.

Table 9.12 The summary of the cost results of all the chemotherapy regimens

	Events No	Cost 1 (exclude complication cost)			Cost 2 (include complication cost)		
		Mean	Min	Max	Mean	Min	Max
Chemotherapy	329 courses	£3440	£59	£13770	£4284	£60	£15030
Clinical trial	265 courses	£5010	£914	£7997	£6220	£914	£10131
Chemotherapy + trial	594 courses	£4140	£59	£13770	£5148	£60	£15030
Inpatient chemotherapy	516 courses	£4678	£638	£13770	£5829	£729	£15030
Outpatient chemotherapy	78 events	£587	£59	£5112	£640	£60	£5112
ADE	47 courses	£4367	£4797	£2553	£5284	£2677	£6036
Course 1	23 courses	£4625	£2553	£4797	£5799	£2677	£6036
Course 2	24 courses	£4120	£3938	£4287	£4790	£4522	£5037
ADE + Mylotarg	10 courses	£6132	£4113	£6418	£7290	£4779	£7657
Course 1	9 courses	£6357	£6069	£6418	£7568	£7060	£7657
Course 2	1 course	£4113	-	-	£4779	-	-
AraC (HD)	40 courses	£4091	£3092	£4405	£4919	£3689	£5315
Course 1	21 courses	£4389	£4204	£4405	£5299	£5114	£5315
Course 2	19 courses	£3761	£3092	£3802	£4499	£3689	£4548
AraC(HD) + Mylotarg	7 courses	£5926	£5316	£6028	£6810	£6044	£6938
Course 1	7 courses	£5926	£5316	£6028	£6810	£6044	£6938
Course 2	-	-	-	-	-	-	-
AraC (LD)	83 courses	£3396	£638	£4895	£4088	£729	£5852
Course 1	39 courses	£3226	£638	£4895	£4002	£729	£5852
Course 2	44 courses	£3547	£1285	£4359	£4164	£1348	£4989
AraC (LD) + Mylotarg	2 courses	£5170	£4359	£5980	£5963	£4989	£6938
Course 1	1 course	£5980	-	-	£6938	-	-
Course 2	1 course	£4359	-	-	£4989	-	-
DA	91 courses	£4458	£750	£4918	£5738	£819	£6405
Course 1	52 courses	£4559	£750	£4918	£5913	£819	£6405
Course 2	39 courses	£4322	£2774	£4751	£5501	£3688	£6055
DA+Mylotarg	8 courses	£6253	£4248	£6539	£7699	£5408	£8026
Course 1	7 courses	£6539	£6539	£6539	£8025	£8025	£8025
Course 2	1 course	£4248	-	-	£5408	-	-
Clofarabine	3 courses	£13256	£12631	£13770	£14516	£13891	£15030
FLA	7 courses	£4713	£3565	£5709	£6551	£4865	£7909
Course 1	4 courses	£4503	£4503	£4503	£6294	£6294	£6294
Course 2	3 courses	£4994	£3565	£5709	£6894	£4865	£7909
FLAG	25 courses	£5305	£4474	£6283	£7100	£5759	£8615
Course 1	16 courses	£5303	£4661	£5479	£6951	£5759	£7402
Course 2	9 courses	£5308	£4474	£6283	£7365	£6233	£8615
FLAG-Ida	40 courses	£6575	£5505	£7582	£8403	£6909	£10131
Course 1	21 courses	£6243	£5505	£6376	£7551	£6909	£7780
Course 2	19 courses	£6943	£5572	£7582	£9344	£7139	£10131
FLAG-Ida + Mylotarg	19 courses	£7807	£7037	£7998	£9449	£8040	£10131
Course 1	14 courses	£7896	£7037	£7997	£9238	£8040	£9401
Course 2	5 courses	£7582	£7582	£7582	£10131	£10131	£10131
MACE	21 courses	£3519	£2829	£3553	£4583	£3480	£4638
MACE + Mylotarg	9 courses	£5175	£5175	£5175	£6259	£6259	£6259
MidAC	31 courses	£3967	£3038	£4094	£4771	£3389	£4971
HAM	1 courses	£5883	-	-	£6949	-	-
Spanish	33 courses	£4636	£3339	£6403	£5799	£3964	£7595
Course 1	10 courses	£5975	£3508	£6403	£7094	£3964	£7595
Course 2	9 courses	£4579	£3339	£4734	£5743	£4285	£5926
Course 3	7 courses	£4019	£3789	£4057	£5211	£4981	£5249
Course 4	7 courses	£3416	£3377	£3645	£4608	£4569	£4837

MRC	35 courses	£4283	£3511	£5500	£5606	£4300	£6795
Course 1	10 courses	£5301	£3511	£5500	£6575	£4594	£6795
Course 2	9 courses	£4160	£4041	£4175	£6143	£6024	£6158
Course 3	9 courses	£3617	£3617	£3617	£4300	£4300	£4300
Course 4	7 courses	£3841	£3841	£3841	£5216	£5216	£5216
Amsacrine	1 courses	£2155	-	-	£3300	-	-
Arsenic trioxide	2 courses	£10391	£10391	£10391	£11537	£11537	£11537
Campath	1 courses	£2211	-	-	£3357	-	-
ATRA	3 events	£334	£106	£757	£405	£124	£922
Anagrelide	1 events	£152	-	-	£152	-	-
Clopidogrel	1events	£92	-	-	£92	-	-
Cyclophosphamide	6 events	£128	£128	£128	£128	£128	£128
Cyclophosphamide + MESNA	1 events	£173	-	-	£173	-	-
Daunorubicin	1 events	£768	-	-	£768	-	-
ETI	2 events	£1440	£786	£2095	£1440	£786	£2095
FC	6 events	£775	£215	£1687	£775	£215	£1687
Fludarabine	2 events	£594	£364	£823	£594	£364	£823
Mylotarg	1 events	£1712	-	-	£1909	-	-
Melphalan	3 events	£228	£128	£382	£228	£128	£382
Aspirin	2 events	£90	£60	£120	£90	£60	£120
Hydroxycarbamide	39 events	£132	£59	£384	£226	£63	£506
Hydroxycarbamide / Aspirin	1 events	£2244	-	-	£2366	-	-
Chelating agents	2 events	£3874	£2636	£5112	£3874	£2636	£5112
Vincristine	1 events	£374	-	-	£374	-	-
Spanish maintenance	5 events	£3165	£914	£4563	£3165	£914	£4563

9.2.2 Supportive therapy

Supportive care had four different sub-types, namely G-CSF, erythropoietin, steroids and transfusion (please refer to chapter 7 for details). The three most commonly used supportive therapies are discussed in the following paragraphs, while the detailed cost results are listed in **Table 9.13** below.

Table 9.13 The detailed cost results of the supportive therapies

	Events No	Cost 1 (exclude complication cost)			Cost 2 (include complication cost)		
		Mean	Min	Max	Mean	Min	Max
Transfusion	267 events	£8861	£530	£67282	£8861	£530	£67282
	190 patients	£12453	£530	£75229	£12453	£530	£75229
G-CSF	62 events	£827	£197	£4765	£827	£197	£4765
	41 patients	£1251	£197	£4765	£1251	£197	£4765
	55 IP events	£748	£197	£1182	£748	£197	£1182
	7 OP events	£1447	£596	£4765	£1447	£596	£4765
Steroids	13 events	£300	£59	£1733	£300	£59	£1733
Dexamethasone	5 events	£110	£62	£289	£110	£62	£289
Prednisolone	7 events	£467	£59	£1733	£467	£59	£1733
Hydrocortisone	1 event	£79	-	-	£79	-	-
Erythropoietin	3 events	£1628	£111	£4440	1628	£111	£4440

a. G-CSF

G-CSF was the second most commonly used supportive therapy. As shown on **Table 9.13**, the average cost of G-CSF per event was found to be £827. According to the purposes of using G-CSF, the G-CSF can be further divided into two sub-types: inpatient and outpatient G-CSF (please refer to chapter 7 for details). When inpatient G-CSF was used as the adjunctive therapy of curative chemotherapy, the average cost was found to be £748. When outpatient G-CSF was used for long-term maintenance purposes, the average cost was found to be £1447. The cost results are illustrated in **Figure 9.14**. As shown in the pie chart, the inpatient G-CSF treatments were the most common (89%). Since the G-CSF was an expensive drug, the drug cost accounted for the highest percentage for both inpatient and outpatient G-CSF treatments.

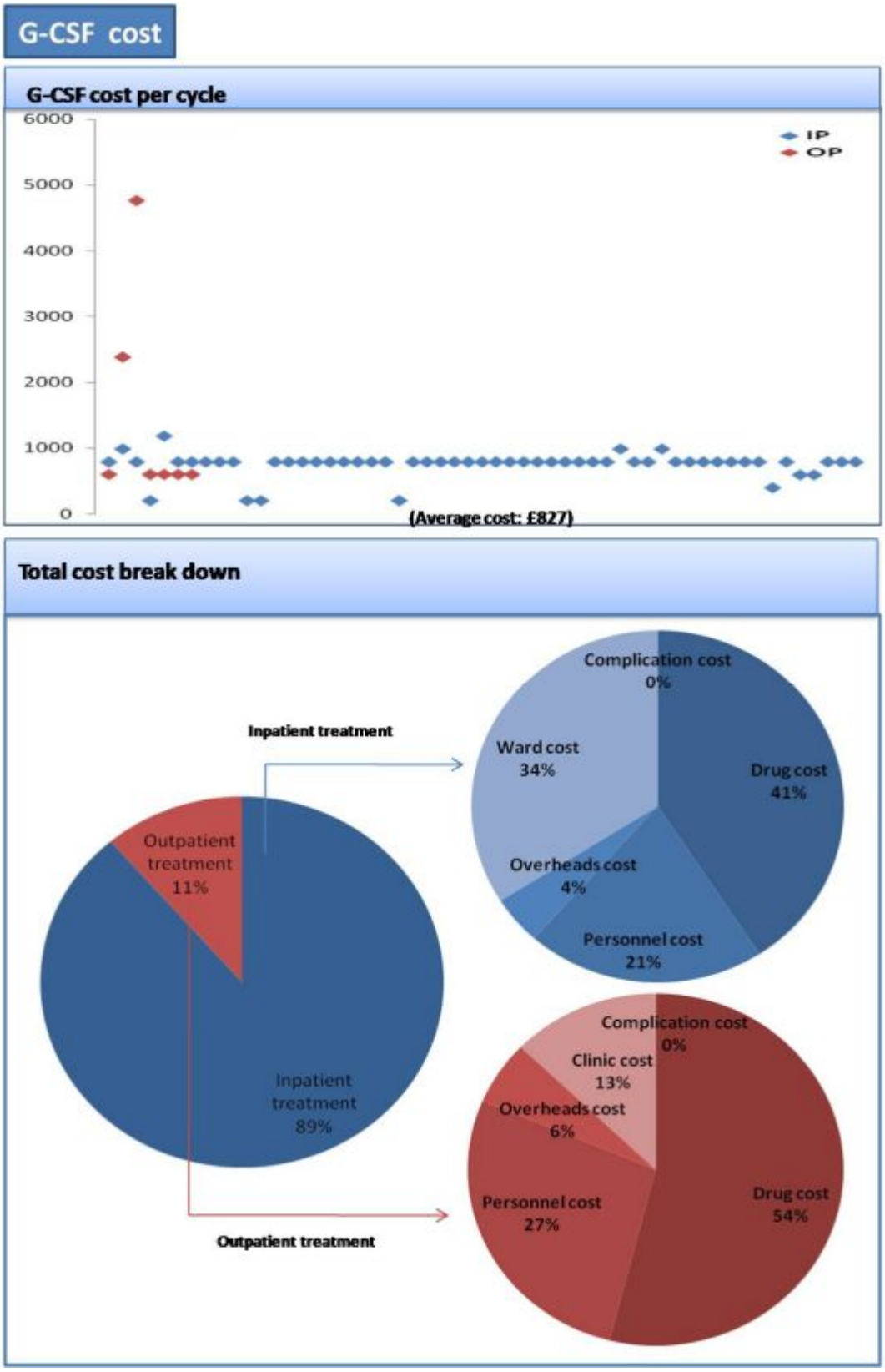


Figure 9.14 The illustration of the G-CSF cost results

b. Steroids

Steroids was another commonly used supportive therapy. **Table 9.13** shows the average costs of the three different drugs that were used on the study patients. Without taking the drug types into consideration, the average steroids cost per event was found to be £300. Taking the drug types into consideration, the average cost result per cycle for Hydrocortisone was the lowest and for the Prednisolone the highest, in sharp contrast with the unit costs of these two drugs which were the exact opposite. This was because the average treatment time per cycle of Hydrocortisone was the shortest, compared to Prednisolone which was the longest. The cost results are illustrated in **Figure 9.15**.

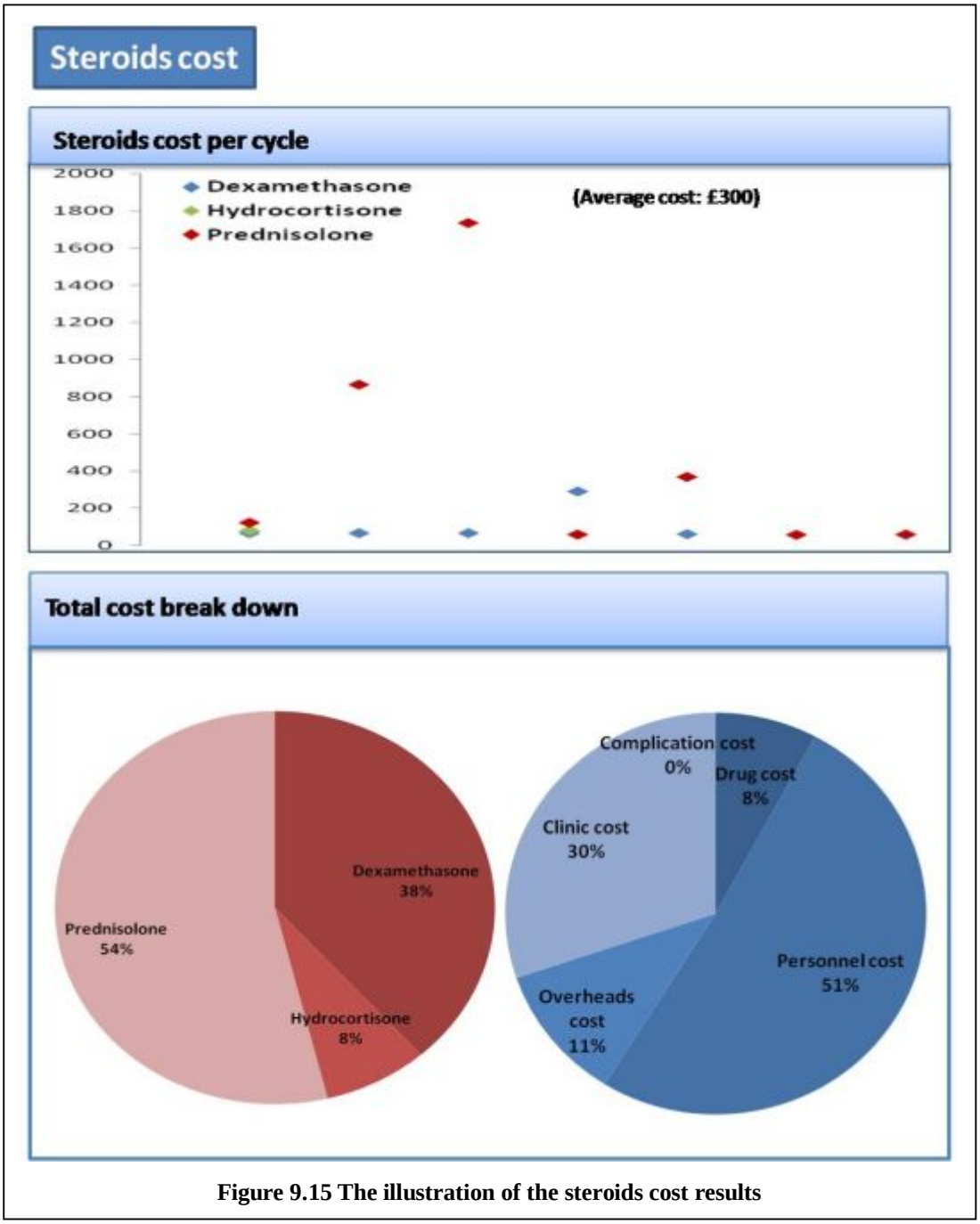


Figure 9.15 The illustration of the steroids cost results

As shown on the pie chart, Prednisolone was the most commonly used drug among three steroids drugs. Also, it can be observed that the personnel cost (51%) and the clinic cost (30%) accounted for the majority of the cost percentage share, while the drug cost accounted for the lowest percentage share, as the unit cost of the drug was low.

c. Transfusion

Transfusion was the most commonly used supportive therapy on the study patients. Based on the unit cost of the transfusion (£414/transfusion as described in chapter 7), **Table 9.13** illustrates the average transfusion costs per event (£8861) and per patient (£12453). The cost results are also illustrated in **Figure 9.16** below.

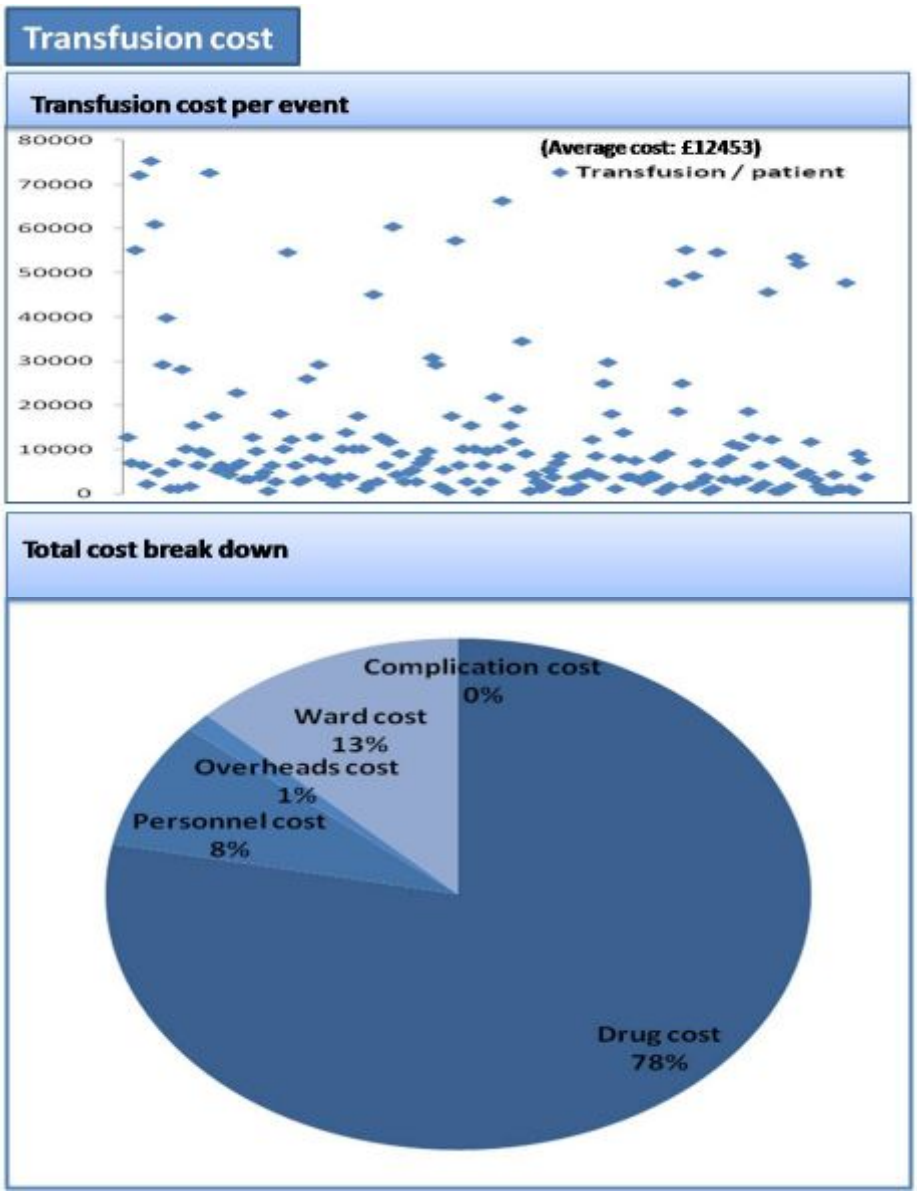


Figure 9.16 The illustration of the transfusion cost results

As shown on the relevant plot, although the transfusion cost varied widely, most of the transfusion costs per person were below £10000. The breaking down pie chart shows the components accounted for the highest percentage (78%).

9.2.3 Palliative care and end-of-life care

189 out of 239 study patients died because of AML. According to the information in the HMRN database, 33 patients had received palliative care before death while 68 died during the treatments. However, the situation of the rest of 88 patients when they were at terminal stage was unknown. In order to avoid underestimating the care cost, the end-of life cost was applied to all cases with the exception of the 22 patients who died at home (please refer to section 7.10 for costing details). The estimated cost results are listed in **Table 9.14** below.

Table 9.14 The detailed cost results of the palliative and end-of-life care

	Events No	Cost 1 (exclude complication cost)			Cost 2 (include complication cost)		
		Mean	Min	Max	Mean	Min	Max
Palliative care	33 patients	£2223	£336	£6313	£2223	£336	£6313
End of life care	66 patients	£938	-	-	£938	-	-

As shown on the table, the average palliative care cost was £2223, while the average cost for the estimated 14-day end of life care was £938. The cost results are illustrated below (**Figure 9.17**).

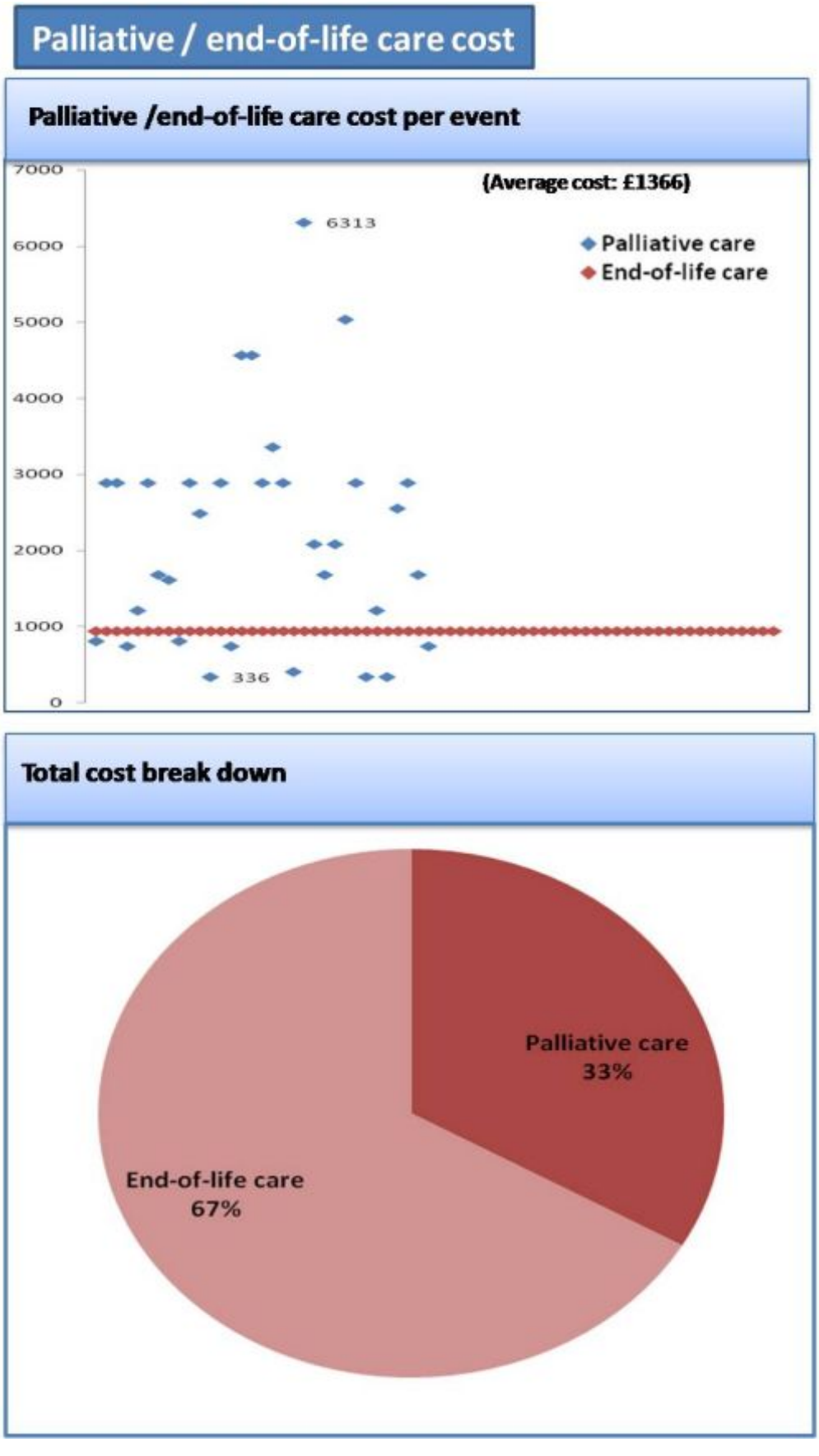


Figure 9.17 The illustration of the palliative and end-of-life care cost results

9.2.4 Stem cell transplantation related treatments

Stem cell transplantation was one of the most important consolidation treatment options for AML/APML. According to the information from the HMRN database, three treatments were related to stem cell transplantation, namely radiotherapy (before transplantation), stem cell transplantation, and immunosuppressive therapy (after transplantation). The cost results of each treatment are listed in **Table 9.15**, while the relevant details are discussed in the following sections.

Table 9.15 The detailed cost results of the stem cell transplantation related treatments

	Events No	Cost 1 (exclude complication cost)			Cost 2 (include complication cost)		
		Mean	Min	Max	Mean	Min	Max
Radiotherapy	14 events	£1318	£635	£2771	£1318	£635	£2771
Stem cell transplant	13 patients	£44199	-	-	£44199	-	-
Immunosuppressive	6 patients	£5302	£82	£16684	£5302	£82	£16684

a. Radiotherapy

According to the HMRN records, 14 radiotherapies were used among 13 patients who received stem cell transplantation. Since no treatment details were avaliable, the radiotherapy cost was directly retreived from the 'Reference Cost Index' (please refer to section 7.13 for costing details). The cost results are illustrated below (**Figure 9.18**).

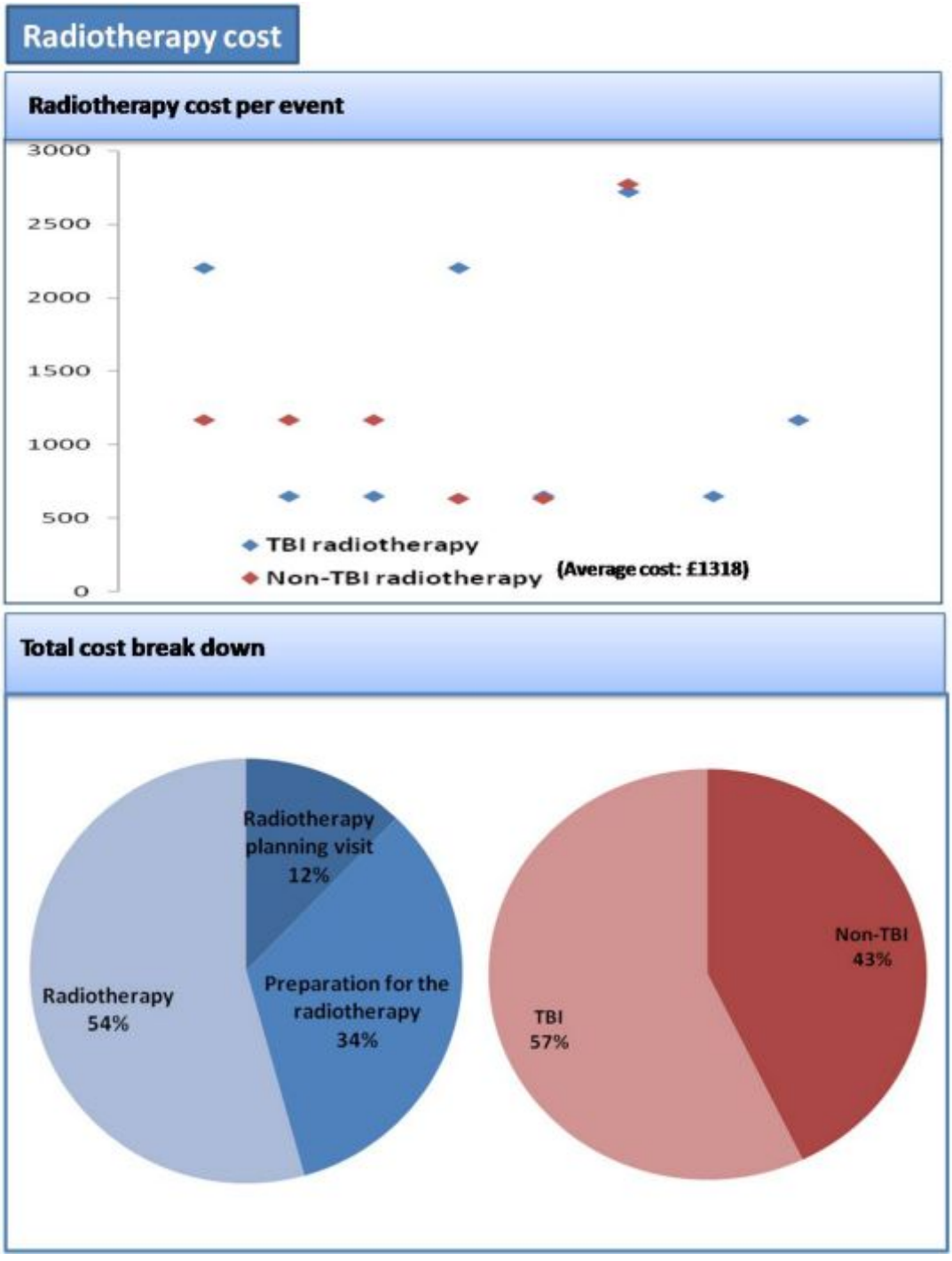


Figure 9.18 The illustration of the Radiotherapy cost results

As illustrated, two types of radiotherapy were used. TBI was slightly more common (57%). The average cost was found to be £1318 per event. This cost included the treatment planning cost (12%), the preparation cost for the radiotherapy (34%), and the radiotherapy itself (54%).

b. Stem cell transplantation

According to the HMRN records, 13 patients were found be received the stem cell transplantation as their consolidation treatment. Since no treatment details were avaliable, the transplantation cost was directly retreived from the 'Reference Cost Index' (please refer to section 7.14 for costing details).

The cost results are illustrated below (**Figure 9.19**). As illustrated, the costs of all stem cell transplantions were the same (£44199). This was the consequence of direct applying the 'Reference Cost Index' as the treatment cost. Therefore, the difference between individuals were not possible to be captured. It is worth noting that the transplantation costconsisted three differe costs, namely consulting visit, stem cell harvest (18%), and the actual stem cell transplantation (82%).

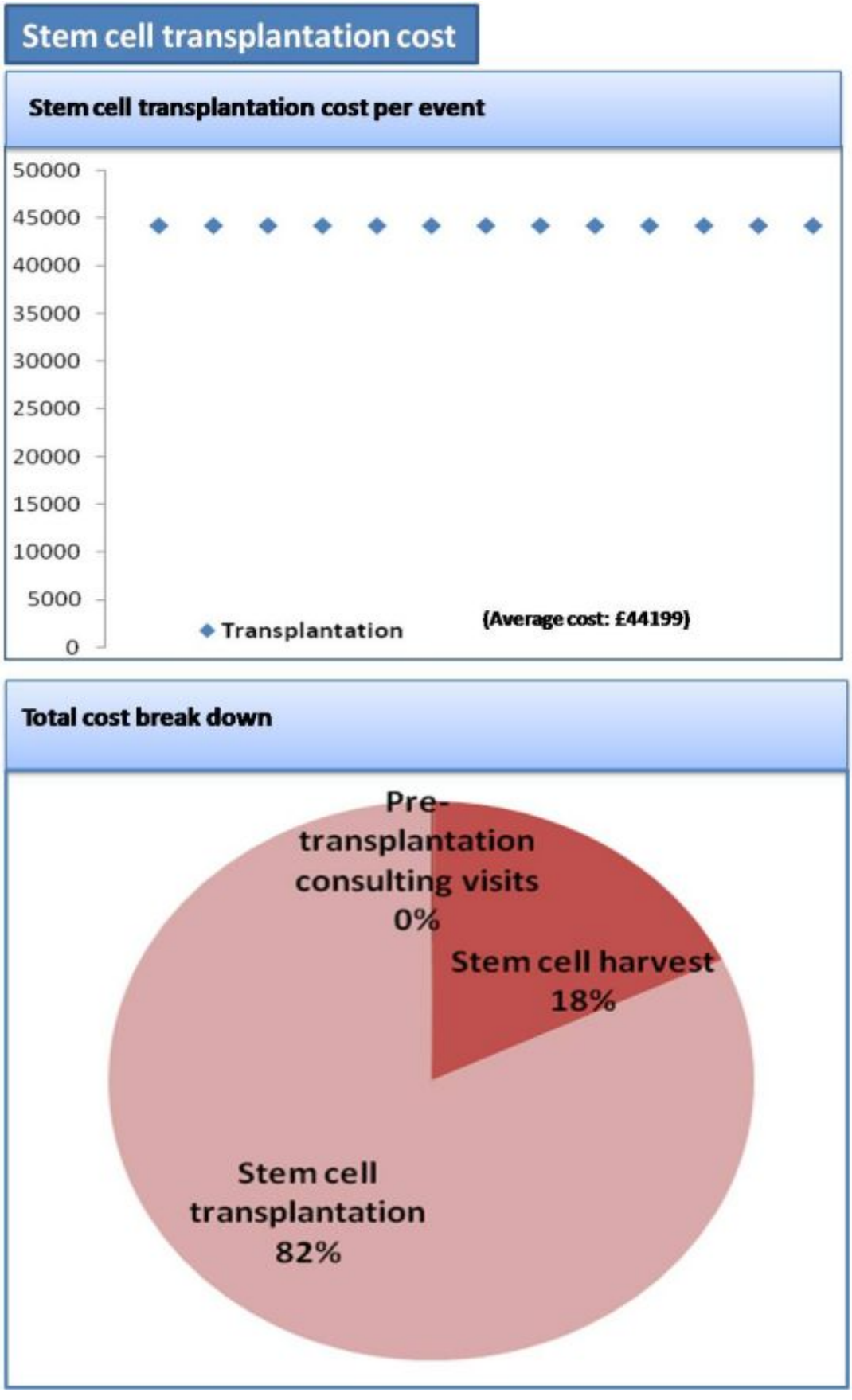


Figure 9.19 The illustration of the stem cell transplantation cost results

c. Immunosuppressive therapy

Immunosuppressive therapy was the treatment that was carried out after stem cell transplantation for preventing or treating the graft-versus-host disease. Among 13 patients who received stem cell transplantations, six were found to be involved in immunosuppressive therapy. The cost results (illustrated in **Figure 9.20**) were obtained based on the assumptions and costing method discussed in section 7.7.

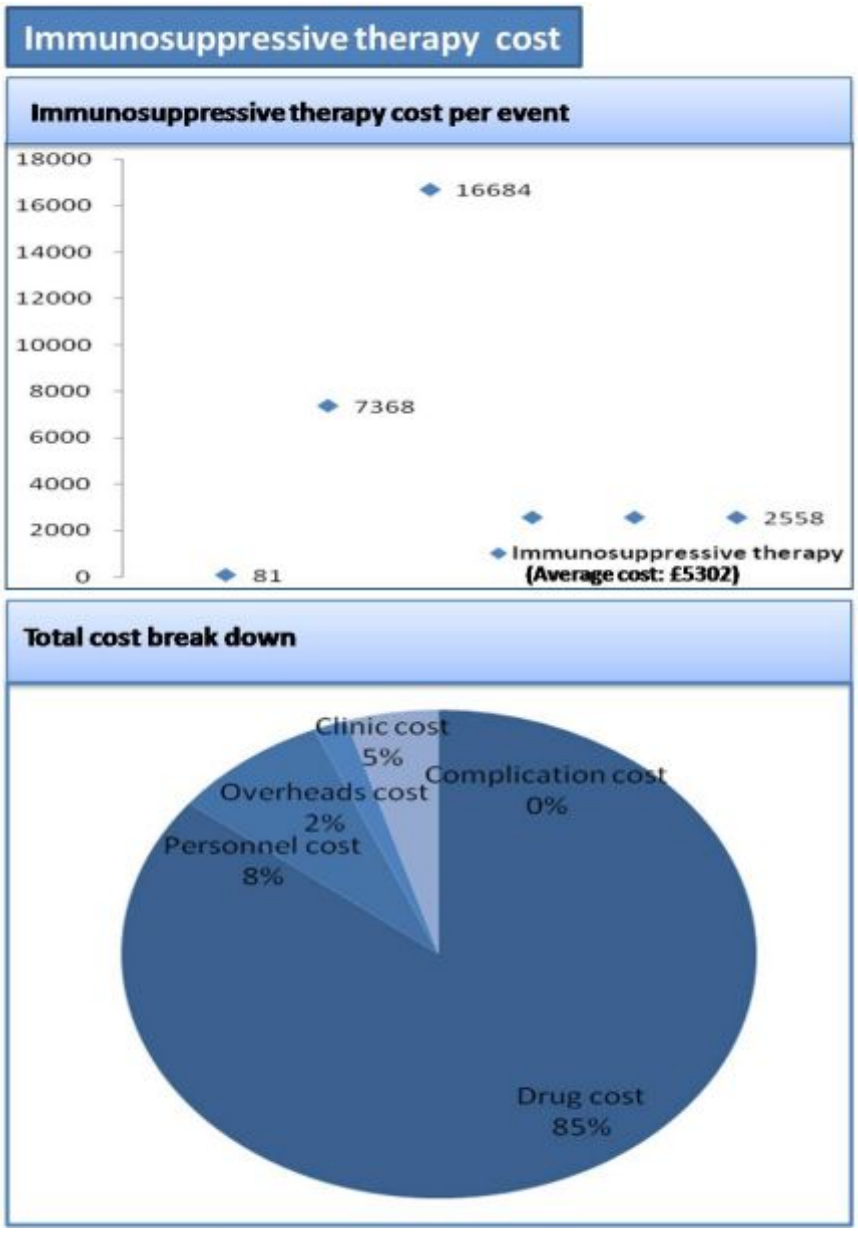


Figure 9.20 The illustration of the immunosuppressive therapy cost results

As shown in the relevant plot, the cost results varied heavily (£82~ £16684). This was due to the difference of the lengths of the treatment time. Finally, the average cost of the immunosuppressive therapy was found to be £5302 (with drug cost accounting for 85%).

9.2.5 Follow-up visit / observation

Follow-up visit was one of the most commonly used interventions in the HMRN database. Since many other interventions also took place during the outpatient visit (such as the outpatient chemotherapy and immunosuppressive therapy), the follow-up time period in the current study was defined as the gap between any treatments, in order to avoid overestimating the cost (please refer to section7.9 for details). The cost results are illustrated in **Figure 9.21** below.

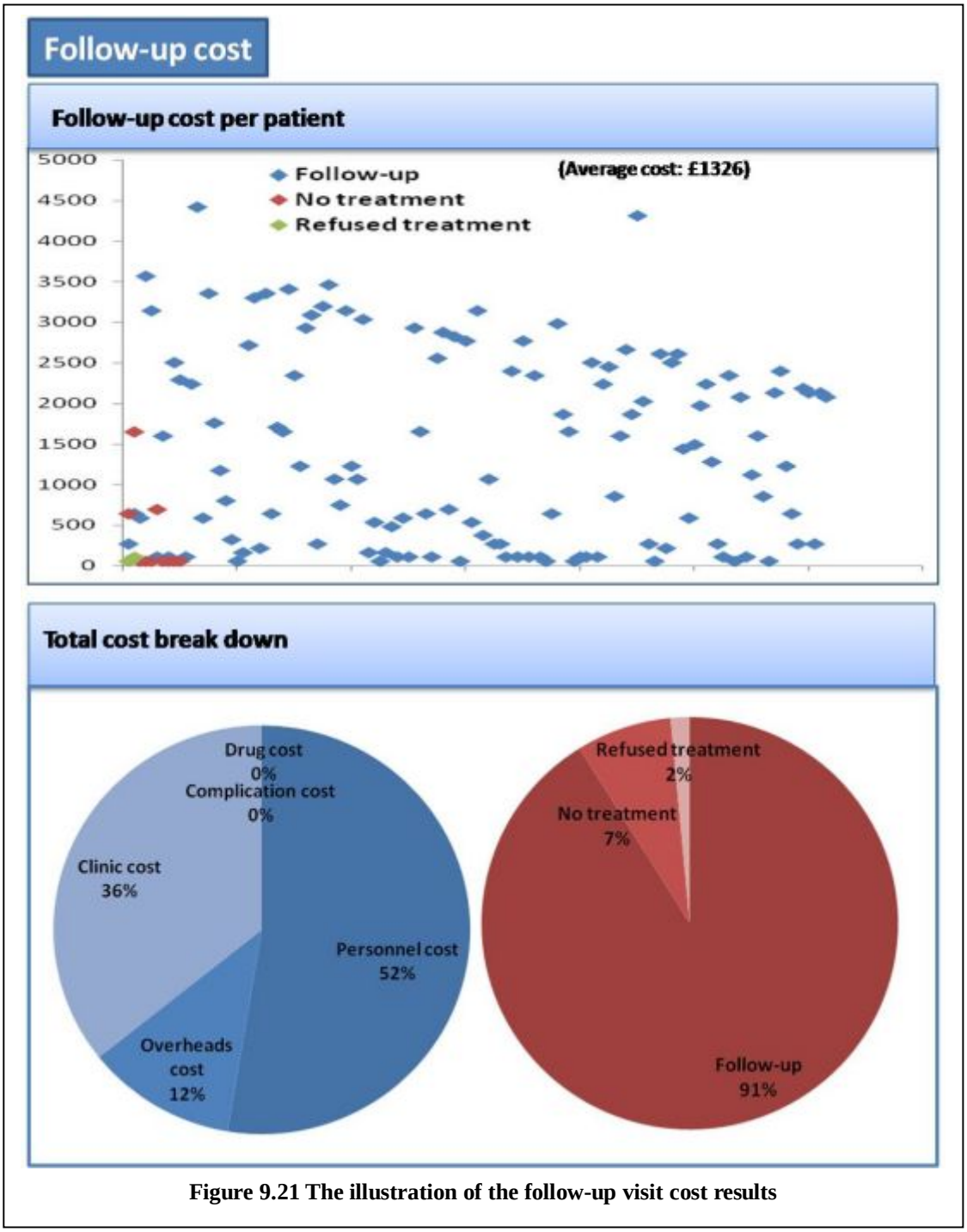


Figure 9.21 The illustration of the follow-up visit cost results

As illustrated, the follow-up costs varied (£53~£4416) depending on the patients' conditions. The average cost of follow-up visits per patient was found to be £1326, and the personnel cost and clinic cost accounted for the highest percentage (88% in total).

Detailed cost results can be found in **Table 9.16** below.

Table 9.16 The detailed cost results of the follow-up visits

	Events No	Cost 1 (exclude complication cost)			Cost 2 (include complication cost)		
		Mean	Min	Max	Mean	Min	Max
Observation	135 patients	£1326	£53	£4416			
No treatment	10 patients	£335	£53	£1649			
Refused treatment	2 patients	£80	£53	£106			
Follow-up	123 patients	£1427	£53	£4416			
	269 events	£653	£53	£3564			

9.2.6 Comparison with previous relevant studies

The current section involves the comparison of the cost results and/or the costing methods of the current study with the results from previous related studies (please refer to chapter 2). The reason for the comparison was to justify the reliability of the costing methods and/or the accuracy of the cost results of the current work.

It must be stressed that there were cases where the comparison was not possible for various reasons, such as the use of different definitions, the inclusion of different cost drivers, differences in the dosages used in regimens, or unreported cost numbers. In cases such as ones described above, detailed cost break down information was not available (such as palliative care), and thus, the comparison was omitted.

a. Chemotherapy

The comparison of the chemotherapy cost of the current work with the ones of other relevant studies was challenging, mainly because of three reasons. Firstly, the studies that focused on chemotherapy costing are limited (please refer to chapter 2 for details). Secondly, the regimens or the dosages of the regimens that were used in the relevant studies were different from the ones used in the current study. Thirdly, the cost drivers involved in each study were different. When the detailed cost information of each cost driver was not available, a comparison was impossible to be carried out. After careful matching, only one study was comparable. The comparison results are presented in **Table 9.17** below.

Table 9.17 The comparison of ADE cost with previous studies

		Clavio's study	The current study
Country		Italy	UK
Regimen		AML 10	ADE cycle 1
Cost drivers	Personnel and services cost	√	√
	Drug cost	√	√
	Complication cost	√	√
	Other costs	√	√
Result		$6671	£5799
Cost in 2007		£5940	£5799

As shown on the table above, in cases where the same cost drivers were involved, the cost results of both studies were relatively consistent. In other wards, Clavio's study [112] validated the cost result of the ADE regimens.

b. G-CSF

The G-CSF costing method contained several assumptions, as the treatment details were unavailable (please refer to section 7.6 for the costing details and assumptions). In order to validate the costing method and the cost result, a comparison with relevant studies was conducted (please refer to chapter 2 for details of the relevant study search). After converting the results into comparable forms, the comparison table was possible to be created (**Table 9.18**).

Table 9.18 The comparison of G-CSF cost with previous studies

Relevant studies					The current study
Study name	Year	Country	G-CSF cost	Value in 2007	
Standaert's study (no ward cost)	1998	UK	£1413 per patient	£1794 per patient	£1251 per patient
Bradstock's study (drug cost only)	2001	Australia	A$3684	£1548 till 1st remission	£1009 till 1st remission

As shown on the table above, compared to the UK study [206], the cost result of the current study (£1251 per patient) was much lower than the result of Standaert's study [206] (£1435.8 per patient), regarding that ward and clinic costs have not included into Standaert's result. Also, compared to Bradstock's study [207] that was carried out in Australia, the average G-CSF cost in first remission time of the current study was much lower too (£1009 vs £1548), regarding that Bradstock et al. [207] calculated the drug cost only. A possible explanation for this significant difference might be the fact that the unit cost was retrieved from the different resources. Also, in the current study, protocol suggestions and expert opinions were used to predict the number of uses (please refer to chapter 7 for details), while in the Standaert's [206] and Bradstock's studies [207], the actual usage data was used as the quantity. Therefore, based on the comparison result, the G-CSF cost in the current study is possible to have been underestimated.

c. Transfusion

Comparing the transfusion cost of the current study with previous relevant studies was challenging, as the settings, the unit cost of blood products, and the involved cost drivers were all different. Therefore, for convenience and availability reasons, it was decided to compare the costing method (such as the uses of resource and the unit cost) instead of the transfusion cost results.

Among all the relevant AML cost studies, only one UK study included information related with platelet transfusion cost [206]. According to Standaert et al [206], it was found that the cost of platelet products were £172.47/day, and the total platelet cost in the induction cycle was £1655.71 in 1998 (roughly 10 transfusions occurred in induction cycle). When compared to the costing method of the current study, the unit cost of the platelet was found to be similar (£153/day vs £172/day), as both studies used the same information resource [181]. Also, based on the extrapolated transfusion frequency of the current study (refer to chapter 5), it was found that the average number of transfusions given to the study patients in induction cycle was 8.5, which is close to the transfusion number in the result of the Standaert et al study [206]. The relevant details can be found in the following table (**Table 9.19**).

Table 9.19 The comparison of transfusion cost with previous studies

Comparison 1

Standaert et al study		The current study	
Unit cost	**Resource use**	**Unit cost**	**Extrapolated frequency (refer to chapter 5)**
Retrieved from the National Blood Service	10 transfusions in induction cycle	Retrieved from the National Blood Service	8.5 transfusions in induction cycle

Comparison 2

Cartoni et.al study		The current study	
Unit cost	**Resource use**	**Unit cost**	**Extrapolated frequency (refer to chapter 5)**
	Disease time /end of life stage: 6.1 (± 3.5) transfusions per month Other status: 1.6 (± 1.4) transfusions per month		Disease time<2 months: 7 transfusion per month Disease time>2 months: 2 transfusion per month

Cartoni et.al [150] has also cost transfusion in Italy in 2007. The study showed that the number of transfusions in disease time or end of life stage was 6.1 (± 3.5) transfusions per month, and in the rest of time were 1.6 (± 1.4) transfusions per month. After a comparison of Cartoni's results [150] with the number of transfusions per month of the current study (7 transfusions per month in short disease time, and 2 transfusions per month in long disease time), it was observed that the numbers of transfusions in both studies were very close. More details can be found in **Table 9.19** above.

Based on the above, it was safe to claim that the extrapolated transfusion frequency used in the current study was close to the real frequency, and thus, it was a reliable piece of information suitable for costing the transfusion.

d. Immunosuppressive therapy

Although there was no relevant immunosuppressive therapy costing study on AML, it was decided that it could be worthwhile to look at the cost from other types of transplantations. According to the NHS report [208], the immunosuppressive therapy cost after kidney transplantation was found to be £870 for first six weeks, which means £145 per week. After comparing the aforementioned cost with the unit cost of the immunosuppressive therapy used in the current study (£23.5 per day, £164.5 per week), it was observed that the cost difference between the two studies was small. This finding support the validity of the costing method used in the current study for immunosuppressive therapy.

e. Transplantation

The transplantation cost was directly derived from the 'Reference Cost Index', which represented the average transplantation cost in the UK. In order to validate the current cost result, a comparison with related international studies was conducted. After the relevant adjustment for the study time period, the currency exchange and the inflation comparison results (please refer to chapter 2 for the details) were obtained (**Table 9.20**).

Table 9.20 The comparison of stem cell transplantation cost with previous studies

	Year	Country	Transplantation cost (from admission to discharge)	Value in 2007
The current study (Reference cost)	2007	UK	£44142	£44142
Agthoven et al. study	1998	Netherland	€39787 (£26880)	£34138
Vicent et al. study	1999	USA	$11820 (£7319)	£9002
Mishra et al. study	1999	Norway	$92272 (£57134)	£70275
Blaise et al. study	1998	France	€37128 (£25084)	£31857
Uyl-de et al. study	1992	Netherland	$51220 (£28101)	£41028

Although the costing methods and costing data varied between different studies, the differences were explainable. As it can be seen in **Table 9.20** above, the estimates from all the studies [209-213] were relatively consistent, except the ones from Vicent's [210] and Mishra's [211] studies. The particularly low estimate from Vicent's study [210] can be explained by the fact that the personnel cost was excluded from the study results. The particularly high estimate from Mishra's study [211] can also be explained by the inclusion of the pre-transplantation cost (which started costing from consulting outpatient visit). Therefore, it can be claimed that relatively consistent SCT cost estimates have been found between the current and most of other involved studies. This finding potentially validates the estimated cost of the current study.

9.2.7 Conclusion

Section 9.2 brings the part of the study results and literature review results (chapter 2) together. In section 9.2, the estimated cost results of the main treatments (section 9.2.1 to section 9.2.5) as well as the results of their comparison with relevant studies (section 9.2.6) were presented. The summarized cost result list of all the treatments can be found below (**Table 9.21**).

Table 9.21 The summarized cost result list of all the treatments/interventions

	Events No	Cost 1 (exclude complication cost)			Cost 2 (include complication cost)		
		Mean	Min	Max	Mean	Min	Max
Chemotherapy +clinical trial	594 courses	£4140	£59	£13770	£5148	£60	£15030
Inpatient chemotherapy	516 courses	£4678	£638	£13770	£5829	£729	£5112
Outpatient chemotherapy	78 events	£587	£59	£5112	£640	£60	£5112
Supportive care							
Transfusion	267 events	£8861	£530	£67282	£8861	£530	£67282
Erythropoietin	3 events	£1628	£111	£4440	£1628	£111	£4440
G-CSF	62 events	£827	£197	£4765	£827	£197	£4765
Steroids	13 events	£300	£59	£1733	£300	£59	£1733
Palliative care	33 patients	£2223	£336	£6313	£2223	£336	£6313
End-of-life care	66 patients	£938	-	-	£938	-	-
Splenectomy	2 patients	£4010	-	-	£4010	-	-
Venesection	3 patients	£1168	£280	£2102	£1168	£280	£2102
Immunosuppressive	6 patients	£5302	£82	£16684	£5302	£82	£16684
Stem cell transplant	13 patients	£44199	-	-	£44199	-	-
Radiotherapy	14 events	£1318	£635	£2771	£1318	£635	£2771
Observation	135 patients	£1326	£53	£4416	£1326	£53	£4416
Laboratory test cost	239 patients	£1746	£140	£16048	£1746	£140	£16048

Due to the limited number of related studies or incomparable cost information, not all the cost results or costing method could be appropriately compared. However, based on the cases that were possible to be compared (in section 9.2.6), it was found that most of the results were consistent, with the exception of the G-CSF cost. This ensured that the overall treatment cost calculation (carried out at later stages of the current study) was reliable. However, it must be stressed that the cases involving G-CSF treatment should be treated with caution when interpreting the results.

9.3 Overall treatment cost results with no treatment overlapping

The current section describes the results of overall treatment cost per patient without taking the treatment overlapping into consideration.

Based on the costing method discussed in section 8.1, the cost results of each treatment (discussed in section 9.2) were linked to the corresponding events in the treatment pathway (please refer to chapter 4). Without taking the treatment overlapping into consideration, those events costs were directly summed up as overall treatment cost. The cost results are illustrated in **Figure 9.22** below.

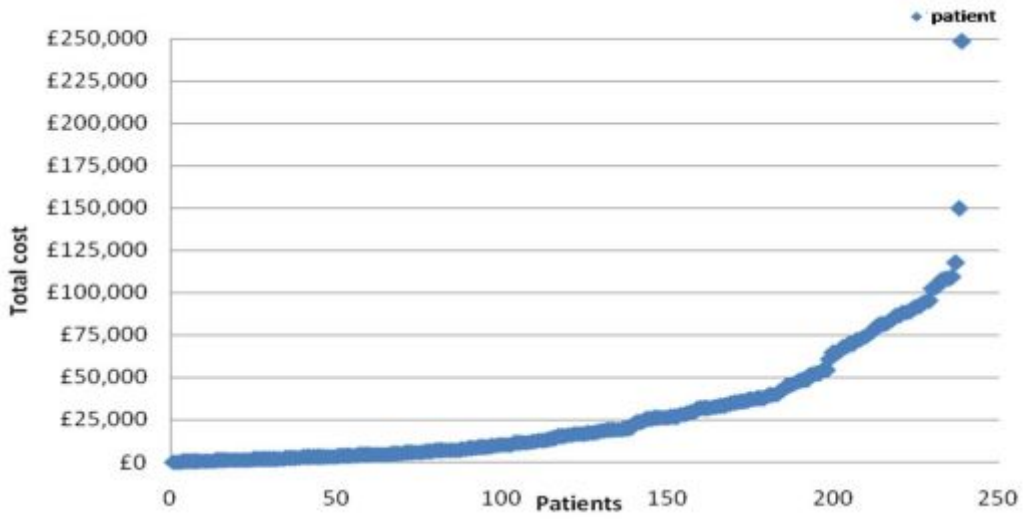


Figure 9.22 The results of total treatment cost per patient (no treatment overlapping)

As shown in the plot, the total cost distribution was like parabola, except two extreme estimates. The detailed cost results by treatment phases are listed in **Table 9.22**.

Table 9.22 The detailed results of total treatment cost (no treatment overlapping)

Treatment phase	No.	Cost results			
		Average	Min.	Max.	SD
Total cost	239	£33192	£246	£254522	35326
First line	239	£21826	£193	£103327	22726
Induction	239	£13976	£193	£88795	17034
Consolidation	103	£18215	£487	£78507	15030
1st relapse-2nd relapse	42	£31749	£2350	£100967	25172
2nd relapse-3rd relapse	6	£46846	£1589	£180446	69412
3rd relapse +	2	£12250	£9257	£15242	4232

As shown in **Table 9.22**, the average cost increased progressively by the number of AML recurrences. The average cost of the first-line treatment was the lowest (£21826), followed by the treatment cost for the 2nd relapse (£31749). The treatment cost for the 2nd relapse period was the highest (£46846). It is worth nothing that the progressive cost increase did not apply to the cost after the 3rd relapse. As demonstrated in **Table 9.22**, the average cost for the 3rd relapse (£12250) was much less than the first line treatment cost. This inconsistence could be explained by two possible reasons. Firstly, the number of cases was too few in the current study (n=2). Therefore, the results might not be able to represent the whole resource use during the 3rd relapse. Secondly, patients might be very ill when they reached the 3rd relapse. Therefore, the average cost was much less as they died very quickly afterward.

To conclude, the study found that the more times the AML recurred the higher the cost would be (before the 3rd relapse). Under this circumstance, the average overall treatment cost was found to be £33192. It is worth noting that all the overall treatment cost results discussed in this section were not the actual cost result, as the treatment overlapping issue was not taken in to consideration. However, these cost results gave a general idea of how the distribution of the overall cost results would be like. The overall cost that included the consideration of the treatment overlapping issue is discussed in the next section.

9.4 Overall treatment cost results with treatment overlapping

The current section deals with the presentation of the results of the overall treatment costs per patient, including the consideration of the treatment overlapping issue.

Based on the costing method discussed in section 8.2, a macro costing method that was included the consideration of the overlapping issue was applied in order to yield more reasonable and accurate cost results. There were two challenges in regards to this matter. Firstly, the overlapping treatments had to be identified and decisions had to be made on how the costs would be re-allocated/shared between them. To resolve this issue, a number of assumptions were made (please refer to section 8.2 for details). Secondly, the calculation (that integrated all the aforementioned definitions and assumptions) had to be executed with the statistical software. To resolve this issue, the SAS program (SAS software program package, version 8.02, SAS Institute, Cary, NC) was used. The cost calculation was carried out in three phases (please refer to section 8.2.3). Details regarding the calculation process can be found in section 9.1, while the cost results are presented in the following sections.

9.4.1 Overall treatment

The overall treatment cost results that were obtained from the aforementioned calculation are plotted in **Figure 9.23** below.

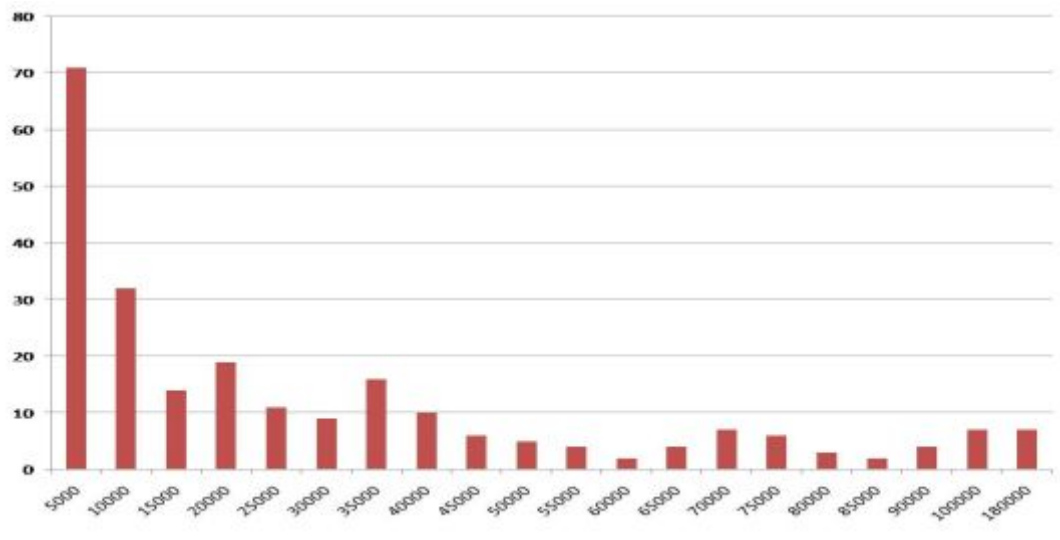


Figure 9.23 The overall treatment cost (with treatment overlapping) over the number of patient

As shown in the plot, the overall cost distribution was parabolic. The contributions of the costs for each treatment phase are illustrated below (**Figure 9.24**).

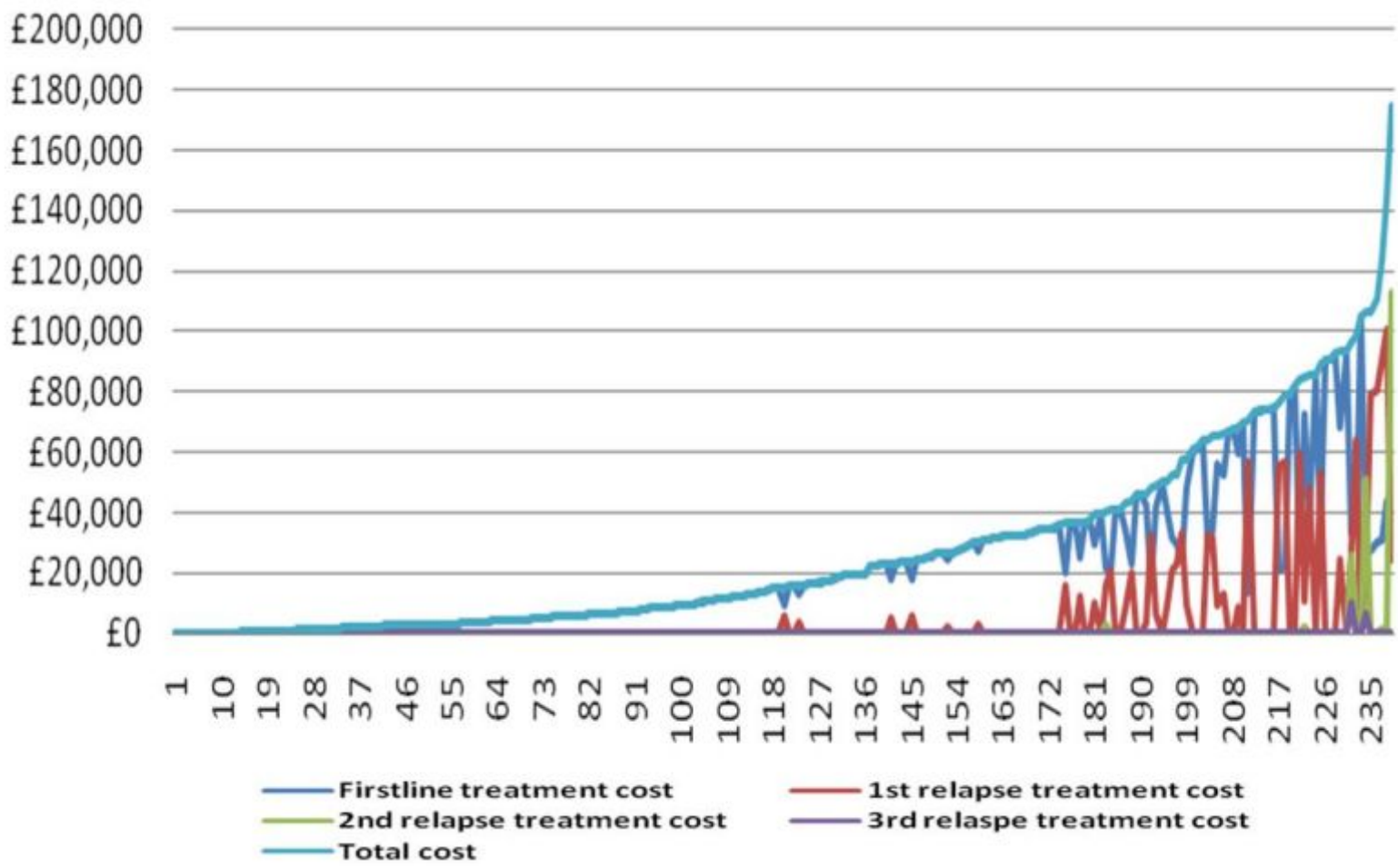


Figure 9.24 The contributions of the costs for each treatment phase

As shown in **Figure 9.24** above, the overall treatment costs were mainly driven by the first-line treatment cost and the number of AML recurrences. The detailed cost results ordered by treatment phases are listed in **Table 9.23**.

Table 9.23 The detailed results of overall treatment cost (with treatment overlapping)

Treatment phase	No.	Cost results			
		Average	Min.	Max.	SD
Total cost	239	£27290	£193	£174286	31025
First line	239	£21340	£193	£105101	22226
Induction	239	£12503	£193	£101205	14788
Consolidation	102	£20505	£106	£73237	18035
1st relapse-2nd relapse	42	£28808	£2063	£100416	26202
2nd relapse-3rd relapse	6	£32582	£1589	£112594	43706
3rd relapse +	2	£8251	£6380	£10121	2645

Table 9.23 demonstrates that the average cost increased progressively by the number of AML recurrences, with the exception of the treatment cost for the 3rd relapse (the reasons for this are discussed in section 9.3). The average cost of the first-line treatment was the lowest (£21340), followed by the treatment cost for the 1nd relapse (£28808). The treatment cost for the 2nd relapse period was the highest (£32582). The raising treatment cost values were caused mainly by the execution of the stem cell transplantation and of other related treatments and follow-up visits.

9.4.2 Comparison with the cost results with no treatment overlapping

The differences of the cost results between the two costing methods (with and without considering the treatment overlapping) are presented in **Table 9.24**.

Table 9.24 The difference of cost results between two costing methods

	No.	Average cost (no treatment overlapping)	Average cost (with treatment overlapping)	Difference
Total cost	239	£33192	£27290	£5902
First line	239	£21826	£21340	£486
Induction	239	£13976	£12503	£1473
Consolidation	102	£18215	£20505	£2290
1st relapse-2nd relapse	42	£31749	£28808	£2941
2nd relapse-3rd relapse	6	£46846	£32582	£14264
3rd relapse +	2	£12250	£8251	£3999

As shown in **Table 9.24**, the cost results that included the consideration of the treatment overlapping were lower than the ones that did not. This was probably because some medical resources were shared during the treatment overlapping. As demonstrated above (**Table 9.24**), the cost differences also increased progressively, with the exception of the cases at the 3rd relapse phase. The cost difference for first-line treatment was the lowest (£486) while the one for the 2nd relapse treatment was the highest (£14264). Possible explanation for this was that most of the treatments that were used in the first line period were the inpatient treatments that had less overlapping problems. Therefore, although ward cost accounted for the highest percentage of inpatient treatments (discussed in section 9.2.1), the cost sharing (especially the ward cost sharing) was not significant. Moreover, plenty of the outpatient treatments were used in 2nd and 3rd relapse periods and they usually overlapped with inpatient treatments or other outpatient treatments. Therefore, more medical resources were shared, something that caused greater cost difference between the two costing methods.

It is worth noting that the consolidation cost difference was not consistent with the aforementioned increasing trends. This was mainly because the cost attributes were slightly changed between two different costing methods when the treatment crossed the cut off point (between induction and consolidation). However, as a whole, the cost difference of first-line treatment cost still followed the increasing trend mentioned before.

9.4.3 Comparison with relevant studies

A small number of studies focusing on costing overall/lifetime treatment for AML (please refer to chapter 2 for details) were available. These studies made use of the hospital accounting system or the national-level database, but did not use the bottom-up costing method. Therefore, it was worthwhile comparing the results of the current study (derived from the bottom-up costing method) with the findings of aforementioned relevant studies. Based on the available cost breakdown information and study period, 3 studies were found to be comparable, after the relevant matching had been carried out. The comparison results are listed in **Table 9.25**.

Table 9.25 The comparison of overall treatment cost with previous studies

	Year	Country	Average cost	Value in 2007
The current study	2007	UK	£27290	£27290
			£21340 (first-line)	£21340
Lang's study	2001	USA	$50320	£29159
Menzin's study	1998	USA	$40270	£31665
Uyl-de's study	1995	Netherlands	$46387 (first-line)	£39274
Katz's study	2003	USA	$115471	£79596

As shown in **Table 9.25**, most of the studies were carried out in USA [35, 214, 215]. The cost results of the first two studies were consistent [35, 214]. Lang's [214] and Menzin's [35] studies showed that the overall treatment costs for AML were £29159 and £31665 respectively. Their results were slightly higher than the one of the current study. This was possibly because the medical supplies / consumables were not included in the current study due to lack of relevant information. Another possible explanation is that there were differences in preferred treatments/regimens between the USA and the UK, with the ones used in the USA being more expensive. It is also worth noting that the cost results of Katz's study [215], which was also carried out in the USA and has the same study period (from the first admission to the last discharge), was not possible to compare with other studies. This was because there was no detailed information about which cost drivers were included in the cost calculation. Uyl-de's study [216] was the only one that carried out in Europe. The authors calculated that the first-line treatment cost was £39274, a value much higher than the cost result of the current study. This difference can be explained partly by the treatment protocol used in Netherlands (the country where the study took place). More specifically, Uyl-de studied the AML patients who were recruited in the HOVON 29 or the EORTC AML-10 trial. The suggested treatments and regimens of these two protocols were much different from the ones used in the UK at present. Also, according to these two protocols, the stem cell transplantation was set as the consolidation treatment for the eligible patients. Therefore, as would be expected, the cost result of Uyl-de's study was much higher than any other studies.

9.4.4 overall treatment cost vs. patient characteristics

The relationship between the cost results and the patient characteristics are presented in **Error! Reference source not found.**. These patient characteristics included the baseline characteristics (age, gender, death or not, diagnosis, history of antecedent haemotalogical disorder, year of enrollment) and treatment related characteristics (number of treatments, type of primary treatment, achieving first remission). The correlation results are also presented in the **Error! Reference source not found.** below.

Table 9.26 The comparison of overall treatment cost with previous studies

	Case number	Mean	Correlation (P value)
Age			<.0001
age≦54	60	£53346	
54< age≦67	61	£29431	
67<age≦77	61	£18527	
age>77	57	£6847	
Number of treatments			<.0001
1-3	167	£12911	
4-6	39	£43958	
7-9	20	£67322	
10-13	13	£100409	
Death			<.0001
Yes	189	£20512	
No	50	£52908	
Achieving first remission			0.0287
Yes	105	£49426	
No	134	£9944	
Type of primary induction treatment			<.0001
With induction intent	132	£42407	
With non-induction intent	47	£12556	
Palliative care only	21	£2550	
Supportive care only	39	£7202	
Gender			0.8401
Male	122	£25140	
Female	117	£29530	
Diagnosis			0.075
AML NOS	197	£24976	*
AML with core binding factors	10	£61057	*
AML - probable therapy related	6	£13190	
AML with MLL (11q23) rearrangement	2	£22339	
APML	24	£36149	
Year of diagnosis			0.7182
2004	29	£33342	
2005	122	£25269	
2006	88	£28095	
History of antecedent haematological disorder			0.7729
Yes	11	25057	
No	228	27397	

As show in **Error! Reference source not found.**, the patient characteristics that were highly associated with the overall treatment cost were age (p<.0001), number of treatments (p<.0001), death (p<.0001), and type of primary induction treatment (p<.0001). Achieving first remission/response to primary induction treatment (p=0.0287) was also significantly associated with the total treatment cost. For the rest of the patient characteristics, although the cost differences existed between groups, these differences were not significant.

As would be expected, patients who were young, still alive at the time of current work, and received many times of treatments were highly associated with high overall treatment cost. It was also observed that the patients who received intensive primary induction treatment and the patients who responded to the induction treatment (reached first remission) were greatly associated with high overall treatment cost. This was related to the common findings that AML progresses very quickly and leads to death very easily, if patients do not receive induction treatments or receive induction treatment but do not respond well [20, 21]. Therefore, these patients spent more medical resources as they survive longer.

9.4.5 Conclusion

The current study was the first attempt to cost the overall AML/APML treatments by using bottom-up method. The study finding showed that the average overall cost was £27290. This result was found to be slightly lower than those of other related studies, but this difference was explainable. By and large, it can be claimed that after comparing the results of the current study with those of other related studies, they were found to be consistent. The comparison results not only justified the costing method used here, but also validated the accuracy of the cost results of the current study.

Chapter 10 Discussion

Summary, study limitation, recommendations, and conclusion

CHAPTER 10 DISCUSSION

AML/APML is the most common form of acute leukemia. It is very expensive to treat, as it involves long hospital stays, expensive treatments (such as stem cell transplantation), and complex complications (such as infection and anemia) [3]. For such an important health issue, it is striking that only seven studies focusing on the lifetime treatment cost were identified since 1995.None of these studies involved discussion of the cost predictors and none was carried out in the UK. Furthermore, these studies used the charging system or the administrative claim database for costing, which had methodology drawbacks (discussed in chapter 1) and means that it is difficult to translate the findings to a UK setting. In this thesis, a bottom-up method was employed to obtain estimates of the total health care cost over the lifetime of care. The lifetime cost results were further analyzed in order to uncover possible cost predictors. The obtained cost results were expected to provide a different perspective from the NHS reference cost, while the possible cost predictor results to provide useful information for health policy makers.

10.1 Contributions of the current study

Several challenges arose during the AML/APML lifetime treatment costing. To overcome these challenges, some innovative methods that had not been used before were applied. This approach, which was unique among all the related studies, was expected to extract more robust results. The contributions of the current study were the following:

10.1.1 First use of the bottom-up costing method on AML/APML lifetime treatment

As it is commonly accepted, the bottom-up costing method produces more precise and reliable cost results [43, 48-50]. However, it was observed that no relevant lifetime treatment cost study has made use of this method in the world (please refer to chapter 2: literature review). Therefore, the current work was the first attempt to cost the AML/APML lifetime treatment by using bottom-up method.

10.1.2. First cost predictor study for AML/APML lifetime treatment

Cost predictor analysis has been used to investigate various other diseases. However, it was observed that no AML study has covered this area in the past. Therefore, the current study was the first attempt of determining the cost predictors.

10.1.3 Breakdown of the hospital barrier

Most of the previous cost studies were restricted to single or specific two to three hospitals, as the detailed information (such as medical records and charging systems) was difficult to obtain from different hospitals. This restriction compromised the robustness of the results, as the cost that patients transfer from hospital to hospital could be overlooked. In the current study, the aforementioned hospital barrier was broken by using the databases covering the medical information of all the hospitals in the network to cost, something that was expected to produce more robust cost result.

10.1.4 Transparency of the costing procedures

Since the current study employed the bottom-up method to cost the AML/APML treatments, all the estimated costs were traceable and the contributions of each cost driver were identifiable. This approach not only prevented costing in black box, but also provided a common ground for comparison with other relevant studies.

10.1.5 Consideration of the treatment overlapping

With the exception of the studies using the charging system or administration claim database for costing, most studies employing the bottom-up costing method faced the treatment overlapping issue. However, no information regarding how the overlapping issue was dealt with was found in the relevant papers (according to the results of the literature review presented in chapter 2). In order to increase the reliability of the cost result, in the current study, the treatment overlapping and cost sharing were taken into account (The details and relevant costing methods can be found in the chapter 8).

10.2 Summary of the main findings of the current study

The methods used for identification, measurement, and valuation of cost in previous economic evaluation studies on AML/APML treatments were reviewed in chapter 2. The review showed that most of the available publications related with economic evaluation of AML/APML treatment made use of the charging system or the administration claim database. The common cost drivers that were used for costing single or overall treatments were hospitalization, drug, personnel, overheads, outpatient visit, transfusion, adverse event treatment, laboratory test, follow-up, materials, and out-of-pocket.

Chapter 3 outlined how the study material was handled. The challenge at this phase was to impute the missing data and the necessary, but insufficient, information for the treatment costing (such as treatment time, hospital stays, and transfusion frequency). In order to yield the robust estimations, the available and reliable information sources (such as the treatment guidelines, expert opinions, and the analysis of the additional data) were used.

In chapter 4, the preliminary analysis results of the study material were presented. The most important finding at this phase was the treatment pathway for AML and APML patients, which not only provided an overview of the AML/APML treatment history of AML/APML patients, but also formed a basis for costing at later stages of the study.

In chapter 5, an overview of the methodology that was used in the current study is described. More specifically, three-level cost classification was applied in order to identify the costs that had to be estimated for the AML/APML lifetime treatments. Finally, 13 treatment/intervention events, with their five cost drivers, were determined, based on cost classification and literature review.

Chapter 6 outlined the derivation of each of the five cost drivers. There were two important challenges at this phase. Firstly, the staff working time had to be obtained in order to calculate the personnel cost. This was dealt with by conducting a staff working time survey. Secondly, the complication treatment costs of each treatment had to be obtained. In order to achieve this, both expert opinion surveys and the meta-analysis of the results of previous studies were used.

Chapter 7 outlined how each of the 13 treatments/interventions were costed. The number of medical resource uses per treatment time was used in order to connect the five cost drivers (discussed in chapter6) to the treatment cost. The challenge in this phase to carefully define the number of uses per treatment time from treatment to treatment, as the relevant actual information was unavailable. To order to address this, all the available and reliable information courses (such as the treatment guidelines, expert opinions, and the database analysis) were used.

Chapter 8 outlined how the lifetime treatment cost of each patient was complied from the components described in the previous chapters. In this phase, a refined cost sharing procedure was established in order to resolve the treatment overlapping issue.
In chapter 9, the cost results of each treatment and the overall treatments per patient were presented. Also, the cost predictors were explored. It was illustrated that age, diagnosis,

deprivation, number of treatment, and death were the important predictors of the lifetime cost for AML/APML, and these cost predictors explained majority part of the cost variance.

10.3 Study limitations

The costing method used in the current study dealt with a number of difficulties successfully. However, it was also subject to a number of disadvantages. These disadvantages are briefly presented below.

10.3.1 Lacking of the information about the cost incurred outside the study sites

It can be claimed that the current work was more successful in ensuring all acute treatment costs were recoded as the data collection was based on a linked regional database rather than being based on data collected from a single hospital site. However, treatment costs from providers outside this network were excluded. For example, treatment of patients who received further intervention in private sectors or went out to other networks could not be costed. During the costing process, 5 patients who received treatments outside the network were detected. Therefore, their lifetime costs were excluded from the cost predictor analysis, in an attempt ensure the reliability of the study results.

10.3.2 Lacking of the detailed information of medical supplies/consumables use

The medical supplies/ hospital consumables / disposables (such as syringe and gloves) were part of the treatment cost. In studies that made use of the charging systems for costing, the consumables were easy to cost. However, in studies employing the bottom-up method, the consumable costs were very difficult to identify, due to lack of detailed quantity information. The current study was not an exception to this. Although some of the relevant studies used the percentage of treatment or the overall cost to predict the consumable costs, during the current work it was decided not to take the consumable costs into consideration. The reason was that its consumable costs were too low, compared to the treatment cost as a whole. Also, restraint time and workforce made it not possible to extract all the consumable cost percentages for each treatment. Therefore, it was decided that the cost can be neglected. Based on cost result comparisons (discussed in chapter 9), the findings of the current study were found to be consistent with and close to the results of other relevant studies. Therefore, it is safe to claim that the omission of the consumable costs was acceptable.

10.3.3 Lacking of the actual unit cost information for estimating ward/clinic cost

Several AML treatment cost studies (including the current study) concluded that the key cost driver of the treatment cost was the length of hospital stay. For such important key cost driver, unfortunately, there was no relevant tariff price or national average cost for basic ward care and clinic care that can be used to cost length of hospital stay in the UK. Therefore, the current study used the ward and clinic costs which involved the simplest treatment from the 'Reference Cost Index' (please refer to chapter 6 for details) as substitutes. However, this approach needed professional opinions in order to justify its accuracy. Moreover, it was impossible to identify the type of the ward (single/multi-bed ward, standard/special ward) patients stayed in for the duration of the treatment, as no relevant information was available. Therefore, all the ward costs used the same unit cost, with the exception of the treatment cost derived from the 'Reference Cost Index' (such as stem cell transplantation and radiotherapy). Although the cost result comparisons (presented in chapter 9) indirectly proved that the costing method for the ward was acceptable, it was believed that further refinements from experts were needed.

10.3.4 Applying a large amount of required assumptions for the costing

Due to the absence of some necessary information (such as transfusion frequency, hospital stays, and antibiotic use), a large number of assumptions and imputations had to be made during the costing.

It is possible that some of these assumptions and imputations might have caused the cost results to be underestimated. For example, as the imputed working time of consultants was underestimated, the personnel cost of outpatient treatment could be also underestimated. This was because the number of consultants who were involved in the working time survey was low. Since the consultants' answers tended to be more conservative than those of other staff, it was considered that the results might have been underestimated.

In contrast, some other assumptions and imputations could have resulted in the cost results being overestimated. For example, due to the lack of detailed relevant information and for the convenience reason, it was assumed that some of the chemotherapy regimens (such as low dose AraC) were only given in inpatient setting, for consistency reasons. However, such regimens can actually be given in both inpatient and outpatient scenarios. In such cases, the treatment cost might have been overestimated.

In other cases, some of the assumptions and imputations (such as the extrapolated transfusion frequency and hospital stay) were justified in the cost result comparisons (please refer to chapter 9). Therefore, further refinements from haematologists and other clinical staff were needed in order to justify the accuracy of these assumptions. If the actual details of medical resource consumption are obtainable, the information would be more desirable for bottom-up costing.

10.3.5 Using literature review to cost the complications of treating AML

Complication treatment cost plays an important role in treatment costing. In the current study, the complication costs were calculated based on the literature review and on the meta-analysis results: incidence rates of complications (please refer to chapter 7). This was because the detailed information of medical resource usage for complication treatment was not available. The advantage of the employed approach was that the cost results of complication treatments were more robust than other estimation approaches, as they were based on a large number of clinical trial studies. However, the drawback of this approach was that it compromised the reliability of the cost results. Firstly, the complication cost results derived from the literature review results (incidence rates of complication) and 'Reference Cost Index' (unit cost of complication treatment) could not reflect the actual consumption of medical resources. Secondly, the detailed incidence rates of complication that derived from the literature review were strongly determined by level of detail the authors reported in the relevant papers not the actual incidences. Although generally it was observed that the extrapolated results were close to those of other related results (chapter 7), approvals by more experts, a sensitivity analysis, or actual information of medical resource consumption would be desirable.

10.3.6 The reliability of using the existing publications for costing

In the current study, a number of existing publications were used for estimating treatment costs when the actual consumption details of medical resources were not available, such as BNF, PSSRU Unit cost, and NHS Reference Cost Index (please refer to section 5.4). The advantage of this approach was that the cost results were more robust than other estimation approaches, as these publications were based on a large number of UK populations or national data. However, the drawback of this approach was that the reliability of these publications was still controversial. For example, the drug prices from the 'BNF' are not always the prices that hospitals actually pay, and the treatment costs from the 'Reference Cost Index' are considered to be under estimated.

Although using the existing publications was not perhaps the optimal alternative, the cost results were still valuable for the current work. This was mainly because the detailed and actual cost data were not available from either the regional databases or the hospitals.

10.4 Recommendations

10.4.1 Recommendation based on the findings of the current study

a. Reveal the gap between real cost and NHS reference cost

The 'Reference Cost Index' is thought to be an alternative information source in relation to the treatment cost in the UK. However, it is always questionable how close its values are to the actual treatment cost. In the current study, relatively reliable treatment costs were obtained with different approach and different perspective from the 'Reference Cost Index'. It was observed that the AML relevant treatment costs in the NHS 'Reference Cost Index' was lower than the cost results of the current study. For example, for the immunosuppressive therapy, the reference cost was £1408, while the cost result of the current study was found to be £5302 per treatment time (please refer to chapter 9). Although further and more detailed comparisons between both costing methods are needed, it is suggested that the NHS should re-measure the treatment cost for AML/APML in order to develop more robust and fair payments.

b. Health policy decision making or clinical guideline development

Based on the findings of the cost results (discussed in chapter 9), the overall treatment cost for AML/APML were very high. Regarding the low survival rate of AML/APML, it is a wasteful use of medical resources with no benefit in terms of increased outcomes. Therefore, it is suggested that the health policy makers or the clinical guideline developers could re-set the treatment guideline in order to conserve medical resources for better use.

10.4.2 Recommendation for future research

The study limitation discussed previously (section 10.2) form the basis of the suggestions for the future study for obtaining more robust results. Based on the costing experience, a

number of recommendations were made. The latter are presented in the following paragraphs.

a. Unit cost

Most of the cost drivers that were used in the current study were derived be means of the bottom-up costing method. This approach required great amounts of research time to obtain reliable results. During the costing procedure, it was observed that existing published national average cost data could be used as the cost drivers directly, as they were found to be very close to the cost results calculated with the bottom-up method. For example, the drug cost for antibiotic use was found to be £69.13 per day. Compared to the antibiotic drug cost in the 'Reference Cost Index', the cost difference was only £2.13. Therefore, it is suggested that the existing national average cost data can be used for the cost drivers for to time and workforce saving.

b. Database improvement

Bottom-up method is a resource-demanding approach. It needs a highly detailed database with a limited amount of unknown factors. In the current study, many challenges and difficulties arose because the detailed resource use information was not available. In order to obtain more robust results and save time/workforce, it is suggested that more detailed information about the resource use (such as admission and discharge dates, transfusion date, transfusion unit, and so on) should be collected and recorded for costing. In addition, it is suggested that database covering more hospitals and more networks would be preferable. This is because the wide coverage of the database could assist in breaking both the hospital and the network barrier, something that can produce more robust cost results.

c. Cost-effectiveness study

In the current study, information related with the patients' quality of life was not available. Therefore, it was impossible to determine whether the increased lifetime cost was caused by prolonged survival or by ineffective and expensive treatments. For better understanding of the causes of the high lifetime cost, it is suggested that further cost-effectiveness study would be preferable.

10.5 Conclusion

During the current study, a number of tasks were completed. The costing methods used in previous relevant studies were reviewed, the relevant bottom-up method was developed and implemented, the treatment cost over patients' lifetime was calculated, and the cost predictors were extracted. The current study not only employed an innovative approach to cost the lifetime treatment for AML/APML, but also overcome many of the difficulties that identified or overlooked in previous studies. It was observed that AML/APML was expensive to treat, but possible predictive factors actually existed. It is expected that these findings could help to bridge the gap between the actual and the NHS reference costs while the cost predictors could assist decision makers in relation with health policy or clinical guideline issues. Also, it is expected that the current study could stimulate the interest of other researchers for more and better economic evaluations of the AML/APML treatment.

Appendix 1.1 WHO classification of AML

WHO Classification of AML
AML with recurrent cytogenetic abnormalities
AML with t(8;21)(q22;q22), (AML1/ETO)
AML with inv(16)(p13;q22) or t(16;16)(p13;q22), (CBF/MYH11)
AML with t(15;17)(q22;q12), (PML/RAR) (APL)
AML with 11q23 (MLL) abnormalities
AML with multilineage dysplasia
With prior myelodysplastic syndrome
Without prior myelodysplastic syndrome
AML and MDS, therapy related
Alkylating agent type
Topoisomerase II inhibitor type
AML, NOS (modified FAB classification)
AML, minimally differentiated
AML without maturation
AML with maturation
Acute promyelocytic leukaemia
Acute myelomonocytic leukaemia
Acute monoblastic and monocytic leukaemia
Acute erythroid leukaemia
Acute megakaryoblastic leukaemia
Acute basophilic leukaemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma

Source: Brunning's study [15]

Appendix 2.1 Search strategies (MEDLINE and EMBASE)

#	Search History
1	Leukemia, Myeloid, Acute.mp. or exp Leukemia, Myeloid, Acute/
2	Leukemia, Myelomonocytic, Acute.mp. or exp Leukemia, Myelomonocytic, Acute/
3	Leukemia, Erythroblastic, Acute.mp.
4	Leukemia, Basophilic, Acute.mp.
5	Leukemia, Eosinophilic, Acute.mp.
6	Leukemia, Erythroblastic, Acute.mp.
7	Leukemia, Mast-Cell.mp.
8	Leukemia, Megakaryoblastic, Acute.mp.
9	Leukemia, Monocytic, Acute.mp.
10	(Acute Myelo$ Leuk$ or Acute Myelo$ Leuc$).mp.
11	(Acute nonlympho$ Leuk$ or Acute nonlympho$ Leuc$).mp.
12	AML.mp.
13	acute disease.mp. or exp Acute Disease/
14	leukemia, myeloid.mp. or exp Leukemia, Myeloid/
15	13 and 14
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 15
17	Leukemia, Promyelocytic, Acute.mp. or exp Leukemia, Promyelocytic, Acute/
18	APML.mp.
19	APL.mp.
20	17 or 18 or 19
21	ph1 negat$.mp.
22	philadelphia negat$.mp.
23	ph1 posit$.mp.
24	philadelphia posit$.mp.
25	21 or 22 or 23 or 24
26	16 or 20 or 25
27	economics.mp. or Economics/
28	Economics, Hospital.mp. or exp Economics, Hospital/
29	Economics, Medical.mp. or exp Economics, Medical/
30	exp Economics, Nursing/ or Economics, Nursing.mp.
31	Economics, Pharmaceutical.mp. or exp Economics, Pharmaceutical/

32	evaluation study.mp. or exp Evaluation Studies/
33	model, economic.mp. or exp Models, Economic/
34	(economic$ or pharmacoeconomic$ or pric$ or cost$).mp.
35	exp "costs and cost analysis"/ or exp "cost allocation"/ or exp cost-benefit analysis/ or exp "cost control"/ or exp "cost savings"/ or exp "cost of illness"/ or exp "cost sharing"/ or exp "deductibles and coinsurance"/ or exp medical savings accounts/ or exp health care costs/ or exp direct service costs/ or exp drug costs/ or exp employer health costs/ or exp hospital costs/ or exp health expenditures/ or exp capital expenditures/ or exp economics, hospital/ or exp hospital charges/ or exp economics, medical/ or exp fees, medical/ or exp economics, nursing/ or exp economics, pharmaceutical/ or exp "fees and charges"/ or exp capitation fee/ or exp fee-for-service plans/ or exp fees, dental/ or exp fees, pharmaceutical/ or exp prescription fees/ or exp "rate setting and review"/
36	budget.mp. or exp Budgets/
37	(low adj cost).mp.
38	(high adj cost).mp.
39	(health?care adj cost$).mp.
40	(cost adj estimate$).mp.
41	(cost adj variable).mp.
42	(unit adj cost$).mp.
43	(fiscal or funding or finacial or finance).mp.
44	value of life.mp. or exp "Value of Life"/
45	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44
46	26 and 45
47	limit 46 to (english language and yr="1995 - 2008")

Appendix 2.2 Sources of search strategy

1. Published study:

MEDLINE, PUBMED, NHS EED, EMBASE, The Cochrane Library, CancerLit, and the Cochrane Center Register of Controlled Trials.

2. Grey literature:

a. Theses: http://www.theses.com/

b. Conference proceedings:

i) ZETOC Conference Search & ISI Proceedings

ii) Conference proceedings:

The International Conference on Malignant Lymphoma (Lugano)
http://annonc.oxfordjournals.org/supplements.dtl

The National Congress of Medical Oncology
http://annonc.oxfordjournals.org/supplements.dtl

The European Conference on Clinical Oncology
http://www.ecco-org.eu/Conferences-and-Events/page.aspx/7

The European Society for Medical Oncology (ESMO)
http://www.esmo.org/

European Hematology Association (EHA)
http://www.ehaweb.org/

The American Society of Clinical Oncology
http://www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Annual+Meeting+Summaries

The American Society of Hematology
http://www.hematology.org/meetings/2008/index.cfm

3. Ongoing trials

http://www.doh.gov.uk/research/nrr.htm
http://clinicaltrials.nci.nih.gov
http://clinicaltrials.gov/ct/gui
www.trialscentral.org/index.html

4 Hand-searching of key journals

Annals of Oncology, European Journal of Cancer, European Journal of Haematology, Journal of Clinical Oncology, and Blood.

Appendix 2.3 Study eligibility form

Study eligibility form

Study No: _____

	Yes	Unclear	No
Type of study			
Q1: Was the study described as economic evaluation?			
Participants in the study			
Q2: Did the participants in the study suffer from AML / APML?			
Intervention			
Q3: Did the study contain the estimation of cost?			
Outcomes in the study			
Q4: Did the study report the measurement methods of costing and health outcome (including the effectiveness, utilities, or no outcome measurement)?			

Final decision	Include	Unclear	Exclude

Appendix 2.4 Quality assessment checklist

Quality Assessment Form

Study ID: _____

	Adequate	Unclear	Inadequate	Not used
First Stage				
Definition of study question				
Q1: Was the cost-measurement the main part of the study?				
Q2: Did it mainly study AML/APML patients?				
Study Design				
Q3: Trial-based study:				
● Were inclusion/exclusion criteria of recruitments outlined clearly				
Q4: Model-based study:				
● Did it outline the model used? If so, did the model reflect the real clinical practice?				
●Were inclusion/exclusion criteria of papers outlined clearly if the data/ parameters collected through systematic review?				
Cost measurement				
Q5: Were the measurement methods of cost and outcome described comprehensively?				
Q6: Were the sources of measurement described clearly?				
Q7: Were costs valued credibly?				
Results Presentation				
Q8: Were the results presented by the raw value or unit-cost?				
Q9: Did the study provide the range or distributions of value for the key study parameters?				
Q10: Were costs adjusted for different timing?				
Q11: Were sensitivity analyses conducted to investigate uncertainty in estimates of cost?				
Second Stage (For Economic Evaluation Study Only)				
Q1: Did the study involve a comparison of alternatives (including do-nothing alternative)?				
Q2: Was the viewpoint for the analysis stated?				
Q3: Were all the important and relevant costs and consequence for each alternative identified?				
Q4: Were costs and consequences measured accurately?				

Appendix 2.5 Data extraction form

Data Extraction Form					Study ID:_____
Notes					
General Info.					
Title					
Author					
Contact E-mail					
Journal		**Price Year**			
Country		**Source type**	**published**	**unpublished**	
Study type	**Trial**	**Observation**	**Model**		
Data type	**Primary** (From:)	**Secondary** (From:)			
Population					
Setting					
Study period					
Initial numbers		**Outcome No.**			
Age	**Elder** ( )	**Young** ( )	**Adult** ( )	**All**	
Treatment stage	**All**				
	Induction	**Consolidation**			
		Post remission	**Maintenance**	**remission continuation**	
Intervention					
Therapy type	**Overall**	**Chemotherapy**	**Supportive**	**Palliative**	
	Complication	**Transplantation**	**Others**		
Analysis type	**Cost analysis**	**CEA / CUA**			
Objective					
Methodology					
Cost type	**Unit cost (Ref)**	**Unit cost (charge)**	**Payments**	**charges**	
Costs	**Categories**	**Source**	**Methods**	**value**	
Outcome	**Categories**		**value**		
Results					
Notes					

Appendix 2.6 The relevant historical currency exchange rates

From	To	Year	Exchange rate
Australia (A$)	USD	2001	0.51822
Canada ($CAN)	USD	1992	0.82845
Canada ($CAN)	USD	2000	0.67398
Euro (€)	USD	1998	1.17160
Euro (€)	USD	2000	0.92492
Euro (€)	USD	2001	1.25622
Euro (€)	USD	2003	1.13208
Euro (€)	USD	2005	1.24539
German (Mark)	USD	1999	0.47985
GBP (£)	USD	1998	1.65763
INR	USD	2006	0.02214
Yen (¥)	USD	2005	0.00903

Source: http://www.x-rates.com/cgi-bin/hlookup.cgi

Appendix 2.7 The inflation conversion table

	Year	Value in 2007
$1 in	1992	1.46
	1993	1.42
	1994	1.38
	1995	1.35
	1996	1.31
	1997	1.29
	1998	1.27
	1999	1.23
	2000	1.19
	2001	1.17
	2002	1.15
	2003	1.13
	2004	1.09
	2005	1.05
	2006	1.03

http://safalra.com/other/historical-uk-inflation-price-conversion/

Appendix 2.8 The summary of overall treatment cost studies

Study	Country	Patients	Type of analysis	Study period	Cost type	Costing Method					Note
						Cost item	Item content	Data source	Method	Value	
Rosenman et al. 2005 [109]	USA	AML Children (36)	Cost analysis	3 years	Hospital charge	1. Hospitalization	Pediatric, Emergency room, Pediatric ICU, SCT room, Neonatal ICU, Burn unit	Hospital accounting system	Sum up	$5,442,100	1. Only focus on inpatient cost. 2. Total inpatient charges per patient (mean): 94,000 (SD: 123,900)
						2. Pharmacy / IV therapy				$3,431,300	
						3. Laboratory / Pathology				$2,102,500	
						4. OR / Recovery room				$1,186,200	
						5. Radiology	Standard diagnostic, CT scan, Nuclear medicine, MRI			$805,300	3. Total AML inpatient charges (mean): 336,600 (40,500-652,800)
						6. Respiratory services / Pulmonary function				$382,000	
						7. Physical therapy / Occupational therapy				$61,000	
						8. All other				$2,183,195	
						Total				$15,566,400	
Lang et al.2002 [103]	USA	AML Elder ≧65 (3439)	Cost analysis	2 years	Payments	1. Hospitalization		SEER and Medicare database	Sum up	$42,103	Payments per month: $9,226
						2. Skilled nursing facility				$767	
						3. Outpatient visit				$2,254	
						4. Physician / supplier				$5,061	
						5. Home health				$890	
						6. Hospice				$678	
						7. medical equipment ayments				$135	
						Total Medicare payments				$51,888	
Menzin et al. 2002 [104]	USA	AML Elder ≧65 (2657)	Cost analysis	2 years	payments	Hospitalization		SEER and Medicare database	Sum up	$34,823±755	
						SNF				$653±52	
						Outpatient visit				$1,799±113	
						Physician				$2,994±78	
						Home health care				$1,004±52	

						Hospice				$320±22	
						Total Medicare payments				$41,594±870	
Yu et al. 2006 [107]	Taiwan	AML Adult ≦60 yrs (94)	CEA	From diagnosis to the end of therapy, either cure or mortality	charges	1. Hospitalization 2. Pharmacy (drug) 3. Laboratory 4. blood transfusion 5. procedure 6. Professional manpower 7. out-of-pocket Mean total treatment cost		Hospital accounting system	Sum up	$9,118 $15,196 $4,776 $5,644 $6,079 $1,737 $868 $43,418 (1,494 – 172,332)	1. Only focus on inpatient cost. 2. Post remission
Katz et al. 2006 [108]	USA	AML Elder ≧ 60 (219)	Cost analysis	From first admission to last discharge	charges	1. Mean charges of first admission 2. Mean charges of subsequent admission 3. Mean admission Mean total charges per person		Hospital accounting system	Sum up	$70,305 ± 204,800 $38,785 ± 142,166 $53,054 ± 173,901 $115,471 ± $334,581	
										HOVON	EORTC
Uyl-de Groot et al. 2001 [105]	Netherlands	AML adult ≦60 (84)	Cost analysis	From diagnosis to 2 years follow-up		Diagnosis Treatment Follow-up Relapse treatment Total cost	Lab tests, consultants Phase I: Chemotherapy, G-CSF Phase II: harvest Phase III: BMT/PBSCT Outpatient visits, lab tests Chemotherapy, palliative care			$2504 $46113 $6148 $19503 $2470 $25010 $101748	$4714 $52409 $7292 $20619 $8127 $22770 $115930
Kuse et al. 2001 [106]	Germany	AML elder ≧60 (100)	Cost analysis	Protocol (2 inductions + 1 consolidation)	charges	Cost (Young adults) Cost (elderly patients)				105KDM (63-204 KDM) 87.6KDM (56-147 KDM)	

Appendix 2.9 The summary of chemotherapy cost studies

Study	Country	Patients	Type of analysis	Study period	Cost type	Costing Method						Note
						Cost item	Item content	Data source	Method	Value		
Yu et al. 2006 [107]	Taiwan	AML Adult ≦60 (54)	CEA	Single period of therapy	Charges	1. Hospitalization 2. Pharmacy (drug) 3. Laboratory 4. blood transfusion 5. procedure 6. Personnel 7. out-of-pocket		Hospital accounting system	Sum up			1. Only focus on inpatient cost. 2. post remission
						Mean total cost				CC: $7670 ± 5865 HiDAC: $13,668 ± 6048		
Katz et al 2006 [108]	USA	AML Elder ≧ 60 (219)	Cost analysis	From first admission until last discharge	charges	1. Mean charges of first admission without chemotherapy		Hospital accounting system	Sum up	$103,483 (211,388)		1. Induction treatment
						2. Mean charges of first admission with chemotherapy				$46,118 (197,039)		
						Mean total cost without chemotherapy				$163,159 (236,486)		
						Mean total cost with chemotherapy				$80,541 (388,194)		
										Protocol	Standard	
Berman et al. 2002 [114]	USA	AML (79)	Cost analysis	From diagnosis until the day before the next phrase of chemotherapy	charges	1. Inpatient bed		Hospital accounting system	Sum up	$34373	$44200	1. Induction treatment
						2. pharmacy	Antiemetics, antibiotics, chemotherapy, and G-CSF			$29214	$25553	
						3. Professional fee				$14723	$16563	
						4. chemistry				$10848	$13061	
						5. Blood bank				$5273	$8537	
						6. All the other	Emergency room, Hospital visit, Laboratory			$13563	$21109	
						Median total cost				$96571	$124868	

										AML10	FLANG	1. Induction therapy
Clavio et al. 2001 [112]	Italy	AML Adult ≦60 (18)	Cost analysis	Beginning of therapy until discharge	charges	1. Personnel and services		Hospital accounting system	Sum up	$5,906	$3,970	2. Only focus on treatment cost; diagnostic cost were excluded
						2. Antiblastic drugs				$453	$1,057	
						3. Infection treatment				$1,366	$721	
						4. Antiemetic drug				$156	$52	
						5. G-CSF				$52	$506	
						6. Transfusion				$4,243	$2,784	
						7. Microbiological test				$70	$43	
						8. Radiological test				$23	$18	
						9. Other costs				$156	$113	
						Mean total cost				$12,424	$9,269	
										Conventional chemotherapy	ATRA	
Takeshifa et al. 1995 [116]	Japan	APML adult 17-65 (36)	Cost analysis	First 2 month of hospitalization	payment	1. Antibiotics		NHI data	Sum up	￥13,174 ± 7136	￥7,341 ± 6442	1. remission induction
						2. Blood products				￥21,846 ± 16,942	￥14150 ± 10688	
						3. Anticoagulants				￥7,492 ± 7051	￥6,788 ± 5980	
						4. Other medical costs	drugs, meals, fee for laboratory tests, basic room, surgery			￥43510 ± 17116	￥34374 ± 13141	
						Total costs				￥86032 ± 33030	￥62653 ± 22312	
Jacob et al. 2007 [115]*	India	AML	Cost analysis	Complete treatment: 2 inductions and 3 consolidations	charges	Mean total cost of complete treatment		Hospital accounting system	Sum up	500,000 INR		1. induction and consolidation treatment
										Conventional chemotherapy	Low dose chemotherapy	
Storti et al. 2005 [113]	Italy	AML elder 65-80 (17)	Cost analysis	N/A	charges	hospitalization (monthly)		Hospital accounting system	Sum up	€3700	€1000	
						Antibiotic (monthly)				€1100	€300	
						Transfusion (monthly)				€1200	€500	
						Chemotherapy				€500	€6	

						(monthly) Total cost (monthly)		€6500	€1806
Stabler et al. 2003 [100]	Germany	Cancer (66)	Cost analysis	3 months	Bottom-up	Hospitalization Personnel	Hospital accounting system	-	

CC: conventional chemotherapy

Appendix 2.10 The summary of transplantation cost studies

Study	Country	Patients	Type of analysis	Study period	Cost type	Costing Method						Note
						Cost item	Item content	Data source	Method	Value		
Yu et al. 2006 [107]	Taiwan	AML Adult ≦60 yrs (54)	CEA	Single period of therapy	charges	1. Hospitalization 2. Pharmacy (drug) 3. Laboratory 4. blood transfusion 5. procedure 6. Personnel 7. out-of-pocket		Hospital accounting system				1. Only focus on inpatient cost. 2. post remission
						Mean total treatment cost				AlloSCT: 29,208 ± 20,901 ASCT: 10,037 ± 7,291		
										MA	NMA	
Cordonnier et al. 2005 [120]	France	AML (23)	Cost analysis	1 year	charges	Care expense	Average daily rate for personnel costs, supplies, and room costs	Hospital accounting system		€59920	€62960	
						Pre-transplantation	Family HLA typing / evaluation of the recipient and donor /conditioning chemotherapy / harvest		Cost of harvest: MA-8.6% of total cost; NMA-5% of total cost			
						Expensive drugs	chemotherapy, cyclosporine, blood products, growth factors, antibacterial and antifungal drugs		Pharmacy expense = 10% of total cost			
						Other resources	TBI, expensive investigations (CT, MRI)		Blood bank = 10% of total cost			
						Overheads	maintenance, administration		step-down method	€100	€100	
						Mean total cost				€74900 ±22600	€78700± 37300	
Schimmer et al. 2002 [127]	Canada	AML (18)	Cost analysis	1.5 year after transplantation	Unit cost	Space requirements	Examination room*2, waiting area and staff work area	1. hospital 2. health insurance	Resource counts * reference unit cost	Fixed costs for overheads $2300		
						Durable equipment	table, equipment, desk and					

							chairs (examining room)						
						General equipment and waiting area	Standard office equipment and lounge furniture						
						personnel	1. operated 0.5 days / week 2. administrative secretary 0.5 FTE, receptionist 0.1 FTE, nurse 0.1 FTE, hematologist 0.1 FTE	FTE: annual full-time-equivalent		Staff $33,300 Physician fees $4,100			
						Incremental diagnostic tests (New patient tests)	Complete blood count, liver function tests, bone mineral density, Mammogram			Initial diagnostic procedures $ 13,200			
						Annual total cost of operating the clinic			Sum up	$53,000 (Can)			
										BMT	MUD	PBSCT	
Agthoven et al. 2002 [124]	Netherlands	ALL & AML adult (97)	Cost analysis	Pre-transplantation until 2-year follow-up	Unit cost	Pre-transplantation: screening cost	HLA typing + confirmation, chemistry, antibody, screening, immunology	Unit cost: Dutch tariff	Resource counts * reference unit cost	€2,342 (excluding haematologist)			1. HLA typing details: Table 5 in the article
						Pre-transplantation: donor cost	Family HLA typing, requesting blood samples, donor graft, harvest	Unit cost: Dutch tariff	Resource counts * reference unit cost	10843	47063	11137	2. donor cost details: table 5 of the article
						Transplantation	Hospitalization, consultations, antibiotics, blood components, immunosuppressants, TBI, laboratory test	1. Unit cost: Dutch tariff 2. wholesale prices 3. the unit of hospital days (regular / isolation / ICU)	1. Resource counts * reference unit cost 2. Hospitalization, day care treatment, outpatient visit included overheads cost	28944	35543	32255	
						Follow-up phase 1: 6 months	outpatient visits, consultations antibiotics, day care, blood components, laboratory test			16587	30292	15051	
						Follow-up phase 2: 6-12 months				10157	18473	12265	
						Follow-up phase 3: 12-24 months				8093	13331	6313	
						Personnel cost	See table 3 of the article	Salary and full-time equivalents	FTEs required * total employer costs				
						Average costs				98334	151754	98977	

										PBPCT	BMT	
Vicent et al. 2001 [125]	Spain	ALL, AML, NHL, and HD children (131)	Cost analysis	From admission for transplantation until discharge	charges	Stem cell collection	Mobilization, harvest, apheresis, cryopreservation	Hospital accounting system	Sum up	$1218	$1071	
						Hospitalization	Hematologic care unit, intensive unit			$3117	$5106	
						Blood products	Platelet transfusion, red blood cell transfusion			$606	$1236	
						Pharmacy	Growth factors, conditioning, antibiotics			$1845	$2061	
						Laboratory test	Blood count, culture			$164	$257	
						Radiological	X-ray, CT			$99	$9	
						Total cost				$7895	$11820	
Chandy et al. 2001 [126]	India	AML, CML, THAL children (4)	Cost analysis	From admission to discharge	charges	Investigations		Hospital accounting system	Sum up	$1735.5		
						Physician fees				$133,475		
						Room charges				$2,866		
						Blood product				$2,112		
						Drugs				$6,869		
						Disposables				$6,362		
						Mean total cost				$16,666.75		
Mishra et al. 2001 [128]	Norway	CML, ALL, AML, MSD (17)	Cost analysis	From pre-transplantation until 1 year follow up	charges	Pre-transplantation	Personnel resource, pharmacy, blood products, diagnostic tests, donor evaluation	Hospital accounting system	1. personnel resource unit cost: with 4 levels of care (OC:IC:LIC:HIC = 1:2:3:4) 2. overhead unit cost: step down key cost and allocate to get the mean cost	$12,077		1. use bottom up costing method 2. outpatient costs were excluded
						Transplantation	Personnel, pharmacy, blood product, operation, laboratory test, radiology			$80,195		
						Post-transplantation (1 year follow-up)	Personnel resource, pharmacy, blood products, laboratory test, radiology			$14,533		
						Total cost				$106,825		
										PBSCT	BMT	
Blaise et al. 2000 [121]	France	AML, ALL, CML	Cost analysis	6 months	Unit cost	Donor graft collection	1. Blood cell collection 2. BM collection: prior study	Medical records	1.Resource count * reference unit cost	€2740±525	€2449±241	

		adult ≦55 (98)				Conditioning regimen (drugs and TBI)		prices of medical technical acts	2. total yearly cost of consumable supplies, hotel cost, personnel cost, and depreciation of equipment (for 5 years) were measured to calculate per diem cost 3. step-down method to calculate the overheads	€1280±453	€1370±367	
						Room cost	Initial and secondary room			€17408±7363	€21759±10087	
						Outpatient visit				€1678±1051	€1463±991	
						Transfusion	Platelet, erythrocyte	Prices		€1802±1957	€3193±3537	
						Post transplantation drug		price		€6450±3193	€7403±2632	
						Parenteral nutrition		Price		€783±832	€1008±1106	
						Laboratory tests		prices of medical technical acts		€5220±1509	€5832±1769	
						Total cost				€37410±12109	€44531±15881	
Farah et al. 1998 [117]	USA	ALL, AML, CML children ≦ 16 (19)	Cost analysis	Treatment period	charges	Hospitalization		Unit bed charges	Sum up			1. TBI charge were similar whether performed in inpatient or outpatient setting
						Ambulance transportation (to and from)		Round trip twice per day,				
						Clinical visit						
						Fluid administration						
						Total cost				Outpatient TBI save $3,250 per patient		
										AlloBMT	Control	
Barr et al. 1996 [118]	Canada	AML (2CR) adult 16-45 (7)	CEA	5 years	Unit cost	Diagnostic and therapeutic costs	laboratory tests, radiologic investigations, clinic visits, emergency department visit		Resource counts * reference unit cost	$32997	$14349	1. the cost to families and to BMT donors were not included, but typing costs were included 2. nursing costs were included in ward costs
						Ward costs	Included nursing cost	Nursing costs: nursing reports	nursing time per patient per day in hour * nursing cost	$51105	$23673	
						Professional fees	Physicianconsultation, visits, laboratory medicine, radiology, and surgical procedures	OHIP schedule of benefits.		$5231	$6682	

						Drug cost				$11267	$7097	
						Total cost				$CAN: 100,600 (SD:48380)	$CAN: 51,800 (SD:17370)	
										Unit treatment cost	Total cost	
Uyl-de Groot et al. 1995 [119]	Netherlands	AML (30)	Cost analysis	2 years	Unit cost	Option 1: no further treatment	40% no relapse		Resource count * reference unit cost	$4220	$1690 (4220*0.4)	
							60% relapse					
							50% re induction cycle			$31160	$9350	
							50% no re induction cycle			0	0	
						Conventional treatment cost					$11040	
						Option 2: autologous BMT	Autologous BMT: pre-transplantation, transfusion, hospitalization, medication,		Hospitalization 55%, Medication 14%, Transfusion 18%	$51220	$51220	
							Follow up					
							60% no relapse			$4220	$2530	
							40% relapse			$4220	$1690	
						Total BMT cost					$55440	
Esperou et al. 2004 [122]	France	CML, AML, ALL (85)	Cost analysis	6 months	charges	Room	Acute care days, ICU days, outpatient visit, home care	Hospital accounting system	step-down method to allocate the overheads costs.	€57703 (11444-149901)		1. Median cost
						Blood bank				€5390 (834-26557)		
						Tests	family HLA typing, pre-transplant evaluation			€791 (48-3947)		
						pharmacy				€4441 (524-34628)		
						Conditioning				€13285		
						Harvesting	BMT, PBSCT			€8501		
						Total cost				€70479 (14761-183758)		
Dagher et al. 1997 [123]	USA	ALL, AML children 9-17 (10)	Cost analysis	Unknown	charges	Inpatient		Hospital accounting system				
						Daily bed charges						
						Transportation	To and from the radiation facility					
						Outpatient						
						Clinic visit						

						Home-care TBI Total difference		$2,400
Stabler et al. 2003 [100]	Germany	Cancer (66)	Cost analysis	3 months	Bottom-up	Diagnosis SCT Conditioning chemo Total cost	1. Hospital accounting system 2. survey	€16672 per outpatient contact €45930 per hospital care day €80820 per inpatient treatment day

Appendix 2.11 The summary of adjunctive care cost studies

Study	Country	Patients	Type of analysis	Study period	Cost type	Costing Method						Note
						Cost item	Item content	Data source	Method	Value		
										induction	Induction + consolidation	
Standaert et al. 2002 [129]	UK	AML adult (82)	Cost analysis	24 hours after chemotherapy until ANC recovery	Unit cost charges	CRF (case report method)						
						1.Hospital stay		Case report forms	Resource count * unit reference cost	£4455.10	£7774	
						2. anti-infective drug				£433.9	£727.16	
						3. Platelet use				£1457.37	£466.44	
						4. Lab test				£267.31	£2345.59	
						5. G-CSF				£918	£1413	
						Total cost				£7531.67	£12726.19	
						PF (medical chart)						
						1. Hospitalization		Hospital accounting system	Sum up	£4485	£7721.10	
						2. iv infective drug				£536.45	£600.25	
						3. Other drug				£308.1	£530.41	
						4. Diagnostic tests	Haematology, biochemistry, microbiology, t			£1147.36	£1531.58	
						5. Blood products				£3223.78	£4477.75	
						Total cost				£9700.69	£14,861.09	
										G-CSF	Placebo	
Bradstock et al. 2001 [130]	Australia	AML adult 15-60 (114)	Cost analysis	Start date until ANC recovery	Payment	Lenograstim	Daily dose and duration of lenograstim	Australian pharmaceutical benefits schedule, case record forms	1. Sum up 2. Exclude: chemotherapy, antibiotics, transfusions, 1-day admission and outpatient visits	A$3684	A$120	Exclude some costs because the authors considered there were no differences between two arms
						Intravenous and oral antibiotics	Duration of administration and standard doses	hospital purchasing costs, case record forms				
						Inpatient admission		Reimbursement				
						Total				Mean increase: A$ 1494 (SE: 1942)		

Bennet et al. 2001 [131]	USA	AML elder 55-70 (207)	Cost analysis	Start date until ANC recovery	charges	Daily cost without infection	Blood bank, hospitalization, lab test, and pharmacy	Unit cost: the hospital billing data of 24 pts at 5 centers	Sum up	$1476 (722)		use cost-to-charge ratio to transform the charges to real cost
						Daily cost with infection	Blood bank, hospitalization, lab test, pharmacy, and antibiotics,	Unit cost: the hospital billing data of 24 pts at 5 centers		$1742 (548)		
						G-CSF		Drug selling price		$200		
						Total cost				Placebo group: $49,693 G-CSF group: $50,593		
										AML10	FLANG	
Clavio et al. 2001 [112]	Italy	AML Adult ≦60 (18)	Cost analysis	Chemo: admission until discharge G-CSF: day 11 until neutrophil recovery	charges	1. Personnel 2. Antiblastic drugs 3. Infection treatment 4. Antiemetic drug 5. G-CSF 6. Transfusion 7. Microbiologic testing 8. Radiological testing		Hospital accounting system	Sum up	$5,906 $453 $1,366 $156 $52 $4,243 $70 $23	$3,970 $1,057 $721 $52 $506 $2,784 $43 $18	1. Induction therapy 2. Only focus on treatment cost; diagnostic cost were excluded 3. Including chemotherapy cost
						9. Other costs				$156	$113	
						Mean total cost				$12,424	$9,269	
										infection	Un-infection	
Bennett et al. 1999 [132]	USA	AML elder 55-70 (117)	Cost analysis	Start date until discharge	charges	Non GM-CSF	Hospital room, laboratory, pharmacy, blood products,	24 patients' hospital charges data (cost to charge ratio)	Median per day cost(exclude the cost of GM-CSF)	$1742	$1467	Use 24 patients' charge data to estimate the mean 117 pts' total cost
						GM-CSF		Hospital charge		$190.8	$190.8	
						Total cost		Resource count * hospital charge unit cost		Overall: $38,412 One cycle: $38,617 Two cycle: $37,467		
										G-CSF	Control	
Ojeda et al. 1999 [133]	Spain	AML, NHL adult	Cost analysis	Transplantation in-patient	charges	Occupied-bed days	personal, laboratory test	Patient medical records	Sum up	€4362 ± 387	€4317 ± 238	Only included in-patient time.

		18-64 (62)		time		Non-prophylactic antibiotics				€711 ± 140	€601 ± 76	Exclude: costs after discharge, conditioning chemotherapy, harvest and cryopreservation.
						TPN (total parenteral nutrition)				€511 ± 38	€483 ± 32	
						Transfusion	RBC, Platelet			€995 ± 133	€993 ± 196	
						G-CSF				€553 ± 37		
						Total cost				€7,449 ± 645 Median: €5,961	€6,689 ± 480 Median: €5,751	
										GM-CSF	Control	
Uyl-de Groot et al. 1998 [134]	Netherlands	AML elder ≧ 60 (103)	Cost analysis	Start date until 2 years follow-up	charges	Induction I						
						1. Hospitalization	Personnel, overheads cost		Sum up	$14,950	$14,270	
						2. Consultation				$101	$83	
						3. Laboratory services	Routine test, blood culture			$2,854	$2,592	
						4. Medical procedures	radiotherapy and surgery			$1,318	$1,437	
						5. Drug (excl. GM-CSF)		Wholesale price		$5,327	$4,412	
						6. GM-CSF		Wholesale price		$3314	0	
						7. Nutrition				$434	$328	
						8. Transfusion	Blood products			$2,301	$2,113	
						Total induction I cost				$30,599	$25.236	
						Total induction II cost				$25,054	$22,965	
						Total consolidation cost				$15,384	$20,891	
						Treatment cost				$40,782	$34,465	
						1st year follow-up	Outpatient visit, day-care			$11,266	$10,831	
						2nd year follow-up				$6,039	$6,571	
						Total cost				$58,087	$51,867	
										1 cycle	2 cycles	
Bennett et al. 1997 [135]	USA	AML elder 56-70 (117)	Cost analysis	Start date until discharge	charges	1. Daily cost without infection	Blood bank, hospitalization laboratory test,	hospital billing data of 7 pts at a center	Sum up	$2,100	$2,100	1. medical cost only 2. use

							pharmacy				cost-to-charge ratio to transform the charges to real cost
						2. Daily cost with infection	Blood bank, hospitalization laboratory test, pharmacy, antibiotics	Unit cost: the hospital billing data of 7 pts at a center		$3,600	$3,600
						3. G-CSF		selling price		$200	$200
						Mean total cost				$66,757	$62,728
Lu et al. 1996 [136]	Unknown	AML (521)	Cost analysis	1st induction (start day until discharge)	charge sunit cost	1. hospitalization 2. anti-infective therapy 3. transfusion 4. G-CSF administration 5. physician visit		Baseline model with hospital accounting system	Resource count * hospital charge unit cost		
						Net cost saving				$2,230	
										G-CSM	placebo
Bennett et al. 1998 [137]	USA	AML elder >55 (207)	Cost analysis	Start date until discharge	charges	1. Median cost per day with infection				$1,840	$1,840
						2. Median cost per day without infection				$1,370	$1,370
						Total cost				$52,070	$51,950
										G-CSF	Placebo
Woronoff-Lemsi et al. 1997 [138]	France	AML elder 55-75 (83)	CEA	Start date until ANC recovery	charges	Overall survival cost		Medical records and hospital accounting system		$97,841	$106,963
										(36,704)	(45,927)
						Disease free survival cost				$53,456	$59,528
										(20,940)	(27,075)

Appendix 2.12 The summary of complication treatment cost studies

Study	Country	Patients	Type of analysis	Study period	Cost type	Costing Method							Note
						Cost item	Item content	Data source	Method	Value			
Nomura et al. 2006 [139]	Japan	AML 40 yrs (30)	CEA	Start of chemotherapy to CR or death	Payment and hospital charge	1. Hospitalization 2. chemotherapy 3. Laboratory test 4. Medication (excluding antifungals) 5. nutrition 6. Transfusion		National health insurance	Sum up	$5093 (3644-5914) $7542 (5394-10600) $1404 (749-1729) $1053 (283-3536) $733 (518-972) $8608 (1338-16211)			Strategy 1: Oral fluconazole Strategy 2: empirical amphotericin B Strategy 3: MCPG
										S1	S2	S3	
						7. Antifungal drug			Resource count * daily hospital charge	$884	$112	$870	
						Cost per patient				$25900	$25400	$25400	
										case	control		
Menzin et al. 2005 [140]	USA	AML elder ≧65 (160)	Cost analysis	Inpatient time and 30 days post discharge	Charges and payment	Total charges for hospitalization	Hospitalization, intensive care	Accounting system	Sum up	$110767 (95592)	$55796 (63462)		
						Medicare payments for hospitalization		SEER + Medicare	Sum up	$34268 (31811)	$21416 (22449)		
										HU	TLS		
Annemans et al. 2003 [141]	Belgium, Netherlands, Spain, UK	ALL, AML, NHL (144)	CEA	Treatment time	Ref Unit cost	1. Medication		Unit cost	Mean of resource count * reference unit cost	€218 (51)	€446 (92)		HU: hyper uricaemia TLS: tumour lysis syndrome
						2. Interventions				€13 (6)	€719 (185)		
						3. Consultations				€32 (3)	€142 (19)		
						4. Laboratory				€32 (4)	€115 (20)		
						5. Imaging				€1 (0)	€83 (18)		
						6. Hospitalization				€376 (142)	€5837 (1421)		
						Total cost				€672 (181)	€7342 (1617)		
						Total cost per treatment with rasburicase		Unit cost	Average body weight *dosage* number of days* unit cost	Adult: €2220 Child: €960			
						Incremental cost of prevention with the		Drug cost – (HU cost*HU incidence*%HU prevented) – (TLS		Adult: €1752 (1425-1924) Child: €492 (165-664)			

						drug Incremental cost of treatment with the drug			cost*TLS incidence*% TLS prevented) Drug cost – (HU cost*% HU prevented) – (TLS cost*TLS incidence in HU case*% TLS prevented)		Adult: - €426 Child: - €1686 (-€965~-€3665)		
Costa et al. 2003 [142]	Brazil	AML, ALL, NHL, HL children ≦21 (22)	Cost analysis	Treatment time plus 20 days after treatment	Ref unit cost	1. Antibacterial 2. drugs excludes disease treatment 3. ambulatory visit 4. cultures 5. transfusions 6. laboratory test 7. Hemogram 8. Hospitalization Total direct cost total cost per episode	Personnel and 3 types of ward		Resource count * reference unit cost Sum up per treatment episode		$41,523 $7,657 $5,337 $3,726 $3,642 $4,420 $2,117 $112,383 $180,805 $2660($2039) (AML: $2917)		
Rosenman et al. 2002 [143]	USA	ALL, AML, CNS children ≦18 (157 episodes)	Cost analysis	Treatment time	charges	Total hospital charges per episode			Mean		$11,967±$16,261 ($40,694±38,831in AML)		
											C+N	C+A	M
Agaoglu et al. 2001 [144]	Turkey	ALL, AML children (87 episodes)	Cost analysis	Treatment time	charges	Daily drug cost for 30kg patient		Hospital accounting system			$53.8	$46.2	$121.4
Horowitz et al. 1996 [145]	USA	ALL, AML, NHL (10)	Cost analysis	Treatment time	charges	1. Antibiotic cost differential 2. Hospital day cost saved	Gentamicin, Ceftazidime, Vancomycin, Ciprofloxacin IV oncology bed	Hospital accounting system	total cost of ciprofloxacin * number of days on ciprofloxacin Cost of oncology bed per day * the number		$1,142 per patient $8,880 per patient		

Agaoglu et al. 2001 [144]	1. cefepime + netilmicin 2. ceftazidime + amikacin 3. meropenem
Horowitz et al. 1996 [145]	1. object is to compare the cost of ciprofloxacin in hospital and at home

						Total cost saved	Antibiotic and hospitalization cost save	of days	$10,022 per patient				
Storti et al. 2005 [113]	Italy	AML elder 65-80 (17)	Cost analysis	unknown	charges	Antibiotic expense (monthly)			ST €2900	CC €1100	LDC €300	ST: supportive care CC: Conservation chemotherapy LDC: low-dose chemotherapy	

Appendix 2.13 The summary of examination cost studies

Study	Country	Patients	Type of analysis	Cost type	Costing Method						
					Cost item	Item content	Data source	Method	Value		
Gonen et al. 2005 [146]	Turkey	AML (33 episodes)	Cost analysis	Hospital charge unit cost	1. Blood cultures		Hospital accounting system	Resource count * hospital charge unit cost	$43*26		
					2. Urine cultures				$36*21		
					3. Chest X-ray				$5.8*6		
					4. Sinus X-rays				$4.9*2		
					5. Oral smear				$14.2*2		
					6. Sterile urine examinations				$14.2*11		
					7. urinalysis				$5.7*6		
					Total cost of	investigation of fever per episode			$2137/33=$64.76		
									cyto	PCR	PCR (add)
Tonnaire et al. 1998 [147]	France	ALL, AML adult 16-91 (107)	CEA	Ref unit cost	1. Equipment	Appliances and supplies		5 year depreciation rate for equipment (20%) and 10 year for materials (10%), average annual rate 8%	$108	$26.6	$0
					2. Labor	technicians, physicians, white collar and maintenance workers	1. White collar workers: annual laboratory charges / no. of analyses completed within the year 2. physicians and technicians: 5 exams per week + 1 hour work for physician to interpret.		$289.8	$123.1	$41.6
					3. Reagents				$163.2	$88	$53.2
					4. Other non expendable laboratory supplies				$15.8	$3	$0
					5. stationery				$0.6	$0.5	$0
					Total				$577.4	$241.2	$94.8

Appendix 2.14 The summary of palliative or supportive care cost studies

Study	Country	Patients	Type of analysis	Study period	Cost type	Costing Method							Note
						Cost item	Item content	Data source	Method	Value			
Yu et al. 2007 [107]	Taiwan	AML Adult ≦60 yrs (54)	CEA	Single period of therapy	Charges	1. Hospitalization 2. Pharmacy (drug) 3. Laboratory 4. blood transfusion 5. procedure 6. personnel 7. out-of-pocket		Hospital accounting system	Sum up				1. Only focus on inpatient cost 2. post remission
						Total treatment cost				Supportive care: $3,013± 4,586 Palliative care: $15,726± 17,083			
										Discharge early	Terminal	Chronic	
Cartoni et al. 2007 [150]	Italy	AML, lymphoma, myeloma (144)	Cost analysis	Unknown	Ref unit cost	1. Health care provider	Physician, nurse,, and co-ordination team (direct cost and overheads in a 60:40 ratio)		Resource count * reference unit cost	€1354.9	€1513.6	€507.3	
						2. Medicines				€1432.2	€1442.6	€728.3	
						3. Transfusion				€1148.2	€1224.3	€227.3	
						4. laboratory	hematology, blood chemistry, microbiology			€51.1	€52.0	€25.4	
						Total monthly cost				€3986.4 (241.2 - 6285.3)	€4232.5 (437 - 14599)	€1488.3 (455.9 - 4769.5)	
Wandt et al. 1998 [148]	Germany	AML adult ≦60 (105)	Cost analysis	Unknown	charge	Platelet transfusion RBC transfusion Leukocyte filters personnel		Hospital accounting system	Sum up	Trigger 1 saved 1/3 cost No difference No difference			
						Transfusion cost per treatment cycle				Trigger 1 is cost saved			
Ruiz-Arguel	Mexico	AML adult	Cost	Start date until	charges	Outpatient setting cost	Transfusion,			$1700 per patient			

les et al. 1995 [149]		14-63 (24)	analysis	granulocyte count recovery		saved by avoiding prolonged hospitalization	antibiotics, physician fee		
Storti et al. 2005 [113]	Italy	AML elder 65-80 (17)	Cost analysis	unknown	charges	hospitalization (monthly) Antibiotic (monthly) Transfusion (monthly) Chemotherapy (monthly) Total cost (monthly)		Hospital accounting system	€5,100 €2,900 €900 €0 €8,900

Appendix 3.1 Database Cleaning

Database Cleaning	Number
Removed problematic cases	
Medical note is not obtainable	2
Extraction form has not been completed	2
Removed duplicated events	
Duplicated records	1
Integrated the records that are likely to be the same	
Integrating Mylotarg	2
Integrating Spanish approach (like)	3
Integrating MRC approach (like)	1
Integrating FC	2
Integrating FLAG	2
Integrating FLAG-Ida	2
Fixed the records that against the definition	
Removing observation record	91
Removing “non-haematological” treatment record	10
Removing “Bisphosphonates” which is not for AML treatment	1
Change the extreme long palliative care to observation	3
Fixed the field input error	
Immunosuppressive therapy miss-input as chemotherapy	1
AraC(LD) miss-input as Cytarabine (IT)	2
Fixing the missing data in the field: place of death	2
Fixed the date input error	
Fixing the missing data in the field: Date of Follow-up	1
Fixing the missing date in the field: treatment date	7
Fixing the miss-input date in the field: treatment date	4
Fixing the miss-input in the field: death date	18
Total	156

Appendix 3.2 Integration information for imputation

	Cycle one		Interval	Cycle two		Imputed treatment time	Numbers of imputed cases
	Treatment time	Hospital stays		Treatment time	Hospital stays		
Intensive inpatient treatment							
ADE	10	30	13	8	25	30+13+8=51	6
AraC (HD)	5	32	17	5	23	32+17+5=54	3
AraC (LD) – clinical trail	10	30	18	10	30	30+18+10=58	3
DA	10	35	14	8	30	35+14+8=57	12
FLA	5	28*	17*	5	46*	28+17+5=50	1
FLAG	7	33	19	7	45	33+19+7=59	2
FALG-Ida	7	28	17	7	46	28+17+7=52	15
HAM	6	30*				30	1
MACE	5	25				25	10
MidAC	5	30				30	3
Spanish Approach	4	31	0	4	23		2
	5	32	0	1	28**		
MRC approach	10	32	11	8	25		0
	5	27	17	5	28		
Clofarabine	5	30**				30	
Mild inpatient treatment							
Amsacrine	5	28				28	0
AraC (LD) -chemotherapy	10	14	18	10	14	14+18+10=42	5
Arsenic trioxide	25	33				33	0
Campath	3	14**				14	
Intensive outpatient treatment							
Mylotarg	1	-	6	1	-	One cycle (1)	1
FC	5	-	23	5	-	One cycle (5)	2
Fludarabine	5	-	28	5	-	One cycle (5)	1
Cyclophosphamide	1	-	6	1	-	One cycle (1)	2
Cyclophosphamide / MESNA	1	-				1	0
ETI	5	-	21	5	-	One cycle (5)	0
Etoposide	7	-	21	7	-	One cycle (7)	2
Vincristine	1	-	6	1	-	1	0
ATRA	Till	-				Till	2
	remission**					remission**	
Melphalane	4	-				4	0
Anagrelide	5	-				5	1
Clopidogrel	7	-				7	1
Mild outpatient treatment							
Aspirine	28**	-				28**	1
Hydroxycarbamide	28**	-				28**	16
Hydroxycarbamide / Aspirin	28**	-				28**	0
Chelating agent	28**	-				28**	0
Non-chemotherapy treatment							
Supportive care							

Erythropoietin	1	-	6	1	-	3 months**	0
G-CSF	4 after chemo**	-	-	4 after chemo**	-		21
Steroids							6
Dexamethasone	14 days**	-				14	
Prednisolone	14 days**	-				14	
Hydrocortisone	14 days**	-				14	
Transfusion							89
Disease time < 2 months	1	-	4	1	-	Till remission**	
Disease time > 2 months	1	-	14	1	-	Till remission**	
Stem cell transplantation	1	28				28	4
Immunosuppressive	14 weeks**	-				98**	3
Radiotherapy	1	-				1	2
Splenectomy	1	8				8	0
Venesection	1	-				1	0
Palliative care							17
<100 days till death	Till death**	Till death**				Till death**	
>100 days till death	2 weeks**	2 weeks**				14**	
Follow up							
End-of life care	14**	14**				14**	

* The length was imputed by similar treatment

** The length was imputed by expert opinions

Appendix 4.1 Types of treatment by numbers of treatment (for AML patients)

	Tx 1	Tx 2	Tx 3	Tx 4	Tx 5	Tx 6	Tx 7	Tx 8	Tx 9	Tx 10	Tx 11
Chemotherapy	**84**	**48**	**21**	**25**	**21**	**17**	**10**	**2**	**3**	**1**	**-**
ADE	3	3	1	6	4	1	-	-	-	--	-
AraC(HD)	-	1	1	-	5	3	-	-	1	-	-
AraC(HD) + Mylotarg	-	-	-	-	-	1	1	-	-	-	-
AraC(LD)	27	5	1	1	-	2	-	-	-	1	-
Clofarabine	-	-	-	1	-	-	1	-	-	-	-
DA	27	8	-	1	1	-	-	1	-	-	-
DA + Mylotarg	-	-	-	-	-	-	1	-	-	-	-
FLA	-	-	-	3	1	-	-	-	-	-	-
FLAG	2	5	3	7	1	-	-	-	-	-	-
FLAG-Ida	1	2	1	1	-	-	-	-	-	-	-
FLAG-Ida + Mylotarg	-	-	-	-	-	1	-	-	-	-	-
HAM	-	-	-	-	-	1	-	-	-	-	-
MACE	-	4	3	-	2	-	-	-	-	-	-
MidAC	-	4	6	-	-	2	-	-	-	-	-
Mini-MidAC	-	2	1	-	-	-	-	-	-	-	-
Amsacrine	-	-	-	-	1	-	-	-	-	-	-
Campath	-	-	-	-	-	1	-	-	-	-	-
Daunorubicin	-	-	-	-	1	-	-	-	-	-	-
Cyclophosphamide	-	-	2	1	1	-	1	-	-	-	-
Cyclophosphamide / MESNA	-	-	-	-	1	1	-	-	-	-	-
ETI	1	1	-	-	-	-	-	-	-	-	-
FC	1	-	1	-	-	2	2	-	-	-	-
Fludarabine	-	-	-	1	-	-	1	-	-	-	-
Vincristine	-	1	-	-	-	-	-	-	-	-	-
Melphalan	1	1	-	1	-	-	-	-	-	-	-
Anagrelide	-	-	-	-	-	-	1	-	-	-	-
Clopidogrel	-	-	-	-	-	1	-	-	-	-	-

Aspirin	-	-	-	-	1	-	-	-	1	-	-
Hydroxycarbamide	21	10	1	1	2	1	1	1	1	-	-
Hydroxycarbamide + Aspirin	-	-	-	1	-	-	-	-	-	-	-
Chelating agent	-	1	-	-	-	-	1	-	-	-	-
Clinical trial	**70**	**45**	**20**	**9**	**1**	**-**	**-**	**-**	**-**	**-**	**-**
AML 14 AraC	4	-	-	-	-	-	-	-	-	-	-
AML 14 AraC + Mylotarg	-	1	-	-	-	-	-	-	-	-	-
AML 14 D35 C200	3	-	-	-	-	-	-	-	-	-	-
AML 14 D35 C400	1	-	-	-	-	-	-	-	-	-	-
AML 14 D50 C200	4	-	-	-	-	-	-	-	-	-	-
AML 15 ADE	7	7	1	-	-	-	-	-	-	-	-
AML 15 ADE + Mylotarg	8	1	-	-	-	-	-	-	-	-	-
AML 15 AraC	-	6	10	3	1	-	-	-	-	-	-
AML 15 AraC + Mylotarg	1	4	2	-	-	-	-	-	-	-	-
AML 15 DA	8	8	-	-	-	-	-	-	-	-	-
AML 15 DA + Mylotarg	6	-	-	-	-	-	-	-	-	-	-
AML 15 FLAG-Ida	15	7	1	-	-	-	-	-	-	-	-
AML 15 FLAG-Ida + Mylotarg	13	-	-	-	-	-	-	-	-	-	-
AML 15 MACE	-	3	7	-	-	-	-	-	-	-	-
AML 15 MACE + Mylotarg	-	7	2	-	-	-	-	-	-	-	-
AML 15 MidAC	-	1	7	6	-	-	-	-	-	-	-
Immunosuppressive	-	-	-	1	-	1	1	2	1	-	-
Radiotherapy	-	-	-	2	1	3	2	3	1	1	1
Stem cell transplantation	-	-	-	1	3	-	2	3	2	2	-
Splenectomy	-	-	1	-	1	-	-	-	-	-	-
Palliative care	11	9	1	2	1	2	2	1	-	-	2
Venesection	-	1	1	-	-	-	-	1	-	-	-
No treatment	10	-	-	-	-	-	-	-	-	-	-
Refused treatment	2	-	-	-	-	-	-	-	-	-	-
Total	**177**	**103**	**54**	**40**	**28**	**23**	**17**	**12**	**7**	**4**	**3**

Appendix 4.2 Types of treatment by numbers of treatment (for APML patients)

	Tx 1	Tx 2	Tx 3	Tx 4	Tx 5	Tx 6	Tx 7	Tx 8	Tx 9	Tx 10	Tx 11
Chemotherapy	**6**	**4**	**2**	**2**	**1**	**-**	**-**	**-**	**-**	**-**	**-**
ADE	-	-	1	-	-	-	-	-	-	-	-
AraC(LD)	-	2	-	-	-	-	-	-	-	-	-
DA	-	1	-	-	-	-	-	-	-	-	-
DA + Mylotarg									-	-	-
MACE	-	-	-	1	-	-	-	-	-	-	-
Arsenic trioxide (ATO)	-	1	-	1	-	-	-	-	-	-	-
Mylotarg	-	-	-	-	1	-	-	-	-	-	-
G-CSF									-	-	-
Cyclophosphamide	-	-	1	-	-	-	-	-	-	-	-
ATRA	3	-	-	-	-	-	-	-	-	-	-
MRC approach (like)	1	-	-	-	-	-	-	-	-	-	-
Spanish approach (like)	2	-	-	-	-	-	-	-	-	-	-
Clinical trial	**17**	**4**	**2**	**2**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
AML 15 MRC approach	9	1	1	1	-	-	-	-	-	-	-
AML 15 Spanish approach	8	2	1	1	-	-	-	-	-	-	-
AML 15 Spanish Maintenance	-	1	-	-	-	-	-	-	-	-	-
Palliative care	1	-	-	-	1	-	-	-	-	-	-
Total	**24**	**8**	**4**	**4**	**2**	**-**	**-**	**-**	**-**	**-**	**-**

Appendix 6.1 National blood and blood components price list

Final National Prices
Impact of Cost Pressures, Developments and Cost Reduction Programmes
For the Financial Year 2009/10

	Baseline National Price 2008/09	Cost Reduction & Efficiency Savings				Development Costs and Cost Pressures				Impact Diagnostic, & Tissues Price Adjustments	Pre-Inflation National Price 2009/10	Price Movement Pre Inflation	Inflation Funding GDP Deflator	National Price 2009/10	Price Movement Post Inflation
		Income Impact Product Demand	Fixed cost Adjustment RC's,Plt's & FFP Demand	DRR & Trans. Adj.	Cash Releasing Efficiency Savings	Estate, Infrastructure & Consolidation	Agenda for Change	Devel. CD Plts 60-80%	Capital Charge Adj.						
Red Cell Components															
Whole Blood	140.02		-3.34	-4.15	-3.89	3.92	0.99	0.00	0.08	-3.69	129.94	-10.08	3.57	133.51	-6.51
Standard Red Cells	139.72		-3.34	-4.15	-3.89	3.91	0.99	0.00	0.08	-3.69	129.63	-10.09	3.56	133.19	-6.53
Neonatal Red Cells	44.97		-0.49	-0.73	-0.60	1.26	0.32	0.00	0.02	-0.57	44.18	-0.79	1.21	45.39	0.42
Frozen Red Cells, Thawed & Washed	393.24		-3.34	-4.15	-3.89	11.02	2.79	0.00	0.21	-3.69	392.19	-1.05	10.79	402.98	9.74
Red Cells for Exchange Transfusion	192.90		-3.34	-4.15	-3.89	5.40	1.37	0.00	0.10	-3.69	184.70	-8.20	5.08	189.78	-3.12
Red Cells for Intra-Uterine Transfusion	179.32		-3.34	-4.15	-3.89	5.02	1.27	0.00	0.10	-3.69	170.64	-8.68	4.69	175.33	-3.99
Red Cell Added Value Services															
Premium for CMV -ve Red Cells	7.13		0.00	0.00	0.00	0.20	0.05	0.00	0.00		7.38	0.25	0.20	7.58	0.45
Premium for Irradiated Red Cells	7.11		0.00	0.00	0.00	0.20	0.05	0.00	0.00		7.36	0.25	0.20	7.56	0.45
Premium for Cell Washing	27.04		0.00	0.00	0.00	0.76	0.19	0.00	0.01		28.00	0.96	0.77	28.77	1.73
Platelet Components															
Platelets (1.0 ATD)	232.29		-7.12	0.00	-5.11	6.51	1.65	1.83	0.12	-6.47	223.70	-8.59	6.15	229.85	-2.44
Neonatal Platelets (0.25 ATD)	89.67		-1.78	0.00	-1.28	2.51	0.64	0.46	0.05	-1.62	88.65	-1.02	2.44	91.09	1.42
Platelets for Intra-Uterine Transfusion	324.07		-7.12	0.00	-5.11	9.08	2.30	1.83	0.17	-6.47	318.75	-5.32	8.77	327.52	3.45
Platelet Added Value Services															
Premium for CMV -ve Platelets	7.13		0.00	0.00	0.00	0.20	0.05	0.00	0.00		7.38	0.25	0.20	7.58	0.45
Premium for Irradiated Platelets	7.11		0.00	0.00	0.00	0.20	0.05	0.00	0.00		7.36	0.25	0.20	7.56	0.45
Premium for Cell Washing	27.04		0.00	0.00	0.00	0.76	0.19	0.00	0.01		28.00	0.96	0.77	28.77	1.73
Premium for HLA Selected Platelets	153.16		0.00	0.00	0.00	4.29	1.08	0.00	0.08		158.61	5.45	4.36	162.97	9.81
Premium for HPA Selected Platelets	153.16		0.00	0.00	0.00	4.29	1.08	0.00	0.08		158.61	5.45	4.36	162.97	9.81
Plasma Components															
Clinical FFP (250/300 mls UK sourced)	36.33		-0.22	0.00	-0.97	1.02	0.26	0.00	0.02	-1.23	35.21	-1.12	0.97	36.18	-0.15
Clinical MBFFP (275 mls US Sourced)	135.79		-0.22	0.00	-0.97	3.80	0.96	0.00	0.07	-1.23	138.20	2.41	3.80	142.00	6.21
Neonatal MBFFP (65mls US Sourced)	72.78		-0.05	0.00	-0.24	2.04	0.52	0.00	0.04	-0.31	74.78	2.00	2.06	76.84	4.06
Cryo-depleted Plasma (UK sourced)	41.93		-0.22	0.00	-0.97	1.17	0.30	0.00	0.02	-1.23	41.00	-0.93	1.13	42.13	0.20
Cryoprecipitate															
Cryoprecipitate (UK Sourced)	43.09		-0.22	0.00	-0.97	0.00	0.00	0.00	0.00	-1.23	40.67	-2.42	1.12	41.79	-1.30
Pooled cryoprecipitate (UK Sourced)	227.36		-1.09	0.00	-4.85	6.37	1.61	0.00	0.12	-6.15	223.37	-3.99	6.14	229.51	2.15
MB Cryoprecipitate-Neonatal (US Sourced)	107.89		-0.22	0.00	-0.97	3.02	0.76	0.00	0.06	-1.23	109.31	1.42	3.01	112.32	4.43
MB Cryoprecipitate-Pooled (US Sourced)	539.44		-1.09	0.00	-4.85	15.11	0.00	0.00	0.00	-6.15	542.46	3.02	14.92	557.38	17.94
Other Components and Services															
Apheresed Granulocytes	421.66		0.00	0.00	0.00	11.81	2.99	0.00	0.23		436.69	15.03	12.01	448.70	27.04
Buffy Coats	57.16		0.00	0.00	0.00	1.60	0.40	0.00	0.03		59.19	2.03	1.63	60.82	3.66
Total (£m's) [price x volume issued]	318.0	12.6 (A)	-7.8 (B)	-7.6 (C)	-8.6 (D)	9.3	2.3	0.4	0.2	-8.7	310.0	-7.9	8.5	318.5	0.6

TOTAL	Closing position NCG Process 2008/09	Total Cost Reduction & Savings on baseline costs	-3.8	12.2	-8.7	-7.9	8.5	0.6
		Net Impact (A) + (B) + (C) = Consumable Cost Reduction from reduced red cell demand, plus reduced DRR value less other product volume adjustments	-2.8			Income Decrease / % Decrease		Net Income Decrease / % Decrease
		+ (C), CRES Programme	-8.6			-2.5%		0.2%

Appendix 6.2 The staff working time survey results

			ADE									DA / AML 15 DA / AML 14 DA									
			In-patient period									In-patient period									
			Indirect contact					Direct contact				Indirect contact					Direct contact				
			No	Min	wages	overheads	capital	No	Min	wages	overheads	capital	No	Min	wages	overheads	capital	No	Min	wages	overheads	capital
Doctor (Modernising Medical Careers)																					
Foundation House Officer 1																					
Foundation House Officer 2																					
Specialty Registrar (StR)								**1**	**15**	£15.9	£0.5	£0.5						**1**	**15**	£15.9	£0.5	£0.5
Clinical Practitioner																					
Consultant																					
Nurse (Agenda for Change)																					
Band 1																					
Band 2	A	Clinical support worker	**2**	**30**	£10.2	£1.8	£0.9	**2**	**30**	£10.2	£1.8	£0.9	**2**	**30**	£10.2	£1.8	£0.9	**2**	**60**	£38.4	£3.6	£1.8
Band 3	B																				
Band 4	C																				
Band 5	D	24-hour ward nurse	**2**	**20**	£12.8	£1.2	£0.6	**2**	**90**	£57.6	£5.4	£2.7	**2**	**10**	£6.4	£0.6	£0.3	**2**	**60**	£38.4	£3.6	£1.8
Band 5	D	Day ward nurse																			
Band 6	E	Nurse team leader	**2**	**10**	£7.8	£0.6	£0.5	**2**	**10**	£7.8	£0.6	£0.5	**1**	**10**	£3.9	£0.3	£0.3	**1**	**10**	£3.9	£0.3	£0.3
Band 7	F,G	Nurse team manager	**1**	**10**	£4.6	£0.3	£0.3	**1**	**10**	£4.6	£0.3	£0.3	**1**	**10**	£4.6	£0.3	£0.3	**1**	**10**	£4.6	£0.3	£0.3
Band 8	H, I																				
Band 9	H, I																				
Pharmacist																					
Pharmacist			**1**	**10**	£4.1	£0.3	£0.5						**1**	**10**	£4.1	£0.3	£0.5					
Pharmacist technician																					

The staff working time survey results (continued)

			AraC (HD) / AML 15 AraC										AraC (LD) / AML 14 AraC									
			In-patient period										In-patient period									
			Indirect contact					Direct contact					Indirect contact					Direct contact				
			No	Min	wages	overheads	capital	No	Min	wages	overheads	capital	No	Min	wages	overheads	capital	No	Min	wages	overheads	capital
Doctor (Modernising Medical Careers)																						
Foundation House Officer 1																						
Foundation House Officer 2																						
Specialty Registrar (StR)								**1**	**15**	£15.9	£0.5	£0.5						**1**	**15**	£15.9	£0.5	£0.5
Clinical Practitioner																						
Consultant																						
Nurse (Agenda for Change)																						
Band 1																						
Band 2	A	Clinical support worker	**2**	**30**	£10.2	£1.8	£0.9	**2**	**90**	£30.6	£5.4	£2.7	**2**	**30**	£10.2	£1.8	£0.9	**2**	**90**	£30.6	£5.4	£2.7
Band 3	B																					
Band 4	C																					
Band 5	D	24-hour ward nurse	**2**	**10**	£6.4	£0.6	£0.3	**2**	**60**	£38.4	£3.6	£1.8	**2**	**30**	£19.2	£1.8	£0.9	**2**	**30**	£19.2	£1.8	£0.9
Band 5	D	Day ward nurse																				
Band 6	E	Nurse team leader	**1**	**10**	£3.9	£0.3	£0.3	**1**	**10**	£3.9	£0.3	£0.3	**1**	**10**	£3.9	£0.3	£0.3	**1**	**10**	£3.9	£0.3	£0.3
Band 7	F,G	Nurse team manager	**1**	**10**	£4.6	£0.3	£0.3	**1**	**10**	£4.6	£0.3	£0.3	**1**	**10**	£4.6	£0.3	£0.3	**1**	**10**	£4.6	£0.3	£0.3
Band 8	H, I																					
Band 9	H, I																					
Pharmacist																						
Pharmacist			**1**	**10**	£4.1	£0.3	£0.5						**1**	**10**	£4.1	£0.3	£0.5					
Pharmacist technician																						

The staff working time survey results (continued)

			FLA/ FLAG / FLAG-Ida										AML 16 DClo / Clofarabine									
			In-patient period										In-patient period									
			Indirect contact					Direct contact					Indirect contact					Direct contact				
			No	Min	wages	overheads	capital	No	Min	wages	overheads	capital	No	Min	wages	overheads	capital	No	Min	wages	overheads	capital
Doctor (Modernising Medical Careers)																						
Foundation House Officer 1																						
Foundation House Officer 2																						
Specialty Registrar (StR)								**1**	**15**	£15.9	£0.5	£0.5						**1**	**15**	£15.9	£0.5	£0.5
Clinical Practitioner																						
Consultant																						
Nurse (Agenda for Change)																						
Band 1																						
Band 2	A	Clinical support worker	**2**	**30**	£10.2	£1.8	£0.9	**2**	**60**	£38.4	£3.6	£1.8	**2**	**30**	£10.2	£1.8	£0.9	**2**	**30**	£10.2	£1.8	£0.9
Band 3	B																					
Band 4	C																					
Band 5	D	24-hour ward nurse	**2**	**10**	£6.4	£0.6	£0.3	**2**	**15**	£9.6	£0.9	£0.5	**2**	**60**	£33.6	£3.6	£1.7	**2**	**60**	£33.6	£3.6	£1.7
Band 5	D	Day ward nurse																				
Band 6	E	Nurse team leader	**1**	**10**	£3.9	£0.3	£0.3	**1**	**10**	£3.9	£0.3	£0.3	**1**	**30**	£11.7	£0.9	£0.8	**1**	**30**	£11.7	£0.9	£0.8
Band 7	F,G	Nurse team manager	**1**	**10**	£4.6	£0.3	£0.3	**1**	**10**	£4.6	£0.3	£0.3	**1**	**10**	£4.6	£0.3	£0.3	**1**	**10**	£4.6	£0.3	£0.3
Band 8	H, I																					
Band 9	H, I																					
Pharmacist																						
Pharmacist			**1**	**10**	£4.1	£0.3	£0.5						**1**	**10**	£4.1	£0.3	£0.5					
Pharmacist technician																						

The staff working time survey results (continued)

			MidAC / AML 15 MidAC / HAM										MACE / AML 15 MACE									
			In-patient period										In-patient period									
			Indirect contact					Direct contact					Indirect contact					Direct contact				
			No	Min	wages	overheads	capital	No	Min	wages	overheads	capital	No	Min	wages	overheads	capital	No	Min	wages	overheads	capital
Doctor (Modernising Medical Careers)																						
Foundation House Officer 1																						
Foundation House Officer 2																						
Specialty Registrar (StR)								**1**	**15**	£15.9	£0.5	£0.5						**1**	**15**	£15.9	£0.5	£0.5
Clinical Practitioner																						
Consultant																						
Nurse (Agenda for Change)																						
Band 1																						
Band 2	A	Clinical support worker	**2**	**30**	£10.2	£1.8	£0.9	**2**	**30**	£10.2	£1.8	£0.9	**2**	**10**	£3.4	£0.6	£3.0	**2**	**30**	£10.2	£1.8	£0.9
Band 3	B																					
Band 4	C																					
Band 5	D	24-hour ward nurse	**2**	**60**	£33.6	£3.6	£1.7	**2**	**60**	£33.6	£3.6	£1.7	**2**	**30**	£19.2	£1.8	£0.9	**2**	**60**	£33.6	£3.6	£1.7
Band 5	D	Day ward nurse																				
Band 6	E	Nurse team leader	**1**	**30**	£11.7	£0.9	£0.8	**1**	**30**	£11.7	£0.9	£0.8	**1**	**10**	£3.9	£0.3	£0.3	**1**	**20**	£7.8	£0.6	£0.5
Band 7	F,G	Nurse team manager	**1**	**10**	£4.6	£0.3	£0.3	**1**	**10**	£4.6	£0.3	£0.3	**1**	**10**	£4.6	£0.3	£0.3	**1**	**10**	£4.6	£0.3	£0.3
Band 8	H, I																					
Band 9	H, I																					
Pharmacist																						
Pharmacist			**1**	**10**	£4.1	£0.3	£0.5						**1**	**10**	£4.1	£0.3	£0.5					
Pharmacist technician																						

The staff working time survey results (continued)

			Campath / ATO / Mylotarg/ Immunosuprresive (IP)										Amsarcrine / Idarubicin / Chelating agent (IP)									
			In-patient period										In-patient period									
			Indirect contact					Direct contact					Indirect contact					Direct contact				
			No	Min	wages	overheads	capital	No	Min	wages	overheads	capital	No	Min	wages	overheads	capital	No	Min	wages	overheads	capital
Doctor (Modernising Medical Careers)																						
Foundation House Officer 1																						
Foundation House Officer 2																						
Specialty Registrar (StR)								**1**	**15**	£15.9	£0.5	£0.5						**1**	**15**	£15.9	£0.5	£0.5
Clinical Practitioner																						
Consultant																						
Nurse (Agenda for Change)																						
Band 1																						
Band 2	A	Clinical support worker						**1**	**60**	£10.2	£1.8	£0.9						**1**	**15**	£2.55	£0.45	£0.2
Band 3	B																					
Band 4	C																					
Band 5	D	24-hour ward nurse	**2**	**5**	£3.2	£0.3	£0.2	**1**	**60**	£19.2	£1.8	£0.9	**2**	**5**	£3.2	£0.3	£0.2	**1**	**15**	£4.8	£0.45	£0.2
Band 5	D	Day ward nurse																				
Band 6	E	Nurse team leader						**1**	**30**	£11.7	£0.9	£0.8						**1**	**10**	£3.9	£0.3	£0.3
Band 7	F,G	Nurse team manager																				
Band 8	H, I																					
Band 9	H, I																					
Pharmacist																						
Pharmacist			**1**	**10**	£4.1	£0.3	£0.5						**1**	**10**	£4.1	£0.3	£0.5					
Pharmacist technician																						

The staff working time survey results (continued)

			APML 15 Spanish										APML 15 MRC									
			In-patient period										In-patient period									
			Indirect contact					Direct contact					Indirect contact					Direct contact				
			No	Min	wages	overheads	capital	No	Min	wages	overheads	capital	No	Min	wages	overheads	capital	No	Min	wages	overheads	capital
Doctor (Modernising Medical Careers)																						
Foundation House Officer 1																						
Foundation House Officer 2																						
Specialty Registrar (StR)								1	15	£15.9	£0.5	£0.5						1	15	£15.9	£0.5	£0.5
Clinical Practitioner																						
Consultant																						
Nurse (Agenda for Change)																						
Band 1																						
Band 2	A	Clinical support worker	2	20	£6.8	£1.2	£0.6	2	20	£6.8	£1.2	£0.6	2	30	£10.2	£1.8	£0.9	2	30	£10.2	£1.8	£0.9
Band 3	B																					
Band 4	C																					
Band 5	D	24-hour ward nurse	2	30	£19.2	£1.8	£0.9	2	60	£38.4	£3.6	£1.8	2	60	£38.4	£3.6	£1.8	2	60	£38.4	£3.6	£1.8
Band 5	D	Day ward nurse																				
Band 6	E	Nurse team leader	2	10	£7.8	£0.6	£0.5	2	10	£7.8	£0.6	£0.5	2	20	£15.6	£0.6	£1.0	2	20	£15.6	£1.2	£1.0
Band 7	F,G	Nurse team manager	1	10	£4.6	£0.3	£0.3	1	10	£4.6	£0.3	£0.3	1	10	£4.6	£0.3	£0.3	1	10	£4.6	£0.3	£0.3
Band 8	H, I																					
Band 9	H, I																					
Pharmacist																						
Pharmacist			1	10	£4.1	£0.3	£0.5						1	10	£4.1	£0.3	£0.5					
Pharmacist technician																						

The staff working time survey results (continued)

			G-CSF / Vincristine / Cyclophosphamide + MESNA / Daunorubicin										Cyclophosphamide / Etoposide / EIT / FC / Melphalan / ATRA / Chelating agent (OP) / Hydroxyurea / Aspirin / steroids									
			Out-patient period										Out-patient period									
			Indirect contact					Direct contact					Indirect contact					Direct contact				
			No	Min	wages	overheads	capital	No	Min	wages	overheads	capital	No	Min	wages	overheads	capital	No	Min	wages	overheads	capital
Doctor (Modernising Medical Careers)																						
Foundation House Officer 1																						
Foundation House Officer 2																						
Specialty Registrar (StR)																						
Clinical Practitioner																						
Consultant								**1**	**15**	£22.5	£4.5	£0.8						**1**	**15**	£22.5	£4.5	£0.8
Nurse (Agenda for Change)																						
Band 1																						
Band 2	A	Clinical support worker						**1**	**30**	£5.1	£0.9	£0.5										
Band 3	B																					
Band 4	C																					
Band 5	D	24-hour ward nurse	**2**	**5**	£3.2	£0.3	£0.2						**1**	**5**	£1.6	£0.15	£0.1					
Band 5	D	Day ward nurse																				
Band 6	E	Nurse team leader	**1**	**10**	£3.9	£0.3	£0.3	**1**	**5**	£2	£0.15	£0.1	**1**	**10**	£3.9	£0.3	£0.3					
Band 7	F,G	Nurse team manager																				
Band 8	H, I																					
Band 9	H, I																					
Pharmacist																						
Pharmacist			**1**	**10**	£4.1	£0.3	£0.5						**1**	**10**	£4.1	£0.3	£0.5					

The staff working time survey results (continued)

			Transfusion										Venesection									
			In-patient period										Out-patient period									
			Indirect contact					Direct contact					Indirect contact					Direct contact				
			No	Min	wages	overheads	capital	No	Min	wages	overheads	capital	No	Min	wages	overheads	capital	No	Min	wages	overheads	capital
Doctor (Modernising Medical Careers)																						
Foundation House Officer 1																						
Foundation House Officer 2																						
Specialty Registrar (StR)								**1**	**15**	£15.9	£0.5	£0.5										
Clinical Practitioner																						
Consultant																		**1**	**15**	£22.5	£4.5	£0.8
Nurse (Agenda for Change)																						
Band 1																						
Band 2	A	Clinical support worker						**1**	**60**	£10.2	£1.8	£0.9						**1**	**60**	£10.2	£1.8	£0.9
Band 3	B																					
Band 4	C																					
Band 5	D	24-hour ward nurse	**2**	**5**	£3.2	£0.3	£0.2	**1**	**10**	£3.2	£0.3	£0.2						**1**	**10**	£3.2	£0.3	£0.2
Band 5	D	Day ward nurse																				
Band 6	E	Nurse team leader	**1**	**10**	£3.9	£0.3	£0.3	**1**	**5**	£2	£0.15	£0.1	**1**	**10**	£3.9	£0.3	£0.3	**1**	**5**	£2	£0.15	£0.1
Band 7	F,G	Nurse team manager																				
Band 8	H, I																					
Band 9	H, I																					
Pharmacist																						
Pharmacist			**1**	**10**	£4.1	£0.3	£0.5															

The staff working time survey results (continued)

			Erythropoietin										Immunosuppresive therapy									
			Out-patient period										Out-patient period									
			Indirect contact					Direct contact					Indirect contact					Direct contact				
			No	Min	wages	overheads	capital	No	Min	wages	overheads	capital	No	Min	wages	overheads	capital	No	Min	wages	overheads	capital
Doctor (Modernising Medical Careers)																						
Foundation House Officer 1																						
Foundation House Officer 2																						
Specialty Registrar (StR)																						
Clinical Practitioner																						
Consultant								**1**	**15**	£22.5	£4.5	£0.8						**1**	**15**	£22.5	£4.5	£0.8
Nurse (Agenda for Change)																						
Band 1																						
Band 2	A	Clinical support worker						**1**	**10**	£1.7	£0.3	£0.2										
Band 3	B																					
Band 4	C																					
Band 5	D	24-hour ward nurse	**2**	**5**	£3.2	£0.3	£0.2						**1**	**5**	£1.6	£0.15	£0.1					
Band 5	D	Day ward nurse																				
Band 6	E	Nurse team leader	**1**	**10**	£3.9	£0.3	£0.3	**1**	**5**	£2	£0.15	£0.1	**1**	**10**	£3.9	£0.3	£0.3					
Band 7	F,G	Nurse team manager																				
Band 8	H, I																					
Band 9	H, I																					
Pharmacist																						
Pharmacist			**1**	**10**	£4.1	£0.3	£0.5						**1**	**10**	£4.1	£0.3	£0.5					

The staff working time survey results (continued)

			Sampling for blood										Sampling for bone marrow									
			Out-patient period										Out-patient period									
			Indirect contact					Direct contact					Indirect contact					Direct contact				
			No	Min	wages	overheads	capital	No	Min	wages	overheads	capital	No	Min	wages	overheads	capital	No	Min	wages	overheads	capital
Doctor (Modernising Medical Careers)																						
Foundation House Officer 1																						
Foundation House Officer 2																						
Specialty Registrar (StR)																						
Clinical Practitioner																						
Consultant								**1**	**5**	£7.5	£1.5	£0.2						**1**	**30**	£45	£9	£1.6
Nurse (Agenda for Change)																						
Band 1																						
Band 2	A	Clinical support worker																				
Band 3	B																					
Band 4	C																					
Band 5	D	24-hour ward nurse	**1**	**5**	£3.2	£0.3	£0.2						**1**	**30**	£19.2	£1.8	£0.9					
Band 5	D	Day ward nurse																				
Band 6	E	Nurse team leader																				
Band 7	F,G	Nurse team manager																				
Band 8	H, I																					
Band 9	H, I																					
Pharmacist																						
Pharmacist																						

The staff working time survey results (continued)

			Follow-up / observation / outpatient visits										Anti-biotic									
			Out-patient period										In-patient period									
			Indirect contact					Direct contact					Indirect contact					Direct contact				
			No	Min	wages	overheads	capital	No	Min	wages	overheads	capital	No	Min	wages	overheads	capital	No	Min	wages	overheads	capital
Doctor (Modernising Medical Careers)																						
Foundation House Officer 1																						
Foundation House Officer 2																						
Specialty Registrar (StR)													**1**	**5**	£5.3	£0.2	£0.2					
Clinical Practitioner																						
Consultant								**1**	**15**	£22.5	£4.5	£0.8										
Nurse (Agenda for Change)																						
Band 1																						
Band 2	A	Clinical support worker						**1**	**5**	£1.6	£0.15	£0.1	**1**	**10**	£1.7	£0.3	£0.2					
Band 3	B																					
Band 4	C																					
Band 5	D	24-hour ward nurse											**2**	**5**	£3.2	£0.3	£0.2					
Band 5	D	Day ward nurse																				
Band 6	E	Nurse team leader						**1**	**10**	£3.9	£0.3	£0.3	**1**	**5**	£1.8	£0.2	£0.2					
Band 7	F,G	Nurse team manager																				
Band 8	H, I																					
Band 9	H, I																					
Pharmacist																						
Pharmacist													**1**	**10**	£4.1	£0.3	£0.5					

Appendix 6.3 The literature review for complication rate of each treatment and regimen

ADE													
		Heil 1995 [217]	Bishop 1996 [218]	Lee 1999 [219]	Heil 1995 [217]	Hann 1997 [220]	Heil 1997 [221]	Heil 1997 [221]	Heil 1997 [221]	Heil 1997 [221]	Heil 1997 [221]	Bishop 1996 [218]	
Number of Patient		30	152	41	39	770	262	67	157	58	26	149	
Age		15-75 yr	15-60 yr	≥ 60 yr	15-75 yr	All age	≥ 16 yr	≥ 16 yr	≥ 16 yr	≥ 16 yr	≥ 16 yr	15-60 yr	
Randomised trial		Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
Controlled trail		Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	
Phrase		-	In	In	-	In	In 1	In 2	Con 1	Con 2	Con 2	In	
Regimens													
AraC	mg/m2	100	100	100	100	100	200	200	200	200	3000	3000	
	Days (dose)	7	7	7	8	10	7	5	5	5	6	4 (8)	
Daunorubicin	mg/m2	45	50	30	60	50	45	45	45	45	30	50	
	Days	2	3	3	3	3	3	2	2	2	2	3	
Etoposide	mg/m2	100	75	100	100	100	100	100	100	100	-	75	
	Days	5	7	3	5	5	5	5	5	5		7	
Complications													
Fever							241	50	99	33	24		78%
Severe		5			2								10%
Infection			96				252	47	85	30	24	128	76%
Severe		2			2	46							6%
Pneumonia													
Severe		2			2								6%
Pain													
Severe		-			1								3%
Nausea / vomiting									144			137	91.8%
Severe (grade 3-4)		0.5			1				49			79	34.5%
Diarrhea									25			34	19.3%
Severe (grade 3-4)		-			1				13			25	11.3%
Severe Stomatitis										4			7%
Severe Cardiac disorder (failure)		0.5			2	8							1.3%
Severe Hepatic disorder		3			4								10.1%
Sever Bilirubin										16			27%
Cerebellum disorder									6	10		10	10.8%
Severe (grade 3-4)							0					3	0.7%
Neurologic disorder								15					22%

The literature review for complication rate (continued)

		AraC (LD)				AraC (HD)					
		Winer 2005 [222]	Burnett 2007 [223]	Stone 2001 [224]		Bassan 1998 [225]	Ossenkoppele 2004 [226]	Curtis 1987 [227]	Mayer 1994 [228]	Estey H 1990 [229]	
Number of Patient		94	103	82		24	69	43	187	53	
Age		≥ 18	> 60	≥ 60		15-60	≥ 45	All age	≥ 16	≥ 18	
Randomised trial		No	Yes	Yes		No	Yes	No	Yes	No	
Controlled trail		No	No	Yes		No	Yes	No	No	No	
Phrase		In	In	Con		Con	-	Con	con	In	
Regimens											
AraC	mg/m2	20	20	100		1000	2000	3000	3000	6000	
	Day (doses)	7	10 (20)	5		6	5	6 (12)	3 (6)	4	
Hydroxyurea	mg/m2	500									
	Day	15									
GM-CSF	Dose	250 µg/m2					5 µg/kg				
	Day	7									
Complications											
Fever		54			57%						
Severe (grade 3-4)											
Infection			46	80	68.1%	14					58%
Severe (grade 3-4)		7		6	7%		40	9		17	40%
Pneumonia / sepsis						2				37	50.6%
Severe (grade 3-4)											
Diarrhea				80	98%						
Severe (grade 3-4)			6	8	7.6%						
Nausea / vomiting											
Severe (grade 3-4)			8								
Malaise				80	98%						
Severe (grade 3-4)				1	1%						
Severe mucositis			8		8%						
Severe alopecia			8		8%						
Serious CNS toxicity									41		22%
Severe neurotoxicity							2				3%
Severe cerebellar toxcitity								2			5%
Respiratory insufficiency		7			7%						
Severe liver disorder							11				16%
Severe cardiac disorder			14		14%		11				16%
Renal disorder		8	5		6.6%			3			7%

The literature review for complication rate (continued)

		DA (Part 1)												
		Atallah 2007 [230]	Dillman 1991 [231]	Takemoto 1999 [232]	Rai 1981 [233]	Rai 1981 [233]	Vogler 1992 [234] 2006 [235]	Dillman 1991 [231]	Rai 1981 [233]	Mitus 1995 [236]	Rai 1981 [233]	Stone 1994 [237]	Rowe 1995 [238] 2008 [239]	
Number of Patient		149	50	26	79	177	60	110	62	94	43	177	47	
Age		All	≥ 60	15-60	< 60	≥ 60	≥ 14	15-60	< 60	≤ 65	≥ 60	≥ 60	55-70	
Randomised trial		No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	
Controlled trail		No	No	No	No	No	No	No	No	No	No	Yes	Yes	
Phrase		In	In	In	In	In	In	In	In	In	In	In	In	
Regimens														
AraC	mg/m2	-	100	100	100	100	100	100	100	100	100	100	100	
	Day (dose)	-	7	7	5	5	7	7	7	7	7	5 (10)	7	
Daunorubicin	mg/m2	-	35	40	45	45	45	45	45	45	45	50	60	
	Day		3	3	2	2	3	3	3	3	3	1	3	
Complications														
Fever				19			17			93			35	72.2%
Severe (grade 3-4)		36		7										24.6%
Infection				16	32	76	58		41		23		32	56.3%
Severe (grade 3-4)		107	10	3				6				32	33	34.2%
Fungal infection										12				13%
Pneumonia														
Severe (grade 3-4)													13	28%
Malaise				2										7%
Severe (grade 3-4)														
Weight gain													10	21%
Weight loss													13	28%
Mucositis							33			37		21		27.5%
Severe (grade 3-4)							5					4		3.8%
Bacteremia										27				29%
Headache							14							24%
Pain				7										25%
Digestive system														
Nausea / vomiting				21			48					94	26	61%
Severe (grade 3-4)				4			2					0		2.3%
Diarrhea				10			41					35	25	35.8%
Severe (grade 3-4)				1			8					4		4.9%
Stomatitis				10									20	41%
Severe (grade 3-4)														

Anorexia			20										75%
Severe (grade 3-4)			6										21%
Skin and appendages													
Alopecia			21			43					122	24	67.7%
Severe (grade 3-4)			6			16					50		27.4%
Rash						24					30		22.8%
Severe (grade 3-4)						1					0		0.4%
Metabolic disorder													
Edema												11	23%
Respiratory system													
Pulmonary						23						10	30.8%
Dyspnea													
Severe (grade 3-4)													
Cardiovascular system													
Hypertension												15	32%
Hypotension												12	26%
Severe (grade 3-4)													
Cardiac disorder				0	2	14		3		0.9	7		4.5%
Severe (grade 3-4)	3					13					7		8.4%
Severe heart failure			1										4%
Renal disorder													
Dialysis													
Severe (grade 3-4)	19												13%
Renal disorder				4	4			6		4			5%
Severe (grade 3-4)	6												4%
Hepatic disorder													
Hepatic disorder				4	4			2		0		39	12%
Severe (grade 3-4)	40	1					-						20.6%
Bilirubinemia			9										36%
Severe (grade 3-4)			0						9				7.5%
Creatinine						15					9		10.1%
Severe (grade 3-4)						0.6					0		0.3%
Neurologic disorder													
Neurologic disorder						5							9%
Severe (grade 3-4)													
Cerebellar dysfunction						2			5				4.5%
CNS toxicity													
Severe (grade 3-4)		1					6						4.4%

The literature review for complication rate (continued)

		DA (part 2)													
		Weick 1996 [240]	Dillman 1991 [231]	Lowenberg 1997 [241]	Usui 2002 [242]	Zittoun 1996 [243]	Dillman 1991 [231]	Rubin 1992 [244]	Weick 1992 [245]	Weick 1996 [240]	Godwin 1998 [246]	Anderson 2002 [247]	Stone 1995 [248]	Dombret 1995 [249]	
Number of Patient		66	50	161	22	26	116	176	168	490	104	161	195	85	
Age		≤ 65	≥ 60	≥ 61	15-60	15-45	15-60	≥ 18	≤ 64	≤ 65	≥ 56	≥ 56	≥ 60	≥ 65	
Randomised trial		No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	
Controlled trail		No	No	Yes	No	Yes	No	No	No	No	Yes	No	Yes	Yes	
Phrase		Con	In	In	In	In	In	In	In	In	In	In	In	In	
Regimens															
AraC	mg/m2	200	200	200	200	200	200	200	200	200	200	200	299	200	
	Day (dose)	7	7	7	7	7	7	7	7	7	7	7	7	7	
Daunorubicin	mg/m2	30	30	30	40	45	45	45	45	45	45	45	45	45	
	Day	3	3	3	7	3	3	3	3	3	3	3	3	4	
Complications															
Fever				114											71%
Severe (grade 3-4)														9	11%
Infection				124		19					67		125		68.9%
Severe (grade 3-4)			10		22		10			49	15	24	35	41	16.8%
Fungal infection															
Pneumonia											25				24%
Severe (grade 3-4)														14	16%
Malaise															
Severe (grade 3-4)													31		16%
Weight gain (≥ 5kg)						2									8%
Weight loss															
Mucositis				39	6										24.6%
Severe (grade 3-4)					1					20					
Bacteremia															
Headache						0									0%
Pain				10							5				5.7%
Digestive system															
Nausea / vomiting				56	18										40.4%
Severe (grade 3-4)					0					15					2.9%
Diarrhea				66	13										43.2%
Severe (grade 3-4)				29	2										9%
Stomatitis															41%
Severe (grade 3-4)												6			10.9%

Anorexia														
Severe (grade 3-4)														
Skin and appendages														
Alopecia														
Severe (grade 3-4)														
Rash														
Severe (grade 3-4)				10										45%
Metabolic disorder														
Edema			90		6									23%
Respiratory system														
Pulmonary														56%
Dyspnea														
Severe (grade 3-4)												35		18%
Cardiovascular system														
Hypertension														
Hypotension			21		1									11.8%
Severe (grade 3-4)												14		7%
Cardiac disorder			35		0									18.7%
Severe (grade 3-4)				1								27		12.9%
Dysrhythmia												27		14%
Severe heart failure														
Renal disorder			39											
Dialysis			5											24%
Severe (grade 3-4)														3%
Renal disorder														
Severe (grade 3-4)														
Hepatic disorder			68											
Hepatic disorder		5	18											42%
Severe (grade 3-4)						-			29					7.4%
Bilirubinemia														
Severe (grade 3-4)												31		16%
Neurologic disorder	11		18											
Neurologic disorder	6						18	7						10.4%
Severe (grade 3-4)									5					2%
Cerebellar dysfunction														
CNS toxicity		3												
Severe (grade 3-4)						5								4.8%

The literature review for complication rate (continued)

		HAM					MidAC		
		Lofgren 2004 [250]	Solary 1995 [251]	Kern 1998 [252]	Buchner 1991 [253]		Buchner 1999 [254]	Buchner 1999 [254]	
Number of Patient		55	154	91	56		365	212	
Age		≥ 60	14-66	≥ 17	≥ 65		16-60	16-60	
Randomised trial		Yes	Yes	No	No		Yes	Yes	
Controlled trail		No	Yes	Yes	Yes		No	No	
Regimen									
Phrase		-	Both	In	Both		In	Con	
AraC	mg/m2	1000	1000	1000 or 3000	1000 or 3000		3000	3000	
	Day (dose)	3 (6)	5 (10)	4 (8)	4 (8)		3 (6)	3 (6)	
Mitoxantrone	mg/m2	12	12	10	10		10	10	
	Days	3	4	4	4		3	3	
Etoposide	mg/m2	200							
	Days	3							
Complications									
Fever					55	98%			
Severe (grade 3-4)					21	38%			
Infection				91	47	93.9%			
Severe (grade 3-4)				44		48%	146	23	29.2%
Pneumonia / sepsis					24	43%			
Mucositis			48	36		34.3%			
Severe (grade 3-4)			15	8		9.4%			
Weight gain					5	9%			
Digestive system									
Nausea / vomiting			83	61		58.8%			
Severe (grade 3-4)			17	17		13.9%	80	19	17.2%
Diarrhea			79	45		50.6%			
Severe (grade 3-4)			25	14		15.9%	37	8	7.8%
Severe Stomatitis							33	6	6.8%
Metabolic disorder									
Edema					7	13%			
Renal disorder									
Renal disorder		9	14			11%			
Severe (grade 3-4)			0			0%			
Hepatic disorder									
Liver disorder		15	51			31.6%			
Severe (grade 3-4)			12			8%			
Bilirubinemia				35	36	48.3%			

Severe (grade 3-4)			4	22	17.7%			
Creatinine			17		19%			
Severe (grade 3-4)			4		4%			
Cardiovascular system								
Cardiac disorder		2		24	12.4%			
Severe (grade 3-4)		2			1%	22	2	4.2%
Heart failure	6				11%			
Neurocortical disorder								
Nurocortical disorder				15	26%			
Severe (grade 3-4)				12	21%			
CNS toxicity			10		11%			
Severe (grade 3-4)			6		7%	7	2	1.6%

The literature review for complication rate (continued)

		FA			FLAG								FLAG-Ida				
		Estey 1994 [255]	Atallah 2007 [230]		Marcucci 2003 [256]	Ossenkoppele 2004 [226]	Huhmann 1996 [257]	Estey 1994 [255]	Visani 1994 [258]	Clavio 1996 [259]	Montillo 1998 [260]		Russo 2005 [261]	Yavuz 2006 [262]	Pastore 2003 [263]	Martin 2009 [264]	
Number of Patient		85	278		20	65	22	112	28	51	38		57	56	46	23	
Age		All	≥ 15		≥ 18	45-75	18-65	All age	17-75	≥ 18	11-70		18-60	-	15-60	18-70	
Randomised trial					No	Yes	No	No	No	No	No		Yes	No	No	No	
Controlled trail					No	Yes	No	Yes	No	No	No		No	No	No	Yes	
Phrase		In	-		-	-	-	In	-	-	-		In	-	Con	-	
Regimen																	
AraC (HD)	mg/m2	2	-		1to2	2	2	2	2	2	2		2	2	2	-	
	Day (dose)	5	-		5	5	5	5	5	5	5		5	5	5	-	
Fludarabine	mg/m2	30			15to30	25	25	30	30	30	30		25	25	30	-	
	Day	5			5	5	5	5	5	5	5		5	5	5		
Idarubicin	mg/m2	-	-					-					10	12	10	-	
	Day	-	-					-					3	3	3		
G-CSF		-	-		5 μg/kg	5 μg/kg	400 μg/m2	-	5mg/kg	300 μg/day	5 μg/kg		-	-	5 μg/kg	-	
Complications																	
Fever							22			16		52%	56		27		80.5%
Severe (grade 3-4)			92	33%			0				17	28%			13		28%
Infection		74		87%			20	102				91%	56		19		72.8%
Severe (grade 3-4)		27	153	49.6%		44	5	25			17	38%			14	2	23%
Pneumonia / sepsis										10		20%		15	13		28%
Mucositis					50%		55%										
Mild (<grade 2)													55		46		98%
Severe (grade 3-4)							0				4	7%			30		65%
Headache					65%							65%					
Severe (grade 3-4)					15%							15%					
Pain					2		15					40%					
Severe (grade 3-4)							14%					14%					
Digestive system																	
Nausea / vomiting					13		14					64%					
Mild (< grade 2)													53		10		61%
Severe (grade 3-4)							32%					32%	3		8		10.7%
Diarrhea					16		8					57%					
Severe (grade 3-4)							2				3	8%	5%				5%

GI disorder					14%						14%					
Skin and appendages																
Rash				30%							30%					
Severe (grade 3-4)				0%							0%					
Skin disorder														17%		17%
Metabolic disorder																
Edema				75%							75%					
Severe (grade 3-4)				1%							1%					
Respiratory system																
Dyspnea				65%							65%					
Severe (grade 3-4)				50%							50%					
Lung disorder																
Renal disorder																
Renal disorder						41%					41%					
Severe (grade 3-4)		11	4%			0%					0%					
Hepatic disorder																
Liver disorder																
Severe (grade 3-4)		61	22%		10					3	12.6%					
Bilirubinemia				8		9					40%			26%		26%
Severe (grade 3-4)				4		1					12%				22%	22%
creatinine				4		6					23.8%			4%		4%
Severe (grade 3-4)				0%		0%					0%					
Acute renal failure									1%		1%					
Cardiovascular system																
Cardiac disorder									8%		8%			4%		4%
Severe (grade 3-4)		3	1%		16%						16%					
Hypertension				2							10%					
Hypotension				4							20%					
Neurocortical disorder																
Nurocortical disorder						9			3		16%					
Severe (grade 3-4)					9	0%		1		1	7%					

The literature review for complication rate (continued)

	Mylotarg					Clofarabine			MACE			Hydroxyurea			Amsacrine	
	Bross 2001 [265]	Bross 2001 [265]	Bross 2001 [265]	Martin 2009 [264]		Faderl 2008 [266]	Kantarjian 2003 [267]		Cassileth 1992 [268]	Sung 2005 [269]		Burnett 2007 [223]	Harousseau 2009 [270]		Lovie 1985 [271]	
Phase	2	2	1							2			3			
Number of Patient	142	80	41	48		16	62		99	51		99	229			
Age	≥ 18	≥ 60	16-70	18-70		≥ 60	≥ 15		15-65	15-65		> 60	≥ 70			
Randomised trial	No	No	No	No		Yes	No		Yes	No		Yes	Yes			
Controlled trail	No	No	No	Yes		No	No		No	No		No	Yes			
Phrase	Con	Con	-			In	In		Con	-		In				
Regimen				FLAG-Ida		30 mg/m2 for 5 days	40 mg/m2 for 5 days									
AraC mg/m2									3	1						
Day (dose)									6 (12)	3 (6)						
amsacrine mg/m2									100	100						
Day									3	3						
Etoposide mg/m2										100						
Day										5						
Complications																
Fever			44%		44%	4	19	30%								
Severe (grade 3-4)	10	4			6.3%											
Infection							50%	50%								
Severe (grade 3-4)	40			9	26%				22%		22%	21%		21%	50%	50%
Pneumonia / sepsis						6	16	28%								
Severe (grade 3-4)	23	13			16%								19%	19%	20%	20%
Mucositis						3	9	15%							32,40,46,80%	
Severe (grade 3-4)	4%				4%	6%		6%				3%		3%		
Malaise															80%	80%
Headache						38%		38%		10%	10%					
Pain			4		10%											
Hemorrage	15%				15%				5	4	6%	3%		3%	13%	13%
Severe (grade 3-4)																
Digestive system																
Nausea / vomiting			13		32%	13	42	71%		82%	82%				30%	30%
Severe (grade 3-4)	11%				11%	0	2	2.5%		29%	29%	8%		8%		
Diarrhea						12	13	32%		26%	26%				3-17%	
Severe (grade 3-4)						0%		0%				20%		20%		

Anorexia						19%		19%							29%	29%
GI disorder																
Severe (grade 3-4)									4%		4%		9%	9%		
Skin and appendages																
Alopecia															4-20%	
Severe (grade 3-4)												5%		5%		
Rash			12%		12%	9	29	49%		24%	24%					
Severe (grade 3-4)						2	6	10%								
Metabolic disorder													10%	10%		
Edema						38%		38%								
Respiratory system																
Dyspnea																
Severe (grade 3-4)	13	10			10%											
Renal disorder																
Renal disorder															1-5%	
Severe (grade 3-4)												3%		3%		
Hepatic disorder																
Liver disorder															30-35%	
Severe (grade 3-4)									17%		1%					
Bilirubinemia						10	31	53%								
Severe (grade 3-4)	33	18		6	21%	6	9	19%								
Creatinine						32%		32%								
Severe (grade 3-4)	1	0			0.5%	13%		13%								
Cardiovascular system																
Cardiac disorder																
Severe (grade 3-4)												16%	14%	15%		
Hypertension																
Severe (grade 3-4)	13	9			10%											
Hypotension																
Severe (grade 3-4)	11	6			7.7%											
Neurocortical disorder																
CNS toxicity															1-5%	
Severe (grade 3-4)	6				4%					2%	2%					
Cerebellar toxicity																
Severe (grade 3-4)									12%		12%					

The literature review for complication rate (continued)

	G-CSF													
	Heil 1997 [221]	Heil 1997 [221]	Heil 1997 [221]	Heil 1997 [221]	Heil 1997 [221]	Godwin 1998 [246]	Dombret 1995 [249]	Ohno 1994 [272]	Ohno 1990 [273]	Kern 1998 [252]	Amadori 2005 [274]	Amadori 2005 [274]	Amadori 2005 [274]	
Patient	AML	AML	AML	AML	AML	AML	AML	AML	AML	AML	AML	AML	AML	
Number of Patient	262	67	157	58	26	104	88	28	48	68	172	173	177	
Age	≥ 16	≥ 16	≥ 16	≥ 16	≥ 16	≥ 56	≥ 65	15-65	13-70	≥ 17	≥ 61 yr	≥ 61	≥ 61	
Randomised trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	
Controlled trail	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
Phrase	In 1	In 2	Con 1	Con 2	Con 2	In	In	In	In	In	In	In	In	
Conjunction treatment	ADE	ADE	ADE	ADE	DA (HD)	DA	DA (after)	HAM (during)	HAM	HAM	HAM (during)	HAM (after)	HAM (during & after)	
Complications														
Fever	238	54	77	27	25			26	41					76%
Severe (grade 3-4)						20	10				40	54	44	24%
Infection	249	52	69	21	23			14	5	65				70%
Severe (grade 3-4)							42			29				46%
Fungal infection						20%								20%
Pneumonia / sepsis						33		3						27%
Severe (grade 3-4)							11		1					8.8%
Mucositis									5	33				33%
Severe (grade 3-4)										15%				15%
Pain						1%								1%
Severe (grade 3-4)											0%	2	2	0.8%
Digestive system														
Nausea / vomiting										36				53%
Severe (grade 3-4)										21	40	29	28	20%
Diarrhea										24				35%
Severe (grade 3-4)										11	3	9	7	5%
Stomatitis								14%						14%
Skin and appendages														
Severe Rash											3	7	7	3.3%
Hepatic disorder														
Liver disorder								4%						4%

Severe (grade 3-4)											14	21	21	11%
Bilirubinemia										27%				27%
Severe (grade 3-4)										6%				6%
creatinine										12%				12%
Cardiovascular system														
Cardiac disorder														
Severe (grade 3-4)											10	16	19	8.6%
Hypotension														
Severe (grade 3-4)											2	9	7	3.4%
Neurocortical disorder														
CNS toxicity										4%				4%
Severe (grade 3-4)										3%				3%

The literature review for complication rate (continued)

	ATRA									MRC approach							
	Shen et.al 2004 [275]	Tallman et.al. 1997 [276]		Medeiros et al 1998 [277]	Mandelli et al 1997 [278]	Tallmanet al 2000 [279]	Castaigne et al 1990 [280]	Kanamaru et al. 1995 [281]		Botton et al 1998 [282]	Jacomo et al 2007 [283]	Fenaux et al 1993 [284]	Fenaux et al 1999 [285]	Ades et al 2005 [286]		Bahar et al 2004 [287]	
Number of Patient	20	172	94	37	240	167	22	109		413	114	54	208	129	404	24	
Age	17-74	1-81	1-81	9-69	2-74	1-81	19-68	15-74		≤65 yr	5-79	6-63	2-64	≧ 60	18-60	17-55	
Randomised trial	Yes	Yes	Yes	No	Yes	Yes	No	No		Yes	No	Yes	Yes	No	No	No	
Controlled trail	Yes	Yes	Yes	No	Yes	Yes	No	No		Yes	No	Yes	Yes	No	No	No	
Phrase	Con	In	M	In	In	In	In	In		In	Con	In	In	In	In	In	
Regimen																	
Dosage (mg/m2)	45	45	45	45	45	45	45	45									
Complications																	
Retinoic Acid Syndrome		45	34			44		7	24%	64			33	16	60	2	15%
Fever				10					27%								
Severe infection		43	7						19%		4	3					4%
Headache	4		5		31			23	14%			16					30%
Severe												1					2%
Severe Pain					14		11	2	7%								
Dryness of mouth	11			28					68%								
Degestive system																	
Severe Nausea / vomiting		11							6%								
Severe Diarrhea		6							3%								
Severe Stomatitis		12							7%								
Skin and appendages	4								20%								
Skin dryness					70				29%			26					48%
Sever skin disorder		5							3%								
Respiratory system																	
Severe Dyspnea								4	4%								
Severe lung disorder		36							21%								
Hepatic disorder																	
Liver dysfunction												46					85%

Severe	1	34	5	1			13%		
Cardiovascular system									
Severe hypertension					17		7%		
Severe cardiac disorder		19					11%		
Nervous system (Severe)		16	11		5		6%		

The literature review for complication rate (continued)

	Spanish approach								
	Miguel et al [288]	Jacomo et al [283]	Mandelli et al [278]	Avvisati et al 1996 [289]	Montesinos et al 2009 [290]	Mandelli et al 2003 [141]	Girmenia et al 2003 [291]	Serna et al 2008 [292]	
Number of Patient	103	157	240	20	739	134	89	732	
Age	1-74	5-79	2-74	≦ 70	2-83	60-75	1-77	2-83	
Randomised trial	No	No	Yes	No	No	No	No	Yes	
Controlled trail	No	No	Yes	No	No	No	No	Yes	
Phrase	Con	In	In	In	In	In	In	In	
Complications									
Retinoic Acid Syndrome	7	4		2	183	5		10	18%
Fever				17					85%
Severe infection		2		6		2	19	17	3%
Severe Mucositis	15						22		19%
Severe headache				2					10%
Pain				2					10%
Skin dryness				3					30%
Degestive system									
Severe Nausea / vomiting			12						5%
Severe Diarrhea	2		5						2%
Severe stomatitis			14						6%
Skin and appendages									
Severe skin disorder	2								2%
Metabolic disorder									
Severe Edema					75				10%
Respiratory system									
Severe Lung disorder	17								17%
Hepatic disorder									
Severe liver disorder	5		7						3%
Cardiovascular system									
Hypotension				1					5%
Severe cardiac disorder	6		6						3%
Urogenital sysem									
Severe renal disorder	1		1						0.6%
Nervous system									
Severe	2								2%

Appendix 6.4 The unit cost list of complications

	Adverse event	ICD-10	HRG 4.0	No of cases	Lower quartile	× 70%	
Cardiovascular (Arrhythmia)	dysrhythmias (Nodal, junctional arrhythmia)	I49	EB07I	4567	£448	£314	
	Atrioventricular heart block (type I / II)	I44.0-I44.3	EB07I	4567	£448	£314	
	Sinus bradycardia	R00.1	EB07I	4567	£448	£314	
	Sinus tachycardia	R00.0	EB07I	4567	£448	£314	
	Supraventricular tachycardia (SVT)	I47.1	EB07I	4567	£448	£314	
	Atrial fibrillation (flutter)	I48	EB07I	4567	£448	£314	
	Ventricular tachycardia	I47.2	EB07I	4567	£448	£314	
	Premature ventricular contraction (PVC)	I49.3	EB07I	4567	£448	£314	
					£448	£314	
Cardiovascular (general)	Hypertension	I11	EB04I	303	£521	£365	
	Hypotension	I95.2 / I95.8	EB01Z	5396	£508	£356	
	Acute myocardial infarction	I21	EB10Z	5999	£758	£531	
	Myocardial ischaemia	I24.x, I25.6	EB10Z	5999	£758	£531	
	Myocarditis	I40, I41, I51.4	EB01Z	5396	£508	£356	
	Pericarditis (pericardial effusion)	I30,I31,I32	EB01Z	5396	£508	£356	
	Phlebitis	I80	EB11Z	685	£424	£297	
	Thrombosis / embolism	I80, I82	EB11Z	685	£424	£297	
	Congestive heart failure (CHF)	I50.0	EB03I	904	£916	£641	
	Left ventricular function decrease	I50.1	EB03I	904	£916	£641	
	Peripheral artery occlusive disease	I73.9	QZ17C	4322	£447	£313	
	Peripheral arterial ischemia	I73.9	QZ17C	4322	£447	£313	
					£520	£364	
Oedema	Oedema, not elsewhere classified	R60	WA18Y	299	£403	£282	
	Cerebral oedema	G93.6	AA25Z	2684	£649	£454	
	Gestational oedema	O12.0	NZ04A	629	£336	£235	
			NZ07A	382	£500	£350	
	Pulmonary oedema	J81	DZ20Z	76	£815	£571	
	Pulmonary oedema due to heart disease	I50.1	EB03I	904	£916	£641	
					£634	£444	
Dermatology / skin	Alopecia	L65.8	JD04C	670	£429	£300	
		L65.9	JD06B	1217	£349	£244	£264
	Rash	R21.x	JD05C	834	£359	£251	
	Flushing	R23.2	WA18Y	299	£403	£282	
	Desquamation	R23.4	JD05C	834	£359	£251	
	Pruritus	L29.8	JD04C	670	£429	£300	
		L29.3, L29.9	JD06B	1217	£349	£244	
		L29.1	LB35B	1340	£352	£246	
		L29.2	MB01Z	412	£379	£265	£257
	Urticaria	L50.8	JD04C	670	£429	£300	
		L50.0	JD05C	834	£359	£251	£273
	Stevens-Johnson syndrome	L51.1	JD03C	654	£498	£349	
	Toxic epidermal necrolysis	L51.2	JD03C	654	£498	£349	
	Vesicular / macular / papular erythema (eruption)	L53.0	JD03C	654	£498	£349	
	Nail disease	L60.1	JD04C	670	£429	£300	
		L60.3	JD05C	834	£359	£251	
		L60.4	JD06B	1217	£349	£244	£260
	Pigmentation change	L80.x	JD05C	834	£359	£251	
					£389	£272	
Gastrointestinal disorder	Anorexia	R63.0	KC03C	983	£174	£122	
	Diarrhea	A09.x	FC06C	161	£195	£137	
		K59.2	FC04C	13526	£168	£130	£130

	Nausea / Vomiting	R11.x	FC02C	4891	£171	£120	
	Stomatitis	K12.2	CZ22Y	1048	£139	£97	
	Mucositis	L23.5	JD04C	670	£429	£300	
	Ascites	R18.x	FC05C	5545	£474	£332	
	Colitis	K50-K52	FC07C	2071	£568	£398	
	Constipation	K59.0	FC04C	13526	£168	£118	
	Dehydration	E86.x	KC02F	27	£308	£216	
	Gastric and duodenal ulcer	K25.0,2,4,6	FC08C	303	£352	£247	
		K25.1,3,5,7,9	FC02C	4891	£543	£380	
		K26.1,3,5,7,9	FC02C	4891	£543	£380	
		K26.0,2,4,6	FC08C	303	£352	£246	
		K27.0,2,4,6	FC08C	303	£352	£246	
		K27.3,5,7,9	FC02C	4891	£543	£380	
		K27.1	FC05C	5545	£474	£332	£362
	Dyspepsia, dysphagia	R13.x	FC01C	6232	£557	£390	
	Heartburn	R12.x	FC01C	6232	£557	£390	
	Fistula-intestinal	K63.2	FC05C	5545	£474	£332	
	Fistula-anal	K60.3	FC11C	3226	£532	£372	
	Fistula-rectal	K60.4	FC04C	13526	£562	£393	
	Flatulence	R14.x	FC02C	4891	£543	£380	
	Gastritis	K29.x	FC02C	4891	£543	£380	
	Taste disturbance	R43.8	AA26Z	4580	£525	£368	
	Smell disturbance	R43.8	AA26Z	4580	£525	£368	
	Pancreatitis	K85.x	GC02C	166	£409	£286	
	Atrophy of salivary gland	K11.0	CZ23Y	957	£508	£356	
	Ileus	K56.0, 3, 7	FC05C	5545	£474	£332	
	Fistula-esophageal or pharyngeal	K38.3	FC10Z	84	£359	£251	
	Procitis	K51.2	FC07C	2071	£568	£398	
					£429	£300	
Hepatic disorder	Bilirubinemia	E80.4, 80.6	GC07C	1761	£307	£215	
	Elevated alkaline phosphatase	R74.8	WA19Y	318	£311	£218	
	Elevation of levels of transaminase	R74.0	WA19Y	318	£311	£218	
	Liver failure	K72.9	GC02C	166	£409	£286	
	Decrease portal vein flow	K76.5,7	GC02C	166	£409	£286	
					£320	£224	
Pulmonary disorder	Dyspnoea	R06.8	DZ19C	1268	£395	£277	
	Cough	R05.x	DZ19C	1268	£395	£277	
	Hiccoughs	R06.6	DZ19C	1268	£395	£277	
	Apnea	R06.8	DZ19C	1268	£395	£277	
	Acute respiratory distress syndrome	J80.x	DZ27F	86	£461	£323	
	Pneumothorax	J93	DZ26B	121	£411	£288	
	Pulmonary fibrosis	J84.9	DZ25B	375	£590	£413	
	Pleural effusion	J90.x-J91.x	DZ16C	802	£616	£431	
	Laryngitis	J04.0	CZ22Y	1048	£437	£306	
	Stridor	R06.1	DZ19C	1268	£395	£277	
	Voice change	R49.8	CZ22Y	1048	£437	£306	
					£430	£301	
Renal / genitourinary disorder	Creatiniemia	R79.8	WA19Y	318	£311	£218	
	Renal failure	N17.x	LA07C	83	£296	£207	
		N18.x,N19.x	LA08B	965	£974	£682	£644
	Bladder spasms	N32.8	LB19B	1885	£361	£253	
	Hematuria	R31.x	LB38B	539	£376	£263	
	dialysis	X40.x	LC02A	1854429	£133	£93	
	Haemoglobinuria	R82.3	LB37B	393	£338	£237	
	Urinary incontinence	R32.x	LB16C	1054	£353	£247	
	Proteinuria	R80.x	LB37B	393	£338	£237	
	Polyuria / urinary frequency	R35.x	LB37B	393	£338	£237	

	Urinary retention	R33.x	LB16C	1054	£353	£247	
	Urinary electrolyte wasting	E72.0	KC04Z	1506	£355	£247	
	Urine color change	R82.9	LB37B	393	£338	£237	
					£134	£94	
Neurology-Sensory	Paresthesia (abnormal touch sensation)	R20.2	AA26Z	4580	£525	£176	
	Arachnoiditis	G03.9	AA22Z	2221	£710	£497	
	meningismus	R29.1	AA22Z	2221	£710	£497	
	Radiculitis	M54.1	HC22C	286	£438	£307	
					£476	£333	
Neurology-Motor	Paralysis	G81	AA25Z	2684	£649	£454	
		G82	HC25C	277	£701	£491	£458
	Extrapyramidal	G20-G26	AA25Z	2684	£649	£454	
	Involuntary movement	R25.x	AA25Z	2684	£649	£454	
	Torticollis	M43.6	HC26C	187	£379	£265	
					£644	£415	
Neurology-cortical	Confusion (disorientation)	R41.0	WA18Y	299	£403	£282	
	delusion	F22	WD22Z	8195	£199	£139	
	Somnolence	R40.0	AA25Z	2684	£649	£454	
	Stupor	R40.1	AA25Z	2684	£649	£454	
	Coma	R40.2	AA22Z	2221	£710	£497	
	dizziness	R42.x	AA26Z	4580	£525	£368	
	Hallucination	R44	WD22Z	8195	£199	£139	
	Restlessness	R45.1	WD22Z	8195	£199	£139	
	Seizure (convulsion)	G40-41, R56.8	AA26Z	4580	£525	£368	
					£357	£250	
Neurology-cerebellar	Ataxia	R27	AA26Z	4580	£525	£368	
	Locomotor ataxia	R26	AA26Z	4580	£525	£368	
	Dysdiadochokinesia (incoordination)	R27	AA26Z	4580	£525	£368	
	Dysmetria	R27	AA26Z	4580	£525	£368	
	Tremor	R25.1	AA25Z	2684	£649	£454	
	Slurred speech	R47.8	AA25Z	2684	£649	£454	
	Dysphasia or aphasia	R47.0	AA22Z	2221	£710	£497	
	Nystagmus	H55	BZ24C	2115	£341	£239	
	Cerebellar necrosis	I67.8	AA22Z	2221	£710	£497	
					£561	£393	
Neurology-hemarrhage	Transient ischemic attack	G45.9	AA29Z	157	£539	£377	
	Stroke (Cerebral vascular accident)	I61-I62	AA23Z	1249	£980	£686	
					£931	£652	
Neurology-Mood	anxiety	F40, F41	WD22Z	8195	£199	£139	
	Agitation	R45.1	WD22Z	8195	£199	£139	
	Depression	F32-F33	WD22Z	8195	£199	£139	
	Euphoria	F02.0	WD22Z	8195	£199	£139	
	Suicidal ideation	R45.8	WD22Z	8195	£199	£139	
					£199	£139	
Neurology-general	Syncope	R55.x	EB08I	445	£413	£289	
	Fatigue, malaise, asthemia	R53	WA18Y	299	£403	£282	
					£409	£286	
					£389	£272	
Local	Weight gain	R63.5	KC03C	983	£174	£122	
	Weight loss	R63.4	KC03C	983	£174	£122	
	swelling	R22	CZ22Y	1048	£437	£306	
Pain (R52)	Headache	R51, R43, R44	AA31Z	765	£231	£162	
	Bone pain	M89.8	HD24C	5876	£436	£305	
	Chest pain	M07.3, M07.4	HD23C	1403	£480	£336	
	Back pain	M54.5	HC24C	5876	£453	£317	
	Abdominal pain or cramping	R25.2	AA25Z	2684	£649	£454	
	Arthralgia (joint pain)	M25.5	HD26C	850	£351	£246	

	Arthritis	M00-M25	HD24C	5876	£436	£305	
			HD25C	65	£493	£345	
			HD26C	850	£351	£246	
		M01.x	HD23C	1403	£480	£336	£305
	Dysmenorrhea	N94.4-N94.6	MB03B	2583	£405	£264	
	Earache (otalgia)	H92.x	CZ21Y	3319	£368	£258	
	Myalgia (muscle pain)	M79.1	HD21C	1515	£367	£257	
	Neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies)	M79.2	AA26Z	4580	£525	£368	
	Pevic Pain	R10.x	FC05C	5545	£474	£332	
	Pleuritic pain	R07.3	EB01Z	5396	£508	£356	
	Rectal or perirectal pain (proctalgia)	K59.4	FC11C	3266	£532	£372	
					£463	£324	
Fever		R50.x	WA04U	30	£390	£273	
Infection	Bacterial	A49	WA09Y	29	£394	£276	
	Fungal	B35-B49	WA09Y	29	£394	£276	
	Viral	B34	WA06Y	87	£529	£370	
					£475	£332	

Appendix 6.5 The summary of unit cost list for complication

	Adverse event	Cost	Total Cost
Cardiovascular	Unspecified		£364
	Arrhythmia	£314	
	Hypertension	£365	
	Hypotension	£356	
	Congestive heart failure (CHF)	£641	
Local	Oedema	£444	
	Weight gain / loss	£122	
Dermatology / skin	Unspecified		£272
	Alopecia	£264	
	Rash	£251	
Gastrointestinal disorder	Unspecified		£300
	Anorexia	£122	
	Diarrhea	£130	
	Nausea / Vomiting	£120	
	Stomatitis	£97	
	Mucositis	£300	
Hepatic disorder	Unspecified		£224
	Bilirubinemia	£215	
	Liver failure	£286	
Pulmonary disorder	Unspecified		£301
	Dyspnoea	£277	
	Apnea	£277	
Renal / genitourinary disorder	Unspecified		£94
	Creatiniemia	£218	
	Renal failure	£644	
	dialysis	£93	
Neurology	Unspecified		£272
	General	£286	
	Fatigue, malaise	£282	
	Sensory	£333	
	Motor	£415	
	Paralysis	£458	
	Cortical	£250	
	Dizziness	£368	
	Seizure (convulsion)	£368	
	Cerebellar	£393	
	Hemarrhage	£652	
	Mood	£139	
	Anxiety	£139	
	Depression	£139	
Pain	Unspecified		£324
	Headache	£162	
	Bone pain	£305	
Fever	Unspecified		£273

Appendix 6.6 The summary of the unit cost list for non-infection complications

	Incidence rate	Unit Cost	Cost	Total cost
ADE				£188
Severe fever	10%	£273	£27	
Severe pain	3%	£324	£10	
Severe Nausea / vomiting	34.5%	£120	£41	
Severe Diarrhea	11.3%	£130	£15	
Severe Stomatitis	7%	£97	£7	
Severe Cardiac disorder	1.3%	£364	£5	
Severe Hepatic disorder	10.1%	£224	£23	
Neurologic disorder (Severe)	22%	£272	£60	
Severe Cerebellum disorder	0.7%	£393		
AraC (LD)				£115
Severe Diarrhea	7.6%	£130	£10	
Severe Malaise	1%	£282	£3	
Severe mucositis	8%	£300	£24	
Severe alopecia	8%	£264	£21	
Severe cardiac disorder	14%	£364	£51	
Severe Renal disorder	6.6%	£94	£6	
AraC (HD)				£184
Severe neurotoxicity	3%	£398	£12	
Severe cerebellar toxcitity	5%	£561	£29	
Severe liver disorder	16%	£320	£51	
Severe cardiac disorder	16%	£520	£83	
Renal disorder	7%	£134	£9	
DA (C100)				£292
Severe Fever	24.6%	£273	£67	
Severe Mucositis	3.8%	£300	11	
Digestive system				
Severe Nausea / vomiting	2.3%	£120	£3	
Severe Diarrhea	4.9%	£130	£6	
Severe Anorexia	21%	£122	£26	
Skin and appendages				
Severe Alopecia	27.4%	£264	£72	
Severe Rash	0.4%	£251	£1	
Cardiovascular system (severe)	8.4%	£364	£31	
Severe heart failure	4%			
Renal disorder (severe)	4%	£94	£4	
Severe Dialysis	13%			
Hepatic disorder (severe)	20.6%	£224	£46	
Severe Bilirubinemia	7.5%			
Severe Creatinine	0.3%			
Neurologic disorder (severe)	9%	£272	£25	
DA (C200)				£356
Severe Fever	11%	£273	£30	
Severe Malaise	16%	£282	£45	
Severe Pain	5.7%	£324	£19	
Digestive system				
Severe Nausea / vomiting	2.9%	£120	£4	
Severe Diarrhea	9%	£130	£12	
Severe Stomatitis	10.9%	£97	£11	
Skin and appendages				
Severe Rash	45%	£251	£113	
Respiratory system				
Severe Dyspnea	18%	£277	£50	

Cardiovascular system (severe)	12.9%	£364	£47	
Severe Hypotension	7%			
Renal disorder				
Severe Dialysis	3%	£93	£3	
Hepatic disorder (severe)	7.4%	£224	£17	
Severe Bilirubinemia	16%			
Neurologic disorder (severe)	2%	£272	£5	
Severe CNS toxicity	4.8%			
HAM				£248
Severe Fever	38%	£273	£104	
Severe Mucositis	9%	£300	£27	
Digestive system				
Severe Nausea / vomiting	13.9%	£120	£17	
Severe Diarrhea	15.9%	£130	£21	
Hepatic disorder (severe)	8%	£224	£18	
Severe Bilirubinemia	17.7%			
Severe Creatinine	4%			
Cardiovascular system (severe)	1%	£364	£4	
Neurocortical disorder (severe)	21%	£272	£57	
Severe CNS toxicity	7%			
MidAC				£59
Digestive system				
Severe Nausea / vomiting	17.2%	£120	£21	
Severe Diarrhea	7.8%	£130	£10	
Severe Stomatitis	6.8%	£97	£7	
Cardiovascular system (severe)	4.2%	£364	£15	
Neurocortical disorder				
Severe CNS toxicity	1.6%	£393	£6	
FA				£147
Severe Fever	33%	£273	£90	
Renal disorder (severe)	4%	£94	£4	
Hepatic disorder (severe)	22%	£224	£49	
Cardiovascular system (severe)	1%	£364	£4	
FLAG				£409
Severe Fever	28%	£273	£76	
Severe Mucositis	7%	£300	£21	
Severe Pain	14%	£324	£45	
Digestive system				
Severe Nausea / vomiting	32%	£120	£38	
Severe Diarrhea	8%	£130	£10	
Metabolic disorder				
Severe Edema	1%	£444	£4	
Respiratory system				
Severe Dyspnea	50%	£277	£139	
Renal disorder (severe)	0%	£94	£0	
Hepatic disorder (severe)	12.6%	£224	£28	
Severe Bilirubinemia	12%			
Severe creatinine	0%			
Cardiovascular system (severe)	8%	£364	£29	
Neurocortical disorder (severe)	7%	£272	£19	
FLAG-Ida				£353
Severe Fever	28%	£273	£76	
Severe Severe Mucositis	65%	£300	£195	
Digestive system				
Severe Nausea / vomiting	10.7%	£130	£14	
Severe Diarrhea	5%	£120	£6	

Hepatic disorder				
Severe Bilirubinemia	22%	£215	£47	
Cardiovascular system (Severe)	4%	£364	£15	
MACE				£103
Severe Headache	10%	£162	£16	
Digestive system				
Severe Nausea / vomiting	29%	£130	£38	
Hepatic disorder (severe)	1%	£224	£2	
Neurocortical disorder				
Severe Cerebellar toxicity	12%	£393	£47	
Mylotarg				£197
Severe Fever	6.3%	£273	£17	
Severe Mucositis	4%	£300	£12	
Digestive system				
Severe Nausea / vomiting	11%	£130	£14	
Respiratory system				
Severe Dyspnea	10%	£277	£28	
Hepatic disorder				
Severe Bilirubinemia	21%	£215	£45	
Severe Creatinine	0.5%	£218	£1	
Cardiovascular system				
Severe Hypertension	10%	£365	£37	
Severe Hypotension	7.7%	£356	£27	
Neurocortical disorder				
Severe CNS toxicity	4%	£393	£16	
G-CSF				£202
Severe Fever	24%	£273	£66	
Severe Mucositis	15%	£300	£45	
Severe Pain	0.8%	£324	£3	
Digestive system				
Severe Nausea / vomiting	20%	£130	£26	
Severe Diarrhea	5%	£120	£6	
Skin and appendages				
Severe Rash	3.3%	£251	£8	
Hepatic disorder (severe)	4%	£224	£9	
Severe Bilirubinemia	6%			
Cardiovascular system (severe)	8.6%	£364	£31	
Severe Hypotension	3.4%			
Neurocortical disorder (severe)	3%	£272	£8	
ATRA				£165
RAS	24%	£194	£47	
Severe Nausea / Vomiting	6%	£130	£8	
Severe Diarrhea	3%	£120	£4	
Severe Stomitis	7%	£97	£7	
Skin disorder (severe)	5%	£272	£14	
Liver disorder (severe)	13%	£224	£29	
Cardiovascular disorder (severe)	11%	£364	£40	
Severe hypertension	7%			
Neurocortical disorder (severe)	6%	£272	£16	
MRC Approach				£29
RAS	15%	£194	£29	
Spanish Approach				£187
RAS	18%	£194	£35	
Severe Mucositis	19%	£300	£57	
Severe edema	10%	£444	£44	
Severe Nausea / vomiting	5%	£130	£15	
Severe Diarrhea	2%	£120	£2	

Severe stomatitis	6%	£97	£6	
Skin disorder (severe)	2%	£272	£5	
Liver disorder (severe)	3%	£224	£7	
Cardiac disorder (severe)	3%	£364	£11	
Neurocortical disorder (severe)	2%	£272	£5	
Clofarabine				£115
Severe Mucositis	6%	£300	£18	
Digestive system				
Severe Nausea / vomiting	2.5%	£130	£3	
Severe Diarrhea	0%	£0	£0	
Skin and appendages				
Severe Rash	10%	£251	£25	
Respiratory system				
Severe Bilirubinemia	19%	£215	£41	
Severe Creatinine	13%	£218	£28	
Hydroxyurea				£52
Severe Mucositis	3%	£300	£9	
Digestive system (severe)	9%	£300	£27	
Severe Nausea / vomiting	8%			
Severe Diarrhea	20%			
Skin and appendages				
Severe Alopecia	5%	£264	£13	
Renal disorder (severe)	3%	£94	£3	

Appendix 6.7 The cost lists of complication cost for each treatment

	Complication cost		Antibiotics Cost			Total cost	
	Type 1 (derived from literatures)	Type 2 (derived from expert opinions)	Antibiotics days	Day cost	Antibiotics cost	Type 1	Type 2
Chemotherapy							
Inpatient							
ADE 10+3+5	£188	£115.1	12 / course	×81.8	£1964	£2152	£2079
Course 1 (10+3+5)	£94	£57.6	14	×81.8	£1145	£1239	£1203
Course 2 (8+3+5)	£94	£57.6	7	×81.8	£573	£667	£631
ADE + Mylotarg	£188	£115.1	12 / course	×81.8	£1964	£2152	£2079
Course 1 (10+3+5)	£94	£57.6	14	×81.8	£1145	£1239	£1203
Course 2 (8+3+5)	£94	£57.6	7	×81.8	£573	£667	£631
AraC (HD)	£184	£115.1	8 / course	×81.8	£1308	£1492	£1423
Course 1	£92	£57.6	10	×81.8	£818	£910	£876
Course 2	£92	£57.6	8	×81.8	£654	£746	£712
AraC (HD) + Mylotarg	£184	£115.1	8 /course	×81.8	£1308	£1492	£1423
Course 1	£92	£57.6	10	×81.8	£818	£910	£876
Course 2	£92	£57.6	8	×81.8	£654	£746	£712
AraC (LD)	£115	£115.1	9 / course	×81.8	£1472	£1587	£1530
Course 1	£57.5	£57.6	11	×81.8	£890	£957	£957
Course 2-4	£57.5	£57.6	7	×81.8	£573	£630	£630
DA	£356	£115.1	14 / course	×81.8	£2290	£2646	£2405
Course 1	£178	£57.6	16	×81.8	£1309	£1487	£1367
Course 2	£178	£57.6	12	×81.8	£982	£1160	£1040
DA + Mylotarg	£356	£115.1	14 / course	×81.8	£2290	£2646	£2405
Course 1	£178	£57.6	16	×81.8	£1309	£1487	£1367

Course 2	£178	£57.6	12	×81.8	£982	£1160	£1040
FLA	£147	£115.1	24 / course	×81.8	£3926	£4073	£4041
Course 1	£73.5	£57.6	21 *	×81.8	£1718	£1792	£1776
Course 2	£73.5	£57.6	26 *	×81.8	£2127	£2200	£2185
FLAG	£409	£115.1	24 / course	×81.8	£3926	£4073	£4041
Course 1	£204.5	£57.6	21	×81.8	£1718	£1792	£1776
Course 2	£204.5	£57.6	26	×81.8	£2127	£2200	£2185
FLAG-Ida	£353	£115.1	22 / course	×81.8	£3599	£3952	£3714
Course 1	£176.5	£57.6	15	×81.8	£1227	£1404	£1285
Course 2	£176.5	£57.6	29	×81.8	£2372	£2549	£2430
FLAG-Ida + Mylotarg	£353	£115.1	22 / course	×81.8	£3599	£3952	£3714
Course 1	£176.5	£57.6	15	×81.8	£1227	£1404	£1285
Course 2	£176.5	£57.6	29	×81.8	£2372	£2549	£2430
HAM	£248	£115.1	10 (MidAC)	×81.8	£818	£1066	£933
MidAC	£59	£115.1	10	×81.8	£818	£877	£933
Mini MidAC	£59	£115.1	10	×81.8	£818	£877	£933
MACE	£103	£115.1	12	×81.8	£982	£1085	£1097
Spanish approach	£187	£115.1	14 / course	×81.8	£4581	£4768	£4696
Course 1	£46.75	£28.78	14	×81.8	£1145	£1192	£1174
Course 2	£46.75	£28.78	14	×81.8	£1145	£1192	£1174
Course 3	£46.75	£28.78	14 *	×81.8	£1145	£1192	£1174
Course 3	£46.75	£28.78	14 *	×81.8	£1145	£1192	£1174
MRC approach	£29 (+350)	£115.1	13 / course	×81.8	£4254	£4633	£4369
Course 1	£7.25 (+94)	£28.78	13	×81.8	£1063	£1165	£2155
Course 2	£7.25 (+94)	£28.78	23	×81.8	£1881	£1983	£1910
Course 3	£7.25(+103)	£28.78	7	×81.8	£573	£683	£602
Course 4	£7.25(+59)	£28.78	16	×81.8	£1309	£1375	£1338
Clofarabine	£115	£115	14 **	×81.8	£1145	£1260	£1260
Inpatient (Mild)							

Amsacrine	-	£115	14 **	×81.8	£1145	£1145	£1260
Campath	-	£115	14 **	×81.8	£1145	£1145	£1260
Arsenic trioxide	-	£115	14 **	×81.8	£1145	£1145	£1260
Outpatient (Intensive)							
Cyclophosphamid	-	-	-	-	-	-	-
Cyclophosphamid/MESNA	-	-	-	-	-	-	-
Daunorubicin							
ETI	-	-	-	-	-	-	-
FC	-	-	-	-	-	-	-
Fludarabine	-	-	-	-	-	-	-
Etoposide	-	-	-	-	-	-	-
Melphalan	-	-	-	-	-	-	-
Vincristine	-	-	-	-	-	-	-
ATRA	£165	-	-	-	£165	£165	-
Mylotarg	£197	-	-	-	£197	£197	-
Anagrelide	-	-	-	-	-	-	-
Clopidogrel	-	-	-	-	-	-	-
Outpatient (Mild)							
Aspirin	-	-	-	-	-	-	-
Hydroxycarbamide	£122	-	-	-	£122	£122	-
Hydroxycarbamide + Aspirin	£122	-	-	-	£122	£122	-
Chelating agents	-	-	-	-	-	-	-
Clinical Trial							
AML 14 AraC	£115	£115.1	9 / course	×81.8	£1472	£1587	£1530
Course 1	£57.5	£57.6	11	×81.8	£890	£957	£957
Course 2-4	£57.5	£57.6	7	×81.8	£573	£630	£630
AML 14 AraC + Mylotarg	£115	£115.1	9 / course	×81.8	£1472	£1587	£1530
Course 1	£57.5	£57.6	11	×81.8	£890	£957	£957
Course 2-4	£57.5	£57.6	7	×81.8	£573	£630	£630

AML 14 D35 C200	£356	£115.1	14 / course	×81.8	£2290	£2646	£2405
Course 1	£178	£57.6	16	×81.8	£1309	£1487	£1367
Course 2	£178	£57.6	12	×81.8	£982	£1160	£1040
AML 14 D35 C400	£356	£115.1	14 / course	×81.8	£2290	£2646	£2405
Course 1	£178	£57.6	16	×81.8	£1309	£1487	£1367
Course 2	£178	£57.6	12	×81.8	£982	£1160	£1040
AML 14 D50 C200	£356	£115.1	14 / course	×81.8	£2290	£2646	£2405
Course 1	£178	£57.6	16	×81.8	£1309	£1487	£1367
Course 2	£178	£57.6	12	×81.8	£982	£1160	£1040
AML 15 ADE	£188	£115.1	12 / course	×81.8	£1964	£2152	£2079
Course 1	£94	£57.6	14	×81.8	£1145	£1239	£1203
Course 2	£94	£57.6	7	×81.8	£573	£667	£631
AML 15 ADE + Mylotarg	£188	£115.1	12 / course	×81.8	£1964	£2152	£2079
Course 1	£94	£57.6	14	×81.8	£1145	£1239	£1203
Course 2	£94	£57.6	7	×81.8	£573	£667	£631
AML 15 AraC	£184	£115.1	8 / course	×81.8	£1308	£1492	£1423
Course 1	£92	£57.6	10	×81.8	£818	£910	£876
Course 2	£92	£57.6	8	×81.8	£654	£746	£712
AML 15 AraC + Mylotarg	£184	£115.1	8 / course	×81.8	£1308	£1492	£1423
Course 1	£92	£57.6	10	×81.8	£818	£910	£876
Course 2	£92	£57.6	8	×81.8	£654	£746	£712
AML 15 DA	£356	£115.1	14 / course	×81.8	£2290	£2646	£2405
Course 1	£178	£57.6	16	×81.8	£1309	£1487	£1367
Course 2	£178	£57.6	12	×81.8	£982	£1160	£1040
AML 15 DA + Mylotarg	£356	£115.1	14 / course	×81.8	£2290	£2646	£2405
Course 1	£178	£57.6	16	×81.8	£1309	£1487	£1367
Course 2	£178	£57.6	12	×81.8	£982	£1160	£1040
AML 15 FLAG-Ida	£353	£115.1	22 / course	×81.8	£3599	£3952	£3714
Course 1	£176.5	£57.6	15	×81.8	£1227	£1404	£1285

Course 2	£176.5	£57.6	29	×81.8	£2372	£2549	£2430
AML 15 FLAG-Ida + Mylotarg	£353	£115.1	22 / course	×81.8	£3599	£3952	£3714
Course 1	£176.5	£57.6	15	×81.8	£1227	£1404	£1285
Course 2	£176.5	£57.6	29	×81.8	£2372	£2549	£2430
AML 15 MidAC	£59	£115.1	10	×81.8	£818	£877	£933
AML 15 MACE	£103	£115.1	12	×81.8	£982	£1085	£1097
AML 15 MACE + Mylotarg	£103	£115.1	12	×81.8	£982	£1085	£1097
APML 15 Spanish approach	£187	£115.1	14 / course	×81.8	£4581	£4768	£4696
Course 1	£46.75	£28.78	14	×81.8	£1145	£1192	£1174
Course 2	£46.75	£28.78	14 *	×81.8	£1145	£1192	£1174
Course 3	£46.75	£28.78	14 *	×81.8	£1145	£1192	£1174
Course 4	£46.75	£28.78	14 *	×81.8	£1145	£1192	£1174
APML Spanish Maintenance	-	-	-	-	-	-	-
APML 15 MRC approach	£29	£115.1	13 / course	×81.8	£4254	£4633	£4369
Course 1	£7.25	£28.78	13	×81.8	£1063	£1165	£2155
Course 2	£7.25	£28.78	23	×81.8	£1881	£1983	£1910
Course 3	£7.25	£28.78	7	×81.8	£573	£683	£602
Course 4	£7.25	£28.78	16	×81.8	£1309	£1375	£1338
Other treatment Group 1							
Supportive care	-	-	-	-	-	-	-
Transfusion	-	-	-	-	-	-	-
Erythropoietin	-	-	-	-	-	-	-
Steroids	-	-	-	-	-	-	-
G-CSF	-	-	-	-	-	-	-
Venesection	-	-	-	-	-	-	-
Immunosupressive therapy	-	-	-	-	-	-	-
Palliative Care							
Duration < 21	-	-	-	-	-	-	-
Duration > 21	-	-	-	-	-	-	-

Follow-up	-	-	-	-	-	-	-
Other treatment Group 2							
Splenectomy	-	-	-	-	-	-	-
Transplant	-	-	-	-	-	-	-
Auto BMT	-	-	-	-	-	-	-
Allo BMT	-	-	-	-	-	-	-
Radiotherapy	-	-	-	-	-	-	-
TBI	-		-	-	-	-	-
Non-TBI	-	-	-	-	-	-	-

* The estimate derived from the value of similar treatment

** The estimate derived from expert survey

Appendix 7.1 International price and data source list of Mylotarg

Country	Resource	Year	Price	Price in UK (£)
USA	http://content.ecast.wyeth.com/msgs/105/April_PI_20090401_1.pdf	2009/03	2,524.24 USD	£1,764.06
Canada	http://www.saverxcanada.com/drugs/Mylotarg/solution/5mg	2009/05	2,833.97 USD	£1,913.55
Chile	http://www.cenabast.cl/ConsultaPrecios/index.asp	2009	-	-
Germany	www.rote-liste.de/Online	2009	- [195]	-
France	http://www.vidalpro.net	2009	- [195]	-
Spain	http://www.buenasalud.com/enc/	2009	- [195]	-
Belgium	http://www.bcfi.be/	2009	- [195]	-
Greece	http://www.mednet.gr/app/index.php	2009	- [195]	-
Switzerland	http://www.kompendium.ch/app/search_d.cfm	2009	- [195]	-
Sweden	http://www.fass.se/LIF/produktfakta/fakta_lakare.jsp	2009	- [195]	-
Japan	http://www.irxmedicine.com/products/pdt.asp?p_unitid=29174	2008/03	310,000 YEN	£1,492.16
	http://www.mhlw.go.jp/shingi/2005/08/txt/s0831-2.txt	2007	241,154 YEN	£1,039.25
Taiwan	http://homepage.vghtpe.gov.tw/~pharm/newdrugreport/96/S-1231.pdf	2009	77,385 TWD	£1,579.23
Korea	www.dailyinfo.co.kr sdic.sookmyung.ac.kr	2007	2,780,000 KRW	£1,507.00
China	www.2007.org.cn/product/Leukemianewspecial/200709/product_32.html	2009/05	3,200 USD	£2,160.70
Thailand	No public website	2009	-	-
Malaysia	http://www.bpfk.gov.my/Search/advsearch.asp	2009	-	-
Australia	www.pbs.gov.au	2009	-	-
New Zealand	http://www.pharmac.govt.nz/Schedule	2009	-	-
Israel	http://www.ima.org.il/imaj/ar06sep-1.pdf	2009	2,213.17 USD	£1,494.38
South Africa	http://www.sapma.co.za/assets/attachments/PIASA/Wyeth_Price_List_2009-02.PDF	2009	20,409.26 Rand	£1,623.90
Average				**£1,619.36**

Appendix 7.2 Detailed cost list of drug items for each treatment (Assumed that an average patient surface area is 1.8 m^2)

		Dose	Unit cost	Frequency	Cost
Intensive Inpatient treatment					
ADE 10+3+5	Cytarabine	100 mg/m2 iv bd day 1-10 (20 doses)	£9.17	Every 12 hours	£1158.58 / course
	Daunorubicin	50 mg/m2 iv day 1, 3, 5 (3 doses)	£262.97	Alternative days	
	Etoposide	100 mg/m2/d iv day 1-5 (5 doses)	£28.55	Once daily	
	Allopurinol	300mg oral OD (1 dose)	£2.15	Once	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	1 mg oral stat (5 doses)	£7.7	Once daily	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
ADE 8+3+5	Cytarabine	100 mg/m2 iv bd day 1-8 (16 doses)	£9.17	Every 12 hours	£1121.90 / course
	Daunorubicin	50 mg/m2 iv day 1, 3, 5 (3 doses)	£262.97	Alternative days	
	Etoposide	100 mg/m2/d iv day 1-5 (5 doses)	£28.55	Once daily	
	Allopurinol	300mg oral OD (1 dose)	£2.15	Once	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	1 mg oral stat (5 doses)	£7.7	Once daily	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
ADE + Mylotarg course 1	Cytarabine	100 mg/m2 iv bd day 1-10 (20 doses)	£9.17	Every 12 hours	£2779.87 / course
	Daunorubicin	50 mg/m2 iv day 1, 3, 5 (3 doses)	£262.97	Alternative days	
	Etoposide	100 mg/m2/d iv day 1-5 (5 doses)	£28.55	Once daily	
	Allopurinol	300mg oral OD (1 does)	£2.15	Once	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	1 mg oral stat (5 doses)	£7.7	Once daily	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
	Mylotarg	5 mg (1 dose)	£1619.39	Once	
ADE course 2	Cytarabine	100 mg/m2 iv bd day 1-8 (16 doses)	£9.17	Every 12 hours	£1121.90 / course
	Daunorubicin	50 mg/m2 iv day 1, 3, 5 (3 doses)	£262.97	Alternative days	
	Etoposide	100 mg/m2/d iv day 1-5 (5 doses)	£28.55	Once daily	

	Allopurinol	300mg oral OD (1 dose)	£2.15	Once	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	1 mg oral stat (5 doses)	£7.7	Once daily	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
AraC (HD): course 1	Cytarabine	3000m g/m2 iv bd day 1, 3, 5 (6 doses)	£274.95	Alternative days	£1699.97 / course
	Dexamethasone	8 mg oral stat (3 doses)	£0.56	Alternative days	
	Granisetron	2 mg oral stat (3 doses)	£15.39	Alternative days	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
	Predsol	0.5% eye drops 1 drop QDS (1 dose)	£2.35	4 times daily	
AraC (HD): course 2	Cytarabine	3000m g/m2 iv bd day 1, 3, 5 (6 doses)	£274.95	Alternative days	£1699.97 / course
	Dexamethasone	8 mg oral stat (3 doses)	£0.56	Alternative days	
	Granisetron	2 mg oral stat (3 doses)	£15.39	Alternative days	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
	Predsol	1 drop QDS (1 does)	£2.35	4 timesdaily	
AraC (HD) + Mylotarg: course 1	Cytarabine	3000m g/m2 iv bd day 1, 3, 5 (6 doses)	£274.95	Alternative days	£3321.26 / course
	Dexamethasone	8 mg oral stat (3 doses)	£0.56	Alternative days	
	Granisetron	2 mg oral stat (3 doses)	£15.39	Alternative days	
	Metoclopramide	10 mg oral QDS prn	£0.07	Once daily	
	Predsol	1 drop QDS	£2.35	Once daily	
	Chlorphenamine	10 mg IV Bolus	£1.90	Once daily	
	Mylotarg	5 mg	£1619.39	Once	
AraC (HD): course 2	Cytarabine	3000m g/m2 iv bd day 1, 3, 5 (6 doses)	£274.95	Alternative days	£1699.97 / course
	Dexamethasone	8 mg oral stat (3 doses)	£0.56	Alternative days	
	Granisetron	2 mg oral stat (3 doses)	£15.39	Alternative days	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
	Predsol	1 drop QDS (1 dose)	£2.35	4 times daily	
AraC (LD): course 1	Cytarabine	20mg PFS (bd for 10 days – 20 doses)	£4.58	Every 12 hours	£9.16 / day (£91.6 / course)

AraC (LD): course 2-4	Cytarabine	20mg PFS (bd for 10 days – 20 doses)	£4.58	Every 12 hours	£9.16 / day (£91.6 / course)
AraC (LD) +Mylotarg: course 1	Cytarabine	20mg PFS (bd for 10 days – 20 doses)	£4.58	Every 12 hours	£9.16 (1630.45) / day
	Chlorphenamine	10 mg IV Bolus (1 dose)	£1.90	Once	£1712.96 / course
	Mylotarg	5 mg (1 dose)	£1619.39	Once	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
AraC (LD) +Mylotarg: course 2-4	Cytarabine	20mg PFS (bd for 10 days – 20 doses)	£4.58	Every 12 hours	£9.16 / day (£91.6 / course)
Clofarabine	Clofarabine	20 mg/m2 in 100ml N/Saline (5 doses)	£2160	Once daily	£10879.82 / course
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	2 mg oral stat (5 doses)	£15.39	Once daily	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
DA 3+10	Cytarabine	100 mg/m2 iv bd day 1-10 (20 doses)	£9.17	Every 12 hours	£1015.83 / course
	Daunorubicin	50 mg/m2 iv od day 1,3,5 (3 doses)	£262.97	Alternative day	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Alternative day	
	Granisetron	1 mg oral stat (5 doses)	£7.70	Alternative day	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
	Allopurinol	300 mg oral od (1 dose)	£2.15	Once	
DA 3+8	Cytarabine	100 mg/m2 iv bd day 1-8 (16 doses)	£9.17	Every 12 hours	£979.15 / course
	Daunorubicin	50 mg/m2 iv od day 1,3,5 (3 doses)	£262.97	Alternative day	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Alternative day	
	Granisetron	1 mg oral stat (5 doses)	£7.70	Alternative day	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
	Allopurinol	300 mg oral od (1 dose)	£2.15	Once	
DA (3+10)+Mylotarg	Cytarabine	100 mg/m2 iv bd day 1-10 (20 doses)	£9.17	Every 12 hours	£2637.12 / course
	Daunorubicin	50 mg/m2 iv od day 1,3,5 (3 doses)	£262.97	Alternative day	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Alternative day	
	Granisetron	1 mg oral stat (5 doses)	£7.70	Alternative day	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
	Allopurinol	300 mg oral od (1 dose)	£2.15	Once	

	Mylotarg	5 mg	£1619.39	Once	
DA (3+8)+Mylotarg	Cytarabine	100 mg/m2 iv bd day 1-8 (16 doses)	£9.17	Every 12 hours	£979.15 / course
	Daunorubicin	50 mg/m2 iv od day 1,3,5 (3 doses)	£262.97	Alternative day	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Alternative day	
	Granisetron	1 mg oral stat (5 doses)	£7.70	Alternative day	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
	Allopurinol	300 mg oral od (1 dose)	£2.15	Once	
FLA : course 1	Fludarabine	30mg/m2 iv. od day 1-5 (5 doses)	£366.60	Once daily	£1978.65 / course
	Cytarabine	2000mg/m2 iv od day 1-5 (5 doses)	£23.69	Once daily	
	Dexamethasone	8 mg oral stat (3 doses)	£0.56	Alternative day	
	Granisetron	1 mg oral stat (3 doses)	£7.70	Alternative day	
	Metoclopramide	10 mg oral QDS (1op)	£0.07	4 times daily	
	Predsol	0.5% eye drops (1op)	£2.35	Daily	
FLA: course 2	Fludarabine	30mg/m2 iv. od day 1-5 (5 doses)	£366.60	Once daily	£1978.65 / course
	Cytarabine	2000mg/m2 iv od day 1-5 (5 doses)	£23.69	Once daily	
	Dexamethasone	8 mg oral stat (3 doses)	£0.56	Alternative day	
	Granisetron	1 mg oral stat (3 doses)	£7.70	Alternative day	
	Metoclopramide	10 mg oral QDS (1op)	£0.07	4 times daily	
	Predsol	0.5% eye drops (1op)	£2.35	Daily	
FLAG: course 1	G-CSF	300 microgram OD for 7 days	£562.67	Once daily	£2557.83 / course
	Fludarabine	30mg/m2 iv. od day 1-5 (5 doses)	£366.60	Once daily	
	Cytarabine	2000mg/m2 iv od day 1-5 (5 doses)	£23.69	Once daily	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Alternative day	
	Granisetron	1 mg oral stat (5 doses)	£7.70	Alternative day	
	Metoclopramide	10 mg oral QDS (1op) (1 dose)	£0.07	4 times daily	
	Predsol	0.5% eye drops (1op) (1 dose)	£2.35	Daily	
FLAG: course 2	G-CSF	300 microgram OD for 7 days	£562.67	Once daily	£2557.83 / course
	Fludarabine	30mg/m2 iv. od day 1-5 (5 doses)	£366.60	Once daily	
	Cytarabine	2000mg/m2 iv od day 1-5 (5 doses)	£23.69	Once daily	

	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Alternative day	
	Granisetron	1 mg oral stat (5 doses)	£7.70	Alternative day	
	Metoclopramide	10 mg oral QDS (1op) (1 dose)	£0.07	4 times daily	
	Predsol	0.5% eye drops (1op) (1 dose)	£2.35	Daily	
FLAG-Ida: course 1	G-CSF	300 microgram OD for 7 days	£562.67	Once daily	£3789.60 / course
	Fludarabine	30mg/m2 iv. od day 1-5 (5 doses)	£366.60	Once daily	
	Cytarabine	2000mg/m2 iv od day 1-5 (5 doses)	£23.69	Once daily	
	Idarubicin	10 mg/m2 od day 4-6 (3 doses)	£410.59	Alternative day	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	1 mg oral stat (5 doses)	£7.70	Once daily	
	Metoclopramide	10 mg oral QDS (1op) (1 dose)	£0.07	4 times daily	
	Predsol	0.5% eye drops (1op) (1 dose)	£2.35	Daily	
FLAG-Ida: course 2	G-CSF	300 microgram OD for 7 days	£562.67	Once daily	£3789.60 / course
	Fludarabine	30mg/m2 iv. od day 1-5 (5 doses)	£366.60	Once daily	
	Cytarabine	2000mg/m2 iv od day 1-5 (5 doses)	£23.69	Once daily	
	Idarubicin	10 mg/m2 od day 4-6 (3 doses)	£410.59	Alternative day	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	1 mg oral stat (5 doses)	£7.70	Once daily	
	Metoclopramide	10 mg oral QDS (1op) (1 dose)	£0.07	4 times daily	
	Predsol	0.5% eye drops (1op) (1 dose)	£2.35	Daily	
FLAG-Ida + Mylotarg: course 1	G-CSF	300 microgram OD for 7 days	£562.67	Once daily	£5410.89 / course
	Fludarabine	30mg/m2 iv. od day 1-5 (5 doses)	£366.60	Once daily	
	Cytarabine	2000mg/m2 iv od day 1-5 (5 doses)	£23.69	Once daily	
	Idarubicin	10 mg/m2 od day 4-6 (3 doses)	£410.59	Alternative day	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	1 mg oral stat (5 doses)	£7.70	Once daily	
	Metoclopramide	10 mg oral QDS (1op) (1 dose)	£0.07	4 times daily	
	Chlorphenamine	10 mg iv Bolus(1 dose)	£1.90	Once	
	Predsol	0.5% eye drops (1op) (1 dose)	£2.35	Daily	
	Mylotarg	5 mg (1 dose)	£1619.39	Once	

FLAG-Ida: course 2	G-CSF	300 microgram OD for 7 days	£562.67	Once daily	£3789.60 / course
	Fludarabine	30mg/m2 iv. od day 1-5 (5 doses)	£366.60	Once daily	
	Cytarabine	2000mg/m2 iv od day 1-5 (5 doses)	£23.69	Once daily	
	Idarubicin	10 mg/m2 od day 4-6 (3 doses)	£410.59	Alternative day	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	1 mg oral stat (5 doses)	£7.70	Once daily	
	Metoclopramide	10 mg oral QDS (1op) (1 dose)	£0.07	4 times daily	
	Predsol	0.5% eye drops (1op) (1 dose)	£2.35	Once	
HAM	Cytarabine	3000 mg/m2 BD day 1-4 (8 doses)	£549.9	Every 12 hours	£2830.82 / course
	Mitoxantrone	10 mg/m2 iv day 2-6 (5 doses)	£36.17	Once daily	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	2 mg oral stat (5 doses)	£15.39	Once daily	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
	Predsol	0.5% eye drops (1op) (1 dose)	£2.35	Once	
MACE	Amsacrine	100 mg/m2 od day 1-5 (5 doses)	£173.32	Once daily	£1180.82 / course
	Cytarabine	200 mg/m2 od day 1-5 (5 doses)	£18.33	Once daily	
	Etoposide	100 mg/m2 od day 1-5 (5 doses)	£28.55	Once daily	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	2 mg oral stat (5 doses)	£15.39	Once daily	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
MidAC	Mitoxantrone	10 mg/m2 in 100ml N/Saline (5 doses)	£117.50	Once daily	£1204.19 / course
	Cytarabine	1000 mg/m2 iv day 1, 3, 5 (6 doses)	£91.65	Every 12 hours	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	2 mg oral stat (5 doses)	£15.39	Once daily	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
	Predsol	0.5% eye drops (1op) (1 dose)	£2.35	Daily	
Mini-MidAC		As full dose of MidAC			£1204.19 / course
Mild Inpatient Treatment					
Amsacrine	Amsacrine	100 mg/m2 iv	£155.75	Daily	£155.75 / day

Arsenic trioxide (ATO): course 1	Arsenic trioxide	0.15 mg/kg/day in 100ml dextrose 5%	£250.90	25 days every course	£250.90 / day
Campath	Campath (alemtuzumab)	30 mg intravenously	£322.93	3 days weekly	£991.22 / week
	Dexamethasone	8 mg oral stat	£0.56	3 days weekly	
	Chlorphenamine	10 mg iv Bolus	£1.90	3 days weekly	
	Allopurinol	300 mg oral od	£2.15	Once daily	
Intensive Outpatient treatment					
Mylotarg	Mylotarg	5 mg (i.v)	£1619.39	weekly	£1619.39 / week (weekly)
Daunorubicin	Daunorubicin	60 mg/m2 in 100ml N/ Saline	£315.56	Once every 21 days	£315.56 / day
Cyclophosphamide	Cyclophosphamide	500mg oral stat weekly	£2.88	weekly	£69.78 / week
	Granisetron	3 mg oral stat dose	£23.09	Once daily	(weekly)
	Metoclopramide	10 mg QDS oral (1op)	£0.07	Daily	
	Prednisolone	40 mg/m2 oral alt days	£44.75	Alternative days	
Cyclophosphamide (HD)	Cyclophosphamide	3000mg/m2 in 500ml N/S daily (2 doses)	£28.08	Once daily	£132.06
	Granisetron	2 mg oral stat dose	£15.39	Once daily	(one off)
	Dexamethasone	8 mg oral stat dose	£0.56	Once daily	
	Dexamethasone	2 mg oral (8 tabs)	£1.12	Once daily	
	Metoclopramide	10 mg oral QDS (1op)	£0.07	Once daily	
	Allopurinol	300 mg oral OD (1op)	£2.15	Once daily	
	Mesna	6000mg/m2 in 1000ml N/S (i.v)	£56.61	Once daily	
ETI	Etoposide, capsules,	80mg/m2 bd	£24.9	Every 12 hours	£40.77 / day
	Tioguanine	100mg/m2 bd	£10.9	Every 12 hours	(5 days every 26 days)
	Idarubicin	15mg/m2 od day	£4.97	5 days every 26 days	
FC	Fludarabine	40 mg/m2 oral OD	£153	5 days every 28 days	£157.13 / day
	Cyclophosphamide	250 mg/m2 oral OD	£0.96	5 days every 28 days	(5 days every 28 days)

	Granisetron Metoclopramide	1mg BD oral 10 mg QDS oral (1op)	£3.1 £0.07	5 days every 28 days 5 days every 28 days	
Etoposide	Etoposide Metoclopramide	100mg oral daily 10 mg oral QDS (1op)	£12.45 £0.07	7 days every 28 days 7 days every 28 days	£12.52 / day (7 days every 28 days)
Fludarabine	Fludarabine Metoclopramide	40mg/m2 oral od daily 10 mg oral QDS (1op)	£153 £0.07	5 days every 33 days 5 days every 33 days	£153.07 / day (5 days every 33 days)
Vincristine	Vincristine	2 mg/m2 once every week (i.v)	£24.87	Once every 7 days	£24.87 / week (weekly)
Melphalan	Melphalan Prednisolone	7 mg/m2 oral OD daily 40 mg/m2 oral days	£3.23 £1.78	Once daily Once daily	£5.01 / day
ATRA	ATRA	45mg/m2 daily	£16.03	Once daily	£16.03 / day
Anagrelide	Anagrelide	1 mg 4 times a day	£3.37	Once daily	£13.48 / day
Clopidogrel	Clopidogrel	75 mg daily	£1.21	Once daily	£1.21 / day
Mild Outpatient Treatment					
Aspirin	Aspirin	75mg oral for 3 doses daily	£0.0339	3 times daily	£0.1 / day
Hydroxycarbamide	Hydroxycarbamide Metoclopramide	2 g Oral OD daily 10 mg oral QDS (four times daily) pm	£0.44 £0.07	Once daily 4 times daily	£0.72 / day
Hydroxycarbamide + Aspirin	Hydroxycarbamide Metoclopramide Aspirin	2 g Oral OD daily 10 mg oral QDS (four times daily) pm 75mg oral 3 doses daily	£0.44 £0.07 £0.0339	Once daily 4 times daily 3 times daily	£0.82 / day
Chelating agent	Desferprioxamine Deferiprone	500 mg daily intramuscularly for 1 week 25mg/kg, oral, 3 times a day	£4.44 £5.33	Once Daily Daily	£31.08 / first week £5.33 / day

Clinical trial					
AML 14 AraC: course 1	Cytarabine	20mg PFS (bd for 10 days – 20 doses)	£4.58	Every 12 hours	£9.16 / day (£91.6 / course)
AML 14 AraC: course 2	Cytarabine	20mg PFS (bd for 10 days – 20 doses)	£4.58	Every 12 hours	£9.16 / day (£91.6 / course)
AML 14 AraC + Mylotarg: course 1	Cytarabine	20mg PFS (bd for 10 days – 20 doses)	£4.58	Every 12 hours	£9.16 (1630.45) / day
	Chlorphenamine	10 mg IV Bolus (1 dose)	£1.90	Once	£1712.96 / course
	Mylotarg	5 mg (1 dose)	£1619.39	Once	
AML 14 AraC + Mylotarg: course 2	Cytarabine	20mg PFS (bd for 10 days – 20 doses)	£4.58	Every 12 hours	£9.16 / day
AML 14 D35 C200 (10+3)	Cytarabine	100 mg/m2 iv bd day 1-10 (20 doses)	£9.17	Every 12 hours	£889.59 / course
	Daunorubicin	35 mg/m2 iv od day 1,3,5 (3 doses)	£220.89	Alternative day	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Alternative day	
	Granisetron	1 mg oral stat (5 doses)	£7.70	Alternative day	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
	Allopurinol	300 mg oral od (1 dose)	£2.15	Once	
AML 14 D35 C200 (8+3)	Cytarabine	100 mg/m2 iv bd day 1-8 (16 doses)	£9.17	Every 12 hours	£852.91 / course
	Daunorubicin	35 mg/m2 iv od day 1,3,5 (3 doses)	£220.89	Alternative day	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Alternative day	
	Granisetron	1 mg oral stat (5 doses)	£7.70	Alternative day	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
	Allopurinol	300 mg oral od (1 dose)	£2.15	Once daily	
AML 14 D35 C400 (10+3)	Cytarabine	200 mg/m2 iv bd day 1-10 (20 doses)	£18.33	Every 12 hours	£1072.79
	Daunorubicin	35 mg/m2 iv od day 1,3,5 (3 doses)	£220.89	Alternative day	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Alternative day	
	Granisetron	1 mg oral stat (5 doses)	£7.70	Alternative day	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
	Allopurinol	300 mg oral od (1 dose)	£2.15	Once daily	
AML 14 D35 C400 (8+3)	Cytarabine	200 mg/m2 iv bd day 1-8 (16 doses)	£18.33	Every 12 hours	£999.47

	Daunorubicin	35 mg/m2 iv od day 1,3,5 (3 doses)	£220.89	Alternative day	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Alternative day	
	Granisetron	1 mg oral stat (5 doses)	£7.70	Alternative day	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
	Allopurinol	300 mg oral od (1 dose)	£2.15	Once daily	
AML 14 D50 C200 (10+3)	Cytarabine	100 mg/m2 iv bd day 1-10 (20 doses)	£9.17	Every 12 hours	£1015.83
	Daunorubicin	50 mg/m2 iv od day 1,3,5 (3 doses)	£262.97	Alternative day	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Alternative day	
	Granisetron	1 mg oral stat (5 doses)	£7.70	Alternative day	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
	Allopurinol	300 mg oral od (1 dose)	£2.15	Once daily	
AML 14 D50 C200 (8+3)	Cytarabine	100 mg/m2 iv bd day 1-8 (16 doses)	£9.17	Every 12 hours	£979.15
	Daunorubicin	50 mg/m2 iv od day 1,3,5 (3 doses)	£262.97	Alternative day	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Alternative day	
	Granisetron	1 mg oral stat (5 doses)	£7.70	Alternative day	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
	Allopurinol	300 mg oral od (1 dose)	£2.15	Once daily	
AML 15 ADE (10+3+5)	Cytarabine	100 mg/m2 iv bd day 1-10 (20 doses)	£9.17	Every 12 hours	£1158.58 / course
	Daunorubicin	50 mg/m2 iv day 1, 3, 5 (3 doses)	£262.97	Alternative days	
	Etoposide	100 mg/m2/d iv day 1-5 (5 doses)	£28.55	Once daily	
	Allopurinol	300mg oral OD	£2.15	Once daily	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	1 mg oral stat (5 doses)	£7.7	Once daily	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
AML 15 ADE (8+3+5)	Cytarabine	100 mg/m2 iv bd day 1-8 (16 doses)	£9.17	Every 12 hours	£1121.90 / course
	Daunorubicin	50 mg/m2 iv day 1, 3, 5 (3 doses)	£262.97	Alternative days	
	Etoposide	100 mg/m2/d iv day 1-5 (5 doses)	£28.55	Once daily	
	Allopurinol	300mg oral OD	£2.15	Once daily	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	1 mg oral stat (5 doses)	£7.7	Once daily	

	Metoclopramide	10 mg oral QDS prn	£0.07	Once daily	
AML 15 ADE + Mylotarg (course1)	Cytarabine	100 mg/m2 iv bd day 1-10 (20 doses)	£9.17	Every 12 hours	£2777.97 / course
	Daunorubicin	50 mg/m2 iv day 1, 3, 5 (3 doses)	£262.97	Alternative days	
	Etoposide	100 mg/m2/d iv day 1-5 (5 doses)	£28.55	Once daily	
	Allopurinol	300mg oral OD	£2.15	Once daily	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	1 mg oral stat (5 doses)	£7.7	Once daily	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
	Mylotarg	5 mg (1 dose)	£1619.39	Once	
AML 15 ADE + Mylotarg (course 2)	Cytarabine	100 mg/m2 iv bd day 1-8 (16 doses)	£9.17	Every 12 hours	£1121.90 / course
	Daunorubicin	50 mg/m2 iv day 1, 3, 5 (3 doses)	£262.97	Alternative days	
	Etoposide	100 mg/m2/d iv day 1-5 (5 doses)	£28.55	Once daily	
	Allopurinol	300mg oral OD	£2.15	Once daily	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	1 mg oral stat (5 doses)	£7.7	Once daily	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
AML 15 AraC: course 1	Cytarabine	3000m g/m2 iv bd day 1, 3, 5 (6 doses)	£274.95	Alternative days	£1699.97 / course
	Dexamethasone	8 mg oral stat (3 doses)	£0.56	Alternative days	
	Granisetron	2 mg oral stat (3 doses)	£15.39	Alternative days	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
	Predsol	0.5% eye drops 1 drop QDS (1 dose)	£2.35	Once daily	
AML 15 AraC: course 2	Cytarabine	3000m g/m2 iv bd day 1, 3, 5 (6 doses)	£274.95	Alternative days	£1699.97 / course
	Dexamethasone	8 mg oral stat (3 doses)	£0.56	Alternative days	
	Granisetron	2 mg oral stat (3 doses)	£15.39	Alternative days	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
	Predsol	1 drop QDS (1 dose)	£2.35	Once daily	
AML 15 AraC + Mylotarg: course 1	Cytarabine	3000m g/m2 iv bd day 1, 3, 5 (6 doses)	£274.95	Alternative days	£3323.05 / course
	Dexamethasone	8 mg oral stat (3 doses)	£0.56	Alternative days	
	Granisetron	2 mg oral stat (3 doses)	£15.39	Alternative days	

	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	Once daily	
	Predsol	1 drop QDS (1 dose)	£2.35	4 times daily	
	Chlorphenamine	10 mg IV Bolus (1 dose)	£1.90	Once daily	
	Mylotarg	5 mg (1 dose)	£1619.39	Once	
AML 15 AraC + Mylotarg: course 2	Cytarabine	3000m g/m2 iv bd day 1, 3, 5 (6 doses)	£274.95	Alternative days	£1699.97 / course
	Dexamethasone	8 mg oral stat (3 doses)	£0.56	Alternative days	
	Granisetron	2 mg oral stat (3 doses)	£15.39	Alternative days	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
	Predsol	1 drop QDS (1 dose)	£2.35	Once daily	
AML 15 DA (10+3)	Cytarabine	100 mg/m2 iv bd day 1-10 (20 doses)	£9.17	Every 12 hours	£1015.83 / course
	Daunorubicin	50 mg/m2 iv od day 1,3,5 (3 doses)	£262.97	Alternative day	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Alternative day	
	Granisetron	1 mg oral stat (5 doses)	£7.70	Alternative day	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
	Allopurinol	300 mg oral od (1 dose)	£2.15	Once daily	
AML 15 DA (8+3)	Cytarabine	100 mg/m2 iv bd day 1-8 (16 doses)	£9.17	Every 12 hours	£979.15 / course
	Daunorubicin	50 mg/m2 iv od day 1,3,5 (3 doses)	£262.97	Alternative day	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Alternative day	
	Granisetron	1 mg oral stat (5 doses)	£7.70	Alternative day	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
	Allopurinol	300 mg oral od (1 dose)	£2.15	Once daily	
AML 15 DA + Mylotarg: course 1	Cytarabine	100 mg/m2 iv bd day 1-10 (20 doses)	£9.17	Every 12 hours	£2637.12 / course
	Daunorubicin	50 mg/m2 iv od day 1,3,5 (3 doses)	£262.97	Alternative day	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Alternative day	
	Granisetron	1 mg oral stat (5 doses)	£7.70	Alternative day	
	Metoclopramide	10 mg oral QDS prn	£0.07	4 times daily	
	Allopurinol	300 mg oral od	£2.15	Once daily	
	Mylotarg	5 mg	£1619.39	Once	
AML 15 DA + Mylotarg: course 2	Cytarabine	100 mg/m2 iv bd day 1-8 (16 doses)	£9.17	Every 12 hours	£979.15 / course

	Daunorubicin	50 mg/m2 iv od day 1,3,5 (3 doses)	£262.97	Alternative day	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Alternative day	
	Granisetron	1 mg oral stat (5 doses)	£7.70	Alternative day	
	Metoclopramide	10 mg oral QDS prn	£0.07	4 times daily	
	Allopurinol	300 mg oral od	£2.15	Once daily	
AML 15 FLAG-Ida: course 1	G-CSF	300 microgram OD for 7 days	£562.67	Once daily	£3789.60 / course
	Fludarabine	30mg/m2 iv. od day 1-5 (5 doses)	£366.60	Once daily	
	Cytarabine	2000mg/m2 iv od day 1-5 (5 doses)	£23.69	Once daily	
	Idarubicin	10 mg/m2 od day 4-6 (3 doses)	£410.59	Alternative day	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	1 mg oral stat (5 doses)	£7.70	Once daily	
	Metoclopramide	10 mg oral QDS (1op)	£0.07	4 times daily	
	Predsol	0.5% eye drops (1op)	£2.35	Daily	
AML 15 FLAG-Ida: course 2	G-CSF	300 microgram OD for 7 days	£562.67	Once daily	£3789.60 / course
	Fludarabine	30mg/m2 iv. od day 1-5 (5 doses)	£366.60	Once daily	
	Cytarabine	2000mg/m2 iv od day 1-5 (5 doses)	£23.69	Once daily	
	Idarubicin	10 mg/m2 od day 4-6 (3 doses)	£410.59	Alternative day	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	1 mg oral stat (5 doses)	£7.70	Once daily	
	Metoclopramide	10 mg oral QDS (1op)	£0.07	4 times daily	
	Predsol	0.5% eye drops (1op)	£2.35	Daily	
AML 15 FLAG-Ida + Mylotarg (course1)	G-CSF	300 microgram OD for 7 days	£562.67	Once daily	£5410.89 / course
	Fludarabine	30mg/m2 iv. od day 1-5 (5 doses)	£366.60	Once daily	
	Cytarabine	2000mg/m2 iv od day 1-5 (5 doses)	£23.69	Once daily	
	Idarubicin	10 mg/m2 od day 4-6 (3 doses)	£410.59	Alternative day	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	1 mg oral stat (5 doses)	£7.70	Once daily	
	Metoclopramide	10 mg oral QDS (1op)	£0.07	4 times daily	
	Chlorphenamine	10 mg iv Bolus	£1.90	Once Daily	
	Predsol	0.5% eye drops (1op)	£2.35	Daily	
	Mylotarg	5 mg	£1619.39	Once	

AML 15 FLAG-Ida + Mylotarg (course2)	G-CSF	300 microgram OD for 7 days	£562.67	Once daily	£3789.60 / course
	Fludarabine	30mg/m2 iv. od day 1-5 (5 doses)	£366.60	Once daily	
	Cytarabine	2000mg/m2 iv od day 1-5 (5 doses)	£23.69	Once daily	
	Idarubicin	10 mg/m2 od day 4-6 (3 doses)	£410.59	Alternative day	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	1 mg oral stat (5 doses)	£7.70	Once daily	
	Metoclopramide	10 mg oral QDS (1op)	£0.07	4 times daily	
	Predsol	0.5% eye drops (1op)	£2.35	Daily	
AML 15 MACE	Amsacrine	100 mg/m2 od day 1-5 (5 doses)	£173.32	Once daily	£1180.82 / course
	Cytarabine	200 mg/m2 od day 1-5 (5 doses)	£18.33	Once daily	
	Etoposide	100 mg/m2 od day 1-5 (5 doses)	£28.55	Once daily	
	Dexamethasone	8 mg oral stat	£0.56	Once daily	
	Granisetron	2 mg oral stat	£15.39	Once daily	
	Metoclopramide	10 mg oral QDS prn	£0.07	4 times daily	
AML 15 MACE + Mylotarg	Amsacrine	100 mg/m2 od day 1-5 (5 doses)	£173.32	Once daily	£2802.11 / course
	Cytarabine	200 mg/m2 od day 1-5 (5 doses)	£18.33	Once daily	
	Etoposide	100 mg/m2 od day 1-5 (5 doses)	£28.55	Once daily	
	Mylotarg	5mg (1 dose)	£1619.39	Once	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	2 mg oral stat (5 doses)	£15.39	Once daily	
	Metoclopramide	10 mg oral QDS prn	£0.07	4 times daily	
	Chlorphenamine	10 mg iv Bolus	£1.90	Once Daily	
AML 15 MidAC	Mitoxantrone	10 mg/m2 in 100ml N/Saline (5 doses)	£117.50	Once daily	£1204.19 / course
	Cytarabine	1000 mg/m2 (6 doses)	£91.65	Every 12 hours	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	2 mg oral stat (5 doses)	£15.39	Once daily	
	Metoclopramide	10 mg oral QDS prn	£0.07	Once daily	
	Predsol	0.5% eye drops (1op)	£2.35	Daily	
APML 15 Spanish: course 1	ATRA	45mg/m2 for 28 days (28 doses)	£448.81	Once daily	£2978.42 / course

	Idarubicin	12 mg/m2 (4 doses)	£615.89	First 4 days	
	Allopurinol	300mg oral OD	£2.15	Daily	
	Dexamethasone	8mg oral stat (4 doses)	£0.56	First 4 days	
	Granisetron	2mg oral stat (4 doses)	£15.39	First 4 days	
	Metoclopramide	10mg oral QDS prn	£0.07	4 times daily	
APML 15 Spanish: course 2	ATRA	45mg/m2 for 15 days (15doses)	£240.43	Once daily	£1915.92 / course
	Idarubicin	7 mg/m2 (4 doses)	£410.59	First 4 days	
	Dexamethasone	8mg oral stat (4 doses)	£0.56	First 4 days	
	Granisetron	1mg oral stat (4 doses)	£7.70	First 4 days	
	Metoclopramide	10mg oral QDS prn	£0.07	4 times daily	
APML 15 Spanish: course 3	ATRA	45mg/m2 for 15 days (15 doses)	£240.43	Once daily	£869.32 / course
	Mitozantrone	10 mg/m2 (5 doses)	£117.50	First 5 days	
	Dexamethasone	8mg oral stat (5 doses)	£0.56	First 5 days	
	Granisetron	1mg oral stat (5 doses)	£7.70		
	Metoclopramide	10mg oral QDS prn	£0.07		
APML 15 Spanish: course 4	ATRA	45mg/m2 for 15 days (15doses)	£240.43	Once daily	£864.60 / course
	Idarubicin	12 mg/m2 (1 doses)	£615.89	Once	
	Dexamethasone	8mg oral stat (4 doses)	£0.56	First 4 days	
	Granisetron	1mg oral stat (4 doses)	£7.70	First 4 days	
Maintenance (1-3 month)	Mercaptopurine	50 mg/m2 oral daily	£1.675	Once daily	£14.81 / week
	Methotrexate	15 mg/m2 IM bolus (weekly)	£3.08	Weekly	
Maintenance (4-24 month)	Mercaptopurine	50 mg/m2 oral daily	£1.675		
	Methotrexate	15 mg/m2 IM bolus (weekly)	£3.08		
	ATRA	45 mg/m2 per day for 15 days every 3 months	£240.45		
APML 15 MRC: ADE+ATRA	Cytarabine	100 mg/m2 iv bd day 1-10 (20 doses)	£9.17	Every 12 hours	£1607.42 / course
	Daunorubicin	100 mg/m2 iv day 1, 3, 5 (3 doses)	£473.34	Alternative days	
	Etoposide	100 mg/m2/d iv day 1-5 (5 doses)	£28.55	Once daily	

	ATRA	45mg/m2 for 28 days (28 doses)	£448.81	Once daily	
	Allopurinol	300mg oral OD (1 dose)	£2.15	Once daily	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	1 mg oral stat (5 doses)	£7.7	Once daily	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
APML 15 MRC : ADE	Cytarabine	100 mg/m2 iv bd day 1-8 (16 doses)	£9.17	Every 12 hours	£1121.90 / course
	Daunorubicin	100 mg/m2 iv day 1, 3, 5 (3 doses)	£473.34	Alternative days	
	Etoposide	100 mg/m2/d iv day 1-5 (5 doses)	£28.55	Once daily	
	Allopurinol	300mg oral OD (1 dose)	£2.15	Once daily	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	1 mg oral stat (5 doses)	£7.7	Once daily	
	Metoclopramide	10 mg oral QDS prn (1 dose)	£0.07	4 times daily	
APML 15 MRC : MACE	Amsacrine	100 mg/m2 od day 1-5 (5 doses)	£173.32	Once daily	£1180.2/ course
	Cytarabine	200 mg/m2 od day 1-5 (5 doses)	£18.33	Once daily	
	Etoposide	100 mg/m2 od day 1-5 (5 doses)	£28.55	Once daily	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	2 mg oral stat (5 doses)	£15.39	Once daily	
	Metoclopramide	10 mg oral QDS prn	£0.07	Once daily	
APML 15 MRC : MidAC	Mitoxantrone	10 mg/m2 in 100ml N/Saline (5 doses)	£117.50	Once daily	£1204.19 / course
	Cytarabine	1000 mg/m2 (6 doses)	£91.65	Every 12 hours	
	Dexamethasone	8 mg oral stat (5 doses)	£0.56	Once daily	
	Granisetron	2 mg oral stat (5 doses)	£15.39	Once daily	
	Metoclopramide	10 mg oral QDS prn	£0.07	Once daily	
	Predsol	0.5% eye drops (1op)	£2.35	Daily	
Other treatments					
Supportive Care					
Erythropoietin	Aranesp	0.45 mcg/kg weekly (injection)	£46.76	weekly	£46.76 / week
Steroids					
Dexamethasone	Dexamethasone	4 mg, twice a day	£0.29	Daily	£0.58 / day

Prednisolone	Prednisolone	20 mg, oral OD	£0.14	Daily	£0.14 / day
Hydrocortisone	Hydrocortisone	20 mg, oral OD	£1.4	Daily	£1.4 / day
G-CSF	G-CSF	300 microgram OD daily	£80.38	4 days after chemo	£80.38 / day (4 days after chemo) (once every 25 days)
Transfusion	Red blood	2 unit (mean)	£261		£414 / transfusion
	Platelet	1 unit (mean)	£153		
Immunosuppresive					
	Cyclosporin	Neoral: 12.5mg/kg oral OD	£23.4	Daily	£23.5 / day
	Prednisolone	10 mg oral OD	£0.08	Daily	
Venesection	-	-	-	monthly	£132.1 / venesection
Palliative care	-	-	-	3 times weekly	£336.3 / day
Transplantation (allo)				Once	£45558 / transplantation
Radiotherapy					
TBI				Once	£651 / radiotherapy
Non-TBI				Once	£635 / radiotherapy
Splenectomy	-	-	-	Once	£4010 / spenectomy

Appendix 7.3 Detailed drug item cost lists

Detailed drug item cost list for ADE related regimen (by day)

Regimen	Day	Drug item	Dosage	Unit cost	Accumulated cost
ADE 10+3+5	Day 1	Granisetron	1mg Oral stat	£7.7	£320
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Metoclopramide	10 mg oral QDS prn	£0.07	
		Allopurinol	300 mg Oral OD	£2.15	
	Day 2	Granisetron	1 mg mg Oral stat	£7.7	£376
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 3	Granisetron	1mg Oral stat	£7.7	£694
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 4	Granisetron	1 mg mg Oral stat	£7.7	£749
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 5	Granisetron	1mg Oral stat	£7.7	£1067
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 6	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£1085
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 7	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£1104
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 8	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£1122
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 9	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£1140
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 10	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£1159
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
ADE 10+3+8	Day 1	Granisetron	1mg Oral stat	£7.7	£320
		Dexamethasone	8 mg Oral stat	£0.56	

		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Metoclopramide	10 mg oral QDS prn	£0.07	
		Allopurinol	300 mg Oral OD	£2.15	
	Day 2	Granisetron	1 mg mg Oral stat	£7.7	£376
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 3	Granisetron	1mg Oral stat	£7.7	£694
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 4	Granisetron	1 mg mg Oral stat	£7.7	£749
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 5	Granisetron	1mg Oral stat	£7.7	£1067
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 6	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£1085
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 7	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£1104
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 8	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£1122
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
ADE + Mylotarg (Course 1)	Day 1	Granisetron	1mg Oral stat	£7.7	£1942
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Metoclopramide	10 mg oral QDS prn	£0.07	
		Allopurinol	300 mg Oral OD	£2.15	
		Chlorphenamine	10 mg IV Bolus	£1.90	
		Mylotarg	3 mg protein/m2	£1619	
	Day 2	Granisetron	1 mg mg Oral stat	£7.7	£1997
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	

		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 3	Granisetron	1mg Oral stat	£7.7	£2315
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 4	Granisetron	1 mg mg Oral stat	£7.7	£2370
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 5	Granisetron	1mg Oral stat	£7.7	£2688
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 6	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£2707
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 7	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£2725
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 8	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£2743
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 9	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£2762
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 10	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£2780
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
ADE + Mylotarg	Day 1	Granisetron	1mg Oral stat	£7.7	£320
(Course 2)		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Metoclopramide	10 mg oral QDS prn	£0.07	
		Allopurinol	300 mg Oral OD	£2.15	
	Day 2	Granisetron	1 mg mg Oral stat	£7.7	£376
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 3	Granisetron	1mg Oral stat	£7.7	£694
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 4	Granisetron	1 mg mg Oral stat	£7.7	£749
		Dexamethasone	8 mg Oral stat	£0.56	

	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
Day 5	Granisetron	1mg Oral stat	£7.7	£1067
	Dexamethasone	8 mg Oral stat	£0.56	
	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
	Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
Day 6	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£1085
	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
Day 7	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£1104
	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
Day 8	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£1122
	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	

Detailed drug item cost list for AraC (HD) related regimen (by day)

Regimen	Day	Drug item	Dosage	Unit cost	Accumulated cost
AraC (HD)	Day 1	Granisetron	2 mg Oral stat	£15.4	£568
(course 1 and 2)		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£275	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£275	
		Metoclopramide	10 mg oral QDS prn	£0.07	
		Predsol	1 drop QDS	£2.35	
	Day 3	Granisetron	2 mg Oral stat	£15.4	£1134
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£275	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£275	
	Day 5	Granisetron	2 mg Oral stat	£15.4	£1700
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£275	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£275	
AraC (HD)	Day 1	Granisetron	2 mg Oral stat	£15.4	£568
(course 2)		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£275	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£275	
		Metoclopramide	10 mg oral QDS prn	£0.07	
		Predsol	1 drop QDS	£2.35	
	Day 3	Granisetron	2 mg Oral stat	£15.4	£1134
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£275	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£275	
	Day 5	Granisetron	2 mg Oral stat	£15.4	£1700
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£275	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£275	
AraC (HD) + Mylotarg	Day 1	Granisetron	2 mg Oral stat	£15.4	£2190
(course 1)		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£275	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£275	
		Metoclopramide	10 mg oral QDS prn	£0.07	
		Predsol	1 drop QDS	£2.35	
		Chlorphenamine	10 mg IV Bolus	£1.90	
		Mylotarg	3 mg protein/m2	£1619	
	Day 3	Granisetron	2 mg Oral stat	£15.4	£2755
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£275	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£275	
	Day 5	Granisetron	2 mg Oral stat	£15.4	£3321
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£275	

		Cytarabine	3000 mg/m2 in 500ml N/Saline	£275	
AraC (HD) + Mylotarg	Day 1	Granisetron	2 mg Oral stat	£15.4	£568
(course 2)		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£275	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£275	
		Metoclopramide	10 mg oral QDS prn	£0.07	
		Predsol	1 drop QDS	£2.35	
	Day 3	Granisetron	2 mg Oral stat	£15.4	£1134
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£275	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£275	
	Day 5	Granisetron	2 mg Oral stat	£15.4	£1700
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£275	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£275	

Detailed drug item cost list for AraC (LD) related regimen (by day)

Regimen	Day	Drug item	Dosage	Unit cost	Accumulated cost
AraC (LD)	Day 1	Cytarabine	20 mg injection	£4.58	£9
		Cytarabine	20 mg injection	£4.58	
	Day 2	Cytarabine	20 mg injection	£4.58	£18
		Cytarabine	20 mg injection	£4.58	
	Day 3	Cytarabine	20 mg injection	£4.58	£28
		Cytarabine	20 mg injection	£4.58	
	Day 4	Cytarabine	20 mg injection	£4.58	£37
		Cytarabine	20 mg injection	£4.58	
	Day 5	Cytarabine	20 mg injection	£4.58	£46
		Cytarabine	20 mg injection	£4.58	
	Day 6	Cytarabine	20 mg injection	£4.58	£55
		Cytarabine	20 mg injection	£4.58	
	Day 7	Cytarabine	20 mg injection	£4.58	£64
		Cytarabine	20 mg injection	£4.58	
	Day 8	Cytarabine	20 mg injection	£4.58	£73
		Cytarabine	20 mg injection	£4.58	
	Day 9	Cytarabine	20 mg injection	£4.58	£82
		Cytarabine	20 mg injection	£4.58	
	Day 10	Cytarabine	20 mg injection	£4.58	£92
		Cytarabine	20 mg injection	£4.58	
AraC (LD) + Mylotarg	Day 1	Cytarabine	20 mg injection	£4.58	£1631
(course 1)		Cytarabine	20 mg injection	£4.58	
		Chlorphenamine	10 mg IV Bolus	£1.90	
		Mylotarg	3 mg protein/m2	£1619	
		Metoclopramide	10 mg oral QDS prn	£0.07	
	Day 2	Cytarabine	20 mg injection	£4.58	£1640
		Cytarabine	20 mg injection	£4.58	
	Day 3	Cytarabine	20 mg injection	£4.58	£1649
		Cytarabine	20 mg injection	£4.58	
	Day 4	Cytarabine	20 mg injection	£4.58	£1658
		Cytarabine	20 mg injection	£4.58	
	Day 5	Cytarabine	20 mg injection	£4.58	£1668
		Cytarabine	20 mg injection	£4.58	
	Day 6	Cytarabine	20 mg injection	£4.58	£1676
		Cytarabine	20 mg injection	£4.58	
	Day 7	Cytarabine	20 mg injection	£4.58	£1686
		Cytarabine	20 mg injection	£4.58	
	Day 8	Cytarabine	20 mg injection	£4.58	£1695
		Cytarabine	20 mg injection	£4.58	
	Day 9	Cytarabine	20 mg injection	£4.58	£1704
		Cytarabine	20 mg injection	£4.58	
	Day 10	Cytarabine	20 mg injection	£4.58	£1713
		Cytarabine	20 mg injection	£4.58	

Detailed drug item cost list for Clofarabine related regimen (by day)

Regimen	Day	Drug item	Dosage	Unit cost	Accumulated cost
Clofarabine	Day 1	Granisetron	2 mg Oral stat	£15.4	£2176
		Dexamethasone	8 mg Oral stat	£0.56	
		Clofarabine	20 mg/m2 in 100ml N/Saline	£2160	
	Day 2	Granisetron	2 mg Oral stat	£15.4	£4352
		Dexamethasone	8 mg Oral stat	£0.56	
		Clofarabine	20 mg/m2 in 100ml N/Saline	£2160	
	Day 3	Granisetron	2 mg Oral stat	£15.4	£6528
		Dexamethasone	8 mg Oral stat	£0.56	
		Clofarabine	20 mg/m2 in 100ml N/Saline	£2160	
	Day 4	Granisetron	2 mg Oral stat	£15.4	£8704
		Dexamethasone	8 mg Oral stat	£0.56	
		Clofarabine	20 mg/m2 in 100ml N/Saline	£2160	
	Day 5	Granisetron	2 mg Oral stat	£15.4	£10880
		Dexamethasone	8 mg Oral stat	£0.56	
		Clofarabine	20 mg/m2 in 100ml N/Saline	£2160	
		Metoclopramide	10 mg oral QDS prn	£0.07	

Detailed drug item cost list for DA related regimen (by day)

Regimen	Day	Drug item	Dosage	Unit cost	Accumulated cost
DA 3+10	Day 1	Granisetron	1mg Oral stat	£7.7	£292
(course 1)		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Metoclopramide	10 mg oral QDS prn	£0.07	
		Allopurinol	300 mg Oral OD	£2.15	
	Day 2	Granisetron	1mg Oral stat	£7.7	£318
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 3	Granisetron	1mg Oral stat	£7.7	£608
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 4	Granisetron	1mg Oral stat	£7.7	£635
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 5	Granisetron	1mg Oral stat	£7.7	£924
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 6	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£943
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 7	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£961
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 8	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£979
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 9	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£998
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 10	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£1016
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
DA 3+8	Day 1	Granisetron	1mg Oral stat	£7.7	£292
(course 2)		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Metoclopramide	10 mg oral QDS prn	£0.07	
		Allopurinol	300 mg Oral OD	£2.15	
	Day 2	Granisetron	1mg Oral stat	£7.7	£318
		Dexamethasone	8 mg Oral stat	£0.56	

		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 3	Granisetron	1mg Oral stat	£7.7	£608
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 4	Granisetron	1mg Oral stat	£7.7	£635
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 5	Granisetron	1mg Oral stat	£7.7	£924
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 6	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£943
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 7	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£961
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 8	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£979
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
DA + Mylotarg (course 1)	Day 1	Granisetron	1mg Oral stat	£7.7	£1913
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Metoclopramide	10 mg oral QDS prn	£0.07	
		Allopurinol	300 mg Oral OD	£2.15	
		Chlorphenamine	10 mg IV Bolus	£1.90	
		Mylotarg	3 mg protein/m2	£1619	
	Day 2	Granisetron	1mg Oral stat	£7.7	£1940
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 3	Granisetron	1mg Oral stat	£7.7	£2229
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 4	Granisetron	1mg Oral stat	£7.7	£2256
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 5	Granisetron	1mg Oral stat	£7.7	£2545
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	

		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 6	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£2564
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 7	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£2582
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 8	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£2600
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 9	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£2619
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 10	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£2637
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
DA + Mylotarg	Day 1	Granisetron	1mg Oral stat	£7.7	£292
(course 2)		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Metoclopramide	10 mg oral QDS prn	£0.07	
		Allopurinol	300 mg Oral OD	£2.15	
	Day 2	Granisetron	1mg Oral stat	£7.7	£318
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 3	Granisetron	1mg Oral stat	£7.7	£608
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 4	Granisetron	1mg Oral stat	£7.7	£635
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 5	Granisetron	1mg Oral stat	£7.7	£924
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 6	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£943
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 7	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£961
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 8	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£979
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
DA (D35 C400)	Day 1	Granisetron	1mg Oral stat	£7.7	£268
(course 1)		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
		Daunorubicin	35 mg/m2 in 100ml N/Saline	£221	
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
		Metoclopramide	10 mg oral QDS prn	£0.07	
		Allopurinol	300 mg Oral OD	£2.15	

	Day 2	Granisetron	1mg Oral stat	£7.7	£313
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
	Day 3	Granisetron	1mg Oral stat	£7.7	£579
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
		Daunorubicin	35 mg/m2 in 100ml N/Saline	£221	
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
	Day 4	Granisetron	1mg Oral stat	£7.7	£624
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
	Day 5	Granisetron	1mg Oral stat	£7.7	£890
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
		Daunorubicin	35 mg/m2 in 100ml N/Saline	£221	
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
	Day 6	Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	£926
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
	Day 7	Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	£963
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
	Day 8	Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	£1000
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
	Day 9	Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	£1036
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
	Day 10	Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	£1073
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
DA (D35 C400)	Day 1	Granisetron	1mg Oral stat	£7.7	£268
(course 2)		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
		Daunorubicin	35 mg/m2 in 100ml N/Saline	£221	
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
		Metoclopramide	10 mg oral QDS prn	£0.07	
		Allopurinol	300 mg Oral OD	£2.15	
	Day 2	Granisetron	1mg Oral stat	£7.7	£313
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
	Day 3	Granisetron	1mg Oral stat	£7.7	£579
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
		Daunorubicin	35 mg/m2 in 100ml N/Saline	£221	
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
	Day 4	Granisetron	1mg Oral stat	£7.7	£624
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
	Day 5	Granisetron	1mg Oral stat	£7.7	£890

		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
		Daunorubicin	35 mg/m2 in 100ml N/Saline	£221	
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
	Day 6	Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	£926
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
	Day 7	Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	£963
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
	Day 8	Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	£1000
		Cytarabine	200 mg/m2 in 100ml N/Saline	£18.33	
DA (D35 C200) (course 1)	Day 1	Granisetron	1mg Oral stat	£7.7	£250
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	35 mg/m2 in 100ml N/Saline	£221	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Metoclopramide	10 mg oral QDS prn	£0.07	
		Allopurinol	300 mg Oral OD	£2.15	
	Day 2	Granisetron	1mg Oral stat	£7.7	£276
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 3	Granisetron	1mg Oral stat	£7.7	£524
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	35 mg/m2 in 100ml N/Saline	£221	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 4	Granisetron	1mg Oral stat	£7.7	£550
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 5	Granisetron	1mg Oral stat	£7.7	£798
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	35 mg/m2 in 100ml N/Saline	£221	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 6	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£816
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 7	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£835
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 8	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£853
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 9	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£871
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 10	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£890
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
DA (D35 C200) (course 2)	Day 1	Granisetron	1mg Oral stat	£7.7	£250
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	

	Daunorubicin	35 mg/m2 in 100ml N/Saline	£221	
	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Metoclopramide	10 mg oral QDS prn	£0.07	
	Allopurinol	300 mg Oral OD	£2.15	
Day 2	Granisetron	1mg Oral stat	£7.7	£276
	Dexamethasone	8 mg Oral stat	£0.56	
	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
Day 3	Granisetron	1mg Oral stat	£7.7	£524
	Dexamethasone	8 mg Oral stat	£0.56	
	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Daunorubicin	35 mg/m2 in 100ml N/Saline	£221	
	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
Day 4	Granisetron	1mg Oral stat	£7.7	£550
	Dexamethasone	8 mg Oral stat	£0.56	
	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
Day 5	Granisetron	1mg Oral stat	£7.7	£798
	Dexamethasone	8 mg Oral stat	£0.56	
	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Daunorubicin	35 mg/m2 in 100ml N/Saline	£221	
	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
Day 6	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£816
	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
Day 7	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£835
	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
Day 8	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£853
	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	

Detailed drug item cost list for FLA related regimen (by day)

Regimen	Day	Drug item	Dosage	Unit cost	Accumulated cost
FLA	Day 1	Granisetron	1mg Oral stat	£7.7	£401
(course 1)		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
		Prednisolone	0.5% 1op	£2.35	
		Metoclopramide	10 mg oral QDS prn	£0.07	
	Day 2	Fludarabine	30 mg/m2 in 100ml N/S	£366.6	£791
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
	Day 3	Granisetron	1mg Oral stat	£7.7	£1190
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
	Day 4	Fludarabine	30 mg/m2 in 100ml N/S	£366.6	£1580
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
	Day 5	Granisetron	1mg Oral stat	£7.7	£1979
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
FLA	Day 1	Granisetron	1mg Oral stat	£7.7	£401
(course 2)		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
		Prednisolone	0.5% 1op	£2.35	
		Metoclopramide	10 mg oral QDS prn	£0.07	
	Day 2	Fludarabine	30 mg/m2 in 100ml N/S	£366.6	£791
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
	Day 3	Granisetron	1mg Oral stat	£7.7	£1190
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
	Day 4	Fludarabine	30 mg/m2 in 100ml N/S	£366.6	£1580
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
	Day 5	Granisetron	1mg Oral stat	£7.7	£1979
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	

Detailed drug item cost list for FLAG related regimen (by day)

Regimen	Day	Drug item	Dosage	Unit cost	Accumulated cost
FLAG	Day 1	G-CSF	300 microgram OD	£80.38	£481
(course 1& 2)		Granisetron	1mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
		Prednisolone	0.5% 1op	£2.35	
		Metoclopramide	10 mg oral QDS prn	£0.07	
	Day 2	G-CSF	300 microgram OD	£80.38	£960
		Granisetron	1mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
	Day 3	G-CSF	300 microgram OD	£80.38	£1439
		Granisetron	1mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
	Day 4	G-CSF	300 microgram OD	£80.38	£1918
		Granisetron	1mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
	Day 5	G-CSF	300 microgram OD	£80.38	£2397
		Granisetron	1mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
	Day 6	G-CSF	300 microgram OD	£80.38	£2478
	Day 7	G-CSF	300 microgram OD	£80.38	£2558

Detailed drug item cost list for FLAG-Ida related regimen (by day)

Regimen	Day	Drug item	Dosage	Unit cost	Accumulated cost
FLAG-Ida	Day 1	G-CSF	300 microgram OD	£80.38	£892
(course 1 & 2)		Granisetron	1mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
		Prednisolone	0.5% 1op	£2.35	
		Metoclopramide	10 mg oral QDS prn	£0.07	
		Idarubicin	10 mg/m2 in 100 ml	£410.6	
	Day 2	G-CSF	300 microgram OD	£80.38	£1371
		Granisetron	1mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
	Day 3	G-CSF	300 microgram OD	£80.38	£2260
		Granisetron	1mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
		Idarubicin	10 mg/m2 in 100 ml	£410.6	
	Day 4	G-CSF	300 microgram OD	£80.38	£2739
		Granisetron	1mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
	Day 5	G-CSF	300 microgram OD	£80.38	£3629
		Granisetron	1mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
		Idarubicin	10 mg/m2 in 100 ml	£410.6	
	Day 6	G-CSF	300 microgram OD	£80.38	£3709
	Day 7	G-CSF	300 microgram OD	£80.38	£3790
FLAG-Ida	Day 1	G-CSF	300 microgram OD	£80.38	£892
(course 2)		Granisetron	1mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
		Prednisolone	0.5% 1op	£2.35	
		Metoclopramide	10 mg oral QDS prn	£0.07	
		Idarubicin	10 mg/m2 in 100 ml	£410.6	
	Day 2	G-CSF	300 microgram OD	£80.38	£1371
		Granisetron	1mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	

		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
	Day 3	G-CSF	300 microgram OD	£80.38	£2260
		Granisetron	1mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
		Idarubicin	10 mg/m2 in 100 ml	£410.6	
	Day 4	G-CSF	300 microgram OD	£80.38	£2739
		Granisetron	1mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
	Day 5	G-CSF	300 microgram OD	£80.38	£3629
		Granisetron	1mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
		Idarubicin	10 mg/m2 in 100 ml	£410.6	
	Day 6	G-CSF	300 microgram OD	£80.38	£3709
	Day 7	G-CSF	300 microgram OD	£80.38	£3790
FLAG-Ida + Mylotarg (course 1)	Day 1	G-CSF	300 microgram OD	£80.38	£2513
		Granisetron	1mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
		Prednisolone	0.5% 1op	£2.35	
		Metoclopramide	10 mg oral QDS prn	£0.07	
		Idarubicin	10 mg/m2 in 100 ml	£410.6	
		Chlorphenamine	10 mg IV Bolus	£1.90	
		Mylotarg	3 mg protein/m2	£1619	
	Day 2	G-CSF	300 microgram OD	£80.38	£2992
		Granisetron	1mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
	Day 3	G-CSF	300 microgram OD	£80.38	£3882
		Granisetron	1mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
		Idarubicin	10 mg/m2 in 100 ml	£410.6	
	Day 4	G-CSF	300 microgram OD	£80.38	£4361
		Granisetron	1mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
	Day 5	G-CSF	300 microgram OD	£80.38	£5250

		Granisetron	1mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
		Idarubicin	10 mg/m2 in 100 ml	£410.6	
	Day 6	G-CSF	300 microgram OD	£80.38	£5331
	Day 7	G-CSF	300 microgram OD	£80.38	£5411
FLAG-Ida + Mylotarg (course 2)	Day 1	G-CSF	300 microgram OD	£80.38	£892
		Granisetron	1mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
		Prednisolone	0.5% 1op	£2.35	
		Metoclopramide	10 mg oral QDS prn	£0.07	
		Idarubicin	10 mg/m2 in 100 ml	£410.6	
	Day 2	G-CSF	300 microgram OD	£80.38	£1371
		Granisetron	1mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
	Day 3	G-CSF	300 microgram OD	£80.38	£2260
		Granisetron	1mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
		Idarubicin	10 mg/m2 in 100 ml	£410.6	
	Day 4	G-CSF	300 microgram OD	£80.38	£2739
		Granisetron	1mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
	Day 5	G-CSF	300 microgram OD	£80.38	£3629
		Granisetron	1mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Fludarabine	30 mg/m2 in 100ml N/S	£366.6	
		Cytarabine	2000 mg/m2 in 500ml N/Saline	£23.69	
		Idarubicin	10 mg/m2 in 100 ml	£410.6	
	Day 6	G-CSF	300 microgram OD	£80.38	£3709
	Day 7	G-CSF	300 microgram OD	£80.38	£3790

Detailed drug item cost list for MidAC related regimen (by day)

Regimen	Day	Drug item	Dosage	Unit cost	Accumulated cost
MidAC	Day 1	Granisetron	2 mg Oral stat	£15.4	£319
Mini-MidAC		Dexamethasone	8 mg Oral stat	£0.56	
		Mitozantrone	10 mg/m2 in 100 ml N/S	£117.5	
		Cytarabine	1000 mg/m2 in 500ml N/Saline	£91.65	
		Cytarabine	1000 mg/m2 in 500ml N/Saline	£91.65	
		Prednisolone	0.5% 1op	£2.35	
		Metoclopramide	10 mg oral QDS prn	£0.07	
	Day 2	Granisetron	2 mg Oral stat	£15.4	£636
		Dexamethasone	8 mg Oral stat	£0.56	
		Mitozantrone	10 mg/m2 in 100 ml N/S	£117.5	
		Cytarabine	1000 mg/m2 in 500ml N/Saline	£91.65	
		Cytarabine	1000 mg/m2 in 500ml N/Saline	£91.65	
	Day 3	Granisetron	2 mg Oral stat	£15.4	£953
		Dexamethasone	8 mg Oral stat	£0.56	
		Mitozantrone	10 mg/m2 in 100 ml N/S	£117.5	
		Cytarabine	1000 mg/m2 in 500ml N/Saline	£91.65	
		Cytarabine	1000 mg/m2 in 500ml N/Saline	£91.65	
	Day 4	Granisetron	2 mg Oral stat	£15.4	£1078
		Dexamethasone	8 mg Oral stat	£0.56	
		Mitozantrone	10 mg/m2 in 100 ml N/S	£117.5	
	Day 5	Granisetron	2 mg Oral stat	£15.4	£1204
		Dexamethasone	8 mg Oral stat	£0.56	
		Mitozantrone	10 mg/m2 in 100 ml N/S	£117.5	
HAM	Day 1	Cytarabine	3000 mg/m2 in 500ml N/Saline	£274.95	£552.32
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£274.95	
		Prednisolone	0.5% 1op	£2.35	
		Metoclopramide	10 mg oral QDS prn	£0.07	
	Day 2	Granisetron	1 mg Oral stat	£7.7	£1228
		Dexamethasone	8 mg Oral stat	£0.56	
		Mitozantrone	10 mg/m2 in 100 ml N/S	£117.5	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£274.95	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£274.95	
	Day 3	Granisetron	1 mg Oral stat	£7.7	£1904
		Dexamethasone	8 mg Oral stat	£0.56	
		Mitozantrone	10 mg/m2 in 100 ml N/S	£117.5	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£274.95	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£274.95	
	Day 4	Granisetron	1 mg Oral stat	£7.7	£2579
		Dexamethasone	8 mg Oral stat	£0.56	
		Mitozantrone	10 mg/m2 in 100 ml N/S	£117.5	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£274.95	
		Cytarabine	3000 mg/m2 in 500ml N/Saline	£274.95	
	Day 5	Granisetron	1 mg Oral stat	£7.7	£2705

	Dexamethasone	8 mg Oral stat	£0.56	
	Mitozantrone	10 mg/m2 in 100 ml N/S	£117.5	
Day 6	Granisetron	1 mg Oral stat	£7.7	£2831
	Dexamethasone	8 mg Oral stat	£0.56	
	Mitozantrone	10 mg/m2 in 100 ml N/S	£117.5	

Detailed drug item cost list for MACE related regimen (by day)

Regimen	Day	Drug item	Dosage	Unit cost	Accumulated cost
MACE	Day 1	Granisetron	2 mg Oral stat	£15.4	£236
		Dexamethasone	8 mg Oral stat	£0.56	
		Etoposide	100 mg/m2 in 500 ml N/S	£28.55	
		Amsacrine	100 mg/m2 in 500 ml Dextrose 5%	£173.32	
		Cytarabine	200 mg/m2 in 1000 ml N/S	£18.33	
		Metoclopramide	10 mg oral QDS prn	£0.07	
	Day 2	Granisetron	2 mg Oral stat	£15.4	£472
		Dexamethasone	8 mg Oral stat	£0.56	
		Etoposide	100 mg/m2 in 500 ml N/S	£28.55	
		Amsacrine	100 mg/m2 in 500 ml Dextrose 5%	£173.32	
		Cytarabine	200 mg/m2 in 1000 ml N/S	£18.33	
	Day 3	Granisetron	2 mg Oral stat	£15.4	£709
		Dexamethasone	8 mg Oral stat	£0.56	
		Etoposide	100 mg/m2 in 500 ml N/S	£28.55	
		Amsacrine	100 mg/m2 in 500 ml Dextrose 5%	£173.32	
		Cytarabine	200 mg/m2 in 1000 ml N/S	£18.33	
	Day 4	Granisetron	2 mg Oral stat	£15.4	£945
		Dexamethasone	8 mg Oral stat	£0.56	
		Etoposide	100 mg/m2 in 500 ml N/S	£28.55	
		Amsacrine	100 mg/m2 in 500 ml Dextrose 5%	£173.32	
		Cytarabine	200 mg/m2 in 1000 ml N/S	£18.33	
	Day 5	Granisetron	2 mg Oral stat	£15.4	£1181
		Dexamethasone	8 mg Oral stat	£0.56	
		Etoposide	100 mg/m2 in 500 ml N/S	£28.55	
		Amsacrine	100 mg/m2 in 500 ml Dextrose 5%	£173.32	
		Cytarabine	200 mg/m2 in 1000 ml N/S	£18.33	
MACE + Mylotarg	Day 1	Granisetron	2 mg Oral stat	£15.4	£1858
		Dexamethasone	8 mg Oral stat	£0.56	
		Etoposide	100 mg/m2 in 500 ml N/S	£28.55	
		Amsacrine	100 mg/m2 in 500 ml Dextrose 5%	£173.32	
		Cytarabine	200 mg/m2 in 1000 ml N/S	£18.33	
		Metoclopramide	10 mg oral QDS prn	£0.07	
		Chlorphenamine	10 mg IV Bolus	£1.90	
		Mylotarg	3 mg protein/m2	£1619	
	Day 2	Granisetron	2 mg Oral stat	£15.4	£2094
		Dexamethasone	8 mg Oral stat	£0.56	
		Etoposide	100 mg/m2 in 500 ml N/S	£28.55	
		Amsacrine	100 mg/m2 in 500 ml Dextrose 5%	£173.32	
		Cytarabine	200 mg/m2 in 1000 ml N/S	£18.33	
	Day 3	Granisetron	2 mg Oral stat	£15.4	£2330
		Dexamethasone	8 mg Oral stat	£0.56	
		Etoposide	100 mg/m2 in 500 ml N/S	£28.55	
		Amsacrine	100 mg/m2 in 500 ml Dextrose 5%	£173.32	

	Cytarabine	200 mg/m2 in 1000 ml N/S	£18.33	
Day 4	Granisetron	2 mg Oral stat	£15.4	£2566
	Dexamethasone	8 mg Oral stat	£0.56	
	Etoposide	100 mg/m2 in 500 ml N/S	£28.55	
	Amsacrine	100 mg/m2 in 500 ml Dextrose 5%	£173.32	
	Cytarabine	200 mg/m2 in 1000 ml N/S	£18.33	
Day 5	Granisetron	2 mg Oral stat	£15.4	£2802
	Dexamethasone	8 mg Oral stat	£0.56	
	Etoposide	100 mg/m2 in 500 ml N/S	£28.55	
	Amsacrine	100 mg/m2 in 500 ml Dextrose 5%	£173.32	
	Cytarabine	200 mg/m2 in 1000 ml N/S	£18.33	

Detailed drug item cost list for Spanish approach related regimen (by day)

Regimen	Day	Drug item	Dosage	Unit cost	Accumulated cost
Spanish approach (course 1)	Day 1	ATRA	45 mg/m2 per day	£16.03	£650
		Metoclopramide	10 mg oral QDS prn	£0.07	
		Allopurinol	300 mg Oral OD	£2.15	
		Granisetron	2 mg Oral stat	£15.4	
		Dexamethasone	8 mg Oral stat	£0.56	
		Idarubicin	12 mg/m2 in 100 ml N/S	£615.89	
	Day 2	ATRA	45 mg/m2 per day	£16.03	£1298
		Granisetron	2 mg Oral stat	£15.4	
		Dexamethasone	8 mg Oral stat	£0.56	
		Idarubicin	12 mg/m2 in 100 ml N/S	£615.89	
	Day 3	ATRA	45 mg/m2 per day	£16.03	£1946
		Granisetron	2 mg Oral stat	£15.4	
		Dexamethasone	8 mg Oral stat	£0.56	
		Idarubicin	12 mg/m2 in 100 ml N/S	£615.89	
	Day 4	ATRA	45 mg/m2 per day	£16.03	£2594
		Granisetron	2 mg Oral stat	£15.4	
		Dexamethasone	8 mg Oral stat	£0.56	
		Idarubicin	12 mg/m2 in 100 ml N/S	£615.89	
	Day 5-28	ATRA	45 mg/m2 per day	£320.60	£2978
Spanish approach (course 2)	Day 1	ATRA	45 mg/m2 per day	£16.03	£435
		Granisetron	1 mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Idarubicin	7 mg/m2 in 100 ml N/S	£410.59	
	Day 2	ATRA	45 mg/m2 per day	£16.03	£870
		Granisetron	1 mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Idarubicin	7 mg/m2 in 100 ml N/S	£410.59	
	Day 3	ATRA	45 mg/m2 per day	£16.03	£1305
		Granisetron	1 mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Idarubicin	7 mg/m2 in 100 ml N/S	£410.59	
	Day 4	ATRA	45 mg/m2 per day	£16.03	£1740
		Granisetron	1 mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Idarubicin	7 mg/m2 in 100 ml N/S	£410.59	
		Metoclopramide	10 mg oral QDS prn	£0.07	
	Day 5-15	ATRA	45 mg/m2 per day (for 11 days)	£176.33	£1916
Spanish approach (course 3)	Day 1	Granisetron	1 mg Oral stat	£7.7	£142
		Dexamethasone	8 mg Oral stat	£0.56	
		Mitozantrone	10 mg/m2 in 100 ml N/S	£117.5	
		ATRA	45 mg/m2 per day	£16.03	
		Metoclopramide	10 mg oral QDS prn	£0.07	
	Day 2	Granisetron	1 mg Oral stat	£7.7	£284
		Dexamethasone	8 mg Oral stat	£0.56	

		Mitozantrone	10 mg/m2 in 100 ml N/S	£117.5	
		ATRA	45 mg/m2 per day	£16.03	
	Day 3	Granisetron	1 mg Oral stat	£7.7	£425
		Dexamethasone	8 mg Oral stat	£0.56	
		Mitozantrone	10 mg/m2 in 100 ml N/S	£117.5	
		ATRA	45 mg/m2 per day	£16.03	
	Day 4	Granisetron	1 mg Oral stat	£7.7	£567
		Dexamethasone	8 mg Oral stat	£0.56	
		Mitozantrone	10 mg/m2 in 100 ml N/S	£117.5	
		ATRA	45 mg/m2 per day	£16.03	
	Day 5	Granisetron	1 mg Oral stat	£7.7	£709
		Dexamethasone	8 mg Oral stat	£0.56	
		Mitozantrone	10 mg/m2 in 100 ml N/S	£117.5	
		ATRA	45 mg/m2 per day	£16.03	
	Day 6-15	ATRA	45 mg/m2 per day (for 10 days)	£160.3	£869
Spanish approach (course 4)	Day 1	ATRA	45 mg/m2 per day	£16.03	£640
		Granisetron	1 mg Oral stat	£7.7	
		Dexamethasone	8 mg Oral stat	£0.56	
		Idarubicin	12 mg/m2 in 100 ml N/S	£615.89	
	Day 2-15	ATRA	45 mg/m2 per day (for 14 days)	£224.42	£865
Spanish maintenance (Month 1-3)		Mercaptopurine	50 mg/m2 OD for 84 days	£148.29	
	Week 1	Methotrexate	15 mg/m2 IM bolus	£3.08	
	Week 2	Methotrexate	15 mg/m2 IM bolus	£3.08	
	Week 3	Methotrexate	15 mg/m2 IM bolus	£3.08	
	Week 4	Methotrexate	15 mg/m2 IM bolus	£3.08	
	Week 5	Methotrexate	15 mg/m2 IM bolus	£3.08	
	Week 6	Methotrexate	15 mg/m2 IM bolus	£3.08	
	Week 7	Methotrexate	15 mg/m2 IM bolus	£3.08	
	Week 8	Methotrexate	15 mg/m2 IM bolus	£3.08	
	Week 9	Methotrexate	15 mg/m2 IM bolus	£3.08	
	Week 10	Methotrexate	15 mg/m2 IM bolus	£3.08	
	Week 11	Methotrexate	15 mg/m2 IM bolus	£3.08	
	Week 12	Methotrexate	15 mg/m2 IM bolus	£3.08	
Spanish Maintenance (month 4-24 per 3 months)		Mercaptopurine	50 mg/m2 OD for 84 days	£148.29	
		Methotrexate	15 mg/m2 IM bolus	£3.08	
		Methotrexate	15 mg/m2 IM bolus	£3.08	
		Methotrexate	15 mg/m2 IM bolus	£3.08	
		Methotrexate	15 mg/m2 IM bolus	£3.08	
		Methotrexate	15 mg/m2 IM bolus	£3.08	
		Methotrexate	15 mg/m2 IM bolus	£3.08	
		Methotrexate	15 mg/m2 IM bolus	£3.08	
		Methotrexate	15 mg/m2 IM bolus	£3.08	
		Methotrexate	15 mg/m2 IM bolus	£3.08	
		Methotrexate	15 mg/m2 IM bolus	£3.08	
		Methotrexate	15 mg/m2 IM bolus	£3.08	
		Methotrexate	15 mg/m2 IM bolus	£3.08	
		ATRA	45 mg/m2 per day for 15 days	£240.43	

Detailed drug item cost list for MRC approach related regimen (by day)

Regimen	Day	Drug item	Dosage	Unit cost	Accumulated cost
MRC approach	Day 1	Granisetron	1mg Oral stat	£7.7	£337
(course 1)		Dexamethasone	8 mg Oral stat	£0.56	
(ADE 10+3+5)		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Metoclopramide	10 mg oral QDS prn	£0.07	
		Allopurinol	300 mg Oral OD	£2.15	
		ATRA	45 mg/m2 per day	£16.03	
	Day 2	Granisetron	1 mg mg Oral stat	£7.7	£406
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		ATRA	45 mg/m2 per day	£16.03	
	Day 3	Granisetron	1mg Oral stat	£7.7	£742
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		ATRA	45 mg/m2 per day	£16.03	
	Day 4	Granisetron	1 mg mg Oral stat	£7.7	£813
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		ATRA	45 mg/m2 per day	£16.03	
	Day 5	Granisetron	1mg Oral stat	£7.7	£1147
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		ATRA	45 mg/m2 per day	£16.03	
	Day 6	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£1181
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		ATRA	45 mg/m2 per day	£16.03	
	Day 7	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£1216
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		ATRA	45 mg/m2 per day	£16.03	
	Day 8	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£1250
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		ATRA	45 mg/m2 per day	£16.03	

	Day 9	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£1285
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		ATRA	45 mg/m2 per day	£16.03	
	Day 10	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£1319
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		ATRA	45 mg/m2 per day	£16.03	
	Day 11-28	ATRA	45 mg/m2 per day (18 days)	£288.54	£1607
MRC approach (course 2) (ADE 8+3+5)	Day 1	Granisetron	1mg Oral stat	£7.7	£320
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Metoclopramide	10 mg oral QDS prn	£0.07	
		Allopurinol	300 mg Oral OD	£2.15	
	Day 2	Granisetron	1 mg mg Oral stat	£7.7	£376
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 3	Granisetron	1mg Oral stat	£7.7	£694
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 4	Granisetron	1 mg mg Oral stat	£7.7	£749
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 5	Granisetron	1mg Oral stat	£7.7	£1067
		Dexamethasone	8 mg Oral stat	£0.56	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
		Daunorubicin	50 mg/m2 in 100ml N/Saline	£263	
		Etoposide	100 mg/m2 in 500ml N/Saline	£28.55	
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 6	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£1085
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 7	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£1104
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
	Day 8	Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	£1122
		Cytarabine	100 mg/m2 in 100ml N/Saline	£9.17	
MRC approach (course 3: MACE)	Day 1	Granisetron	2 mg Oral stat	£15.4	£236
		Dexamethasone	8 mg Oral stat	£0.56	
		Etoposide	100 mg/m2 in 500 ml N/S	£28.55	
		Amsacrine	100 mg/m2 in 500 ml Dextrose 5%	£173.32	
		Cytarabine	200 mg/m2 in 1000 ml N/S	£18.33	

		Metoclopramide	10 mg oral QDS prn	£0.07	
	Day 2	Granisetron	2 mg Oral stat	£15.4	£472
		Dexamethasone	8 mg Oral stat	£0.56	
		Etoposide	100 mg/m2 in 500 ml N/S	£28.55	
		Amsacrine	100 mg/m2 in 500 ml Dextrose 5%	£173.32	
		Cytarabine	200 mg/m2 in 1000 ml N/S	£18.33	
	Day 3	Granisetron	2 mg Oral stat	£15.4	£709
		Dexamethasone	8 mg Oral stat	£0.56	
		Etoposide	100 mg/m2 in 500 ml N/S	£28.55	
		Amsacrine	100 mg/m2 in 500 ml Dextrose 5%	£173.32	
		Cytarabine	200 mg/m2 in 1000 ml N/S	£18.33	
	Day 4	Granisetron	2 mg Oral stat	£15.4	£945
		Dexamethasone	8 mg Oral stat	£0.56	
		Etoposide	100 mg/m2 in 500 ml N/S	£28.55	
		Amsacrine	100 mg/m2 in 500 ml Dextrose 5%	£173.32	
		Cytarabine	200 mg/m2 in 1000 ml N/S	£18.33	
	Day 5	Granisetron	2 mg Oral stat	£15.4	£1181
		Dexamethasone	8 mg Oral stat	£0.56	
		Etoposide	100 mg/m2 in 500 ml N/S	£28.55	
		Amsacrine	100 mg/m2 in 500 ml Dextrose 5%	£173.32	
		Cytarabine	200 mg/m2 in 1000 ml N/S	£18.33	
MRC approach	Day 1	Granisetron	2 mg Oral stat	£15.4	£319
(course 4: MidAC)		Dexamethasone	8 mg Oral stat	£0.56	
		Mitozantrone	10 mg/m2 in 100 ml N/S	£117.5	
		Cytarabine	1000 mg/m2 in 500ml N/Saline	£91.65	
		Cytarabine	1000 mg/m2 in 500ml N/Saline	£91.65	
		Prednisolone	0.5% 1op	£2.35	
		Metoclopramide	10 mg oral QDS prn	£0.07	
	Day 2	Granisetron	2 mg Oral stat	£15.4	£636
		Dexamethasone	8 mg Oral stat	£0.56	
		Mitozantrone	10 mg/m2 in 100 ml N/S	£117.5	
		Cytarabine	1000 mg/m2 in 500ml N/Saline	£91.65	
		Cytarabine	1000 mg/m2 in 500ml N/Saline	£91.65	
	Day 3	Granisetron	2 mg Oral stat	£15.4	£953
		Dexamethasone	8 mg Oral stat	£0.56	
		Mitozantrone	10 mg/m2 in 100 ml N/S	£117.5	
		Cytarabine	1000 mg/m2 in 500ml N/Saline	£91.65	
		Cytarabine	1000 mg/m2 in 500ml N/Saline	£91.65	
	Day 4	Granisetron	2 mg Oral stat	£15.4	£1078
		Dexamethasone	8 mg Oral stat	£0.56	
		Mitozantrone	10 mg/m2 in 100 ml N/S	£117.5	
	Day 5	Granisetron	2 mg Oral stat	£15.4	£1204
		Dexamethasone	8 mg Oral stat	£0.56	
		Mitozantrone	10 mg/m2 in 100 ml N/S	£117.5	

Detailed drug item cost list for mild inpatient regimen (by day)

Regimen	Day	Drug item	Dosage	Unit cost	Accumulated cost
Amsacrine	Day 1	Amsacrine	100 mg/m2 iv	£155.75	£156 / day
Daunorubicin	Day 1	Daunorubicin	60 mg/m2 in 100ml N/S	£315.56	£316 / day
Arsenic trioxide	Day 1	Arsenic trioxide	0.25 mg/kg/day	£615.89	£616 / day
Campath	Day 1	Campath	30 mg iv	£322.93	£328
		Dexamethasone	8 mg oral stat	£0.56	
		Chlorphenamine	10 mg iv bolus	£1.90	
		Allopurinol	300 mg oral OD	£2.15	
	Day 2	Allopurinol	300 mg oral OD	£2.15	£330
	Day 3	Campath	30 mg iv	£322.93	£657
		Dexamethasone	8 mg oral stat	£0.56	
		Chlorphenamine	10 mg iv bolus	£1.90	
		Allopurinol	300 mg oral OD	£2.15	
	Day 4	Allopurinol	300 mg oral OD	£2.15	£659
	Day 5	Campath	30 mg iv	£322.93	£987
		Dexamethasone	8 mg oral stat	£0.56	
		Chlorphenamine	10 mg iv bolus	£1.90	
		Allopurinol	300 mg oral OD	£2.15	
	Day 6	Allopurinol	300 mg oral OD	£2.15	£989
	Day 7	Allopurinol	300 mg oral OD	£2.15	£991

Appendix 7.4 The treatment cost list for chemotherapy

	Treatment cost								
	Drug cost		Personnel cost		Overheads cost		Ward/clinic cost		Complication (incl. antibiotic cost)
	Per Day	Quantity	Per Day	Qauntity	Per Day	Quantity	Per Day	Quantity	
Chemotherapy									
Inpatient									
ADE									
10+3+5	£1158.46 (full course)		£135.6	× treatment time	£20.5	× treatment time	£67	× hospital stay	£1239
8+3+5	£1121.90 (full course)		£135.6	× treatment time	£20.5	× treatment time	£67	× hospital stay	£667
ADE + Mylotarg									
Course 1	£2779.87 (full course)		£135.6	× treatment time	£20.5	× treatment time	£67	× hospital stay	£1239
Course 2	£1121.90 (full course)		£135.6	× treatment time	£20.5	× treatment time	£67	× hospital stay	£667
AraC (HD)									
Course 1	£1699.97 (full course)		£122.5	× treatment time	£21.3	× treatment time	£67	× hospital stay	£910
Course 2	£1699.97 (full course)		£122.5	× treatment time	£21.3	× treatment time	£67	× hospital stay	£746
AraC (HD) + Mylotarg									
Course 1	£3321.12 (full course)		£122.5	× treatment time	£21.3	× treatment time	£67	× hospital stay	£910
Course 2	£1699.97 (full course)		£122.5	× treatment time	£21.3	× treatment time	£67	× hospital stay	£746
AraC (LD)									
Course 1	£91.60 × treatment time		£116.2	× treatment time	£20.4	× treatment time	£67	× hospital stay	£957
Course 2 +	£91.60 × treatment time		£116.2	× treatment time	£20.4	× treatment time	£67	× hospital stay	£630
Clofarabine	£17879.82 (full course)		£140.2	× treatment time	£22.4	× treatment time	£67	× hospital stay	£1260
DA									
Course 1	£1015.83 (full course)		£130.4	× treatment time	£18.6	× treatment time	£67	× hospital stay	£1487
Course 2	£979.15 (full course)		£130.4	× treatment time	£18.6	× treatment time	£67	× hospital stay	£1160
DA + Mylotarg									

Course 1	£2637.12 (full course)	£130.4	× treatment time	£18.6	× treatment time	£67	× hospital stay	£1487
Course 2	£979.15 (full course)	£130.4	× treatment time	£18.6	× treatment time	£67	× hospital stay	£1160
FLA								
Course 1	£1978.65 (full course)	£101.6	× treatment time	£14.6	× treatment time	£67	× hospital stay	£1792
Course 2	£1978.65 (full course)	£101.6	× treatment time	£14.6	× treatment time	£67	× hospital stay	£2200
FLAG								
Course 1	£2557.83 (full course)	£101.6	× treatment time	£14.6	× treatment time	£67	× hospital stay	£1792
Course 2	£2557.83 (full course)	£101.6	× treatment time	£14.6	× treatment time	£67	× hospital stay	£2200
FLAG-Ida								
Course 1	£3789.60 (full course)	£101.6	× treatment time	£14.6	× treatment time	£67	× hospital stay	£1404
Course 2	£3789.60 (full course)	£101.6	× treatment time	£14.6	× treatment time	£67	× hospital stay	£2549
FLAG-Ida + Mylotarg								
Course 1	£5410.89 (full course)	£101.6	× treatment time	£14.6	× treatment time	£67	× hospital stay	£1404
Course 2	£3789.60 (full course)	£101.6	× treatment time	£14.6	× treatment time	£67	× hospital stay	£2549
HAM	£2830.82 (full course)	£140.2	× treatment time	£22.4	× treatment time	£67	× hospital stay	£1066
MidAC	£1204.19 (full course)	£140.2	× treatment time	£22.4	× treatment time	£67	× hospital stay	£877
Mini MidAC	£1204.19 (full course)	£140.2	× treatment time	£22.4	× treatment time	£67	× hospital stay	£877
MACE	£1180.82 (full course)	£107.3	× treatment time	£18.8	× treatment time	£67	× hospital stay	£1085
Spanish approach								
Course 1	£2978.42 (full course)	£116	× treatment time	£16.9	× treatment time	£67	× hospital stay	£1192
Course 2	£1915.92 (full course)	£116	× treatment time	£16.9	× treatment time	£67	× hospital stay	£1192
Course 3	£869.32 (full course)	£116	× treatment time	£16.9	× treatment time	£67	× hospital stay	£1192
Course 4	£864.60 (full course)	£116	× treatment time	£16.9	× treatment time	£67	× hospital stay	£1192
MRC approach								
Course 1	£1607.42 (full course)	£157.6	× treatment time	£22.8	× treatment time	£67	× hospital stay	£1165
Course 2	£1121.90 (full course)	£157.6	× treatment time	£22.8	× treatment time	£67	× hospital stay	£1983
Course 3	£1180.2 (full course)	£157.6	× treatment time	£22.8	× treatment time	£67	× hospital stay	£683
Course 4	£1204.19 (full course)	£157.6	× treatment time	£22.8	× treatment time	£67	× hospital stay	£1375
Inpatient (Mild								

Amsacrine	£155.75	× treatment time	£134.2	× treatment time	£20.4	× treatment time	£67	× treatment time	£1145
Arsenic trioxide	£250	× treatment time	£134.2	× treatment time	£20.4	× treatment time	£67	× treatment time	£1145
Campath	£991.22	× treatment time/7d	£134.2	× treatment time/7d	£20.4	× treatment time/7d	£67	× treatment time/7d	£1145
Outpatient (Intensive)									
Cyclophosphamid	£69.78	× treatment time /7 d	£26.6	× treatment time /7 d	£6.05	× treatment time /7 d	£19	× treatment time /7 d	-
Cyclophosphamid/MESNA	£132.06		£26.6		£6.05		£19		-
Daunorubicin	£315.56	× treatment time /21d	£134.2	× treatment time /21d	£20.4	× treatment time/21d	£19	× treatment time /21d	-
ETI	£203.85	× treatment time /26d	£133	× treatment time /26d	£30.25	× treatment time /26d	£95	× treatment time /26d	-
FC	£157.13	× treatment time /28d	£133	× treatment time /28d	£30.25	× treatment time /28d	£95	× treatment time /28d	-
Fludarabine	£765.35	× treatment time /33d	£133	× treatment time /33d	£30.25	× treatment time /33d	£95	× treatment time /33d	-
Etoposide	£87.64	× treatment time /28d	£186.2	× treatment time /28d	£42.35	× treatment time /28d	£133	× treatment time /28d	-
Melphalan	£5.01	× treatment time	£26.6	× treatment time	£6.05	× treatment time	£19	× treatment time	-
Vincristine	£24.87	× treatment time /7d	£26.6	× treatment time /7d	£6.05	× treatment time /7d	£19	× treatment time /7d	-
ATRA	£16.03	× treatment time	£26.6	× treatment time /28d	£6.05	× treatment time /28d	£19	× treatment time /28d	£165
Mylotarg	£1619.36	× treatment time /7d	£134.2	× treatment time /7d	£20.4	× treatment time /7d	£19	× treatment time /7d	£197
Anagrelide	£3.37	× treatment time	£26.6	× treatment time /28d	£6.05	× treatment time /28d	£19	× treatment time /28d	-
Clopidogrel	£1.21	× treatment time	£26.6	× treatment time /28d	£6.05	× treatment time /28d	£19	× treatment time /28d	-
Outpatient (Mild)									
Aspirin	£0.1	× treatment time	£26.6	× treatment time/28d	£6.05	× treatment time/28d	£19	× treatment time/28d	-
Hydroxycarbamide	£0.72	× treatment time	£26.6	× treatment time/28d	£6.05	× treatment time/28d	£19	× treatment time/28d	£122
Hydroxycarbamide + Aspirin	£0.82	× treatment time	£26.6	× treatment time/28d	£6.05	× treatment time/28d	£19	× treatment time/28d	£122
Chelating agents									
First week	£31.08	× treatment time	£26.6	× treatment time	£6.05	× treatment time	£67	× treatment time	-
After 8 days	£5.33	× treatment time	£26.6	× treatment time/28d	£6.05	× treatment time/28d	£19	× treatment time/28d	-
Clinical Trial									
AML 14 AraC									
Course 1	£91.60 × treatment time		£116.2	× treatment time	£20.4	× treatment time	£67	× hospital stay	£957
Course 2	£91.60 × treatment time		£116.2	× treatment time	£20.4	× treatment time	£67	× hospital stay	£630
AML 14 AraC + Mylotarg									

Course 1	£91.60 × treatment time+£1619	£116.2	× treatment time	£20.4	× treatment time	£67	× hospital stay	£957
Course 2	£91.60 × treatment time	£116.2	× treatment time	£20.4	× treatment time	£67	× hospital stay	£630
AML 14 D35 C200								
Course 1	£889.59 (full course)	£130.4	× treatment time	£18.6	× treatment time	£67	× hospital stay	£1487
Course 2	£852.91 (full course)	£130.4	× treatment time	£18.6	× treatment time	£67	× hospital stay	£1160
AML 14 D35 C400								
Course 1	£1072.79 (full course)	£130.4	× treatment time	£18.6	× treatment time	£67	× hospital stay	£1487
Course 2	£999.47 (full course)	£130.4	× treatment time	£18.6	× treatment time	£67	× hospital stay	£1160
AML 14 D50 C200								
Course 1	£1015.83 (full course)	£130.4	× treatment time	£18.6	× treatment time	£67	× hospital stay	£1487
Course 2	£979.15 (full course)	£130.4	× treatment time	£18.6	× treatment time	£67	× hospital stay	£1160
AML 15 ADE								
10+3+5	£1158.46 (full course)	£135.6	× treatment time	£20.5	× treatment time	£67	× hospital stay	£1239
8+3+5	£1121.90 (full course)	£135.6	× treatment time	£20.5	× treatment time	£67	× hospital stay	£667
AML 15 ADE + Mylotarg								
10+3+5	£1158.46 (full course)	£135.6	× treatment time	£20.5	× treatment time	£67	× hospital stay	£1239
8+3+5	£1158.46 (full course)	£135.6	× treatment time	£20.5	× treatment time	£67	× hospital stay	£1239
AML 15 AraC								
Course 1	£1699.97 (full course)	£122.5	× treatment time	£21.3	× treatment time	£67	× hospital stay	£910
Course 2	£1699.97 (full course)	£122.5	× treatment time	£21.3	× treatment time	£67	× hospital stay	£746
AML 15 AraC + Mylotarg								
Course 1	£3321.12 (full course)	£122.5	× treatment time	£21.3	× treatment time	£67	× hospital stay	£910
Course 2	£1699.97 (full course)	£122.5	× treatment time	£21.3	× treatment time	£67	× hospital stay	£746
AML 15 DA								
10+3	£1015.83 (full course)	£130.4	× treatment time	£18.6	× treatment time	£67	× hospital stay	£1487
8+3	£979.15 (full course)	£130.4	× treatment time	£18.6	× treatment time	£67	× hospital stay	£1160
AML 15 DA + Mylotarg								
10+3	£2637.12 (full course)	£130.4	× treatment time	£18.6	× treatment time	£67	× hospital stay	£1487
8+3	£979.15 (full course)	£130.4	× treatment time	£18.6	× treatment time	£67	× hospital stay	£1160

AML 15 FLAG-Ida									
Course 1	£3789.60 (full course)		£101.6	× treatment time	£14.6	× treatment time	£67	× hospital stay	£1404
Course 2	£3789.60 (full course)		£101.6	× treatment time	£14.6	× treatment time	£67	× hospital stay	£2549
AML 15 FLAG-Ida + Mylotarg									
Course 1	£5410.89 (full course)		£101.6	× treatment time	£14.6	× treatment time	£67	× hospital stay	£1404
Course 2	£3789.60 (full course)		£101.6	× treatment time	£14.6	× treatment time	£67	× hospital stay	£2549
AML 15 MidAC	£1204.19 (full course)		£140.2	× treatment time	£22.4	× treatment time	£67	× hospital stay	£877
AML 15 MACE	£1180.82 (full course)		£107.3	× treatment time	£18.8	× treatment time	£67	× hospital stay	£1085
AML 15 MACE + Mylotarg	£2799.82 (full course)		£107.3	× treatment time	£18.8	× treatment time	£67	× hospital stay	£1085
APML 15 Spanish approach									
Course 1	£2978.42 (full course)		£116	× treatment time	£16.9	× treatment time	£67	× hospital stay	£1192
Course 2	£1915.92 (full course)		£116	× treatment time	£16.9	× treatment time	£67	× hospital stay	£1192
Course 3	£869.32 (full course)		£116	× treatment time	£16.9	× treatment time	£67	× hospital stay	£1192
Course 4	£864.60 (full course)		£116	× treatment time	£16.9	× treatment time	£67	× hospital stay	£1192
APML Spanish Maintenance	£425.66		£26.6	× duration / 14 d	£6.05	× duration / 14 d	£19	× duration / 28d	
APML 15 MRC approach									
Course 1	£1607.42 (full course)		£157.6	× treatment time	£22.8	× treatment time	£67	× hospital stay	£1165
Course 2	£1121.90 (full course)		£157.6	× treatment time	£22.8	× treatment time	£67	× hospital stay	£1983
Course 3	£1180.2 (full course)		£157.6	× treatment time	£22.8	× treatment time	£67	× hospital stay	£683
Course 4	£1204.19 (full course)		£157.6	× treatment time	£22.8	× treatment time	£67	× hospital stay	£1375
Supportive care									
Erythropoietin	£46.76	× treatment time /7d	£45.3	× treatment time /7d	£9.95	× treatment time /7d	£19	× treatment time /7d	-
Transfusion									
Duration < 100 days	£414	× treatment time/4d	£41.9	× treatment time/4d	£6.2	×treatment time/4d	£67	× treatment time/4d	-
Duration > 100 days	£414	× treatment time/14d	£41.9	× treatment time/14d	£6.2	× treatment time/14d	£67	× treatment time/14d	-
G-CSF	£322	× frequency	£40.8	× frequency	£8.9	× frequency	£268	× frequency	-
Steroids									
Dexamethasone:	£0.58	× treatment time	£26.6	× treatment time /28d	£6.05	× treatment time /28d	£19	× treatment time /28d	-

Prednisdone	£0.14	× treatment time	£26.6	× treatment time /28d	£6.05	× treatment time /28d	£19	× treatment time /28d	-
Hydrocortisone	£1.4	× treatment time	£26.6	× treatment time /28d	£6.05	× treatment time /28d	£19	× treatment time /28d	-
Other treatment Group 1									
Venesection	£0	once	£41.9	once	£9.4	once	£19	once	-
Immunosupressive therapy	£23.5	× treatment time	£32.1	× treatment time /28d	£6.95	× treatment time /28d	£19	× treatment time /28d	-
Other treatment Group 2									
Palliative Care									
Duration <30				£336 × 3× treatment time /7d					
Duration >30				Follow-up					
End of life				£938 for 14 days					
Follow-up				£53 × gap between treatments / 28 day					
Other treatment Group 3									
Splenectomy				£4,010					
Transplant				£45558					
Radiotherapy									
TBI				£635					
Non-TBI				£651					

Appendix 9.1 The detailed cost results of each treatment

	Events No	Cost 1 (exclude complication cost)			Cost 2 (include complication cost)		
		Mean	Min	Max	Mean	Min	Max
Average cost	**239 pts**	**£26081**	**£193**	**£236310**	**£28584**	**£193**	**£248227**
Chemotherapy	329 courses	£3440	£59	£13770	£4284	£60	£15030
Clinical trial	265 courses	£5010	£914	£7997	£6220	£914	£10131
Chemo+trial	594 courses	£4140	£59	£13770	£5148	£60	£15030
Inpatient chemotherapy	516 courses	£4678	£638	£13770	£5829	£729	£5112
Outpatient chemotherapy	78 events	£587	£59	£5112	£640	£60	£5112
ADE	47 courses	£4367	£4797	£2553	£5284	£2677	£6036
Course 1	23 courses	£4625	£2553	£4797	£5799	£2677	£6036
Course 2	24 courses	£4120	£3938	£4287	£4790	£4522	£5037
Chemotherapy	26 courses	£4395	£2553	£4797	£5361	£2677	£6036
Course 1	16 courses	£4562	£2553	£4797	£5708	£2677	£6036
Course 2	10 courses	£4310	£4113	£4287	£4805	£4779	£5037
AML 15	21 courses	£4331	£3938	£4797	£5189	£4522	£6036
Course 1	7 courses	£4768	£4596	£4797	£6007	£5835	£6036
Course 2	14 courses	£4113	£3938	£4287	£4779	£4522	£5037
ADE + Mylotarg	10 courses	£6132	£4113	£6418	£7290	£4779	£7657
Chemotherapy	-	-	-	-	-	-	-
AML 15	10 courses	£6132	£4113	£6418	£7290	£4779	£7657
Course 1	9 courses	£6357	£6069	£6418	£7568	£7060	£7657
Course 2	1 course	£4113	-	-	£4779	-	-
AraC (HD)	40 courses	£4091	£3092	£4405	£4919	£3689	£5315
Course 1	21 courses	£4389	£4202	£4405	£5299	£5114	£5315
Course 2	19 courses	£3761	£3092	£3802	£4499	£3689	£4548
Chemotherapy	15 courses	£4199	£3735	£4405	£5055	£4481	£5315
Course 1	10 courses	£4405	£4405	£4405	£5315	£5315	£5315
Course 2 +	5 courses	£3788	£3735	£3802	£4535	£4481	£4548
AML 15	25 courses	£4025	£3092	£4405	£4838	£3689	£5315
Course 1	11 courses	£4374	£4204	£4405	£5284	£5114	£5315
Course 2	14 courses	£3751	£3092	£3802	£4487	£3689	£4548
AraC(HD) + Mylotarg	7 courses	£5926	£5316	£6028	£6810	£6044	£6938
Chemotherapy	-	-	-	-	-	-	-
AML 15	7 courses	£5926	£5316	£6028	£6810	£6044	£6938
Course 1	7 courses	£5926	£5316	£6028	£6810	£6044	£6938
Course 2	-	-	-	-	-	-	-
AraC (LD)	83 courses	£3396	£638	£4895	£4088	£729	£5852
Course 1	39 courses	£3226	£638	£4895	£4002	£729	£5852
Course 2	44 courses	£3547	£1285	£4359	£4164	£1348	£4989
Chemotherapy	72 courses	£3267	£638	£4895	£3951	£729	£5852
Course 1	35 courses	£3096	£638	£4895	£3851	£729	£5852
Course 2+	37 courses	£3430	£1285	£4359	£4045	£1348	£4989
AML 14	11 course	£4237	£3019	£4359	£4986	£3649	£5316
Course 1	4 courses	£4359	£4359	£4359	£5316	£5316	£5316
Course 2+	7 courses	£4168	£3019	£4359	£4798	£3649	£4989
AraC (LD) + Mylotarg	2 courses	£5170	£4359	£5980	£5963	£4989	£6938
Chemotherapy	-	-	-	-	-	-	-
AML 14	2 courses	£5170	£4359	£5980	£5963	£4989	£6938
Course 1	1 course	£5980	-	-	£6938	-	-
Course 2	1 course	£4359	-	-	£4989	-	-
DA	91 courses	£4458	£750	£4918	£5738	£819	£6405

Course 1	52 courses	£4559	£750	£4918	£5913	£819	£6405
Course 2	39 courses	£4322	£2774	£4751	£5501	£3688	£6055
DA (D50 C200)	85 courses	£4454	£750	£4918	£5726	£819	£6405
Chemotherapy	57 courses	£4349	£750	£4918	£5591	£819	£6405
Course 1	34 courses	£4397	£750	£4918	£5689	£819	£6405
Course 2 +	23 courses	£4279	£2774	£4751	£5447	£3688	£6055
AML 14	7 courses	£4631	£4248	£4918	£5977	£5408	£6405
Course 1	4 courses	£4918	£4918	£4918	£6405	£6405	£6405
Course 2	3 courses	£4248	£4248	£4248	£5408	£5408	£5408
AML 15	21 courses	£4679	£4248	£4918	£6008	£5408	£6405
Course 1	10 courses	£4884	£4751	£4918	£6341	£6089	£6405
Course 2	11 courses	£4492	£4248	£4751	£5704	£5408	£6055
DA (D35 C200)	5 courses	£4470	£3854	£4792	£5826	£5014	£6278
AML 14	5 courses	£4470	£3854	£4792	£5826	£5014	£6278
Course 1	3 courses	£4792	£4792	£4792	£6278	£6278	£6278
Course 2	2 courses	£3988	£3854	£4122	£5148	£5014	£5282
DA (D35 C400)	1 course	£4707	-	-	£6194	-	-
AML 14	1 course	£4707	-	-	£6194	-	-
Course 1	1 course	£4707	-	-	£6194	-	-
Course 2	-	-	-	-	-	-	-
DA+Mylotarg	8 courses	£6253	£4248	£6539	£7699	£5408	£8026
Chemotherapy	1 course	£6539	-	-	£8026	-	-
Course 1	1 course	£6539	-	-	£8026	-	-
Course 2 +	-	-	-	-	-	-	-
AML 15	7 courses	£6212	£4248	£6539	£7652	£5408	£8026
Course 1	6 courses	£6539	£6539	£6539	£8025	£8025	£8025
Course 2	1 course	£4248	-	-	£5408	-	-
Clofarabine	3 courses	£13256	£12631	£13770	£14516	£13891	£15030
Chemotherapy	3 courses	£13256	£12631	£13770	£14516	£13891	£15030
Course 1	2 courses	£13200	£12631	£13770	£14461	£13891	£15030
Course 2	1 course	£13368	-	-	£14628	-	-
FLA	7 courses	£4713	£3565	£5709	£6551	£4865	£7909
Chemotherapy	7 courses	£4713	£3565	£5709	£6551	£4865	£7909
Course 1	4 courses	£4503	£4503	£4503	£6294	£6294	£6294
Course 2	3 courses	£4994	£3565	£5709	£6894	£4865	£7909
FLAG	25 courses	£5305	£4474	£6283	£7100	£5759	£8615
Chemotherapy	25 courses	£5305	£4474	£6283	£7100	£5759	£8615
Course 1	16 courses	£5303	£4661	£5479	£6951	£5759	£7402
Course 2	9 courses	£5308	£4474	£6283	£7365	£6233	£8615
FLAG-Ida	40 courses	£6575	£5505	£7582	£8403	£6909	£10131
Course 1	21 courses	£6243	£5505	£6376	£7551	£6909	£7780
Course 2	19 courses	£6943	£5572	£7582	£9344	£7139	£10131
Chemotherapy	6 courses	£6503	£6153	£7582	£7963	£7155	£10131
Course 1	5 courses	£6287	£6153	£6376	£7530	£7155	£7780
Course 2 +	1 course	£7582	-	-	£10131	-	-
AML 15	34 courses	£6588	£5505	£7582	£8480	£6909	£10131
Course 1	16 courses	£6230	£5505	£6376	£7558	£6909	£7780
Course 2	18 courses	£6907	£5572	£7582	£9300	£7139	£10131
FLAG-Ida + Mylotarg	19 courses	£7807	£7037	£7998	£9449	£8040	£10131
Chemotherapy	1 course	£7774	-	-	£8777	-	-
Course 1	1 course	£7774	-	-	£8777	-	-
Course 2 +	-	-	-	-	-	-	-
AML 15	18 courses	£7809	£7037	£7997	£9486	£8040	£10131

Course 1	13 courses	£7896	£7037	£7997	£9238	£8040	£9401
Course 2	5 courses	£7582	£7582	£7582	£10131	£10131	£10131
MACE	21 courses	£3519	£2829	£3553	£4583	£3480	£4638
Chemotherapy	11 courses	£3488	£2829	£3553	£4533	£3480	£4638
Course 1	10 courses	£3481	£2829	£3553	£4522	£3480	£4638
Course 2 +	1 course	£3553	-	-	£4638	-	-
AML 15	10 courses	£3553	£3553	£3553	£4638	£4638	£4638
Course 1	10 courses	£3553	£3553	£3553	£4638	£4638	£4638
Course 2	-	-	-	-	-	-	-
MACE + Mylotarg	9 courses	£5175	£5175	£5175	£6259	£6259	£6259
AML 15	9 courses	£5175	£5175	£5175	£6259	£6259	£6259
Course 1	9 courses	£5175	£5175	£5175	£6259	£6259	£6259
Course 2	-	-	-	-	-	-	-
MidAC	31 courses	£3967	£3038	£4094	£4771	£3389	£4971
Chemotherapy	17 courses	£3913	£3038	£4094	£4687	£3389	£4971
Course 1	15 courses	£3889	£3038	£4094	£4649	£3389	£4971
Course 2 +	2 courses	£4094	£4094	£4094	£4971	£4971	£4971
AML 15	14 courses	£4032	£3518	£4094	£4872	£4044	£4971
Course 1	14 courses	£4032	£3518	£4094	£4872	£4044	£4971
Course 2	-	-	-	-	-	-	-
HAM	1 courses	£5883	-	-	£6949	-	-
Chemotherapy	1 courses	£5883	-	-	£6949	-	-
Course 1	1 courses	£5883	-	-	£6949	-	-
Course 2 +	-	-	-	-	-	-	-
Spanish	33 courses	£4636	£3339	£6403	£5799	£3964	£7595
Course 1	10 courses	£5975	£3508	£6403	£7094	£3964	£7595
Course 2	9 courses	£4579	£3339	£4734	£5743	£4285	£5926
Course 3	7 courses	£4019	£3789	£4057	£5211	£4981	£5249
Course 4	7 courses	£3416	£3377	£3645	£4608	£4569	£4837
Spanish like	6 courses	£4951	£3645	£6403	£6143	£4837	£7595
Course 1	2 courses	£6403	£6403	£6403	£7595	£7595	£7595
Course 2	2 course	£4734	£4734	£4734	£5926	£5926	£5926
Course 3	1 course	£3789	-	-	£4981	-	-
Course 4	1 course	£3645	-	-	£4837	-	-
AML 15	27 courses	£4566	£3339	£6403	£5722	£3964	£7595
Course 1	8 courses	£5868	£3508	£6403	£6968	£3964	£7595
Course 2	7 courses	£4534	£3339	£4734	£5691	£4285	£5926
Course 3	6 courses	£4057	£4057	£4057	£5249	£5249	£5249
Course 4	6 courses	£3377	£3377	£3377	£4569	£4569	£4569
MRC	35 courses	£4283	£3511	£5500	£5606	£4300	£6795
Course 1	10 courses	£5301	£3511	£5500	£6575	£4594	£6795
Course 2	9 courses	£4160	£4041	£4175	£6143	£6024	£6158
Course 3	9 courses	£3617	£3617	£3617	£4300	£4300	£4300
Course 4	7 courses	£3841	£3841	£3841	£5216	£5216	£5216
AML 15	31 courses	£4283	£3511	£5500	£5606	£4300	£6795
Course 1	9 courses	£5279	£3511	£5500	£6550	£4594	£6795
Course 2	8 courses	£4159	£4041	£4175	£6141	£6024	£6158
Course 3	8 courses	£3617	£3617	£3617	£4300	£4300	£4300
Course 4	6 courses	£3841	£3841	£3841	£5216	£5216	£5216
MRC-like	4 courses	£4283	£3617	£5500	£5617	£4300	£6795
Course 1	1 course	£5500	-	-	£6795	-	-
Course 2	1 course	£4175	-	-	£6158		
Course 3	1 course	£3617	-	-	£4300	-	-

Course 4	1 course	£3841	-	-	£5216	-	-
Amsacrine	1 courses	£2155	-	-	£3300	-	-
Arsenic trioxide	2 courses	£10391	£10391	£10391	£11537	£11537	£11537
Campath	1 courses	£2211	-	-	£3357	-	-
ATRA	3	£334	£106	£757	£405	£124	£922
Anagrelide	1	£152	-	-	£152	-	-
Clopidogrel	1	£92	-	-	£92	-	-
Cyclophosphamide	6	£128	£128	£128	£128	£128	£128
Cyclophosphamide + MESNA	1	£173	-	-	£173	-	-
Daunorubicin	1	£768	-	-	£768	-	-
ETI	2	£1440	£786	£2095	£1440	£786	£2095
Etoposide	0	-	-	-	-	-	-
FC	6	£775	£215	£1687	£775	£215	£1687
Fludarabine	2	£594	£364	£823	£594	£364	£823
Mylotarg	1	£1712	-	-	£1909	-	-
Melphalan	3	£228	£128	£382	£228	£128	£382
Aspirin	2	£90	£60	£120	£90	£60	£120
Hydroxycarbamide	39	£132	£59	£384	£226	£63	£506
Hydroxycarbamide / Aspirin	1	£2244	-	-	£2366	-	-
Chelating agents	2	£3874	£2636	£5112	£3874	£2636	£5112
Vincristine	1	£374	-	-	£374	-	-
Spanish maintenance	5	£3165	£914	£4563	£3165	£914	£4563
Supportive care							
Transfusion	267 courses	£8861	£530	£67282	£8861	£530	£67282
	190 events	£12453	£530	£75229	£12453	£530	£75229
Erythropoietin	3	£1628	£111	£4440	1628	£111	£4440
G-CSF	62	£827	£197	£4765	£827	£197	£4765
	55 IP events	£748	£197	£1182	£748	£197	£1182
	7 OP events	£1447	£596	£4765	£1447	£596	£4765
Steroids	13	£300	£59	£1733	£300	£59	£1733
Dexamethasone	5	£110	£62	£289	£110	£62	£289
Prednisolone	7	£467	£59	£1733	£467	£59	£1733
Hydrocortisone	1	£79	-	-	£79	-	-
Palliative care	33 patients	£2223	£336	£6313	£2223	£336	£6313
End of life care	66 patients	£938	-	-	£938	-	-
splenectomy	2	£4010	-	-	£4010	-	-
venesection	3	£1168	£280	£2102	£1168	£280	£2102
immunosuppressive	6	£5302	£82	£16684	£5302	£82	£16684
stem cell transplant	13	£44199	-	-	£44199	-	-
radiotherapy	14	£1318	£635	£2771	£1318	£635	£2771
Observation	135 pts	£1326	£53	£4416			
When no treatment	10 pts	£335	£53	£1649			
Refused treatment	2 pts	£80	£53	£106			
Follow-up	123 pts	£1427	£53	£4416			
	269 events	£653	£53	£3564			
Lab cost	239 pts	£1662	£140	£12288	£1662	£140	£12288

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