The Optimisation of Pre-Chemotherapy Blood Assessments through Prognostic Modelling

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Declaration

UCL statement

I, Pinkie Pranlal Chambers, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature _____ Date _____

Abstract

Background

Evidence guiding pre-chemotherapy blood assessments would enable accurate patient-planning and support the growing numbers of patients treated with chemotherapy. The aim of this PhD was to guide chemotherapy providers on the appropriate timing of pre-treatment blood assessments and develop a prognostic model to predict dose delays, mitigating the need for multiple assessments.

Methods and analysis

A literature review guided retrospective data collection of risk factors for cancer patients receiving chemotherapy from four hospitals in England. Descriptive analysis was used to demonstrate changes in laboratory values of pre-chemotherapy blood tests, specifically neutrophils, when taken at different times. Using multivariable logistic regression, the relationship between potential risk factors and the outcome of a chemotherapy dose-administration delay was determined.

Results

The study included 4,604 patients (2,022 breast cancer patients, 1,904 colorectal cancer patients and 678 diffuse large B-cell lymphoma patients) between 1 January 2013 and 1 January 2018. Of these, 616 patients had two neutrophil values within 7 days of treatment. 23% of neutrophils assessed 4-6 days prior to treatment did not meet the required threshold; these were repeated nearer to the treatment time.

Among all patients, 628 (14%) experienced a second cycle treatment delay of 7 days or more. Significant variability was noted in the rate of delays at different hospitals ranging from 8% for hospital 4 to 22% for hospital 1 (P<0.005). Fourteen risk factors were pre-selected for the development of the prognostic model and fair predictive performance (concordance index 0.67) with good calibration was found.

A net benefit analysis demonstrated the model was most beneficial in predicting patients receiving treatment for colorectal cancer; here the model would have value in 50% of all patients.

Conclusions

The use of prognostic modelling offers an alternative to understanding a patient's likeliness to encounter a dose delay, aiding service providers to plan accordingly and negating the need for inappropriate blood tests.

Impact statement

The research presented in this thesis primarily has an impact on clinical practice, but also has impact in the academic setting. These are described with anticipated timescales on impact realisation.

Clinical impact

An output of this research has been the generation of evidence to guide practitioners in the correct timing of blood assessments prior to chemotherapy. My findings were used to influence changes required during the COVID-19 pandemic where social distancing in the workplace led to capacity pressures in the service. Changing processes within services was crucial and the dissemination of my findings at meetings was valued by service providers. Longer-term benefits are likely to be experienced by patients. A secondary output is the development of a prognostic model, enabling practitioners to stratify patients and offer more personalised care pathways. Expressions of interest in the developed model have been received from pharmacists, medical oncologists and chemotherapy nurses around the United Kingdom (UK) and Canada.

Impact within the academic setting

The new knowledge created in this field includes a quantifiable understanding of the impact of age on neutropenic events; the incidence of treatment dose delays for three major cancer types; and implications for safety and hospital attendances when blood assessments are undertaken too far in advance of treatment. One manuscript has been published and three further manuscripts are planned.

I have been awarded a Research for Patient Benefit grant to examine the implications of dose delays on 5-year progression-free survival, using nationally collected chemotherapy data. A second research project (supported by the UK Chemotherapy Board) is due to commence in May 2021, to develop a consensus on timing and thresholds for blood assessments in the UK.

Realisation of impact

Some findings from my research have already had impact; however, the prognostic model will require further development prior to implementation. I plan to carry out a temporal validation in my own clinical setting and I will be funded to achieve this. In addition, I have identified and been in contact with a further site to enable a fuller validation. I estimate that this will take approximately 12-18 months. The usability of the final model is paramount, and with electronic systems driving processes there is an opportunity for the model to co-exist alongside.

In addition to disseminating further findings in appropriate journals, I plan to give conference presentations at cancer-specific meetings and presentations to cancer alliance boards. I have strong professional networks in both the UK and internationally, who have followed and been interested in my research and findings. I shall continue to work with these networks to enable implementation within 5 years

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Acknowledgments

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Abbreviations

ACP	Association of Cancer Physicians
AE	Adverse event
ALT	Alkaline transaminase
AST	Aspartate transaminase
ANC	Absolute neutrophil count
ASCO	American Society for Clinical Oncology
BMI	Body mass index
BOPA	British Oncology Pharmacists Association
BSA	Body surface area
CHF	Coronary Heart Failure
CI	Confidence interval
CITL	Calibration-in-the-large
C-statistic	Concordance statistic
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CIT	Chemotherapy induced thrombocytopenia
CRN	Clinical Research Network
CSF	Colony Stimulating factor
CTCAE	Common Toxicity Criteria for Adverse Events
CVI	Content Validity Index
DLBCL	Diffuse large B-cell lymphoma
ECOG	The Eastern Cooperative Oncology Group
EMtree	Embase subject headings
E/O	Expected/observered
EP	Electronic prescribing
EPV	Events per variable
ESMO	European Society for Clinical Oncology
FBC(s)	Full blood count(s)
FMI	Fraction missing information
FN	Febrile neutropenia
GCSF	Granulocyte-colony stimulating factor
GFR	Glomerular filtration rate
HR	Hazard ratio

HRA	Health Research Authority
IV	Intravenous
LFTs	Liver function tests
MAR	Missing at random
MICE	Multiple imputation chained equation
MNAR	Missing not at random
MASCC	Multinational Association of Supportive Care in Cancer
MeSH	Medical Subject Headings
NCCN	National Comprehensive Cancer Network
N	Numbers of patients
Ne	Neutrophils
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NE	Neutropenic events
NHL	Non-Hodgkin's lymphoma
NS	Neutropenic sepsis
NHL	Non-hodgkins lymphoma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NOS	Newcastle-Ottawa scale
OR	Odds ratio
P-Value	Calculated probability
PEG	Polyethylene glycol
PI	Principal investigator
PICO	Population, Intervention, Comparison, Outcome Model
Plts	Platelets
PPI	Proton-pump inhibitor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PROGRESS	PROGnostic RESearch Strategy
PROSPERO	International Prospective Register for Systematic Reviews
PS	Performance status
R-CHOP	Rituximab cyclophosphamide, doxorubicin, vincristine, and prednisone
RCT	Randomised controlled trial
RDI	Relative dose intensity
RR	Relative risk

RVI	Relative increase in variance
SACT	Systemic anticancer therapy
SC	Subcutaneous
SQL	Structured Query Language
TRIPOD	Transparent Reporting of multivariable prediction models for Individual Prognosis and Diagnosis
UCLH	University College London Hospitals NHS Foundation Trust
UK	United Kingdom
USA	United States of America
U&Es	Urea and electrolytes
VIF	Variance inflation factor
VBA	Validity blood assessment
WHO	World Health Organization

Preface

The basis of this research has originated from my passion to improve the services delivered to patients. I have worked within cancer services for over a decade and blood testing for chemotherapy patients is an area that causes many logistical issues for services and patients. As chair of the *Chemotherapy Expert Reference Group* at the *North Central London Cancer Alliance*, I have experienced these challenges first-hand across London. This research is important in the United Kingdom, but also internationally, where practice does vary, but research can bring understanding that can lead to other positive outcomes.

During the course of the research, I faced challenges posed by the COVID-19 pandemic. The surge of COVID-19 patients admitted to hospitals in April 2020 meant that the commencement of studies and recruitment to studies were deprioritised. The main impact on this research was in the planning of my survey study, presented in Chapter 4.

Some planned presentations of findings were postponed. However, I was pleased to share my findings of the analysis of duplicate bloods with several hospitals, as many were seeking ways to facilitate social distancing in the workplace through early planning of treatments.

Summary of publications, presentations and grants:

- Chambers, P., Jani, Y., Wei, L., Kipps, E., Forster, M.D. & Wong, I.C.K. (2019). Patient factors and their impact on neutropenic events: a systematic review and meta-analysis. *Supportive Care in Cancer*, 27(7), 2413−2424. doi:10.1007/s00520-019-04773-6.

- International Society Oncology Pharmacy Practice Conference, London October 2019, 'Patient factors and their impact on neutropenic events.' Selected for oral presentation in top 10 poster presentation session.

- National Cancer Research Institute Conference, Glasgow 2019. 'Do neutrophil counts pre-chemotherapy treatment provide clinical value?' Selected for oral presentation in silent theatre session.
- UK Chemotherapy Board meeting, London, November 2020 – Presented findings from Chapters 4 and 7 and gained approval for consensus in blood testing to be within the board work plan.

Additionally, the following publications were achieved through collaborations formed during the course of this PhD:

- Vindrola-Padros, C., Brage, E. & Chambers, P. (2018). On the road and away from home: a systematic review of the travel experiences of cancer patients and their families. *Supportive Care in Cancer,* 26, 2973–2982. https://doi.org/10.1007/s00520-018-4266-2.
- Chambers, P., Man, K.K.C., Lui, V.W.Y. Mpima, S., Nasuti, P. Forster, M.D. & Wong, I.C.K. (2020). Understanding molecular testing uptake across tumor types in eight countries: results from a multinational cross-sectional survey. *JCO Oncology Practice,* 16:8, e770−e778.
- Payne, H., Jamieson, L., Prentice, M., & O'Connor, A. (2018). Preferences for toxicity monitoring of patients on abiraterone acetate plus prednisone, *Clinical Oncology.*
- Jamieson, L., Forster, M.D., Zaki, K. et al. (2020). Immunotherapy and associated immune-related adverse events at a large UK centre: a mixed-methods study. *BMC Cancer* 20, 743. https://doi.org/10.1186/s12885-020-07215-3

The research was to enable the optimisation of pre-chemotherapy blood assessments using prognostic modelling. The chapters are presented as follows:

Chapter 1. Introduction

The introductory chapter provides the rationale for the study as a whole. It provides medical context around processes and the current evidence available for

laboratory monitoring of bloods and the relationship to treatment delays, highlighting the clinical consequences. In this chapter, I introduce prognostic research and the use of clinical decision rules as an approach to increasing capacity whilst retaining safety.

Chapter 2. Research objectives and methods

The aims and objectives for the research were created to address the gap in evidence described in the introductory chapter. In this chapter, I describe the arrangements for clinical input and patient and public involvement that was received throughout the PhD. A broad overview of methods used to meet each objective is presented and relates to the PROGnostic RESearch Strategy (PROGRESS) framework—a framework developed to improve the implementation of prognostic research.

Chapter 3. Factors associated with neutropenic events: a systematic review

In this chapter, I synthesise the existing literature on the factors that influence neutropenic events, which are adverse events believed to be the primary reason for treatment dose delays. The results of the review were synthesised by way of meta-analysis, underlining the influence of patient factors. The review was instrumental in developing my data collection strategy, through an understanding of the important factors needed to develop a prognostic model.

Chapter 4. A survey to understand current practices in the United Kingdom

In this chapter, I examine the timing and threshold values used for assessments of neutrophils and platelets. Both timing and threshold values can have an influence on treatment delays, and, in turn, dose intensity. The results presented here together with results in subsequent chapters could influence future policy decisions.

Chapter 5. Retrospective data collection and preparation for analysis

In this chapter I describe the data collection processes for studies that required patient-level data, including the selection of study hospitals, key characteristics of each hospital in relation to the cancers studied and data extraction processes; quality checks and missing data checks undertaken and any findings that guided the development of the final prognostic model are also included here.

Chapter 6. Analysis of repeated blood tests

Here I aimed to understand current blood testing practices and evaluate both safety and efficacy of extending any timeframe.

Chapter 7. Exploring causes of dose delays

Using detailed data from one hospital across six cycles I explored dose delays (the main outcome event) and evaluated the proportion that were attributed to low neutrophils. Analysis of variables not available at other hospitals, as factors influencing dose delays, were examined.

Chapter 8. Model development

In this chapter, I describe the use of multivariable logistic regression in the development of a prognostic model. This chapter includes sample size considerations, exploratory data analysis, use of multiple imputations to handle missing data, model development and assessment of model performance.

Chapter 9 Model Assessments

In this chapter, I detail the ways in which the developed model would be beneficial in practice, using net benefit. I demonstrate how external validation of the model can be easily achieved and how the model could be used in practice.

Chapter 10. Discussion and conclusion

The final chapter is where I consider the results of this research with reference to the defined objectives. Findings are discussed in the context of previous literature,

and limitations are also discussed. This is followed by implications for future research, and an overall conclusion.

Chapter 1. Introduction

In 2020, there were approximately 19 million new cancer cases and 10 million deaths caused by cancer, globally (World Health Organization, 2020); with the incidence increasing and projected to affect 26 million patients by 2040 (Wilson et al., 2019; Arnold et al., 2019). Encouragingly, alongside this, survival rates have also risen steadily in high-income countries and this is partly due to advances in cancer treatments (Allemani et al., 2018). However, the proportion of people with cancer receiving systemic anticancer treatment (SACT) for various tumour types varies substantially worldwide (Chambers et al., 2020; Gakwaya et al., 2008; Yang et al., 2014; Elferink et al., 2010), attributed partly to the inadequate infrastructure to support cancer care. Nonetheless, significant rises are expected in this treatment modality in the next two decades (Wilson et al., 2019).

SACT is a term used to incorporate all drugs with antitumour activity including traditional chemotherapy, immunotherapy or targeted anticancer therapies. The delivery of all classes of SACT remains similar; they are administered either singularly or in combination with the intention of cure, for the prolongation of life, or for palliation. Administration is carried out intravenously in cycles, either orally or via injection, often over a number of months (Oncolink, 2018).

A study conducted by Wilson et al. (2019) investigated the global changes in chemotherapy utilisation in different cancers between 2018-2040. Breast cancer, colorectal cancer, and the haematological malignancy non-Hodgkin's lymphoma (NHL) are among those cancers where the proportion of patients receiving SACT treatment is predicted to rise over the next two decades. The study reported that a total of 15 million patients would require SACT treatment from the projected 26 million new cases of cancer. A breakdown of percentage increase in treatments, per tumour type, between 2018-2040, predicted rises of between 36-62% for breast cancer, colorectal cancer and NHL, combined. These three cancers are also common in the United Kingdom (UK) (World Health Organization, 2020) and as the utilisation of SACT grows (Cancer Research UK, 2017), chemotherapy service providers will be required to meet

these demands through delivering an efficient service. One mechanism by which this could be achieved is through the reduction of patient hospital attendances.

Treatment with all SACT is limited by toxicities, and, in most cases, a review of these involves blood tests to assess bone marrow, renal and hepatic function. Hospital attendances for blood tests in addition to treatment visits can be troublesome to patients and their carers, yet there is a sparsity of evidence guiding the frequency of these assessments.

This chapter discusses the practice around justification, nature, timing, and frequency of blood tests, acknowledging routinely collected data and the role that this can play in changing processes of care, guiding future delivery models.

1.1 Toxicities associated with SACT and monitoring

Toxicities are adverse events (AEs) that occur during and following SACT treatment. The Common Terminology Criteria for Adverse Events (CTCAE) (National Cancer Institute, 2017) is an international grading system, which defines the severity of the AEs. The mechanism of action of SACT, like all drugs, will dictate the toxicity experienced (Oncolink, 2018; Panchal, 2017) and this, in turn, will influence the timing of treatment dosing. SACT is therefore administered in cycles where a 'rest period' follows each administration. A common cycle length for treatment is 21 days, where SACT is administered at day 1 then again at day 22, 43, etc. This rest period (e.g. of 21 days) between administrations allows time for the patient to recover between treatment exposures.

Patients undergoing SACT treatment frequently experience a range of AEs (or toxicities) that can reduce the quality of life (Arnold et al., 2019), some of which are measured through laboratory testing and some that are reported to clinicians during assessments by patients. The reliability of patient accurately reporting toxicities to clinicians at scheduled visits can vary, depending on cancer type and treatment centre (Maguire et al., 2017); delays to reporting can lead to administration delays and dose reductions. A scoping review conducted by Wagland et al. (2015) found that the most commonly reported toxicities were

nausea, vomiting, sore mouth, taste disturbances and diarrhoea; with an incidence ranging from 5-76%. The impact of these AEs on patient experience and treatment outcome has led to numerous research studies and the development of tools to enable both the rapid reporting and subsequent amelioration of AEs (Absolom et al., 2017; Basch et al., 2017).

The most common toxicity that is routinely measured through laboratory monitoring and the cause of treatment-related mortality is myelosuppression. Myelosuppression is the suppression of bone marrow activity, resulting in the reduction of red blood cells, white blood cells and platelets. The condition has clinical impacts for a patient in terms of reduced immunity, bleeding and anaemia (Merrium-Webster, 2018). Reductions in white blood cells, namely the absolute neutrophil count (ANC), is termed neutropenia (Caggiano et al., 2005), which can be tolerated by a patient for short periods (Lyman, 2003). However, the condition leaves a patient vulnerable to opportunistic infections (Osmani et al., 2017), leading to neutropenic sepsis (NS). NS is internationally recognised to be a leading cause of morbidity and mortality (Herbst et al., 2009) and there is an understanding that the risk of developing NS increases with the degree and duration of the neutropenic episode (NE) experienced (Lyman, 2003).

To prevent NEs and, in turn, unnecessary hospitalisations, SACT is not routinely administered without the prior attainment of threshold values for neutrophils and other markers of myelosuppression: these are referred to as 'critical tests'. The pattern of the absolute neutrophil count during multiple administrations or cycles of chemotherapy are shown with different regimens in Figure 1.1. The lowest point is described as a nadir (Ozer, 2003). Count recovery is when full blood count has reached a certain level, specific to the regimen administered (Pether et al., 2017), for example, neutrophils of 1×10^9/L and platelets 100×10^9/L (Thwaites et al., 2017). Where count recovery is not at the appropriate level, the CTCAE (National Cancer Institute, 2017) grading is used in the decision-making for actions. Like the non-laboratory measured toxicities, actions would include the use of dose reductions and delays to treatment. Renal and hepatic function can additionally influence treatment dosing decisions and are again assessed using laboratory values.

1.1.1   Neutrophils and platelets

Neutrophils are one of three types of white blood cell in the circulating blood that are classified as granulocytes and are present in the bone marrow, peripheral blood and intracellularly (Pether et al., 2017). Eosinophils and basophils constitute the remaining granulocytes, all of which are distinguished morphologically from other differential white blood cells, by the presence of multilobular nuclei and granules in the cytoplasm. In a healthy individual, neutrophils are the most abundant white blood cell, forming 40-80% of the total white blood cell count (Summers et al., 2010). All types of granulocyte are involved in the immune defence against invading pathogenic organisms, with neutrophils performing the main anti-bacterial function through phagocytosis (Rosales, 2018), hence monitoring and increasing neutrophils is considered important in the prevention of NS.

Platelets are small, anucleated blood cell fragments released from bone marrow that circulate in the bloodstream at concentrations of 150 to 350 $\times$ 10^9/L. After any vascular injury, platelets rapidly adhere to sites where endothelial disruption has occurred and consequently are crucial in clotting
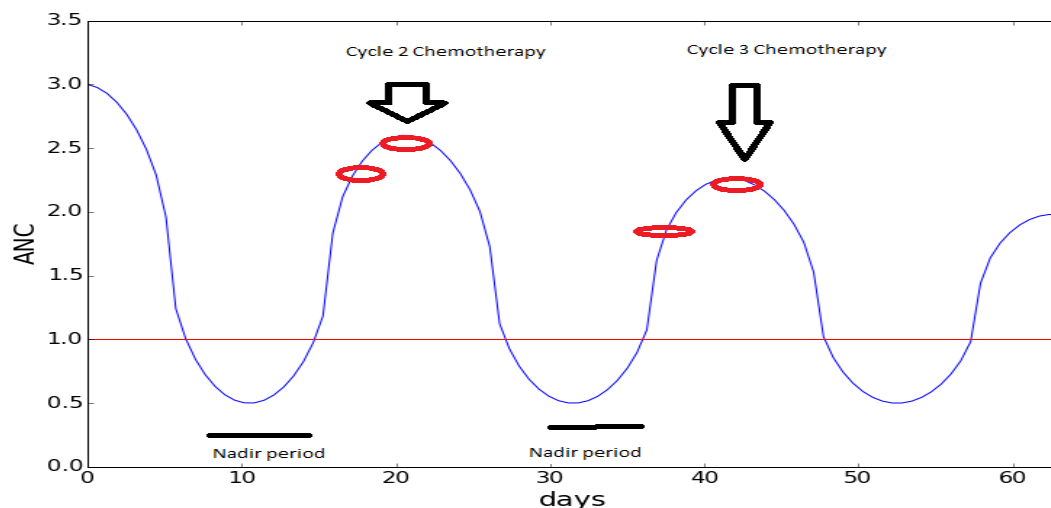
Figure 1-1. Absolute neutrophil count over the course of a 21 day cycle of chemotherapy treatment

Notes: Figure re-drawn from Elamin, 2017. ANC. denotes absolute neutrophil count. The diagram depicts the rise and fall of ANC over repeated chemotherapy administrations, where the nadir period is observed at around 10-14 days after administration. The nadir is when a patients' ANC is at its lowest level, predisposing the patient to life threatening infections. The red circles show the timing of blood assessments prior to administrations, assessing that the nadir period has passed.

(Mezouar et al., 2016). Thrombocytopenia is when an abnormally low blood platelet count is observed, and like NS can be potentially serious, although the occurrence of this complication is not as well researched. Thrombocytopenia in a patient would result in delays to treatments or platelet transfusions (Weycker et al., 2019); chemotherapy-induced thrombocytopenia (CIT) is related to the cancer type and treatment. SACT can interrupt platelet production through multiple pathways, including DNA synthesis, DNA repair, platelet shedding, and clearance of platelets (Deutsch and Tomer, 2006). Some chemotherapies may act to increase the rate of platelet destruction. Wu et al. (2009) conducted a retrospective study of 47,159 patients and found the incidence of CIT was highest in those receiving treatment with gemcitabine, platinum-based treatments and anthracyclines, and the solid tumours that were most affected were colorectal, non-small cell lung, ovarian and breast cancers. A further retrospective study of 158 patients with primary epithelial ovarian, peritoneal, or fallopian tube carcinomas, found that CIT was the second leading cause of dose delays after neutropenia. However, it was not clear in the publication at what grade of thrombocytopenia a delay occurred or if CIT was in the absence of a NE (Nagel et al., 2012).

1.1.2 Renal and hepatic function

The renal and hepatic function profiles of patients will influence dosing of most chemotherapy agents. The importance of measuring markers of renal function (creatinine levels) or hepatic impairment (bilirubin, alanine transaminase) prior to commencement of treatment is established (Krens et al., 2019). Tests are also conducted periodically, and doses are adjusted where deterioration is present. The pharmacokinetic profile of SACT in patients with renal or hepatic impairments can impact drug exposure. Understanding the effect of these pharmacokinetic changes on the disposition of specific anticancer drugs is essential in ensuring correct patient dosing. A recent systematic review collated and synthesised pharmacokinetic and clinical studies and provided practical information on starting doses of 160 chemotherapeutic agents at the initiation of treatment. However, this review did not address any chemotherapy-induced renal and hepatic toxicity (Krens et al., 2019). As there is currently little

published on the occurrence of chemotherapy-induced renal and hepatic impairment, laboratory tests assessing for this are required prior to every SACT treatment administration.

1.2 Relative dose intensity

Relative dose intensity (RDI) represents the ratio of the delivered dose intensity to the standard for a SACT regimen, as established in phase III trials. The dose intensity is dependent on two key factors: (1) the proportion of full dose received by a patient, and (2) time density.
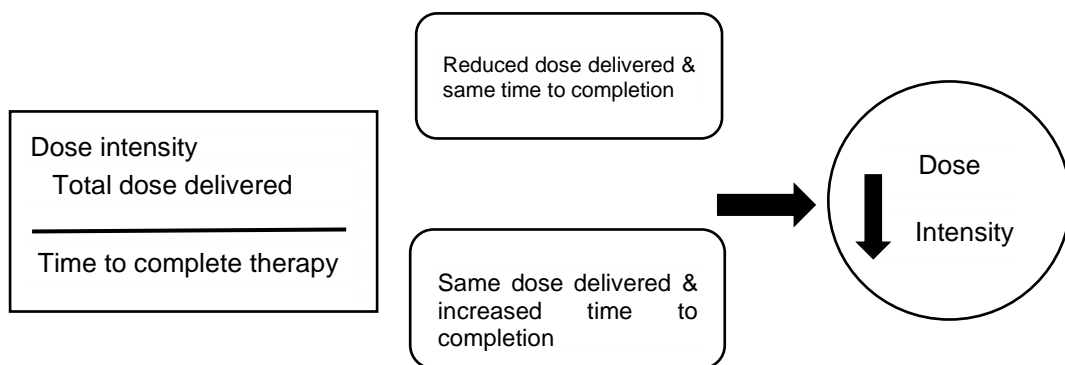
Figure 1-2. Dose intensity calculation and impact of timing and dose of treatment

This diagram shows that dose intensity can be effected in two ways: through a dose reduction or through increasing the time to completion of treatment. Time to completion usually refers to time taken to receive six cycles of chemotherapy treatment.

There is growing evidence that outcomes for patients are enhanced through increasing the RDI of treatment regimens. RDI has been shown to improve survival in breast, colorectal and lung cancers (Bonadonna et al., 1995; Kwak et al., 1990; Luciani et al., 2009), and for the chemotherapy specific to haematological malignancies there is evidence of impact in rituximab cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), although it is assumed for many others (Citron et al., 2003). Various studies have demonstrated that an RDI of less than 85% is associated with shorter survival (Bonadonna et al., 1995; Kwak et al., 1990). In many cancers (e.g. breast cancer), there is evidence that treatment can be further optimised through intensification, i.e., administration as soon as count recovery occurs (Foukakis et al., 2016). To achieve dose intensity while continuing to prevent neutropenia in patients, colony stimulating factors (CSF) are utilised.

1.3   Prophylactic colony stimulating factors

CSFs were introduced into clinical trials 20 years ago and are now used widely in both adults and children. They are a family of glycoproteins that include granulocyte colony stimulating factors (GCSF) and granulocyte-macrophage CSFs. GCSFs are more commonly used in the UK and work by expanding the pool of circulating neutrophils by stimulating proliferation and hastening maturation of myeloid progenitor cells in the bone marrow. They are used successfully in the treatment of chronic and cyclical neutropenia (Baig et al., 2019). If used appropriately, CSFs will reduce the length of time of a nadir, meaning subsequent doses can be administered earlier.

Filgrastim is the generic drug name of a synthetic analogue of GCSF that is administered either subcutaneously or intravenously. Another long-acting preparation of filgrastim, containing polyethylene glycol (PEG), is pegfilgrastim. The long-acting pegfilgrastim is only required as a single injection compared to the recommended single dose on five consecutive days for un-pegylated filgrastim (Vogel et al., 2005).

Much research has been done evaluating the effectiveness of primary prophylaxis of chemotherapy-induced neutropenia, through the use of GCSF, and the majority supports the use of agents such as filgrastim to decrease the severity and duration of NEs (Vogel et al., 2005; Gabrilove et al., 1988; Morstyn et al., 1989; Crawford et al., 2005), including a systematic review (Kuderer et al., 2007) based on 17 randomised controlled trials (RCTs). Consequently, current international practice favours the prophylactic use of GCSF, with numerous chemotherapy regimens; on an international level guidelines are produced by The American Society of Clinical Oncology (ASCO) (Neuss et al., 2016), The Multinational Association of Supportive Care in Cancer (MASCC) (Klastersky et al., 2016) and The National Comprehensive Cancer Network (NCCN) (2012). In the UK, the National Institute for Health and Care Excellence (NICE, 2012) has also published guidance for CSF use. Despite guidelines being present for the use of CSFs, there remains a variation in the practice of prescribing.

1.4 Delayed doses and impact on blood testing

Internationally, capacity pressures are present in all chemotherapy services. These pressures partly dictate the processes or pathways that healthcare providers adopt.

Figure 1.3 depicts the basic treatment pathway that exists in most countries. Stages include prescribing, reconstitution, administration and assessments. Each stage depends on the prior, and assessments are key in ensuring that

Chemotherapy Prescribing
Prescribing by specialist trained professional

Reconstitution /Preparation of SACT
Aseptic procedures used where treatment is intravenous

Administration
Specialist trained health professionals to administer intravenous SACT

Assessment visit(s)
Questionnaire for assessment of toxicity such as nausea and vomiting, mucositis. Blood monitoring to assess renal, liver and bone marrow dysfunction.

Figure 1-3. A basic treatment SACT pathway

Abbreviation: SACT, systemic anticancer therapy. The figure shows the SACT pathway commencing at prescribing, in the United Kingdom this step must be followed by clinical verification by an appropriately trained pharmacist prior to reconstitution. The assessment visit usually occurs prior to prescribing of the next dose and can occur up to a week before the next treatment.

subsequent treatment processes can commence. Lags at any stage will result in an inefficient service.

The occurrence of dose delays ranges between 5-20%, depending on a patient's cancer type and chemotherapy received (Xu et al., 2015). Uncertainty surrounding delayed doses, due to toxicity, poses a challenge for chemotherapy providers, especially with a rising demand. In an attempt to meet capacity requirements and reduce patient waiting times, many hospitals in England request that patients attend assessment visits in advance of their treatment day; but with a lack of evidence guiding the timing of these assessments, it is unknown how far in advance they can occur. Outside the UK, countries have reported similar processes (de Mendonca et al., 2013; Lau, Watson & Hasani, 2014). Where treatments and assessment are conducted on the same day, high drug wastage and patient waiting times have been reported (Kallen et al., 2012).

In the UK, a pragmatic period of 72 hours is accepted as an appropriate timeframe during which a blood test assessing for myelosuppression should be undertaken, before receiving chemotherapy (Chambers, Jenkinson & Gallagher, 2013) in a 21-day cycle. Many clinical trials use this period and it is considered an acceptable timeframe as stated in the National Institute of Health Research (NIHR) Chemotherapy and Pharmacy Advisory Service (2015) guidelines. However, increasingly, clinical visits to assess for toxicity and blood testing are being scheduled four or sometimes five days prior to receiving treatment (Chambers et al., 2013) due to clinic capacity pressures and national shortages of specialist clinicians (Garcia-Alonso, 2011; National Cancer Action Team, 2009). In cases where the 72-hour window or 'validity period' has passed, a new blood result will be obtained to assure safe chemotherapy administration, with the results of the initial blood test guiding safe prescribing and giving confidence that prepared treatment will not be wasted.

The approach that hospitals are adopting in the UK may result in service gains, but it is unclear whether this approach accurately determines a patient's readiness for treatment, or what impact there will be on their experience. Additionally, there are no published reports to define the proportion of patients

who undergo these repeated blood assessments; but there is evidence that duplication exists and that hospitals are extending periods, guided by local service evaluations, beyond 72 hours (Thwaites et al., 2017; Bayliss, 2017).

The mandatory prescribing of chemotherapy on electronic prescribing systems provides opportunities to develop clinical decision rules to identify the patients who are likely to encounter dose delays, and tailor blood assessments for these patients.

1.5   Clinical decision rules

Clinical decision rules are clinical tools designed to be used to assist decision making and can be either diagnostic or prognostic (Moons et al., 2009). The development of such a rule to predict those patients who are likely to encounter dose delays would be considered a prognostic model; data held within National Health Service (NHS) systems could enable the development of such a model. A well-known example of a prognostic model is QRISK® (Hippisley-Cox et al., 2010); this model estimates the lifetime risk of cardiovascular disease in a given individual. However, within the field of cancer, many developed models have been methodologically criticised (Collins et al., 2014), limiting their perceived reliability and applicability. Prognostic models are developed through derivation studies where rules or equations are created. Further studies have determined their discriminatory validity (i.e., do they actually tell the difference between the groups of affected and unaffected individuals) and predictive accuracy (i.e., do they predict at the same sorts of proportions of individuals as they were created to do). Validations can occur at different times, within the same institution (temporal validation) or in different physical locations but with similar clinical settings (geographical validation) or across different clinical settings (domain validation). Finally, efficacy in routine practice can be assessed through RCTs.

The PROGRESS partnership is a UK Medical Research Council-funded collaboration that has highlighted concerns of a gap arising between the potential and actual impact of prognostic studies (Hemingway et al., 2013). A developed framework, created by the group, consisting of four key themes would improve this shortcoming and could support the integration of prognosis

research findings to clinical decision making, healthcare policy and discovering and evaluating new approaches to the management of patient health.

The four themes are as follows:

1. **Fundamental prognosis:** research that describes and explains the future outcomes in people with a disease or health condition in relation to current diagnostic and treatment practices (Hemingway et al., 2013). Under this theme, patterns of healthcare and variation are described. Although the theme is relatively broad it is understood to be highly influential in the impact of any developed prognostic tool.

2. **Prognostic factor research:** research that identifies factors associated with a subsequent clinical outcome in people with a particular disease or health condition (Riley et al., 2013).

3. **Prognostic model research:** the combination of predictors to calculate individual risk of a future outcome (Steyerberg et al., 2013).

4. **Stratified medicine research:** research around the use of prognostic information in guiding treatment decisions in patients with similar characteristics (Hingorani et al., 2013).

The consideration of these themes within the framework in the development of research will assure the future impact.

1.6   Summary

The increase in SACT usage has driven service changes, particularly around the assessments of chemotherapy toxicity assessments, with unknown implications. In the UK, there is a known high utilisation of SACT for patients with breast cancer, colorectal cancer and NHL, and usage is predicted to increase. Data available from electronic prescribing systems could enable research into approaches to optimise blood testing and other pathways to improve patient care, utilising prognostic modelling.

Chapter 2.   Research aims, objectives and overall methodological approach

2.1   Overview

In this chapter, I provide the overall aims and objectives for my thesis and a broad description of methods used. Specific applications of methods are described in the relevant study chapters. I also outline the roles and contributions of clinicians, patients and carers throughout this research.

2.2   Aims and objectives

The optimisation of blood testing schedules for chemotherapy patients is complex, as described in Chapter 1, and highly interconnected with the uncertainty that chemotherapy will proceed on the intended day. With this knowledge, my aim was to guide the optimisation of pre-chemotherapy blood assessments through prognostic modelling. This approach would identify those patients who would require less blood monitoring, in those cancers where SACT treatment is common. These cancers were early breast cancer, colorectal cancer and diffuse large B-cell lymphoma (DLBCL), a subtype of NHL.

2.2.1   Specific research objectives

1. To identify whether and how patient physiological factors have an influence on chemotherapy treatment delays using evidence from previous research.

2. To examine the current practices for pre-chemotherapy blood assessments and identify any existing national variation.

3. To determine, through the evaluation of repeated blood measurements for neutrophils and platelets, the safety and appropriateness of assessing bone marrow suppression beyond a 72-hour time window for treatments with a 21-day cycle, and beyond a 48-hour timeframe for treatments with a 14-day cycle.

4. To use prognostic modelling to develop clinical decision rules, for use by chemotherapy providers to support more personalised pathway decisions based on the patient's risk of a dose delay occurrence.

5. To assess the predictive performance of the developed prognostic model using calibration and discrimination.

2.3   Overview of methods

In this chapter, I describe how the PROGRESS approach was applied and enabled me to organise my study objectives.

Table 2-1. Research objectives arranged under the themes of the PROGRESS framework

Research objective	PROGRESS theme
Identification of factors and their potential influence on treatment delays (objective 1)	Fundamental prognosis research Prognostic factor research
Examination of practices (objectives 2 and 3)	Fundamental prognosis research
Development of prognostic model (objective 4)	Prognostic model research
Assessment of predictive performance (objective 5)	Prognostic model research

As shown in Table 2.1, this research was informed principally by three of the four PROGRESS themes: fundamental prognosis research, prognostic factor research and prognostic model research (Hemingway et al., 2013; Riley et al., 2013; Steyerberg et al.,2013).

The cancer types studied in this research were three identified as being of high incidence in the UK, with projected increases over the next two decades in SACT (see chapter 1). Within these tumour types, there were many stages of disease and an increasing number of treatments available. For this reason, I decided to limit the population studied to those receiving specific SACT treatments. These treatments are further detailed in Chapter 5.

2.3.1   Identification of factors influencing treatment delays

There is a need for a systematic review to inform prognostic modelling studies for a number of reasons. Firstly, there has been a proliferation of prediction

models developed in the last 5 years; however, only a small proportion are externally validated, thereby limiting their use. To avoid undue duplication, the applicability of current models should be assessed. Secondly, a systematic review will bring the prognostic research into context and enable an understanding of the influence of factors on patient and health outcomes, which will facilitate the adoption of a developed model. Thirdly, a review is essential for model development: to understand the factors that need to be collected or obtained to develop a model successfully.

With these three purposes guiding the systematic review it was important to formulate the correct research question. To define the systematic review question, I considered the population of interest, types of studies and the outcome of interest. An unpublished scoping review conducted in 2016 as part of a pre-doctoral fellowship found that there were few studies addressing dose delays in general, but that neutropenic events were a well-researched area. This specific toxicity is understood to influence dose delays greatly. Although my objectives were focused on three major tumour types, I decided to include all cancers in this systematic review.

In summary, the systematic review provided not only a guide to the factors influencing dose delays but described consequences of current practice, highlighting the clinical importance of this research and areas of potential application. The review also included prognostic modelling studies and enabled me to decide whether development of a new model was needed. The review was the first piece of work to be completed and informed future objectives.

2.3.2 Examination of practices

The examination of practices around blood testing and threshold values would be pertinent in the justification of future implementation of the developed prognostic model. Hemingway et al. (2013) describe this type of research as being essential in the adoption of future changes to practice and policy. To examine practices and meet objectives 2 and 3, I conducted three studies:

1. A national survey to examine hospital policies around threshold values and timing of blood assessments for neutrophils and platelets before SACT administration. This study employed descriptive statistics to examine the variation in practice.

2. Analysis of duplicated blood tests at different time points; using data collected from four hospitals I investigated the implications on safety and efficiency when an earlier blood test was performed. Descriptive statistics were used in this evaluation.

3. Analysis of dose delays using detailed data from one hospital. I evaluated the occurrence of delays at each treatment cycle and the occurrence of dose delays with neutropenia.

2.3.3   Development and validation of a prognostic model

Prognostic models can be impactful and lead to improvements in health, safety, and efficiency at different stages in care pathways. The use of a prognostic model can support a stratified medicine or pathway approach that enables more personalisation of processes. In the development of my model, I aimed to assist those involved in SACT delivery through predicting dose delays, leading to some patients needing less blood monitoring through their SACT journey.

The methods for developing the model are discussed in detail in Chapter 9. In summary, prognostic models are usually developed with multivariable regression techniques using data; logistic and Cox regression modelling are the most common, and for my purpose, a logistic regression was the model of choice as the outcome I was assessing was dichotomous: dose delay yes/no.

In development, I addressed complex issues including modelling continuous variables, decisions in choosing whether multi-level modelling would be appropriate, handling missing data and adhering and checking model assumptions. Consideration was given to overfitting and the future use and adoption, throughout every decision made. Upon development, I ensured external validation options were assessed so that this could occur.

Lastly, a comparison with other models and understanding the benefits to certain cohorts of patients was assessed using net benefit analysis.

2.3.4 Governance and patient and public involvement

A steering panel guided the decisions made during all phases of the research. This panel included lead clinicians (in haematology, colorectal and breast cancer treatment, and chemotherapy commissioning) and national chemotherapy leaders. The panel also included three lay members: two patients and one carer, who enabled me to understand the study's impact. The panel of patients/carers were consulted when making methodological decisions, and they also provided feedback on the results relating to each study. Consideration of the views of patients and carers is important for the potential future adoption of any health research. In addition to the steering panel, other experts and stakeholders were regularly updated on the progress of the research and provided advice when necessary.

Chapter 3. The factors associated with neutropenic events: a systematic review and meta-analysis

3.1 Chapter overview

In prognostic research, it is essential to understand the influence of prognostic factors on the desired outcome. The understanding is not only pertinent in model development but will enable the implementation of any model. In this chapter, I detail a systematic review that I conducted in 2018 and published (see Figure 3.1) to understand the factors that influence neutropenic events, a leading cause of treatment delays. I updated the searches in November 2020 and findings from this update are reported in the results.

Patient factors and their impact on neutropenic events: a systematic review and meta-analysis

Pinkie Chambers[1] · Yogini Jani[1] · Li Wei[2] · Emma Kipps[3] · Martin D. Forster[4] · Ian C. K. Wong[2,5]

Figure 3-1. Manuscript published from work undertaken in this chapter

3.2 Background

Timely administration is essential in attaining the best possible outcomes for patients. In Chapter 1, I described ways in which timely administration is achieved and the problems associated with not anticipating those patients likely to receive treatment on time; highlighting that prognostic research could enable better stratification of patients.

Prognostic factor research aims to discover and evaluate variables that would be of value when developing interventions and serve as 'building blocks' for prognostic models (Steyerberg et al., 2013). Biomarkers include a range of biological, pathological, imaging, clinical and physiological variables and are

the most researched prognostic factors (Steyerberg et al., 2013). Few studies exist on the influence of biomarkers on treatment delays; however, a primary cause of delays, neutropenic events, was extensively researched. A systematic review in this area was considered clinically important in guiding practices around CSF prescribing, where internationally recognised guidelines acknowledge patient factors (i.e. age) have influence on NEs but fail to detail how these could guide management decisions (Smith et al., 2015; McNeil, 2005). Additionally, inconsistencies exist in the reported studies for associations with factors such as increasing age and neutropenic events, where one study showed an increase in neutropenia risk and another reported a reduced risk (Julius et al., 2017; Agiro et al., 2016). Moreover, there is no quantification of risk associated between factors and neutropenic events within guidelines, which is essential for clinical decision-making.

In Chapter 1, I indicated that very few developed prognostic models are implemented into clinical practice. The identification and appraisal of already developed studies through this review would offer guidance as to whether it is essential to develop a unique prognostic model or simply validate one that is existing. Overall, the systematic review I present in this chapter was necessary to guide the development of subsequent studies presented in this thesis.

3.3 Aim

This review aimed to investigate factors that have demonstrated influence on neutropenic episodes, quantifying the significance of factors where possible.

3.4 Methods

3.4.1 Search strategy

This was a systematic review that includes a meta-analysis based on peer-reviewed academic articles. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Liberati et al., 2009) were followed for reporting the methods and findings. The review protocol was registered in the PROSPERO: International Prospective Register of Systematic Reviews (CRD42018097263).

Studies were identified through a literature search, guided by the Population-Intervention-Comparison-Outcomes (PICOs) framework, using MEDLINE, EMBASE and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases, from inception to December 1st 2017. An example of the terms used for the search strategy is shown in Table 3.1. Results from searches were combined into EndNote® and duplicates removed. The reference lists of articles included were screened to identify additional relevant publications.

3.4.2   Inclusion and exclusion criteria

Studies were included if they were published in English and included human subjects aged 18 years and over, who were receiving cancer chemotherapy. I included studies that were systematic reviews, RCTs or observational studies. The studies must have quantitatively evaluated the association between individual factors and any NE, i.e., febrile neutropenia (FN), FN associated admissions, dose delays due to neutropenia or, laboratory-tested myelosuppression. Exclusions included early phase pharmacological studies where the purpose was to evaluate a drug or drug effect. Additionally, book reviews, opinion articles, editorial reviews and articles published in only abstract form were excluded.

3.4.3   Selection

I screened articles against the inclusion criteria in two phases: titles and abstracts, followed by full texts; a duplicate screen of 10% of articles were screened by a second researcher, Misha Ladva. Any conflict or uncertainty was resolved through a consensus agreement with my supervisor, Dr Yogini Jani.

Table 3-1. Example based on OVID-Medline

Cancer Chemotherapy identification
1. exp Neoplasms/
2. cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$ or sarcoma$ or leukaemi$
3. 1 or 2
4. exp Antineoplastic Agents/
5. exp Drug Therapy/
6. Antineoplastic Combined Chemotherapy Protocol* or Chemotherap*
7. 4 or 5 or 6 or 7
8. 3 and 7
Risk factors
9. risk$ or risk factor$ or odds or caus$ or etiolog$ or predict$
10. Exp risk factors/
11. Exp causality/
12. Exp etiology
13. 9 or 10 or 11 or 12
Myelosuppression
14. Leukopenia, this term only
15. Exp Agranulocytosis/
16. Granulocytopen$ or agranulocyto$ or neutropen* or leu*open* or aplasia,aplastic,aplasion or nadir*
17. 14 or 15 or 16 or 17
Final Search
18. 8 and 13 and 17

3.4.4   Data extraction and management

A data extraction tool (see Appendix 2) was developed after the initial screening of full-text articles. This tool was then piloted using a random sample of five articles. The data extraction form was modified based on the findings from the pilot run.

I extracted the following data for each article: study design, method of data collection, setting, population characteristics (tumour group), method of analysis, all risk factors investigated, outcomes measured, and strengths of association reported for significant factors. Data was extracted for the adjusted

odds ratios, relative risk and hazard ratios, 95% confidence intervals and calculated probability (P-values), where reported.

3.4.5   Quality assessment

The quality assessment stage in this systematic review and meta-analysis was essential to assure a clear understanding of the evidence base. I assessed the methodological quality of studies to assess for them for bias. Examples of potential biases were the inaccurate selection of participants, data collection, analysis and selective reporting.

As there were no RCTs that met the eligibility criteria I used a modified version of the Newcastle-Ottawa tool to assess the quality of the articles (Luchini et al., 2017). The original Newcastle-Ottawa scale (NOS) has been used for the assessment of methodological quality and bias of the observational studies as recommended by The Cochrane Handbook for Systematic Reviews of Interventions (The Cochrane Collaboration, 2011). Due to the nature of the review, it was believed that a modified version used previously in other work would provide a more comprehensive understanding for the quality of the study and any bias that may exist (Quigley et al., 2018). This assessment tool focused on observational studies and included crucial factors in the assessment such as handling of missing data. Each study was scored between zero (high risk of bias) and three (low risk of bias) in five domains of evaluation. These domains were methods for selecting study participants (i.e., selection bias), methods to control for confounding (i.e., performance bias), statistical methods (i.e., detection bias), methods of measuring outcome variables (i.e., information bias) and subject follow-up. Scores were then categorised (Page, McKenzie & Higgins, 2018) in the same way as other authors, into low, moderate or high risk of bias if the total scores were ≥17, 12-16 and <12 out of the total score of 21, respectively. I conducted all of the quality reviews, and 5% of these were independently duplicated by my supervisor, Dr Yogini Jani, with agreement on all those that were double reviewed.

3.4.6   Analysis

Studies were divided into two categories according to the method of analysis: univariable and multivariable. It was understood from previous studies that confounders can impact the strength of associations (Li et al., 2014). For this reason, only studies that adjusted for confounders using appropriate statistical techniques were thought to be relevant for inclusion in any meta-analysis. Studies that were non-adjusted were descriptively analysed.

The pooled odds ratio was calculated for neutropenic effects at different age groups using random effects models. Due to the heterogeneity of the studies, it was not possible to aggregate other factors in the same way. The Q-test was performed to assess between-study heterogeneity, and calculated using the I^2 statistic, which expresses the percentage of the total observed variability due to study heterogeneity. Subgroup analyses were necessary to explore variations from the effect of age on neutropenic events. The subgroups were cancer type, comorbidities, and renal function. The analysis was only considered if subgroups that included more than two studies were available. All analyses were conducted using STATA version 15.1 SE.

3.5   Results

3.5.1   Identification of articles

The initial search returned 4,415 published articles (see Figure 3.1). Following screening for title and abstract, 161 full-text articles were assessed against the inclusion and exclusion criteria. Following this phase of screening, 38 articles met the inclusion criteria. Figure 3.2 is the PRISMA flow diagram that shows the excluded studies at each phase.

3.5.2   Main characteristics of studies

Tables 3.2 and 3.3 include details of studies that met the inclusion criteria. The articles were published between 2000 and 2017, and all articles were published in English. The locations of these studies included the US (n=11) (Julius et al., 2017; Agiro et al., 2016; Li et al., 2016; Phippen et al., 2011; Chao et al., 2014; Lyman et al., 2011; Hosmer, Malin & Wong, 2011; Lyman, et al., 2003; Laskey

et al., 2012; Hurria et al., 2005; Rivera et al., 2003), Japan (n=8) (Shiota et al., 2014; Mitani et al., 2016; Ikesue et al., 2015; Ichikawa et al., 2015; Shigeta et al., 2015; Watanabe et al., 2012; Fujiwara et al., 2017; Naito et al., 2017), UK (n=3) (Crawford et al., 2005; Jenkins, Scaife & Freeman, 2012; Jenkins, 2009), Korea (n=2) (Kim et al., 2016; Choi, 2014), France (n=1) (Voog et al., 2000), Canada (n=3) (Assi et al., 2014; Altwairgi, Hopman & Mates, 2013; Shirdel,
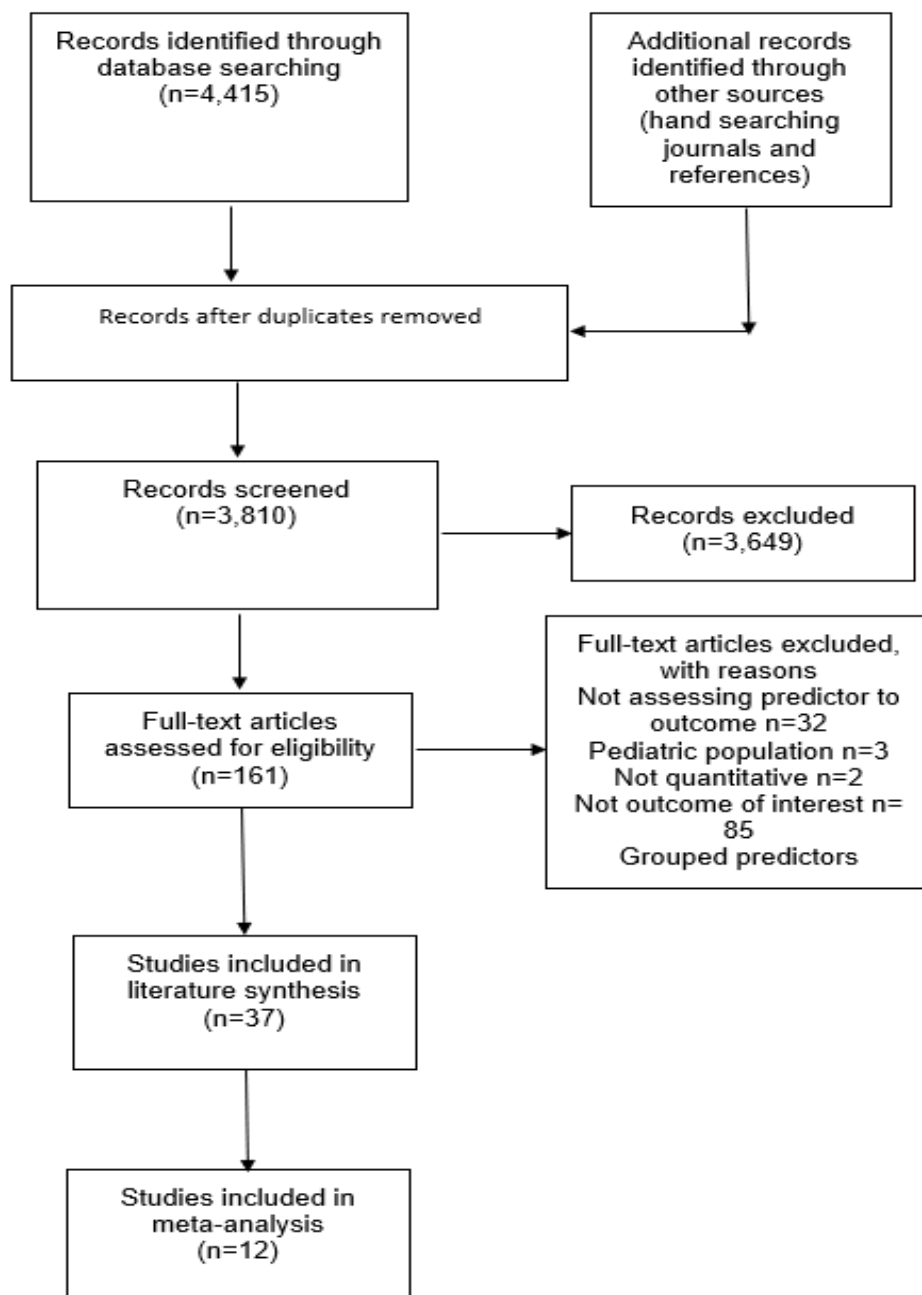
Figure 3-2. PRISMA flow diagram

2011), Belgium (n=1) (Pfeil et al., 2014), India (n=1) (Gupta et al., 2013), China (n=1) (Jiang, Chen & Zhao, 2013) and Spain (n=1) (Lopez-Pousa et al., 2010). Other studies involved multiple countries either through collection utilising collaboration (Schwenglenks et al., 2006; Schwenglenks et al., 2011; Pettengell et al., 2009) or utilising data available from RCTs (Dranitsaris et al., 2008; Meyerhardt et al., 2004; Lalami et al., 2006).

Most studies focused on neutropenic sepsis (Crawford et al., 2005; Li et al., 2016; Phippen et al., 2011; Hosmer et al., 2011; Laskey et al., 2012; Shiota et al., 2014; Laskey et al., 2012; Shiota et al., 2014; Jenkins et al., 2012; Jenkins & Freeman, 2009; Kim et al., 2016; Shirdel et al., 2011; Pfeil, 2014; Lopez-Pousa et al., 2010; Meyerhardt et al., 2004; Kim et al., 2016; Chao et al., 2014; Ikesue et al., 2015; Ichikawa et al., 2015; Fujiwara et al., 2017; Choi et al., 2014; Assi et al., 2014; Pettengell et al., 2009; Lalami et al., 2006) as their primary outcome measure. However, there were a number of studies that did define the outcome as neutropenic episodes (Agiro et al., 2016; Lyman et al., 2011; Lyman et al., 2003; Voog et al., 2000; Altwairgi et al., 2013; Gupta et al., 2013; Dranitsaris et al., 2008), grade 3 neutropenia (Julius et al., 2017; Naito et al., 2017) or above (Chao et al., 2014; Hurria et al., 2005; Rivera et al., 2003; Mitani et al., 2016; Ikesue et al., 2015; Shigeta et al., 2015; Watanabe et al., 2012; Jiang et al., 2013; Schwenglenks et al., 2011), or dose delays (Julius et al., 2017; Jenkins et al., 2009; Schwenglenks et al., 2006; Rivera et al., 2003) and reductions (Julius et al., 2017; Ikesue et al., 2015).

Fifteen studies found were for breast cancer, namely early breast cancer (Hurria et al., 2005; Jenkins & Freeman, 2009; Kim et al., 2016; Assi et al., 2014; Altwairgi et al., 2013; Shirdel et al., 2011; Pfeil et al., 2014; Schwenglenks et al., 2006; Schwenglenks et al., 2011), and a further six focused on non-specific breast cancer (Agiro et al., 2016; Li et al., 2016; Hosmer et al., 2011; Rivera et al., 2003; Dranitsaris et al., 2008). Other groups investigated were patients with lung cancer (Crawford et al., 2005; Ikesue et al., 2015; Watanabe et al., 2012; Fujiwara et al., 2017; Jenkins et al., 2012; Jiang et al., 2013), patients with gynaecological malignancies (Julius et al.,

2017; Phippen et al., 2011; Laskey et al., 2012), oesophageal cancers (Naito et al., 2017), myeloma (Mitani et al., 2016), colorectal (Ichikawa et al., 2015; Meyerhardt et al., 2004), prostate cancer (Shiota et al., 2014; Shigeta et al., 2015), non-Hodgkin's lymphoma (Lyman et al., 2003; Choi et al., 2014; Voog et al., 2000; Pettengell et al., 2009) and glioblastoma (Gupta et al., 2013). Four studies grouped three or more tumour types together (Chao et al., 2014; Lyman et al., 2011; Lopez-Pousa et al., 2010; Lalami et al., 2006).

Table 3-2. Studies found utilising univariable analysis methods (by year of publication)

First author and year of publication	Study design, and country	Population (N), description of study sample	Outcome assessed	Predictors found significant
Li 2016	Retrospective Observational US	N=3,672 neutropenic, N=2,640 control Breast cancer	Febrile neutropenia	Only comorbidity assessed: renal dysfunction, liver disease, and osteoarthritis
Shiota 2014	Prospective Observational Japan	N=37 Metastatic prostate cancer	Febrile neutropenia	Low serum albumin and low lymphocyte count
Shirdel 2012	Retrospective Observational Canada	N=35 Early Breast Cancer	Febrile neutropenia	Pre-cycle blood tests and day 8
Jenkins 2012	Retrospective Observational UK	N=263 Lung cancer	Febrile neutropenia	Baseline neutrophils and leukocytes
Phippen 2011	Retrospective Observational US	N=58 Gynaecological malignancies	Febrile neutropenia	Baseline haemoglobin and albumin. Score of patient-generated global assessment
Jenkins 2009	Retrospective Observational UK	N=740 Early Breast	Febrile neutropenia, chemotherapy delay	Low baseline neutrophils, platelets or white cell counts.
Crawford 2005	Prospective Observational UK	N=120 control, N=111 intervention Lung cancer	Febrile neutropenia	Gender

First author and year of publication	Study design, and country	Population (N), description of study sample	Outcome assessed	Predictors found significant
Hurria 2005	Retrospective Observational US	N=1,405 Early breast cancer	Febrile neutropenia or grade 4 haematological toxicity.	Increasing creatinine
Meyerhardt 2004	Retrospective Observational Multinational data from RCT	N=291 Colorectal cancer	Febrile neutropenia	Bilirubin level
Lalami 2004	Retrospective Observational Multinational	Multiple tumour groups N=203	Febrile neutropenia	Intensive chemotherapy treatment
Abbreviations: RCT, Randomised Controlled Trials; US, United States; UK, United Kingdom; N, numbers of patients.				

Table 3-3. Studies found using multivariable methods (by year of publication)

First author and year of study *denotes included in meta-analysis	Study design and country	Population (N), description of study sample	Outcome assessed	Significant factors	Factors assessed in multivariable model	Comments on quality
Fujiwara 2017 *	Retrospective Observational Japan	N=244 Lung cancer	Febrile neutropenia	Male, radiotherapy pre-treatment	Age, gender, PS, cancer type, stage, albumin, AST, total bilirubin, baseline neutrophils, smoking, radiotherapy, surgery, chemotherapy treatment	High Authors failed to report missing data handling
Julius 2017 *	Retrospective Observational US	N=635 Gynaecological cancers	Chemotherapy-induced neutropenia Treatment delays Treatment dose reductions	Metabolic comorbidities ** mainly diabetes mellitus, age negative effect, number of cycles	Age, BMI, treatment, cancer type, stage, prior treatment (cycles received previously and regimen)	Moderate Authors failed to report missing data handling Population studied may influence generalisability
Naito 2017 *	Retrospective Observational Japan	N=66 Oesophageal cancer	Grade 3/4 neutropenia	Baseline platelet count, ALT	Age, PPI treatment, baseline neutrophils and platelets, albumin, ALT	Moderate Authors failed to report missing data handling Inadequately powered study.

First author and year of study *denotes included in meta-analysis	Study design and country	Population (N), description of study sample	Outcome assessed	Significant factors	Factors assessed in multivariable model	Comments on quality
Agiro 2016 *	Retrospective Observational USA	N=8745 Breast Cancer	Neutropenic episodes	GCSF, age effect, comorbidity	Age, comorbidity, stage, CSF use, prophylactic antibiotics	High Authors failed to report missing data handling
Kim 2016 *	Retrospective Observational Korea	N=610 Early breast cancer	Febrile neutropenia	GFR <60 ml/min, age, comorbidity	Age, comorbidity, stage, renal function, FBC, CSF use	High Authors failed to report missing data handling
Mitani 2016	Retrospective Observational Japan	N=13 with outcome, N=34 control Myeloma	Grade 3/4 neutropenia	Haemoglobin level	Treatment, stage, renal, haemoglobin level	Moderate Authors failed to report missing data handling Inadequately powered study
Ikesue 2015	Retrospective Observational Japan	N=77 Lung cancer	grade 3-4 neutropenia or dose reduction or Febrile neutropenia	Baseline haemoglobin and neutrophils	Neutrophils, platelets and haemoglobin	High Inadequately powered study

First author and year of study *denotes included in meta-analysis	Study design and country	Population (N), description of study sample	Outcome assessed	Significant factors	Factors assessed in multivariable model	Comments on quality
Ichikawa 2015	Retrospective Observational Risk model development Japan	N=1,312 Colorectal	Febrile Neutropenia	Genetic factors, baseline bilirubin, and neutrophils, age but no quantification given	Genetic subtypes, regimen, gender, age neutrophils and bilirubin	Moderate Inadequately powered study and missing data not fully reported
Shiegeta 2015	Prospective Observational Japan	N=95 Metastatic prostate cancer	Severe neutropenia, febrile neutropenia	Age ≥75 years number of comorbid conditions, history of radiotherapy	Age, comorbidity, stage	High Inadequately powered study
Assis 2014	Retrospective Observational Canada	N=251 Early breast cancer	Febrile neutropenia	Treatment, CSF	Treatment, PS, CSF	Moderate Inadequately powered study Study did not fully address confounders
Choi 2014	Retrospective Observational Korea	N=181 DLBCL	Febrile neutropenia	Female gender, bone marrow involvement and comorbid condition	Weight, gender, comorbidity, gender, stage	High Missing data not fully reported

First author and year of study *denotes included in meta-analysis	Study design and country	Population (N), description of study sample	Outcome assessed	Significant factors	Factors assessed in multivariable model	Comments on quality
Chao 2014	Retrospective Observational US	N=19 160, 963 with neutropenia Multiple tumour groups	Febrile neutropenia, grade III and IV neutropenia combined, and grade IV neutropenia alone	COPD, CHF, autoimmune disease, peptic ulcer disease renal disease and thyroid disorder	Only comorbidities	High Missing data not fully reported
Pfiel 2014	Retrospective Observational Belgium	Early breast cancer Total N=994, of which N=166 febrile neutropenia	Febrile neutropenia	Lower platelet count, haemoglobin at baseline, and patient height. Genetics: certain polynucleotide polymorphisms	Weight, height, platelets, ALT, haemoglobin, genetic factors	High Missing data not fully reported
Altwairgi 2013 *	Retrospective Observational Canada	N=239 Early breast Cancer	Prescribing of GCSF Neutropenic episodes	Treatment and pegylated filgrastim	Age, treatment, GCSF	High Missing data not fully reported
Gupta 2013	Retrospective Observational India	N=107 Glioblastoma	Neutropenic episodes	Gender, BSA, BMI, serum creatinine histologic grade	Weight, gender, stage, renal	High Missing data not fully reported

First author and year of study *denotes included in meta-analysis	Study design and country	Population (N), description of study sample	Outcome assessed	Significant factors	Factors assessed in multivariable model	Comments on quality
Jiang 2013 *	Retrospective Observational China	N=141 Non-small cell lung	Grade 3-4 neutropenia	Age, albumin (g/dl)	Age, weight, gender, PS, renal, diabetes, albumin, BSA	High Missing data not fully reported
Laskey 2012 *	Retrospective Observational USA	N=326 Epithelial ovarian cancer	Severe neutropenia or neutropenic sepsis	Age >60 treatment	Weight, treatment, RDI	High Missing data not fully reported
Schwenkglenks 2012	Prospective Observational curative breast Multinational	N=2358 Curative breast	Grade 4 neutropenia	Age, lower weight, higher planned dose intensity number of planned cycles, vascular comorbidity, lower baseline WBC count, and higher baseline bilirubin	Age, weight, comorbidity, liver, renal, FBC, RDI, CSF	High All criteria met in assessment
Watanabe 2012	Prospective Observational advanced lung treated with anthracycline Japan	N=61 Advanced lung cancer treated with anthracycline	Grade 3-4 neutropenia	Gender and lower haematocrit values	Gender, haematocrit value RDI	Moderate Inadequately powered study Study did not fully address confounders Missing data not reported

First author and year of study *denotes included in meta-analysis	Study design and country	Population (N), description of study sample	Outcome assessed	Significant factors	Factors assessed in multivariable model	Comments on quality
Lyman 2012 *	Prospective Observational Small cell lung US	N=3760	Neutropenic episodes	Prior chemotherapy, immunosuppressive medications, high AST, ALT or bilirubin, reduced white blood count or estimated GFR, patients with small-cell lung cancer, with planned RDI 85%, CSFs	Prior chemotherapy, immunosuppressive medications, high AST, ALT or bilirubin, reduced white blood count or estimated GFR, Patients with small-cell lung cancer, with planned RDI 85% CSFs	High All criteria met
Lopez-Pousa 2012	Retrospective Observational Spain	N=1,194 Breast, trachea, colorectal, ovary and stomach cancer	Febrile neutropenia	Baseline lymphocyte and neutrophil counts (negative effect) PS	Gender, PS, FBC, radiotherapy	High Missing data not reported

First author and year of study *denotes included in meta-analysis	Study design and country	Population (N), description of study sample	Outcome assessed	Significant factors	Factors assessed in multivariable model	Comments on quality
Petengell 2009 *	Retrospective Observational Belgium, France, Germany, Spain and the UK	N=749 Non-Hodgkin's lymphoma	Febrile neutropenia	Older age, RDI, prior chemotherapy, recent infection, low baseline albumin <35 g/l CSF use higher weight associated protective effect. Replacing age with GFR and replacing weight with height yielded similar models	Age, dose intensity, Cycle 1 FN, CSF, renal, comorbidity	High
Hosmer 2009	Retrospective Observational US	N=86,693 Breast cancer	Febrile neutropenia	Cancer type, cancer stage (2 or greater), an increasing number of comorbid conditions, and less than 1 month from time of diagnosis to initiation of chemotherapy	Treatment, comorbidity, cancer type, stage	High

First author and year of study *denotes included in meta-analysis	Study design and country	Population (N), description of study sample	Outcome assessed	Significant factors	Factors assessed in multivariable model	Comments on quality
Dranitsaris 2008 *	Prospective Observational Data from multicentre RCT	N=509 Metastatic breast cancer	Any neutropenic complication	Age, PS increased, cycle and baseline neutrophil	Age, treatment, PS, stage, number of cycles	Moderate Study did not fully address confounders. Missing data not reported
Schwenkglenks 2007 *	Retrospective Observational Luxenberg, Belgium, France, Germany, Spain and the UK	N=2,860 Early breast cancer	Neutropenic events delays or hospitalisations	Higher age, higher BSA, lower BMI, regimen type, more planned chemotherapy cycles, normal to high SDI concomitant radiotherapy	Age, weight, treatment, diarrhoea, regimen, cycles, radiotherapy	High All criteria addressed
Lyman 2003	Retrospective Observational US	N=577 Intermediate grade NHL	Neutropenic episodes	1st FN associated with >65 age Cardiovascular disease, baseline haemoglobin and no CSF use	Age, comorbidity, renal, platelets, CSF and RDI	High All criteria addressed

First author and year of study *denotes included in meta-analysis	Study design and country	Population (N), description of study sample	Outcome assessed	Significant factors	Factors assessed in multivariable model	Comments on quality
Rivera 2003	Prospective Observational US	N=143 Breast cancer	ANC < 0.5×109/litre neutropenia-related dose reduction of 15% or neutropenia-related dose delay of 7 days or more, or febrile neutropenia	First cycle ANC effect	Neutrophils, treatment	High Missing data not reported
Voog 2000	Prospective Observational France	N=101 Non-Hodgkin's lymphoma	Grade 4 neutropenic event	Chemotherapy treatment (high doses, Performance status and high levels of soluble p75-R-TNF	Chemotherapy treatment, neutrophils	Moderate Study did not fully address confounders. Missing data not reported
*Abbreviations: ANC, absolute neutrophil count; ALT, alkaline transaminase; AST, aspartate transaminase; BMI, body mass index; BSA, body surface area; CSF, colony stimulating factors; ECOG, Eastern cooperative oncology group; FBC, full blood count; FN, febrile neutropenia; GFR, glomerular filtration rate; GCSF, granulocyte colony stimulating factor; N, numbers of patients; PPI, proton pump inhibitor; PS, performance status; RCT, randomised controlled trials; RDI, relative dose intensity; UK, United Kingdom; US, United States; WBC, white blood cells. **Authors did not detail statistics of finding.*						

3.5.3   Study designs and methods

Table 3.2 details the studies that only used univariable methods, i.e., those that looked at the association between one variable and the outcome. This approach was utilised as a method of selection in studies that later investigated the association of multiple predictors. Where studies used only univariable methods, authors reported baseline full blood counts (Phippen et al., 2011; Jenkins et al., 2012; Jenkins et al., 2009; Shirdel et al., 2011; Pfeil et al., 2014), markers of liver function (Shaikh et al., 2016), treatment (Lalami et al., 2006) and gender (Crawford et al., 2005) as significant factors influencing the event. The odds of occurrence were, however, unadjusted for confounders, and associations were found to be insignificant in some larger multivariable studies (Fujiwara et al., 2017; Kim et al., 2016; Pfeil et al., 2014).

The 28 studies listed in Table3.3 utilised multivariable regression analysis methods for more than one variable: either Cox (Lyman et al., 2003; Laskey et al., 2012; Shigeta et al., 2015) or logistic regression (Julius et al., 2017; Agiro et al., 2016; Chao et al., 2014; Lyman et al., 2011; Hosmer et al., 2011; Mitani et al., 2016; Ikesue et al., 2015; Ichikawa et al., 2015; Watanabe et al., 2012; Fujiwara et al., 2017; Naito et al., 2017; Kim et al., 2016; Choi et al., 2014; Assi et al, 2014; Gupta et al., 2013; Jiang et al., 2013; Lopez-Pousa et al., 2010; Schwenkglenks et al., 2006; Schwenkglenks et al., 2011; Pettengell et al. 2009; Dranitsaris et al., 2008; Rivera et al., 2003). Some of these analyses were performed in order to develop a predictive risk model (Lyman et al., 2011; Hosmer et al., 2011; Ichikawa et al., 2015; Pfeil et al., 2014; Pettengell et al., 2009; Rivera et al., 2003). Where there was a focus on a specific factor such as comorbidity (Chao et al., 2014) and genetic factors (Ichikawa et al., 2015) articles only reported details of these associated hazard or odds ratios despite recognising that other factors were associated with the event.

3.5.4 Study quality

A quality assessment identified that many studies did not document their use of missing data (Julius et al., 2017; Agiro et al., 2016; Chao et al., 2014; Laskey et al., 2012; Mitani et al., 2016; Watanabe et al., 2012; Fujiwara et al., 2017; Naito et al., 2017; Choi et al., 2014; Altwairgi et al., 2013; Jiang et al., 2013; Lopez-Pousa et al., 2010; Dranitsaris et al., 2008; Kim et al., 2016) and some failed to meet the minimum required sample necessary to draw conclusions (Mitani et al., 2016; Ikesue et al., 2015; Ichikawa et al., 2015; Shigeta et al., 2015; Watanabe et al., 2012; Naito et al., 2017). In addition, when using univariable methods to choose factors to build into the multivariable models, some studies used a standard 95% significance level test (Julius et al., 2017; Agiro et al., 2016; Laskey et al., 2012; Mitani et al., 2016; Ikesue et al., 2015; Shigeta et al., 2015; Fujiwara et al., 2017; Naito et al., 2017; Choi et al., 2014; Altwaitgi et al., 2013; Lopez-Pousa et al., 2010; Kim et al., 2016). Although this is standard, in these studies it is preferable to use a less stringent cut-off and to include factors that may become significant when adjusted for confounders. Despite this, on all other domains of the assessment the majority of studies were strong.

Table 3.3 shows the predictors for each for the multivariable studies, where all odds or hazard ratios were reported. These variables fell into the following categories: patient, cancer or treatment-related. These categories were utilised in another similar systematic review (Lyman et al., 2014).

3.5.5 Factors identified

3.5.5.1 Treatment-related factors

Studies either sought to understand real-world treatment-related risks of neutropenic events or controls for this factor by using one or two regimens of interest only. Treatment-related risk is undisputed as a risk factor in clinical practice; however, one study concluded their population incidence to be different from that expected, and, in some populations, actually lower (Julius et al., 2017).

Many studies focused on combinations with anthracyclines and taxanes (Agiro et al., 2016; Assi et al., 2014; Schwenkglenks et al., 2006; Schwenkglenks et al., 2011; Dranitsaris et al., 2008; Kim et al., 2016; Watanabe, 2003). These agents are commonly used in breast cancer, where treatment intent is curative, which may have guided this choice. Concomitant chemo-radiotherapy treatment was explored in a number of studies (Shigeta et al., 2015; Fujiwara et al., 2017; Schwenkglenks et al., 2006) with some exploring the association to events in lung cancer patients and found to be significant in these (Shigeta et al., 2015; Fujiwara et al., 2017). However, all these studies were relatively small and excluded many potential confounders in their analyses.

Dose intensity of treatment and addition of CSFs (Agiro et al., 2016; Lyman et al., 2011; Lyman et al., 2003; Laskey et al., 2012; Voog et al., 2000; Assi et al., 2014; Altwairgi et al., 2013; Schwenkglenks et al., 2011; Kim et al., 2016) were studied by some authors, but not all. The intensity referred to any dose modifications that the patient may have received to reduce their risk of neutropenic episodes.

3.5.5.2   Cancer-related factors

Many studies controlled for cancer type and many chose early-stage cancers to avoid confounders such as previous treatments (Ichikawa et al., 2015; Pfeil et al., 2014). Bone marrow involvement was explored as a risk in a small myeloma population but found to be non-significant (Mitani et al., 2016). The stage of treatment was investigated by most authors initially but was only included in seven multivariable models due to the cut-off level of significance (Julius et al., 2017; Agiro et al., 2016; Hosmer et al., 2011; Shigeta et al., 2015; Fujiwara et al., 2017; Choi et al., 2014; Gupta et al., 2013). Of these investigations, only two (Hosmer et al., 2011; Gupta et al., 2013) reported this to be of significance, one of which was in the glioblastoma population and reported odds of 3.8 (CI 1.05-14.4). Advanced disease was mainly investigated by authors in gynaecological malignancies (Julius et al., 2017; Laskey et al., 2012).

3.5.5.3   Patient-related factors

Figure 3.3 displays the patient-related factors that were studied. It can be seen that age (Agiro et al., 2016; Lyman et al., 2011; Lyman et al., 2003; Laskey et al., 2012; Ichikawa et al., 2015; Shigeta et al., 2015; Jiang et al., 2013; Schwenkglenks et al., 2006; Schwenkglenks et al., 2011; Pettengell et al., 2009; Dranitsaris et al., 2008; Kim et al., 2016) was a factor investigated in many of these studies, with the majority of research finding age to be significant. However, there were investigations where age was not studied as it was found to be non-significant in univariable analysis (Hosmer et al., 2011; Pfeil et al., 2014). Pettengell et al. (2009) found age to be significant in their risk model development study but actually noted that it could be interchanged with a marker of renal function. Conversely, another study reported decreasing age would increase the risk of neutropenic events (Julius et al., 2017).
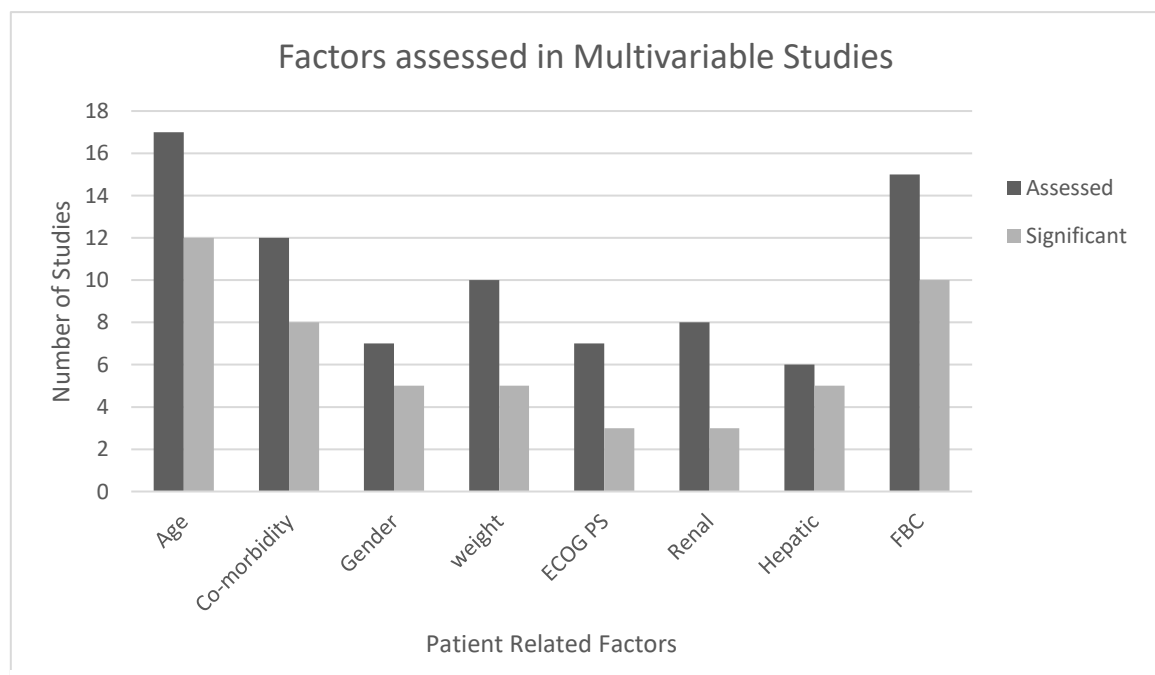
Figure 3-3. Factors assessed and found significant in multivariable studies

Notes: A large proportion of studies assessed and found age and the baseline full blood count as significant factors affecting neutropenic events.

Abbreviations: ECOG PS, Eastern Co-operative Oncology Group Performance Status; FBC, full blood count.

There was variation in the way that age was analysed. Some authors opted to use linear chronological age (Ichikawa et al., 2015), whereas others used an age greater than 65 (Agiro et al., 2016; Lyman et al., 2011; Lyman et al., 2003) years as a suitable threshold in line with the World Health Organization guidelines (WHO).

A high proportion of studies showed that comorbidity (Julius et al., 2017; Agiro et al., 2016; Lyman et al., 2011; Hosmer et al., 2011; Choi et al., 2014; Schwenkglenks et al., 2011) was a significant factor. Despite this, I was unable to pool the results; as each study measured comorbidity in different ways, characterised by either number of comorbid conditions (Hosmer et al., 2011; Shigeta et al., 2015; Choi et al., 2014), patients receiving medication for comorbidities (Lyman et al., 2011), patients with diabetes (Jiang et al., 2013) or cardiovascular disease (Schwenkglenks et al., 2011). One very large study only reported the odds of individual comorbidities and found that having three or more comorbidities would produce a hazard ratio of 1.73 (1.33-2.26) for febrile neutropenia but had a non-significant result for grade 4 neutropenias (Chao et al., 2014). The authors concluded that this may be due to comorbidities impacting febrile neutropenia via other mechanisms. This same study additionally developed and calculated bone marrow suppression scores based on the baseline levels of neutrophils, platelets and haemoglobin. Scores of 1 were assigned to those patients who had been previously treated with chemotherapy and had baseline neutrophil values of <1.5 x 10^9/L. This score was noted to have a significant statistical impact on neutropenic sepsis risk but not on all neutropenic events.

Others found baseline bone marrow function to be an indicator of events (Lyman et al., 2011; Ikesue et al., 2015; Naito et al., 2017; Lopez-Pousa et al., 2010; Rivera et al., 2003). This included a smaller study, where the numbers of patients were less than 500 (Ikesue et al., 2015). The pre-chemotherapy full blood count result was investigated and demonstrated statistical significance as reported by a number of authors (Lyman et al., 2003; Mitani et al., 2016; Ichikawa et al., 2015;

Pfeil et al., 2014; Dranitsaris et al., 2008). In these articles, a low level of neutrophils was defined as either $<2 \times 10^9$/L (Mitani et al., 2016) or $<1.5 \times 10^9$/L (Ichikawa et al., 2015) prior to treatment; dichotomisation in this way may have impacted the results obtained. Low haemoglobin values were also thought to be a factor influencing neutropenic events (Lyman et al., 2003; Mitani et al., 2016; Ikesue et al., 2015; Watanabe et al., 2012; Altwairgi et al., 2013; Pfeil et al., 2014). A larger study (Schwenkglenks et al., 2011) reported a baseline white blood cell counts, greater than 5×10^9/L to reduce neutropenic events. However, with an OR of 0.87 (0.76-0.99), this would be difficult to translate into a change in clinical practice. Again, the level of heterogeneity in these studies, e.g., cut-off levels and the exact parameter used to measure baseline bone marrow function meant that the results could not be aggregated via meta-analysis.

3.5.6   Meta-analysis

A pooled analysis of age where odds ratios were available yielded a combined odds ratio of 1.22 (1.08-1.38) (Figure 3.4). When I^2 was calculated, this identified a high degree of heterogeneity. A subanalysis (Figure 3.5) that only included results from studies that adjusted for comorbidity and either renal or liver function actually produced a higher pooled odds ratio of 1.51 (1.17, 1.95). However, the level of heterogeneity indicated by I^2 was 37.5%, interpreted as a mid-range level. A final subanalysis, including only breast and lymphoma tumour groups (Figure 3.6), yielded an OR of 1.39 (1.11, 1.76), with an acceptable level of heterogeneity ($I^2 = 24.1\%$).

The pooled odds ratios of gender, ethnicity and other variables of interest could not be aggregated due to the heterogeneity of articles that evaluated these factors.

Study ID		OR (95% CI)	% Weight
Fujiwara (2017)		1.68 (0.61, 5.35)	1.23
Julius (2017)		0.87 (0.79, 0.95)	18.22
Naito (2017)		1.07 (0.98, 1.19)	18.02
Agiro (2016)		1.92 (1.18, 3.23)	4.67
Agiro (2016)		1.09 (0.55, 2.17)	2.81
Agiro (2016)		1.25 (0.58, 2.70)	2.31
Kim (2016)		2.80 (1.16, 6.81)	1.79
Altwairgi (2013)		2.80 (1.00, 7.70)	1.38
Jiang (2013)		3.82 (1.23, 11.83)	1.13
Laskey (2012)		2.84 (0.99, 8.13)	1.30
Lyman (2012)		1.30 (0.96, 1.75)	9.26
Schewenglenks (2012)		1.35 (1.06, 1.73)	11.32
Pentegell (2009)		2.20 (1.21, 4.01)	3.54
Dranitisaris (2008)		1.90 (0.95, 3.78)	2.78
Shewenglensks (2007)		1.02 (1.01, 1.03)	20.24
Overall (I-squared = 74.1%, p = 0.000)		1.22 (1.08, 1.38)	100.00

NOTE: Weights are from random effects analysis
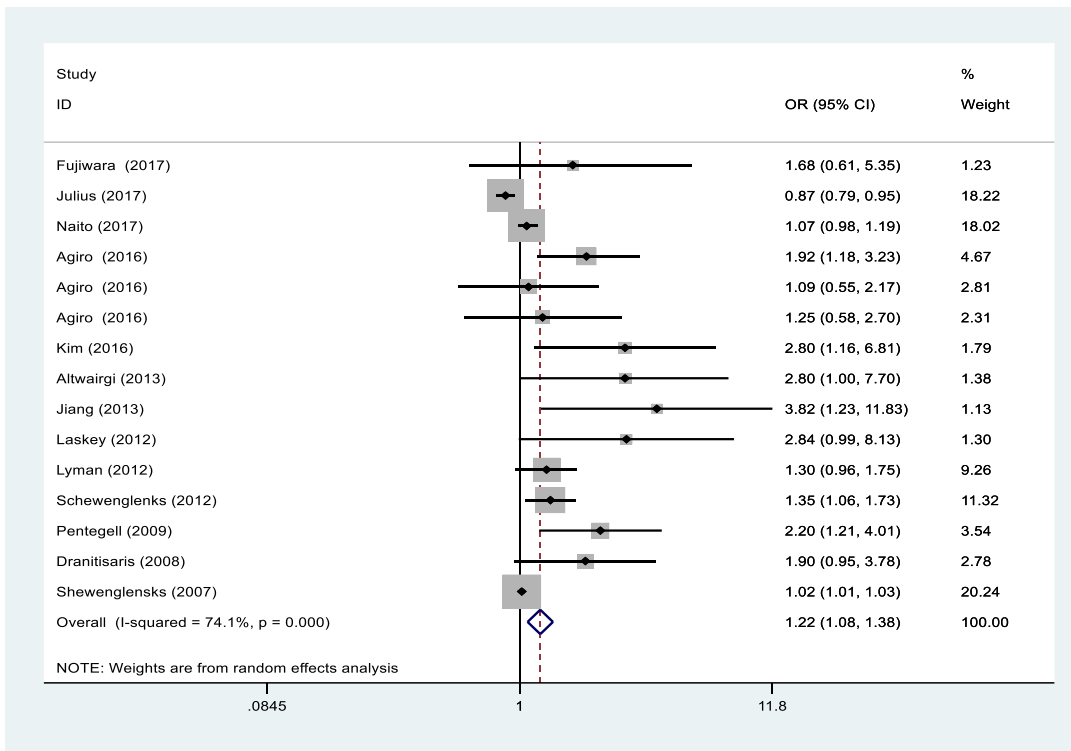
Figure 3-4. Forest plot of all studies investigating age utilising multivariable analysis methods and detailing odds ratios

Study		OR (95% CI)	% Weight
Kim (2016)		2.80 (1.16, 6.81)	6.52
Lyman (2011)		1.30 (0.96, 1.75)	40.72
Schewenkglenks (2010)		1.35 (1.06, 1.73)	52.76
Overall (I-squared = 24.1%, p = 0.268)		1.39 (1.11, 1.76)	100.00

NOTE: Weights are from random effects analysis
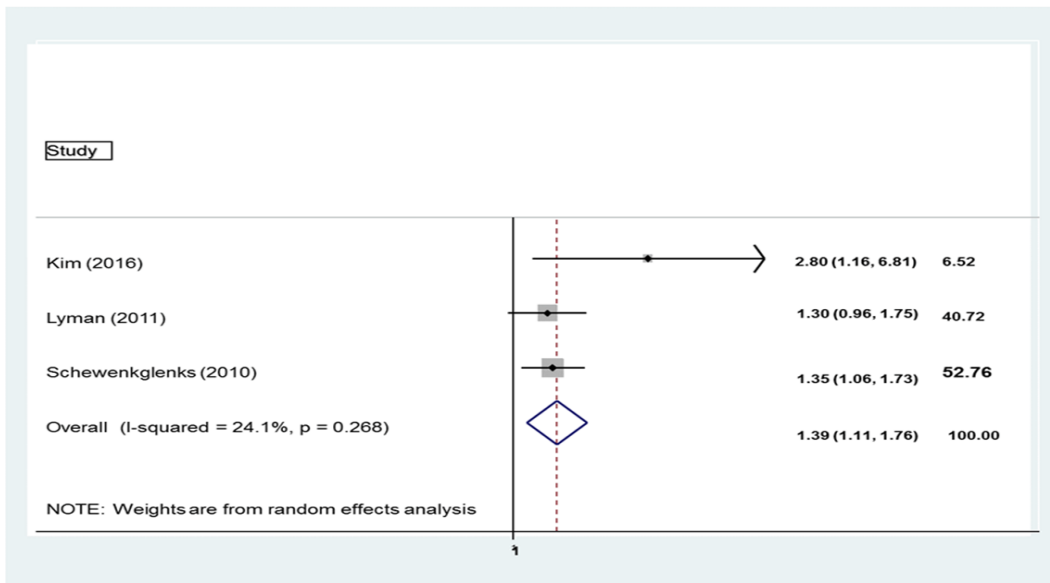
Figure 3-5. Forest plot of all studies investigating age, comorbidity and renal function in the breast and lymphoma subgroup only utilising multivariable analysis methods and detailing odds ratios
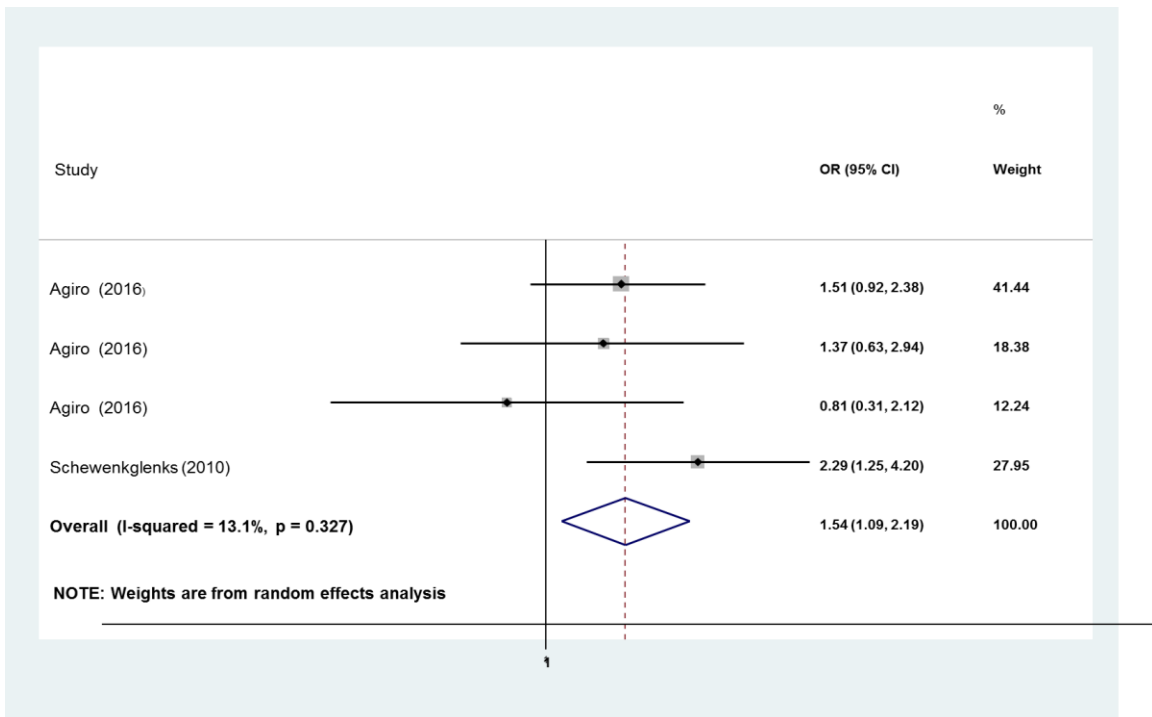
Figure 3-6. Forest plot of all studies investigating age, comorbidity and renal function in the breast and lymphoma subgroup only utilising multivariable analysis methods and detailing odds ratios

3.5.7 Results from updated searches

In November 2020, I updated my searches using the same search strategy indicated in the methodology section. A further 1,850 articles were found and these were screened to identify further risk factors. Although these factors could not be retrospectively collected from hospitals to develop the final model, they could be used to guide any future validation recommendations of the model.

One new factor found was nutritional status. A relatively small study reported a low prognostic nutritional status to increase the risk of neutropenic events (OR 8.39, CI 1.9-37). However, as only 202 patients were included in this study the validity was compromised (Xiao et al., 2020). A further study, with only 226 patients and 44 events of FN, concluded that changes in body weight and albumin were predictive factors to the event (Kayauchi et al., 2020).

3.6   Discussion

Through this work I have demonstrated the influence of a multitude of factors influencing neutropenic events, underlining the importance of prognostic research. Furthermore, I have demonstrated that univariable analysis methods in this complex environment should be used with caution when guiding practice.

Factors found in the review guided my data collection and enabled the development of a model, but findings were still relevant and applicable to current practice. I found that chronological age does seem to influence the occurrence of neutropenic episodes and clinicians can use this finding as a guide to managing patients. Implications of these findings are more pronounced in treatments that fall marginally short of the 20% neutropenic risk threshold that indicates the use of CSFs. An additional risk of 40% could lead to a patient receiving primary CSF prophylaxis, whereas this would not be the case where only treatment-related risk is used. This is true for some treatments used for early breast cancer patients; the regimen docetaxel /cyclophosphamide for example, demonstrated only an 18% neutropenic risk to patients (Gerlier et al., 2010) in the trial setting. Clinicians might want to consider primary prophylaxis for these patients when other predisposing factors are present.

Chronological age might not necessarily be the influencing factor, but rather comorbidity, or frailty (Belani & Fossella, 2005). In my meta-analysis, I used studies that controlled for these potential confounders and an aggregated odds ratio of 1.4 was still seen. Despite this, these studies used a threshold age of 65 years and over, which may not be appropriate. These limitations of other studies guided the development of my analysis methods.

There are differences in the factors that influence a dose delay and those that affect neutropenic events and neutropenic sepsis; this was highlighted in a large study on comorbidity (Chao et al., 2014). The influence on different comorbidities was investigated on either neutropenic events or neutropenic sepsis. The influence

of comorbidities was different for these two outcomes and so although many authors combine neutropenia and dose delay, they are not necessarily the same. There may be other factors that are less researched that influence non-haematological delays.

A number of prognostic models were found and assessed for transferability; however, the models developed were specific for neutropenic sepsis only and could not be used more broadly for any dose delay. Lyman et al. (2011) produced a model that was externally validated to predict neutropenic sepsis (Jenkins et al., 2012). Methodological decisions made in this model did not, however, comply with current guidance and therefore raised concerns regarding its validity. Methodological decisions made included dismissing predictors at the univariable screening stage and dichotomisation of factors without justification. The model is not widely used in the UK.

Neutropenia is one of the most common and most dangerous toxicities of chemotherapy. For this reason, a strategy to prevent the event from occurring is essential. Trial data of new treatment regimens can guide the understanding of the treatment effects on the bone marrow; however, these studies are often undertaken in a controlled group of patients and it is difficult to assess other patient-related factors that increase risk. The work presented in this chapter has demonstrated that many patient-related variables influence the risk of developing neutropenic episodes and the identification of these factors will guide the development of a prognostic model. Risk model development studies were included in this work; however, some were excluded as individual factors were not reported independently. An additional limitation was also that I only included full-text published studies and there may have been other work published in abstract form.

3.7   Summary

The findings from this review can guide clinicians to manage their patients by highlighting the evidence behind the common risks that are broadly understood but not fully quantified. I identified that in order to predict a dose delay, I would need to collect the variables age, performance status, comorbidity, renal and hepatic function, cancer stage and treatment, cancer type, weight and haemoglobin.

Chapter 4. A survey study to understand current practices in the United Kingdom

4.1 Overview

The effect of the sparse understanding of blood tests has anecdotally led to national variation. In this chapter, I present the results from a survey conducted to understand the current practices surrounding blood assessments for neutrophils and platelets, in terms of both threshold values and timing. This is the first survey of its kind examining variation in practices surrounding pre-chemotherapy blood assessments.

4.2 Background

In an attempt to improve cancer care, the National Comprehensive Cancer Network (NCCN) and the National Institute of Clinical Excellence (NICE) present clinical practice guidelines that are evidence based and consensus driven recommendations relating to prevention, diagnostic and treatment strategies. These strategies are implemented through the development of treatment protocols at the hospital level in the UK. The purpose of national guidance is to provide evidence to reduce undue variation in treatments received and information given. However, local protocols and guidelines that are essential to the delivery of treatments vary. In 2008, variations in toxicity assessments were found to lead to an increase in deaths within 30 days of commencing SACT (Khoja et al., 2015). Inquiries at individual hospitals, since this was reported, have found that patient outcomes have been hindered as a result of local practice (Select Committee on-off protocol, 2016). In Australia, the prescribing practices of one clinician, who deviated from national protocols, reduced the chances of survival in patients (Select Committee on-off protocol, 2016). Additionally, in 2019 an inquiry carried out in Scotland (Scottish Government, 2019) found that clinicians were underdosing patients to prevent the occurrence of toxicity instead of adhering to

the nationally accepted standard of prescribing CSF; the practice in this curative setting was strongly condemned. As with these cases of underdosing, therapeutic treatment strategies are often variable and a reflection of clinical experience or intuition, which would have a consequential effect on the timing of treatments, and, in turn, relative dose intensity received.

Laboratory tests are required during the course of any SACT to ensure safety, ensuring adequate bone marrow, renal and hepatic function throughout the period of treatment, as detailed in Chapter 1. Ideally, these tests would be conducted on the day of treatment administration; however, this is not always practical. As the numbers of patients receiving SACT treatment has increased, it is more common for patients to undergo assessments prior to the treatment day. Threshold values for laboratory tests are implemented locally, guiding clinicians to delay treatment where a patient does not attain these values. Threshold values that are set too high, and a policy that recommends a patient undergoes toxicity assessments five or six days prior to administration, may result in the individual being delayed from treatment and inadvertently reduce their dose intensity and treatment outcome. Alternatively, the patient may require a repeat assessment and this can affect the patient's treatment experience.

A service evaluation undertaken by *London Cancer* (Chambers & Gallagher, 2013) reported that the number of blood tests required by hospitals ranged from three to nine over a 21-day cycle for exactly the same treatment; the report showed the consequences of the dearth of evidence on patient attendances. Other local service evaluations presented at conferences have suggested the need for hospitals to change practice through increasing the timeframe between blood tests and treatment in the UK where there is a lack of evidence (Thwaites et al., 2017; Bayliss, 2017). The Covid-19 pandemic further challenged hospitals in 2020 with the implementation of pre-treatment COVID screening and social distancing (Curigliano et al., 2020); advanced blood tests were a tool that would enable services to maximise capacity.

To date, no evidence exists to guide how far in advance of treatment pre-chemotherapy blood assessments should be conducted, and there is uncertainty around the threshold values that need to be attained to assure safe treatments (Brooks et al., 2015).

4.3 Aims

The purpose of this study was to understand the main policies or guidelines relating to pre-chemotherapy assessments being implemented for patients receiving treatment for early breast cancer, colorectal cancer, and DLBCL.

4.4 Objectives

The objectives of this study were:

1. To examine the maximum period that is accepted as safe to assess neutrophils and platelets prior to chemotherapy at hospitals in the UK.

2. To evaluate any differences in threshold values for neutrophils and platelets across hospitals in the UK.

4.5 Methods

This was a cross-sectional survey study that was developed and distributed to healthcare professionals who manage cancer patients receiving SACT in England, Scotland, Wales and Northern Ireland. The questionnaire was designed to capture local practice around the timing and threshold values of blood tests rather than individual practices. The study was carried out using an online survey tool, Qualtrics®.

4.5.1 Participants

My intention was to capture a response around local policies, from at least one health professional at each National Health Service (NHS) hospital in the UK. I, therefore, engaged with and targeted the distribution through two key societies

whose members would have a strong working awareness of these policies. The two societies were the British Oncology Pharmacists Association (BOPA) and the Association of Cancer Physicians (ACP). These are professional societies for pharmacists (BOPA) with an interest in cancer care and medical oncology (ACP). At the time of the survey, BOPA reported having 831 members. BOPA members stretch beyond the UK; however, 631, 50, 22, and 13 members are pharmacists based in England, Scotland, Wales and Northern Ireland, respectively. A total of 490 members were based in NHS hospitals at the time of the survey. The ACP has a membership of around 1,000 doctors in the UK and is recognised by the Royal College of Physicians. Although a breakdown of members was not obtainable, every medical oncologist in training in the UK is believed to be a member.

4.5.2   Questionnaire development

The survey was developed to capture local hospital policies related to the timing and threshold values of pre-chemotherapy haematological tests for treatments related to breast cancer, colorectal cancer and DLBCL; specifying the exact treatment regimens within these cancers, detailed in the inclusion criteria.

I designed the study questionnaire to be short, as it was understood that participants would be busy at the time of dissemination, which was during the COVID-19 pandemic. The questionnaire consisted of seven questions in total: four multiple-choice matrix questions; one open-ended free-text question (allowing respondents to expand on answers in addition to raising concerns or issues that may have been overlooked); and questions enquiring about the respondent professional group and the name of the hospital where they were employed. Details of the survey are reported in Appendix 3.

4.5.2.1   Content validity

Content validity for the questionnaire was quantified using the content validity index (CVI) as recommended by Polit, Beck & Owen (2007). Content validity

involves a panel rating three domains, as recommended by Grant and Davis (1997): the relevance of each question, the clarity of each question, and the comprehensiveness of the entire survey. A CVI is then calculated by dividing the number of raters, rating 3 and 4 on a 4-level Likert scale, by the total number of raters; a CVI score greater than 0.7 is considered acceptable (Halek, Holle & Bartholomeyczik, 2017).

An expert panel was assembled, which included two experts with a background in survey design, and three experts in chemotherapy treatment. Chemotherapy experts included members of BOPA and the ACP. All questions were found to have a CVI >0.78, therefore not requiring question revision. Revisions were made to the wording of the questions, however, to improve clarity and understanding, based on feedback from the expert panel. The panel unanimously agreed that the questionnaire was comprehensive and covered the important areas.

4.5.3   Survey administration

The survey was open between July 1st and July 31st, 2020 and was disseminated to BOPA and ACP members via email and through snowball-sampling techniques to target healthcare professionals who had a role in delivering chemotherapy treatment. In addition, I used Twitter to disseminate the survey, and I received 5,363 impressions, 387 engagements, and 34 retweets. After 2 weeks of being open, a follow-up email was sent to members of BOPA and the ACP reminding them to complete the survey. A further tweet was also sent encouraging specific regions of the country to respond, such as the northwest, from which no responses had been received. BOPA and the ACP also used their social media platforms to disseminate the survey and retweeted my tweets. These societies are followed on Twitter by other professional bodies, such as the UK Oncology Nursing Societies, who retweeted the survey to their membership.

The survey introduction page acted as a consent form and participant information sheet (see Appendix 4). It stated that consent given for data being used for

specified purposes was implied by participation in the survey. All respondents remained anonymous and no identifiable data was collected. There was no direct benefit for participants, and this was explained in the prefacing information of the online survey. Participants were informed of the benefits in terms of improving the use of evidence to inform cancer care delivery models.

4.5.4 Inclusion and exclusion

To capture the policies at individual hospitals, I included all healthcare professionals who completed the survey, including medical and clinical oncologists (registrar consultant level), haematologists (registrar or consultant level), chemotherapy nurses, clinical nurse specialists, and oncology and haematology pharmacists. As the questionnaire was only in English and intended for those working in the UK, participants were required to respond to answers in English. There was no age limit affecting the inclusion of participants.

4.5.5 Missing data

I did not use 'forced answering' to avoid 'missing data' from the online questionnaire, but allowed respondents to leave questions blank, as I believed forced answering was both unethical and could result in inaccurate data. Missing data are therefore presented within the results.

4.5.6 Data analysis

4.5.6.1 Desired sample size

I calculated the sample size (n=131) based on the total population being the number of hospitals in the UK (n=256), a 95% confidence interval and a 10% margin of error, which is acceptable for surveys where answers are not binary but in multiple categories. I, therefore, needed responses from 71 different hospitals.

Data were exported and analyses were conducted using STATA 15®. A response rate was calculated using individual hospitals as a numerator and total NHS chemotherapy treatment hospitals as the denominator. Results were presented as

counts and percentages. As my inclusion criteria allowed for more than one response from each hospital, answers from multiple respondents at particular hospitals were grouped and I planned to assess and present the agreement through a calculation of the Cohen-Kappa statistic where warranted (Warrens, 2015).

For the questions relating to the timing of treatment, I grouped the respondent's answers into three main groups: those receiving blood tests within 3 days, those who require closer timing (<2 days), and those who required timing from 4-7 days. These values were then presented as percentages. Those participants who answered that a guideline was not available, or the regimen was not used, were retained in separate groups.

Again, in relation to threshold values, I used a value of 1 x 10^9/L and 100 x 10^9/L as index values for neutrophils and platelets, respectively. Here, I grouped those participants who responded to using threshold values lower, equal to and greater than the index; separate groups were kept when the participant did not use the regimen or did not have any guidance.

Free-text answers were compiled in a single list and were left unedited and described using percentages.

4.6   Results

A total of 208 participants opened the survey and 170 started the first question. 91 participants completed the questionnaire. The mean time for full completion of the survey was 5 minutes. Table 4.1 details the professional group of the participants who commenced the survey and those who completed the survey fully. As the survey was anonymised, I could not contact individuals to understand the reasons for non-completion. However, 50% of those who did not complete the survey stopped answering questions when they were asked to name their employing hospital.

Table 4-1. Professional groups completing the survey

Professional group	Number starting survey	Number completing survey
Pharmacist	107 (63%)	55 (60%)
Oncologist (medical or clinical)	40 (23%)	23 (25%)
Chemotherapy nurse or Clinical nurse specialist	14 (8%)	8 (9%)
Haematologist	3 (2%)	2 (2%)
Other (unspecified)	6 (4%)	3 (3%)
Total participants	170 (100%)	91 (100%)

The number of participants completing the survey from independent NHS hospitals was 77; a minimum sample of 71 hospitals was needed. There were five hospitals in total where more than one respondent completed the survey. There are 220 hospitals commissioned to deliver chemotherapy treatment in England, approximately 30 in Scotland, four in Wales and two in Northern Ireland (a total of 256 hospitals). I therefore approximately captured 25% of the hospitals in the UK in my sample.

Where there were duplicate participants, different questions were answered; for example, a clinician may have only answered for breast cancer treatments and listed 'not used' for the other cancer types. Therefore, results are not presented per site but per participant.

Table 4.2 shows the responses to blood tests regarding timelines. Most participants in the breast cancer treatments stated that a 72-hour period was used (27-34%). In the colorectal cancers, where the cycle is 14 days there are similar proportions using a one to two-day period (24-29%). Interestingly, some participants did report extending up to 7 days where the standard cycle length was 14 days. A small proportion of the hospitals stated that there was no guidance for the timing of blood tests. 32% of participants who reported on the regimen R-CHOP, used for DLBCL, reported timing of blood assessments to be four days or beyond, implying a shift in practice for this tumour group. In the four hospitals

where three participants completed the survey, I found a disparity between solid cancers and haemato-oncology. Complete agreement was found in this timing of blood tests between those treating breast cancer and colorectal cancer; however, a different, extended period was reported for those treating DLBCL.

Table 4-2. Number of days pre-treatment a patient would have a blood test

Chemotherapy	Within 1-2 days	Within 72 hours	4 days or above	No guidance	Not used/unknown
FEC (breast cancer) N=91	20 (22%)	25 (27%)	13 (14%)	4 (4%)	29 (32%)
EC (breast cancer) N=91	23 (25%)	29 (32%)	14 (15%)	3 (3%)	22 (24%)
Docetaxel (breast cancer) N=91	23 (25%)	31 (34%)	15 (16%)	3 (3%)	19 (21%)
IrMDG (colorectal cancer -palliative) N=91	26 (29%)	26 (29%)	15 (16%)	2 (2%)	22 (24%)
OXMDG (colorectal cancer -palliative) N=91	26 (29%)	26 (29%)	15 (16%)	2 (2%)	22 (24%)
OXMDG N=88 *(colorectal cancer - Adjuvant)	25 (27%)	27 (30%)	14 (15%)	1 (1%)	21 (24%)
OXCAP21 (colorectal cancer) N=91	24 (26%)	27 (30%)	17 (19%)	2 (2%)	21 (23%)
OXCAP14 (colorectal cancer) N=91	22 (24%)	22 (24%)	13 (14%)	1 (1%)	33 (36%)
R-CHOP (DLBCL) N=91	13 (14%)	22 (24%)	29 (32%)	2 (2%)	25 (27%)

Three respondents missed this question. Abbreviations: FEC, fluorouracil, epirubicin and cyclophosphamide; T FEC, docetaxal, fluorouracil, epirubicin and cyclophosphamide; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; FOLFOXIRI, fluorouracil, oxaliplatin and irinotecan; IRMDG, irinotecan and fluorouracil; OXCAP, oxaliplatin and capecitabine, where 14 and 21 refer to the respective cycle length; OXMDG, oxaliplatin and fluorouracil for palliative and adjuvant indications.
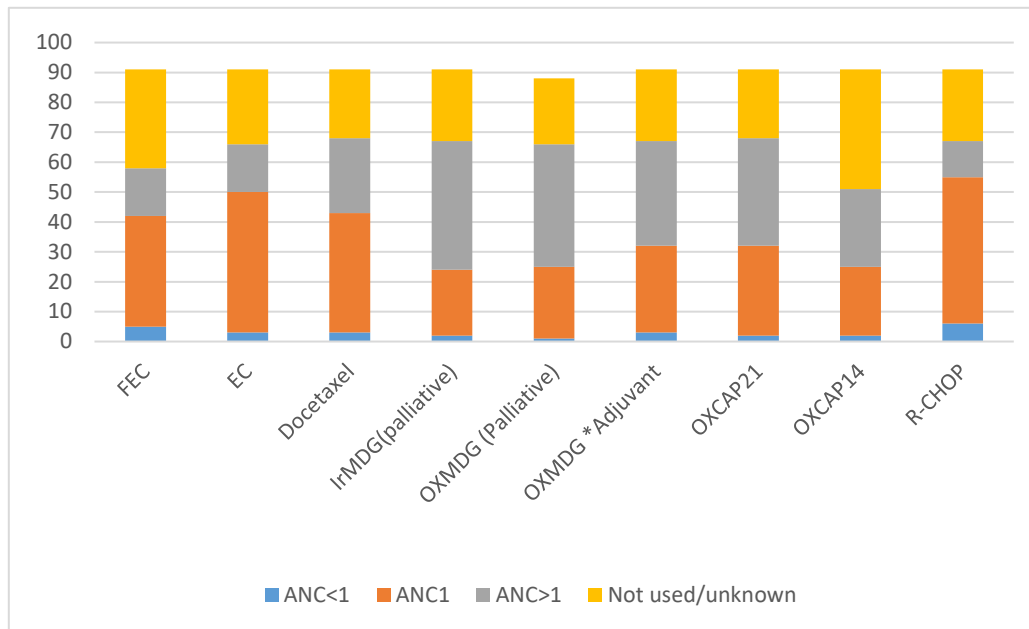
Figure 4-1. Showing number of respondents using threshold values below 1, equal to 1 and greater than 1 for different chemotherapy treatments

Notes: An absolute neutrophil count greater than 1 is used frequently in colorectal cancer treatments whereas a count of 1 is more frequent for the breast and diffuse large b-cell lymphoma treatments.

Abbreviations: FEC, fluorouracil, epirubicin and cyclophosphamide; T FEC, docetaxal, fluorouracil, epirubicin and cyclophosphamide; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; FOLFOXIRI, fluorouracil, oxaliplatin and irinotecan; IRMDG, irinotecan and fluorouracil; OXCAP, oxaliplatin and capecitabine, where 14 and 21 refer to the respective cycle length; OXMDG, oxaliplatin and fluorouracil for palliative and adjuvant indications.

Figure 4.1 shows a divide in the thresholds employed for neutrophils. For patients with breast cancer and DLBCL, a threshold of 1 x 10^9/L is more commonly used, indicated by the orange bar, whereas for the colorectal cancer treatments >1 x
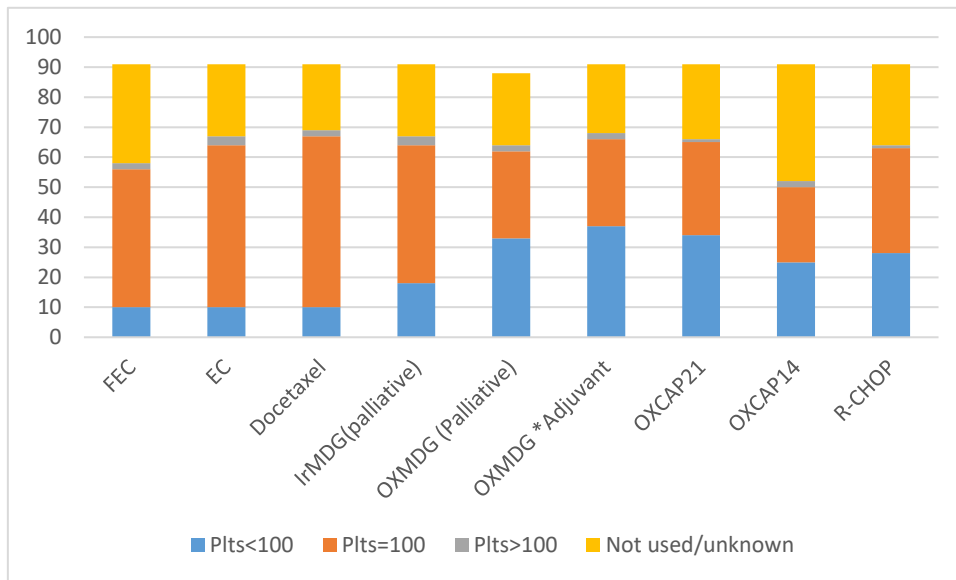
Figure 4-2. Number of respondents using threshold values below 100x109/L, equal to 100 x 109/L and greater than 100X 109/L for different chemotherapy treatments

Notes: Platelet counts below 100X 109/L are frequently used in colorectal cancer and DLBCL.

Abbreviations: FEC, fluorouracil, epirubicin and cyclophosphamide; T FEC, docetaxal, fluorouracil, epirubicin and cyclophosphamide; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; FOLFOXIRI, fluorouracil, oxaliplatin and irinotecan; IRMDG, irinotecan and fluorouracil; OXCAP, oxaliplatin and capecitabine, where 14 and 21 refer to the respective cycle length; OXMDG, oxaliplatin and fluorouracil for palliative and adjuvant indications.

10^9/L, the more common threshold, is indicated in grey, irrespective of treatment intent.

Figure 4.2 shows that it is very rare that platelet counts above 100x10^9/L are used as threshold values. In this figure, it is also noted that many participants used thresholds lower than 100x10^9/L in both the colorectal and DLBCL regimens.

In total, 31 (34%) respondents left further remarks in the section related to "other comments". 26 of these comments were describing exceptions to thresholds that were documented in local policies; respondents described practices where the prescribing consultants would be contacted where patients did not meet threshold values and may make the decision to treat irrespective of laboratory values. Ten out of 26 (38%) of those answering these questions were doctors and they detailed interventions that would occur when threshold values were not met, such as the

assessment of white blood cell count (reported by eight out of ten doctors) and use of CSF (reported by two of the ten doctors). One respondent who was not medically trained stated that they were based in a hospital where medical staff were unavailable, meaning many deferments were necessary for patients.

16% (5 out of 31) of respondents mentioned "pathway challenges" in their comments. These included challenges around bank holidays when the availability of blood testing and clinical assessments is limited. Two of these respondents mentioned moving the blood testing validity period changing from four days to seven days at their hospitals and the positive impact this had had on the pathway.

13% (four out of 31) of respondents described the use of community laboratory tests as an option to save patients undergoing multiple attendances.

4.7   Discussion

Policies relating to the timing of laboratory assessments and threshold values used for neutrophils and platelets have the potential to impact the occurrence of a dose delay and consequently their dose intensity. Through this survey, I found variation with regards to timing of pre-chemotherapy blood tests. At some hospitals, patients are required to have a blood test within a day of treatment administration and at others this can be within 7 days. Counterintuitively, the practice seems to be irrespective of whether a cycle length is 14 days or 21 days. Thresholds that are used in decisions to treat a patient seem to be much more personalised. Guidelines are available, but these threshold values are used to trigger discussions with the treating clinician rather than serving as definitive thresholds. There is, however, a lack of standardisation in these values and again this can lead to variations in dose delays.

A benefit of the ACP and BOPA memberships are the training resources for those new to oncology; I, therefore, speculated that reasons for non-completion would be uncertainty by the junior staff of local policies and apprehension around detailing their place of employment. Additionally, the survey was distributed at the

time of the COVID-19 pandemic and when cancer treatments and trials were recommencing. The increase in workload in chemotherapy services at this time may have made individuals reluctant to answer a survey where information needed to be sought out.

I aimed to capture hospital policies rather than individual practices, and, ideally, I would have used NHS distribution lists for heads of chemotherapy to delegate completion. Unfortunately, due to the COVID-19 pandemic, this was not a feasible option. Health Research Authority (HRA) approvals are required to distribute surveys to clinicians via the NHS, and although in normal circumstances this is relatively straightforward, during the pandemic backlogs at research offices would not have permitted timely execution of such distributions. Using two professional societies was a viable option for the distribution of the surveys, and the overall response rate was adequate, meeting the desired sample size. Nonetheless, by targeting individuals through membership societies some bias was introduced. Paid members of these societies may be individuals that keep up to date with national policies and understand the practice of others. Those healthcare professionals who are not members may not be aware that they are outliers in their practice and treatment of patients. The high rate of non-respondents was concerning and may also imply some bias, including only those participants with documented policies. Some participants did, however, answer that there were no policies available, but this proportion may be higher.

A study evaluating the causes of dose delays at one large hospital in the US noted variation in threshold values used for neutrophils by individual clinicians at the same institution, noting sparse evidence available guiding thresholds (Kogan, Davis & Brooks, 2019), and, importantly, the influence that variation has on delays. Similarly, I have described how variation exists nationally for threshold values, but I did not receive enough responses within one tumour group at hospital level to demonstrate further variation, if any. This may be an area that could be evaluated within hospitals, or cancer alliances, to standardise practices.

Sambrook and Girling (2001) examined variations in treatments prescribed for small-cell lung cancer in 2006, by surveying 1,070 clinicians in the UK. In this study, there was noticeable variation in the way that the same treatments were administered at different institutions. The authors described differences in doses and the number of cycles planned for similar patients at different hospitals. Likewise, the variation shown in this study has a likely impact on dose intensity through variation in delays; however, due to the lack of research in the real world, the impact of dose delays on dose intensity and outcomes is unclear and there is a lack of inertia to change policies and practice.

The main strength of this study was that I had acceptable engagement and participation, capturing around 25% of hospitals in the UK. The findings of this study combined with others presented in this thesis can be used to develop a proposal for consensus in this area. Ideally, the survey would have been distributed to NHS organisations and through an examination of written policies rather than relying on participants to complete the survey. Nonetheless, this was the first study of its kind, examining practices in three different cancers and being important in raising awareness of existing variation.

4.8   Summary

There is notable variation in the timing and thresholds used for assessments of neutrophils and platelets underlining the absence of evidence in this area, including the impact on dose delays and dose intensity. The work presented in subsequent chapters will aim to produce evidence and guide future national policy.

Chapter 5.   Retrospective data collection and preparation for analysis

5.1   Overview

In Chapter 1, I discussed the data that is stored within e-prescribing (EP) systems at chemotherapy-delivering hospitals within the NHS; data could enable a better understanding of real-world patients, prognostic research and service improvements. In this chapter, I detail the acquisition and quality of the data I collected to fulfil objectives 3 and 4: the evaluation of duplicate blood assessments and the development of a prognostic model. This chapter provides an understanding of data quality, explaining decisions made around data manipulation and analysis. The quality of this hospital-collected data was important to assess, and was essential prior to analysis. The work presented in this chapter guided methodological decisions about the definition and classifications of the outcome measures and the predictors used in the model development.

5.2   Site selection

To fulfil the objectives of the study, I required hospital data containing laboratory values for neutrophils across at least two treatment cycles and containing the variables needed to develop a prognostic model. I used the SACT data to guide site selection.

The SACT dataset, introduced in Chapter 1, is an amalgamation of chemotherapy delivery data across England and is managed by Public Health England. To incentivise hospitals to submit accurate reports, hospital data quality is publicly available from the National Cancer Registration and Analysis Service. Quality reports show the numbers of treatments administered at each NHS hospital in England and the percentage of fields completed and submitted to the national dataset. I used these reports to select the hospitals invited to join the study; those administering over 2,500 treatments per annum and known to submit high-quality

data to the SACT dataset, and which were geographically diverse to strengthen generalisability.

5.2.1   Recruitment of hospitals

BOPA facilitated the contact of individual lead pharmacists at these hospitals. Initially, eight hospitals were invited to join the study in September 2017, seven of which responded. Of these seven, one did not hold all blood testing records locally and another did not believe the research would benefit its patient population.

I visited the six remaining hospitals to understand their local chemotherapy processes, view their EP databases and explain the data required. I identified local principal investigators and obtained standard operating procedures at the hospitals to enable future analysis.

It was believed to be practical for only four of the high-volume hospitals to be involved with the study and these would yield enough data to meet my required sample size of 3,000. This sample would mean that each hospital would need to have data over 5 years for 750 patients who were new to treatment for the treatments that I included in my model. Four hospitals (hospitals 1, 3, 4 and 5) were chosen based on their location and their EP systems. One (hospital 6) was not selected because it used a chemotherapy prescribing system, Chemocare, where blood test results were not extracted in the way proposed in this study, and also that the two other hospitals using this prescribing system had higher patient numbers (hospitals 3 and 5). As a pharmacist who has worked with this system, I understood there to be a risk that data may not be extractable from the Chemocare database. Hospital 2 could not ascertain whether data from their EP system (a bespoke system) would be extractable and so I initially decided not to include them for the development study. However, during the capacity and capability process, hospital 5 withdrew due to a lack of capacity and so I contacted hospital 2 and worked with analysts to establish extraction, coding and information governance

procedures, enabling their inclusion. Finally, hospitals 1-4 were included in the study.

5.3   Ethics considerations

As this study was based on retrospective datasets that would be fully anonymised, the study was exempt from NHS ethics approval. Health Research Authority (HRA) approvals were required and granted on 24 November 2017 (IRAS 226078; Appendix 1). A minor amendment was completed to include hospital 4 in April 2018 (see Appendix 1 for details). Local governance committees approved the study and I developed procedures for data handling, transfer and storage to meet NHS information governance requirements (see Appendix 5).

5.4   Summary of included sites

Using publicly available SACT reports, I established that the four hospitals treated a combined number of 18,251 patients for the three cancer types over one year

Table 5-1. Details of hospitals and numbers of patients treated and cycles delivered at the four hospitals recruited in the study

Facility details			Total numbers across all cancers		Total patients in each included cancer		
No	Institution type	E-prescribing system	Patients	Cycles	Breast	Lower GI	Lymphoma
1	Cancer only	Hospital specific in-house developed	8,703	47,460	1,950	1,470	292
2	Acute Hospital & Cancer regional centre	Hospital specific in-house developed	1,866	7,564	327	227	80
3	Acute Hospital & Cancer regional centre	Chemocare	3,885	16,168	221	160	561
4	Acute Hospital & Cancer regional centre	Aria	3,797	23,286	571	360	308

Table adapted from SACT 2017 data quality report.

(January 2016-December 2017). The breakdown by hospital and cancer type is detailed in Table 5.1, however, this data did not provide data on cycles or individual treatments. Hospital 1 is a leading cancer treatment hospital; however, numbers for lymphoma are relatively low as it mainly delivers treatments for solid tumours. In the case of hospital 2, many patients receiving lymphoma treatment were not recorded on EP records. I contacted hospital 2 to confirm that they could provide data for the chemotherapy regimen I had included for this cancer type. Hospitals 3 and 4 were of similar sizes for total patients treated, but case mixes varied within cancer types.

5.4.1   Site policies that would influence the research

At the initial site visits, policies and procedures relating to the delivery of the included protocols were obtained and several areas were identified to influence the proposed research.

1. All sites recognised that repeat blood testing existed, but all had implemented different policies. At hospital 1, patients were seldom brought back to the treatment hospital for a repeat blood test but attended local GP surgeries. These results would be filed as paper medical records rather than electronic ones. Tests for renal and liver function were conducted at the point of receiving treatment and assessed before a subsequent treatment administration. This was also true at hospital 4.

2. Differences in the threshold values for neutrophil counts existed, and this is true nationally (see Chapter 4).

3. There were differences in CSF prescribing. In hospital 2, CSF prescribing was not built into EP systems when the regimen guidelines indicated, possibly leading to accidental omission. In addition, there is no standard guidance on how many days of CSF a patient should receive, leading to variations in lengths of treatments both between

consultants at the same hospital and nationally. Hospitals 1 and 2 used long-acting versions of the CSF (PEG-filgrastim) when indicated, whereas hospitals 3 and 4 only had access to daily treatments (filgrastim).

5.5 Variables required

Guided by the systematic review (Chapter 3) and discussions with clinicians and patients on the study steering panel, I determined that I would need several factors to evaluate the appropriate timing of blood assessments and in the development of a prognostic model.

5.5.1 Cancer treatment-related factors

The collection of the cancer type and exact chemotherapy administered, including any dose reduction and administration of CSFs were essential. These factors are universally recognised by clinicians as important to dose delays (Lyman et al., 2014) and they were additionally identified in my review (Chambers et al., 2019). Treatments for cancers are dependent on the cancer stage and I considered how the data for this would be collected and analysed. In my model, I limited chemotherapy regimens used in specific cancers to achieve this. For early breast cancer, the standard first-line treatment was fluorouracil, epirubicin and cyclophosphamide; however, the practice had changed at some hospitals as new evidence was showing the doublet combination of epirubicin and cyclophosphamide (EC) demonstrated equivalent outcomes with less toxicity (Cardoso et al., 2019). Some patients would receive a doublet or triplet combination for three cycles at this stage followed by docetaxel, whereas some patients would receive six cycles. The final combination of treatment was that patients would start treatment with three cycles of docetaxel and complete the treatment with three cycles of FEC or EC. All these regimens were included in my model.

For the colorectal cancer patients, there were three standard initial treatments available; combinations of oxaliplatin, irinotecan, and fluoruracil (or its pro-drug, capecitabine). A triplet or doublet combination is usually standard for this group of patients, but during data collection, I found cases where a four-drug combination had been used. This is uncommon for colorectal cancer but is standard care for pancreatic cancers. On discussions with clinicians, I became aware that there was a period within which the combination was used for colorectal cancers and therefore it was included in all analyses. The treatments included were either used in the adjuvant setting (post-surgery) or for metastatic patients where the intent was symptom control with the aim of stabilisation of the cancer rather than cure. Data around intent was poor, but I intended to collect data regarding treatment intent in this patient group, where possible.

DLBCL treatment was simpler. There was one standard treatment, R-CHOP. Occasionally, clinicians would prescribe an iteration called mini-CHOP, which included lower doses. I classified this as a dose reduction.

Each treatment category would act as one candidate predictor in my model and the date stamps of administration was required to calculate dose delays.

5.5.2   Patient-related factors

The patient factors of interest in my research were: age, body mass index (BMI), gender, ethnicity, performance status (PS) and comorbidity.

Age was a clear variable associated with neutropenic events in the systematic review (Chambers et al., 2019) and one that I assessed in the meta-analysis. BMI, however, was under-researched, particularly for patients with DLBCL. Obesity is a common problem among cancer patients and is a leading cause of cancers globally (Renehan, Lloyd & Renehan, 2019). Weight and height are routinely collected, as they are used to guide treatment dosing. This factor was easy to calculate and collect from hospital data and therefore the study steering group believed it would be appropriate to evaluate the effect of BMI on dose delays.

Similarly, few studies existed examining gender as an influencing factor to delay; however, there is a link between gender and toxicity for several cancers and therefore it was important to collect data for this factor (Ozdemir et al., 2018).

Ethnicity was a factor that the patients in the study steering panel considered to be important, although I found no direct evidence of its influence. At the time of data collection, it was not considered that the interaction of ethnicity and socioeconomic status could have determined dose delays and therefore socioeconomic data was not collected. This theory emerged during the COVID-19 pandemic when risks to chemotherapy patients were being investigated (Razai et al., 2021).

The Eastern Cooperative Oncology Group Performance Status (ECOG PS) was not found to be associated with NEs in the literature; however, it was commonly included as a confounder. It should also indicate a patient's overall ability to tolerate treatment and is a synthesised scale of symptoms and mobility. However, there is variation in the way PS is recorded and what it means in practice. The ECOG PS is widely used in UK oncology, and in a recent survey, 90% of healthcare professionals managing older patients with cancer used it as part of their assessment (Simcock and Wright, 2020).

Based on the available evidence presented in the systematic review on comorbidity (Chambers et al., 2019), it was understood that febrile neutropenia is mediated through bone marrow suppression, impaired neutrophil and other immune cell function, disturbances of barrier function (skin/mucosal integrity), and availability of pathogenic microbes. Coronary heart failure (CHF) may impair neutrophil function via the impaired release of oxygen radicals (Chao et al., 2014). Diabetes impairs neutrophil function through defects in chemotaxis, phagocytosis and other microbicidal activities (Alenzi and Kelley, 2017). It was therefore also important to collect this factor.

Ideally, I would have preferred to collect data on any comorbidity and then calculated how it was presented in the model using indices such as the Charlson

Index (Charlson et al., 1994), the prevalence of vascular comorbidity or simple counts of conditions. However, I was limited by the differences in the way comorbidity was recorded in hospitals.

5.5.3   Laboratory values

It was essential to collect neutrophils as these were key to achieving one of my research objectives. A low level of neutrophils at baseline was identified as important to neutropenic events (Lyman et al., 2011). Conversely, platelets at baseline were not commonly studied; only two authors had included them in their models (Naito et al., 2017; Pfeil et al., 2014). Haemoglobin measurements were found to be significant by many authors and these could be a marker for overall baseline bone marrow function.

Measures of renal and hepatic function were considered important as these could be factors that were more determinant to delays than age. In practice, it is understood that elevations would cause a patient to be delayed from treatment (Krens et al., 2019).

5.6   Data extraction processes

Table 5.2 describes the information that was given to each site to aid them in the extraction of the required variables.

The hospitals recruited for this study had not previously attempted to extract the breadth of data that was required for this research. I visited them to understand their data flows and worked closely with their analysts to understand blood testing recording and storage to facilitate extractions and troubleshoot coding queries. In three of the hospitals, an analyst worked with me, and at my clinical base hospital, I worked independently, taking advice and direction from local analysts. At hospitals 1 and 2 where in-house EP systems were used, analysts were able to extract data quickly (<1 day). However, at hospital 3, where Chemocare was used as the EP system, I found that blood result data was incomplete. Automated

extraction through linking of other systems was not possible at this hospital and I manually collected laboratory data from other electronic sources to ensure a high-quality dataset. Laboratory and performance status data was collected for 980 patients for all cycles received up to six cycles. 10% of manually collected data was double-checked by a clinical colleague, Benjamin Thwaites.

Table 5-2. Fields be extracted at recruited sites

Chemotherapy regimens	Approved names: FEC or FEC+Docetaxel or FEC+Docetaxel +Trastuzumab (Breast) Epirubicin + Cyclophosphamide (Breast Cancer) CHOP- R or CHOP (indication DLBCL) Irinotecan + Fluorouracil (Colorectal) Oxaliplatin + Fluorouracil (Colorectal) Oxaliplatin + Capecitabine (Colorectal)
Demographic information	Age at start of chemotherapy treatment Gender Ethnicity Height at start of chemotherapy Weight at start of chemotherapy Comorbidity at start of treatment
Related to cancer	Stage Performance status
Related to treatment	Dates of chemotherapy and doses administered Cycle number If filgrastim or lenograstim was included
Blood test results	**Cycle 1** Creatinine bilirubin, ALT, albumin, absolute neutrophil count, platelet count, haemoglobin level – dates and results (-14 days) prior to 1st chemotherapy. **Cycle 2+** Creatinine (assay method), bilirubin, ALT, albumin, absolute neutrophil count, platelet count, haemoglobin level – dates and results (-7 days) prior to each cycle and including the day of chemotherapy. There may be more than one result.

Abbreviations: FEC, fluorouracil, epirubicin and cyclophosphamide; T FEC, docetaxal, fluorouracil, epirubicin and cyclophosphamide; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; FOLFOXIRI, fluorouracil, oxaliplatin and irinotecan; IRMDG, irinotecan and fluorouracil; OXCAP, oxaliplatin and capecitabine, where 14 and 21 refer to the respective cycle.

At all sites, the first chemotherapy treatment from the EP data was used as an index date for entry to the cohort during the study period of 1 January 2013 to 1 January 2018. All these patients were followed up until the administration of the sixth cycle of treatment. Data was restricted to the following three tumour groups: breast cancer, colorectal cancer and DLBCL, identified using the ICD10 coding of C50 for breast cancer, C83 for colorectal cancer, and C19-C21 for DLBCL (WHO, 2004). Only first-line treatments were included, and these were epirubicin and cyclophosphamide with or without fluorouracil; docetaxel with or without

cyclophosphamide; irinotecan-modified de Gramont; oxaliplatin-modified de Gramont and combinations including irinotecan; oxaliplatin and capecitabine; line rituximab, cyclophosphamide, vincristine and prednisolone. Laboratory values for liver, kidney and bone marrow function were extracted in addition to other demographic information for these patients from 7 days before the index date to 4 weeks following their last chemotherapy date or their sixth chemotherapy cycle.

Analysts at hospital 4 identified early in the extraction process that there would be problems extracting blood results; however, they were able to provide comprehensive baseline values that could be used in the analysis.

5.7   Data harmonisation and exclusion of patients

I expected that there would be differences in the way that each hospital named its regimens. Names of the regimens were defined by approved names that should be mapped on all EP systems. However, at hospital 4 this mapping was not extractable and therefore all regimens containing drugs for indications specified were extracted and transferred. When data was received, the names given to the regimens were checked from all hospitals with doses and individual drug names. It also became apparent that there were duplicate entries for patients receiving first-line chemotherapy for two different cancers. Here, I identified the date of treatment and used the first cancer diagnosis and treatment data, excluding any second entry. This duplication occurred in 45 patients across all hospitals.

In hospital 3, 40 out of 958 patients had undergone two blood tests on the same day for neutrophils. On all these occasions, both test results were greater than the threshold neutrophil value of $1x10^9$/L. For these patients, the mean result was used. Two blood results taken on the same day may have meant that the patient received chemotherapy as an in-patient. They may also signify that the patient was having some other procedure or investigation. Occasionally, blood results were analysed twice, even though only one sample was taken. This was to validate the

results analysed on point-of-care testing. For these reasons, I believed it appropriate to use the mean average.

5.8 Cycles administered

When developing the analysis plan, it was important to understand data completeness for the number of cycles received by a patient. I included data for up to six cycles, as for most chemotherapy this is the number administered. However, in the case of colorectal cancer, there can be many more. In this cancer type, a patient may have a block of cycles (between 6 and 8) followed by a break in treatment, which is then followed by another block. This dosing strategy has shown success at reducing disease recurrence (Braun and Seymour, 2011). Reasons why patients did not receive assigned treatments included patient choice, toxicity, progression and patients choosing to have their treatment elsewhere (Braun and Seymour, 2011).

Table 5.3 shows that hospital 1 may be an outlier in the number of patients who do not receive more than three cycles. Hospital 1 is one of three hospitals in England solely dedicated to cancer care. The specialist centre will therefore treat a high volume of complex patients who may be more likely to have a poor response to treatment (Khoja et al., 2015). There may also be patients who travel a significant distance, and once treatment had been established further treatment cycles could be administered closer to home (Tralongo et al., 2011). For hospitals 2, 3 and 4, around three-quarters of patients did receive six cycles of treatment, which would be expected for the population of patients included (Sandra-Petrescu et al., 2018; Wasterlid et al., 2018; Janni et al., 2016).

Table 5-3. Total number of cycles received by patients

Hospital	Cycles recorded						Total Patients
	1	**2**	**3**	**4**	**5**	**6 or more**	
1	326 (16%)	321 (15%)	540 (26%)	145 (7%)	102 (5%)	656 (31%)	2,090
2	41 (3%)	51 (4%)	78 (6%)	119 (9%)	99 (7%)	938 (71%)	1,326
3	50 (5%)	50 (5%)	87 (9%)	88 (9%)	35 (3%)	697 (69%)	1,008
4	30 (5%)	25 (4%)	56 (9%)	53 (8%)	15 (2%)	450 (72%)	627

5.9 Blood testing data

I found that there was a large volume of missing data about neutrophils following cycle 3 at the three hospitals where data was not manually collected; hospitals 1 and 2 had respectively 54% and 66% missing data at cycle 3, and there was no neutrophil data beyond cycle 2 for hospital 4. At cycle 4, the missing data at hospital 1 increased to 89% and was 67% in hospital 2. Following this cycle, there were no further data available for neutrophils at any hospital except hospital 3. This may have been due to how reports were executed during extraction. I suspected that this was the case and suggested alterations to extraction methods. However, due to time constraints at the hospitals, re-extraction was not feasible. Other reasons for the high proportion of missing data here are the use of local testing
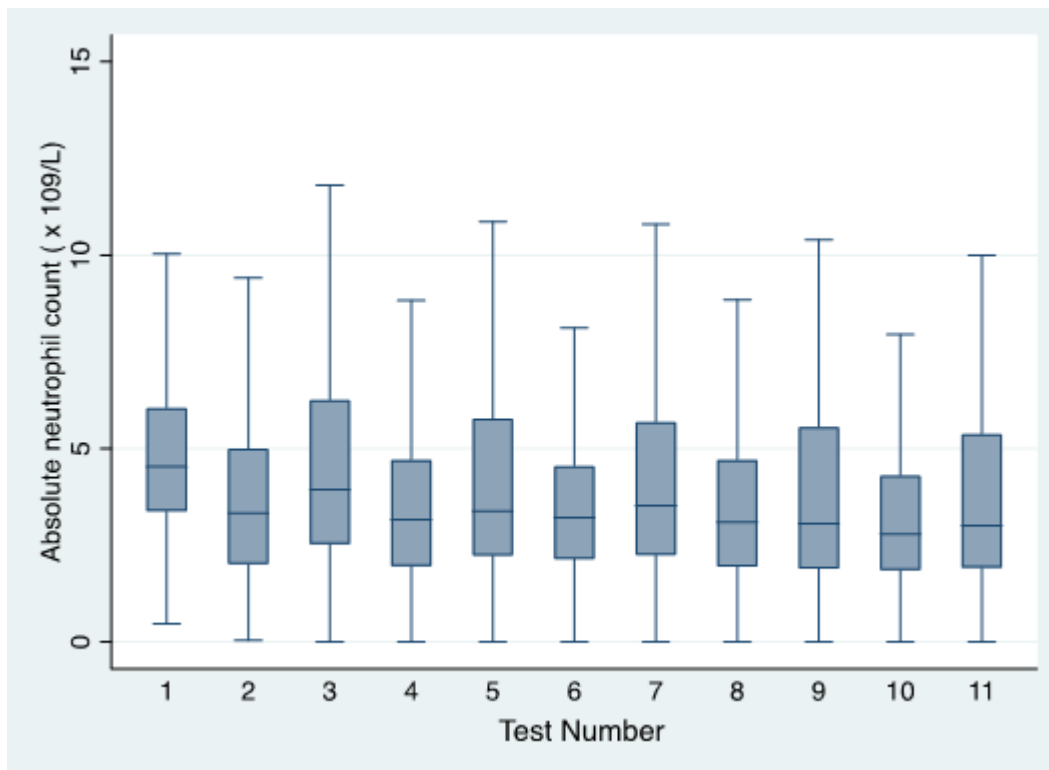
Figure 5-1. Box plot showing average neutrophil count values in three tumour types

Box plot shows tests performed across six cycles. Tests 1, 3, 5, 7, 9 and 11 correspond to pre-treatment tests. N.B. Not all patients received all six cycles of treatment and total patients receiving each test varies. Number of patients who received test 1 and 3=958; total test 5=871; total test 7=783; test 9=748; test 11=697, combining all cancer types.

facilities situated away from the hospitals, as indicated in the comments in the survey reported in Chapter 4. These bloods may have not been recorded on EP systems. At hospital 4, I worked closely with the analyst to establish ways of extracting blood results following baseline; unfortunately, its data was stored on another system that had been archived, meaning extraction was impossible. As laboratory data at hospital 3 was manually collected, neutrophil values were available for every cycle administered to patients. Using data for hospital 3 only, I was able to understand neutrophil fluctuations between cycles.

Figure 5.1 shows neutrophil values obtained from hospital 3 at different points across the six chemotherapy cycles in the three cancer types studied. The time points relate to the pre-treatment blood tests taken and therefore the total number of patients represented at each time point varies. However, the data is broadly consistent with the literature in that that the greatest fall in neutrophil concentration is experienced by patients between cycles 1 and 2 (Silber et al., 1998). This analysis was important to enable me to understand if the missing data would hinder me to meet my overall research objectives.

5.10 Missing data of baseline values

A total of 4,604 eligible patients (1,764 from hospital 1, 1,285 from hospital 2, 958 from hospital 3 and 597 from hospital 4) were included in the study. Table 5.4 shows the baseline variables and the percentage of missing data available, combining data from all hospitals. Concerning treatment-related variables, I expected to observe a complete dataset as this data is collected nationally and incomplete data results in financial penalties. Similarly, many patient factors such as age, gender and ethnicity had either no missing data or very few cases of missing data. The variables of concern to me were platelets where 1,300 (28%) were missing. For this variable, 96% of the missing values originated from one hospital (hospital 2). I was also concerned with comorbidity where 100% of the missing data originated from hospital 1. Missing data for alanine transaminases

(ALT) and albumin were also high and hospital-related. Albumin was only collected at hospital 1 and not routinely tested at other hospitals. Likewise, ALT was not routinely used at hospitals 1 and 4. Imputation of missing data where one site is completely missing is impractical as it would not be possible to understand heterogeneity in the missing values at all hospitals. In Chapters 7 and 8, I discuss how issues with missing baseline data were addressed.

Table 5-4. Variables collected and missing data

Treatment-related factors	Categorical or continuous	Complete	Missing	%age Missing
Chemotherapy	Categorical	4,604	0	0
Chemotherapy administration dates	Continuous	4,604	0	0
Use of CSF	Categorical	4,604	0	0
Dose reductions	Continuous	4,604	0	0
Proportion of dose received	Continuous	4,604	0	0
Patient-related factors				
Age at start of chemotherapy	Continuous	4,604	0	0.02
Gender	Categorical	4,604	0	0
Height	Continuous	4,459	145	3.2
Weight	Continuous	4,173	431	9.3
Body surface area	Continuous	4,025	579	12.6
Performance status	Categorical	4,392	212	4.6
Ethnicity	Categorical	4,604	0	0
Comorbidity	Categorical	2,840	1,764	38
Laboratory values				
Neutrophils	Continuous	4,598	6	0.1
Platelets	Continuous	3,304	1,300	28
Haemoglobin	Continuous	4,505	99	2.2
Creatinine	Continuous	4,555	49	1.1
ALT	Continuous	1,776	2,828	39
Albumin	Continuous	1,581	3,023	34
Bilirubin	Continuous	4,564	40	0.9

Abbreviations: CSF, colony-stimulating factor; ALT, alanine transaminase. Variables created.

5.11 Creation and categorisation of variables

Several variables needed to be calculated using the hospital data to conduct my analysis. Additionally, there was an element of harmonisation needed to be able to pool together all the hospital data.

The new variables that were generated are listed here. STATA commands were used to generate these variables and are available in Appendix 5.

1. **Cycle length** was created using the approved cycle length associated with each chemotherapy regimen used (see Appendix 6). Cycle length was cross-checked with date difference to understand if unusually high differences were observed for a particular regimen, indicating that the regimen was used as standard with a different cycle length. This was the case for OXCAP, where a standard cycle length would be 21 days. However, at one hospital a 14-day cycle was commonly used. This was confirmed with the hospital.

2. **Dose delay.** I used the date of administration provided by the hospitals to calculate the difference in days between the first (index date) and second cycle of chemotherapy. Using this difference and subtracting it from the standard cycle length of chemotherapy regimens (see Appendix 6), I established if there was a delay in the administration of the second cycle and, if so, by how many days. Two levels of dose delay were created: the first was of 3 days or more, and the second was of 7 days or more. A 7-day period was the standard used in the literature; however, through discussions with patients involved in this study, I came to realise that investigating a 3-day period was also justified, as this delay has an impact on a patient's experience.

3. **Body mass index (BMI)** was calculated by dividing the patient's weight in kilograms and dividing it by the square of their height in metres (Calle et al., 2003).

4. **Dose reduction**. To verify the dose reduction, each patient's body surface area was calculated to determine a theoretical dose. Following this calculation, the dose of drug administered to each patient at the first cycle was compared with the theoretical dose. If the received doses of all of the drugs were within 10% of the theoretical dose, the patient was considered to have received full doses. If the received dose of any of the drugs was <90%, the patient was considered to have been dose reduced. This 10% cut-off is commonly recognised as an acceptable margin of error to ascertain whether or not doses have been reduced.

Four variables needed to be manipulated to ensure standardisation of naming across all four hospitals. All numerical variables were retained on numerical scales. It was, however, necessary to re-categorise some of the categorical variables to enable analysis.

1. **Regimen name**. Usually, hospitals name treatments as a protocol; for example, FEC-T would be three administrations of FEC followed by three of docetaxel. I needed to separate these protocols into the name of the drug that was administered. In the case of the FEC-T protocol, cycles 1-3 were named FEC and cycles 4-6 were named docetaxel. In the case of T-FEC, the docetaxel cycles are administered first, followed by FEC, and therefore cycles 1-3 were named docetaxel and cycles 4-6 were named FEC (see Appendix 6 for details).

2. **Performance status (PS)**. There are many limitations to the use of PS. Generally, it is allocated by the treating clinician and indicates how well a patient can carry out their day-to-day tasks. The ECOG provides guidance on how to assess PS on a scale of 0 to 4. A patient with a PS of 4 would be bedridden, whereas a patient in the PS 0 category would be functioning normally. There was a relatively small volume of missing data for PS (<5%). It is thought that missing data for PS is often related to patients with high PS where a clinician is eager to offer a patient

treatment options that may not always be appropriate given the patient's inability to conduct day-to-day tasks. Therefore, rather than entering a high PS on EP systems, this value would simply be omitted. Patients receiving first-line curative treatment, like the ones in this study, tend to have a lower PS than those who are late-stage palliative patients (Simcock and Wright, 2020).

3. **Comorbidity**. Comorbidity data was not collected at one of the four hospitals and at two others it may have not been comprehensive as it was derived only from the hospital rather than primary care data. During my literature review, I found little consensus on the handling of comorbidity data. There were several approaches found to categorise comorbidity, including simply counting cases (Koczwara, 2016), organ-based approaches (Salvi et al., 2008) and the use of weighted indices (Charlston et al., 1994). On review of the literature in cancer studies, I chose to categorise the variables based on vascular comorbidity which has been shown to affect chemotherapy toxicity in several studies, whereas other comorbidities have been shown to have little or no effect (Sarfati, Koczwara & Jackson, 2016).

4. **Ethnicity**. The Office for National Statistics provides options for grouping ethnicity and this was standardised across the datasets (see Appendix 6). There was a complete dataset for ethnicity, but only 0.6% were categorised as Chinese, 3.5% as black and 4.8% as Asian. Such small proportions of non-white patients would prohibit detailed analysis. With the data available, ethnicity was categorised as white and non-white to enable a sufficient statistical sample size but at the cost of detail.

5.12 Summary

In this chapter, I have described recruitment, data collection processes, data completeness and any new variables created that would be used in the analysis presenting in subsequent chapters.

Chapter 6.   Analysis of repeated blood tests

6.1   Chapter overview

In this chapter, I explore the available laboratory data to assess for bone marrow, renal and liver function. The chapter details how I used the data to understand the implications of undertaking blood assessments too far in advance of treatment. In Chapter 5, I described the data collection procedures from hospital electronic prescribing (EP) system. I also discussed the level of missing data in blood assessments; for this reason, I was only able to focus this analysis on cycles 1-2. This work was of particular importance at the beginning of the COVID-19 pandemic when I communicated my work to the hospitals who urgently sought evidence in this area.

6.2   Background

Blood tests are required during the course of any SACT to ensure safety. These tests are assessed regularly to ensure adequate bone marrow, renal and hepatic function throughout chemotherapy. Bone marrow function is assessed through the monitoring of neutrophil counts where threshold values must be achieved prior to treatment. Assessments for renal and liver function, on the other hand, are an evaluation of a trend away from the baseline value.

As most chemotherapy is administered in cycles (an administration followed by a period of recovery), blood monitoring should be timed to be as close to the administration day as possible; however, this is not always practical. As discussed in Chapter 1, the number of patients receiving SACT has increased and it is common for patients not to have blood tests taken on the day of treatment. In the UK, a patient may have their bloods assessed on a different day to their treatment in order to streamline the process of prescribing and reconstitution of treatment. The optimal timing for these blood assessments in relation to a treatment administration is, however, currently unknown. Similarly, it is unknown whether

these blood assessments should even determine the doses or timing of treatments.

In Chapter 4, data from a survey shows that assessments for neutrophils and platelets are commonly undertaken 72 hours prior to treatment, but there is variation and some hospitals use an extended window of time. Likewise, it is anecdotally understood that a period of 7 days is regarded as appropriate to assess the renal and liver functions. However, some clinicians believe that this window of time can be extended further.

At the time of the analysis (May 2020) there was an immediate need to change current processes of care for cancer patients as we were amidst the COVID-19 pandemic. Many institutions were investigating how to reduce healthcare interactions for those patients who required treatment to reduce nosocomial infections. Additionally, during the pandemic, it was a requirement for everyone to adhere to social distancing and this had further implications on the preparation and administration of treatments. An initiative to assist with these interventions was the amendment of blood testing schedules for chemotherapy patients, allowing an extended time window for treatment preparation, flexibility in terms of the date of administration, and meant that infection screening could be concurrently undertaken for patients without additional healthcare interactions.

6.3 Aims and objectives

Using the data collected from EP systems, I aimed to understand whether the time window for assessing pre-chemotherapy blood levels for neutrophils, platelets, renal and hepatic function tests, could be extended without compromising patient safety. This investigation was guided by the following objectives:

- To evaluate the difference in neutrophil grade when taken at different time points prior to chemotherapy.

- To evaluate the patients who achieve the critical threshold of 1 x 10^9/L at different time points.

- To evaluate platelet values and understand how thresholds impact dosing.

- To investigate grade changes of renal and liver function tests over two cycles to understand if significant changes are seen.

6.4   Methods

This was a retrospective descriptive study, using routinely collected chemotherapy data collected from EP systems from hospitals recruited in England. Details of data collection are described in Chapter 5 and an overview of the data is given in Chapter 6. The work presented in this chapter aimed to evaluate the need for multiple blood tests; hospital 4 did not have sufficient data to meet the aims for this chapter and was therefore excluded. Additionally, when investigating trends across the six cycles of treatment, data from hospital 3 was the only complete data to enable this analysis.

6.4.1   Analysis

Data for treatment and blood tests were transferred to STATA® 15SE and analysed using descriptive statistics. I compared changes in blood count values using the Common Terminology Criteria for Adverse Events (CTCAE) grading (National Cancer Institute, 2017). I considered day 1 (the date of the first cycle) as the index date, and each blood test date was ordered in terms of days from the index. Baseline results were regarded as any results that either preceded the index date by 7 days or were taken within 72 hours following the index. In the event that there was more than one baseline value available, I used the closest value to the index.

The variables used in this analysis were regimen name, cancer type and cycle length as well as laboratory values for neutrophils, platelets, creatinine and bilirubin. All the included regimens had a standard length of either 14 or 21 days, as described in Appendix 6. Using cycle length, I was able to determine if treatments were delayed by comparing the date of the second administration to the index date.

In this analysis, I only used data for the first two administrations (cycles) as described above; however, other cycle data were available and I described this where appropriate.

6.4.1.1 Neutrophils and platelets

I grouped the days of the blood tests for neutrophils and platelets. For patients receiving a 21-day cycle, I considered a test result from days 15, 16 or 17 as being outside the approved period and named these 'test 1'. Results from days 18-22 were within the approved period and I referred to these as 'test 2'. In the case of a 14-day cycle I considered days 11 and 12 as being outside the approved period (test 1) and days 13, 14 and 15 as within the approved period (test 2). If there were two tests within the same grouping, I chose the closest value to the treatment date. Each neutrophil value was categorised as per CTCAE grading (National Cancer Institute, 2017). Additionally, for all the regimens, I included the absolute neutrophil count threshold of 1×10^9/L (grade 3), as this determined whether treatment would be administered or not. A threshold of 1×10^9/L was the lowest threshold value for the regimens included. I used this threshold to understand if test 1 would have resulted in the same treatment decision as test 2. In the scenarios where the earlier test would have resulted in treatment being administered but the results of test 2 would result in a different outcome, I described subsequent treatments received for these patients, from the data available.

From the questionnaire discussed in Chapter 2, it was unclear as to the value of platelet measurement in the decision to treat a patient. Thresholds as low as 75×10^9/L were reported as suitable values. I tabulated the numbers of treatments that were administered at thresholds below 100×10^9/L to determine any patterns in regimen where this practice was used.

6.4.1.2 Creatinine and bilirubin

I investigated the changes in creatinine and bilirubin from baseline results to just prior to the administration of the second cycle (either a 14-day or 21-day period), to detect any significant grade change, defined using CTCAE grade changes,

warranting amendments or reductions. For creatinine, in particular, a clinician may, in practice, often choose to monitor patients more intensely when a 10% or more grade change is noted and therefore, I reported figures for this.

For neutrophils, platelets, creatinine and bilirubin, I plotted the median laboratory value obtained over six cycles at hospital 3 only where sufficient data were available. I used this visual plot to understand trends in values over the course of six treatments by chemotherapy regimen.

6.4.1.3   Missing data

Not all patients had duplicated blood tests and therefore I have described the distribution of this as much as possible.

6.5   Results

A total of 4,007 patients were included in the analysis from the three hospitals, of which 66% were female, consistent with a large proportion of patients having breast cancer (40%). A total of 45% of the patients were receiving treatment for colorectal cancer, and 6.5% of patients had two neutrophil results within 7 days of treatment administration. Table 6.1 shows that patients were similar demographically, but the repeated test may have been a consequence of hospital policy.

Grade changes were assessed where two assessments were available (Table 6.2). 40% of patients' neutrophils reduced by 10% or more between assessments; however, grade was only worsened in 2.6% of patients. The downward trend could signify delayed nadirs in some patients. Interestingly, grade improved for neutrophils in 23% of patients; patients having an earlier assessment may not attain threshold values and therefore require a further test to meet the requirements to receive SACT.

Table 6-1. Overview of patient characteristics

Parameter		Patients without two neutrophil results	Patients with two neutrophil counts
Number of patients (N)		3,391	616
Hospital		Hospital 1 1,690 (50%) Hospital 2 1,178 (34%) Hospital 3 523 (15%)	Hospital 1 75 (12%) Hospital 2 107 (17%) Hospital 3 434 (70%)
Age, median (range)		56 (18-90)	56 (18-90)
Gender		Female: 2,242 (66%) Male: 1,149 (34%)	395 (64%) 221 (36%)
Tumour type		Breast: 1,441 (42%) DLBCL: 363 (11%) Colorectal: 1,587 (47%)	Breast: 1,618 (40%) DLBCL: 572 (14%) Colorectal: 1,817 (45%)
Regimen received		FEC: 713 (21%) EC: 501 (15%) T-FEC: 230 (7%) *R-CHOP: 363 (11%) FOLFOXIRI: 8 (0.2%) IRMDG: 576 (17%) *OXCAP: 324 (10%) OXMDG: 679 (20%)	FEC: 130 (21%) EC: 17 (3%) T-FEC: 31 (5%) *R-CHOP: 207 (33%) FOLFOXIRI: 13 (2%) IRMDG: 631 (9%) *OXCAP: 32 (5%) OXMDG: 809 (22%)
Baseline absolute neutrophil count, median (range?)		4.62 range (0.4-72)	Median 4.63 range (0.5-51)
Performance status 0-2 >2		3,384 (99.8%) 7 (0.2%)	611 (99%) 5 (0.8%)
Chemotherapy cycle length 14 days 21 days		1,355 (40%) 2,036 (60%)	204 (33%) 412 (67%)

Denotes combined for patients on a 14-day and 21-day schedule. Abbreviations: DLBCL, diffuse large B-cell lymphoma; FEC, fluorouracil, epirubicin and cyclophosphamide; T-FEC, docetaxal, fluorouracil, epirubicin and cyclophosphamide; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; FOLFOXIRI, fluorouracil, oxaliplatin and irinotecan; IRMDG, irinotecan and fluorouracil; OXCAP, oxaliplatin and capecitabine; OXMDG, oxaliplatin and fluorouracil.

Table 6-2. Grade changes in neutrophils, bilirubin and creatinine

	Neutrophils	**Platelets**	**Bilirubin**	**Creatinine**
Total patients with more than one result within a defined period*	616	436	3,973	3,828
Result worsened by 10% or more	246 (40%)	1	725 (18%)	721 (19%)
Grade worsened by 1 grade	16 (2.6%)	0	6 (0.15%)	24 (0.6%)
Grade worsened by 2 or more grades	5 (0.8%)	0	12 (0.3%)	25 (0.7%)
Grade improved	142 (23%)	6	-	-

Neutrophil grade changes between two levels taken within 7 days; both prior to the second chemotherapy administration. Creatinine and bilirubin changes prior to first and second chemotherapy cycles. Grade improvements in creatinine and bilirubin not reported as only applicable where values were initially abnormal.

Table 6.3 shows that relatively few patients experienced changes that would impact treatment administration. Here, only 0.8% of patients experienced a drop in neutrophils below 1×10^9/L (CTCAE grade 3), signifying an earlier blood assessment was safe. I conducted a Fisher's exact test and reported a P-value of 0.62, demonstrating no statistical significance between the repeated tests taken at these different periods. However, there may still be clinical significance. In an earlier test, 18% of patients did not meet the threshold of 1×10^9/L, and only 0.3% of these continued with this grade 3 toxicity at a test taken closer to the time of planned administration.

Table 6-3. Showing those eligible for treatment at test 1 and test 2

	Test 2: ANC>=1	**Test 2: ANC<1**
Test 1: ANC>=1	498 (81%)	5 (0.8%)
Test 1: ANC<1	111 (18%)	2 (0.3%)

Fisher's exact test showed P=0.62. Abbreviation: ANC, absolute neutrophil count.

In total, only five patients did not meet the threshold value to receive treatment on their second test, when their earlier test had indicated a value above this threshold. Out of these five, three patients fell marginally short of the threshold of 1×10^9/L

but did achieve neutrophils greater than 0.9×10^9/L. These three patients had a record of receiving chemotherapy without delay or future delay. One further patient had a record of receiving treatment (EC) but subsequent cycles were not recorded. The final patient, receiving FEC, received a dose reduction of 25% at cycle 2 and no further cycles were recorded in their treatment record.

Table 6.2 shows that of the 436 patients who had two blood tests within 7 days of each other, only one patient was noted to have lowered platelets from the earlier assessment. I investigated further the threshold values that patients attained when receiving treatment, and although there were no changes between tests, there were occasions where platelets were consistently below 100×10^9/L and treatment was received (Table 6.4). In total, three patients, all receiving R-CHOP chemotherapy for DLBCL, received treatment when platelets were below 50 x 10^9/L but neutrophils were above 1×10^9/L; all patients had initiated treatment with platelets below 50×10^9/L. These patients all received subsequent treatments, with no occurrences of delays recorded.

Table 6-4. Platelet values and corresponding regimens

Platelet value ($x\ 10^9$/L)	Number of patients	Regimens
75-100	2	R-CHOP OXMDG
<75 and >=50	0	N/A
<50	3	R-CHOP

A subgroup analysis of creatinine and bilirubin is presented in Table 6.5, showing very little fluctuation in terms of toxicity grade for the tests used to assess renal and hepatic function. I found that in those patients with breast cancer, there were no cases of grade changes for bilirubin. These fluctuations in median values over the course of six chemotherapy cycles by regimen received are displayed in figure 6.1 and 6.2. Here, I observed that, generally, creatine and bilirubin values are either stable or improve. For bilirubin, the regimen OXCAP may require closer monitoring as here there is an increase in median bilirubin over the cycles. This

increase may be an effect of the disease that this regimen is treating rather than the pharmacological effect of the treatment.

Table 6-5. Renal and hepatic function difference in grade by tumour group

	Cancer	Total number of patients	1 grade change	2 or more grade change	Missing (no second blood test)
Creatinine	Breast	1,618	4 (0.2%)	3 (0.2%)	4 (0.2%)
	Colorectal	1,817	11 (0.6%)	15 (0.8%)	11 (0.6%)
	DLBCL	572	9 (1.6%)	7 (1.2%)	50 (8.7%)
Bilirubin	Breast	1,618	0 (0%)	0 (0%)	11 (7%)
	Colorectal	1,796	5 (0.3%)	10 (0.6%)	16 (0.9%)
	DLBCL	564	1 (0.2%)	2 (0.4%)	7 (1.2%)
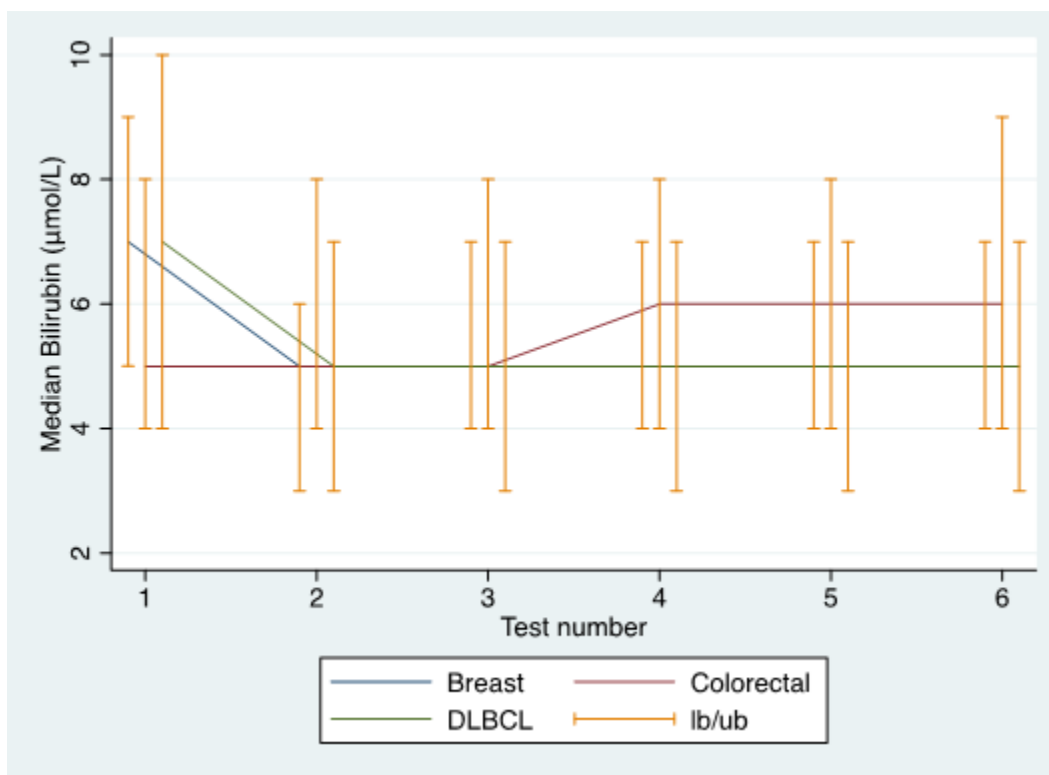
Figure 6-1. Bilirubin over six cycles

Notes: For the majority of protocols the median bilirubin and creatinine are stable across cycles. Values only obtained for cycles received by patients, in total cycle 1 and 2=958; cycle 3=871, cycle 4=783; cycle 5=748; cycle 6=697, combining all cancer types.

Abbreviations: DLBCL: Diffuse large b-cell lymphoma. lb/ub: lower and upper boundaries (denotes the interquartile range).
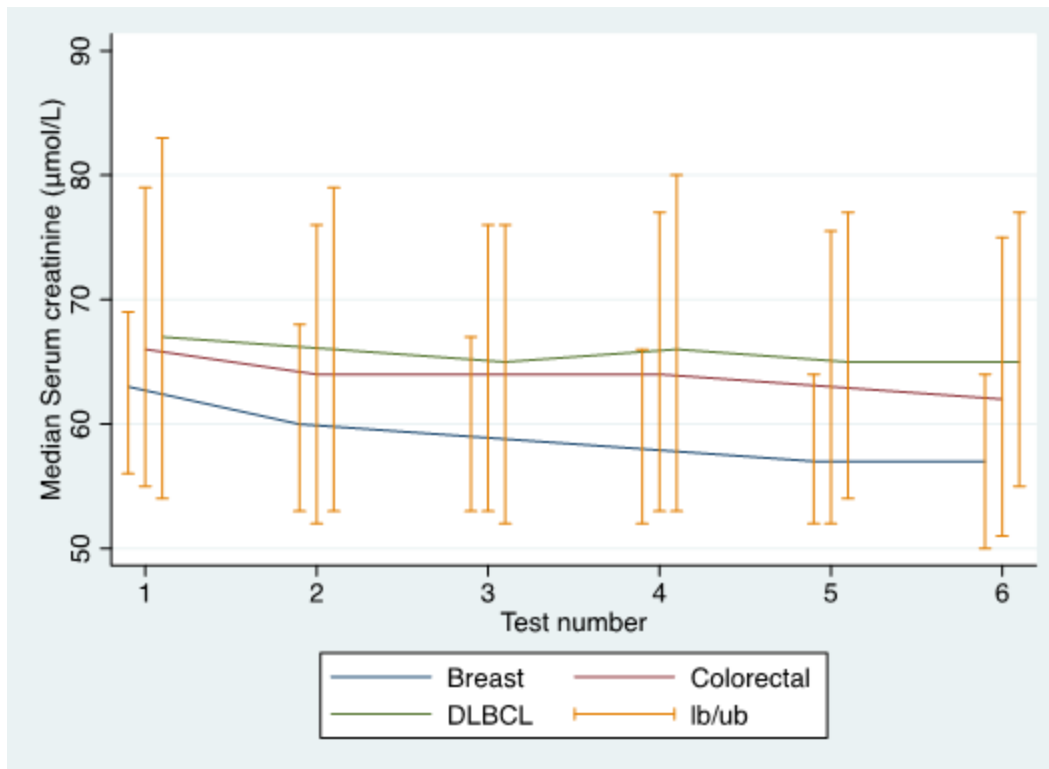
Figure 6-2. Creatinine over six cycles

Notes: For the majority of protocols the median bilirubin and creatinine are stable across cycles. Values only obtained for cycles received by patients, in total cycle 1 and 2=958; cycle 3=871, cycle 4=783; cycle 5=748; cycle 6=697, combining all cancer types.

Abbreviations: DLBCL: Diffuse large b-cell lymphoma lb/ub: lower and upper boundaries (denotes the interquartile range).
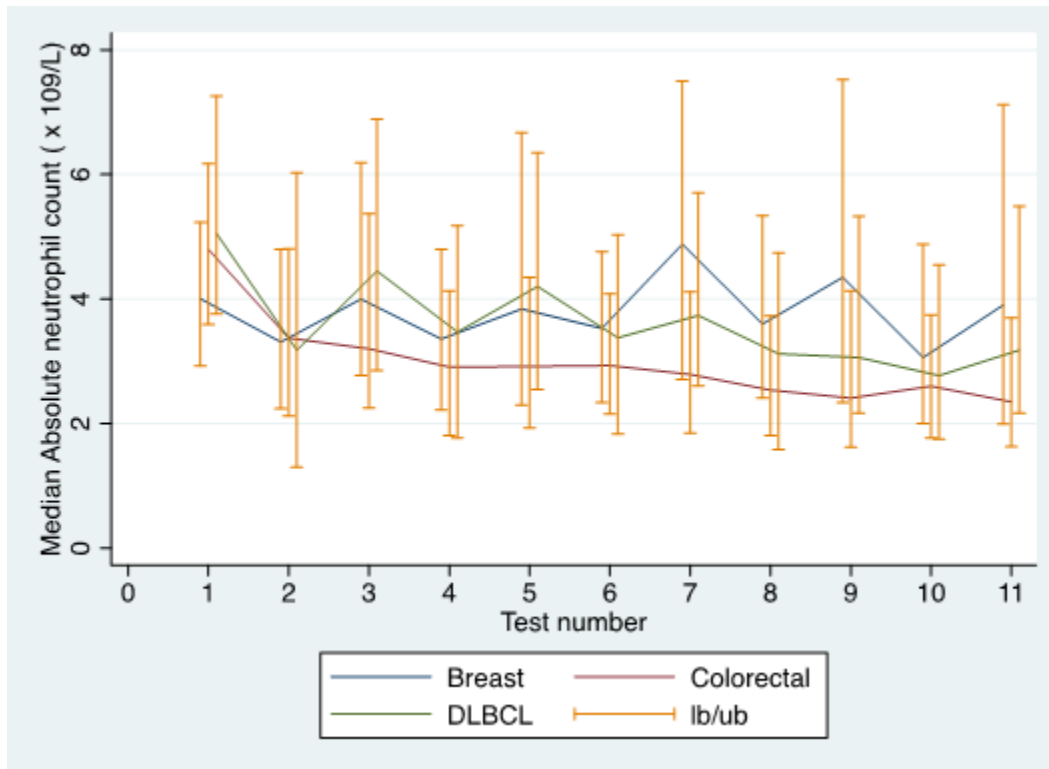
Figure 6-3. Neutrophil counts over six chemotherapy cycles

Notes: The for the majority of protocols the greatest drops to counts are between cycle 1-2. Values only obtained for cycles received by patients, in total cycle 1 and 2=958; cycle 3=871, cycle 4=783; cycle 5=748; cycle 6=697, combining all cancer types.

Abbreviations: DLBCL: Diffuse large b-cell lymphoma lb/ub: lower and upper boundaries (denotes the interquartile range).
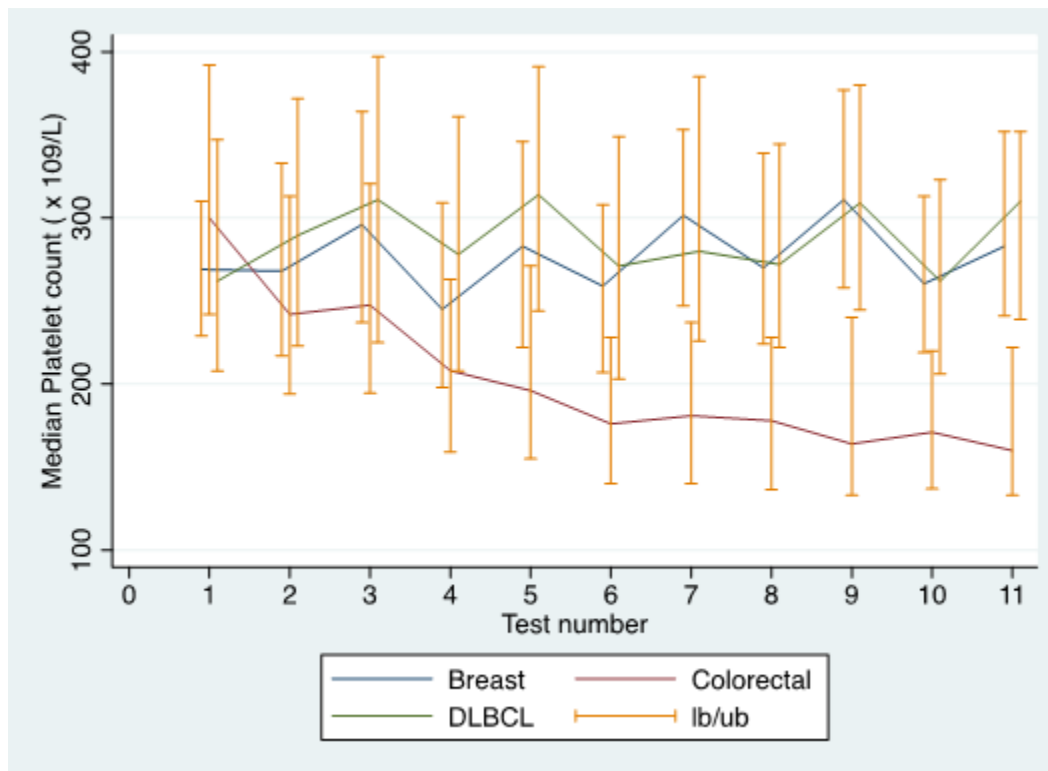
Figure 6-4. Platelet counts over six chemotherapy cycles

Notes: The for the majority of protocols the greatest drops to counts are between cycle 1-2. Values only obtained for cycles received by patients, in total cycle 1 and 2=958; cycle 3=871, cycle 4=783; cycle 5=748; cycle 6=697, combining all cancer types.

Abbreviations: DLBCL: Diffuse large b-cell lymphoma lb/ub: lower and upper boundaries (denotes the interquartile range).

The profile plot in Figure 6.3 indicates that there seems to be the largest change in neutrophils between cycles 1-2 and following this there is some stabilisation. For platelets (figure 6.4) the change is less clear and in the colorectal cancer regimens (OXCAP, OXMDG, IRMDG and FOLFOXIRI) there seems to be a downward trend in all cycles.

6.6 Discussion

The purpose of the investigations in this chapter was to understand whether the time window for assessing pre-chemotherapy bloods could be extended, whilst maintaining safety. In the case of neutrophils, the lowest counts, theoretically, should be experienced from days 7-10 after treatment (referred to as the nadir); thereafter, these counts should start to rise again (Cancer Research UK, 2017). I found that in patients who had two blood tests taken within 7 days of treatment, less than 1% had a CTCAE grade reduced by two or more grades. Although statistically there was no difference between a neutrophil count taken at an earlier period to one taken within 72 hours of the day of treatment, there may be clinical consequences; in 23% of cases, blood tests taken closer to the treatment day showed grade improvements for neutropenia. For 18% of these patients, an earlier test indicated the patient ineligible for treatment (the neutrophil count was below 1 x 10^9/L) and a repeat assessment was necessary closer to the treatment day. Extending the blood assessment window beyond 72 hours may result in many additional tests for patients as threshold values are not achieved. Worryingly, earlier assessments could cause doses to be withheld, impacting dose intensity.

There were a small number of occasions where the earlier neutrophil count would have resulted in treatment being received even though the count had subsequently fallen below the threshold. This runs counter to the theorised rise and fall of neutrophils and could be the effect of a delayed nadir for some patients. Interestingly, for this relatively small number of patients, where the neutrophil count was above 0.9 x 10^9/L, treatment was still received but it was unclear whether these patients suffered any toxicity. It is also undetermined whether the treating clinician believed this low count to be disease-related where delay to treatment would be counterproductive.

Apart from conference proceedings (Bayliss, 2017; Thwaites et al., 2017; Agapinaki and Streetly, 2020), there was little evidence found to support the practice of extending the time window of blood tests beyond 72 hours. One study

from the US investigated blood assessments prior to initiation of chemotherapy and concluded that a 7-day window was safe (Warr et al., 2013) but did not investigate subsequent dosing. Another small study (Waight and Cain, 2014) of 27 patients receiving bortezomib treatment investigated whether blood tests could be reduced in frequency. The authors here concluded that a reduced frequency could be achieved when values for neutrophils and platelets were at an adequate level upon treatment initiation. This study is comparable with others; however, the large sample allowed me to highlight potential clinical implications over extended periods. Drops beyond threshold values are very rare and may not be captured in small single site evaluations.

The results presented have shown that there are benefits associated with reducing the frequency of some kidney and liver function tests, as for many patients there is little variation seen across six cycles of chemotherapy. Reduction in these assessments would result in reduced cost and reduced interventions for the patients; the cost implications are an area for future research. Implementation of this strategy should also be considered to reduce workload for phlebotomy and laboratory staff during the COVID-19 pandemic to ensure safe working.

The findings of my work had an immediate impact on clinical practice during the COVID-19 pandemic; all hospitals were challenged with planning local blood assessments to reduce patient footfall, outsource SACT preparation as a countermeasure for staff absences, and through sharing my findings on safety, hospitals were able to make evidence-based decisions on blood assessments.

In this chapter, I have presented a descriptive analysis using detailed data on blood results taken from three large hospitals; however, I was limited by the number of patients who had these repeated blood results available on EP systems, as detailed in Chapter 6. Demographic differences were not seen between those patients who had undergone repeated assessments and those who had not, but there were differences between hospitals, which could relate to individual hospital policy. Additionally, it is unclear whether those with repeated blood tests are a

biased sample as clinicians may have repeated tests as they believed them to be likely to encounter a delay. Lastly, without access to medical notes, I was unclear as to any admissions or serious AEs that may have subsequently occurred in those patients who had neutrophils below 1×10^9/L; I could only report the impact on subsequent treatments.

6.7 Summary

The COVID-19 pandemic continues to pose capacity challenges to chemotherapy services. Additional distancing requirements add to an already pressed service. It is important, therefore, to prepare to work efficiently and reduce nosocomial infections. Multiple interactions for blood assessments are not necessary, and ideally, these would be taken on the day of chemotherapy treatment to reduce visits; however, as COVID-19 swabbing for all patients becomes a pre-treatment test and as hospital staff need to adhere to distancing rules, hospitals are seeking ways to prepare treatments in advance. My results supported retaining the current standard window for the assessment of neutrophil counts as this would allow for concurrent screening; but extending beyond this period may result in unnecessary cancellations to treatments. In the case of renal and hepatic function, for the tumour groups and treatments studied, the findings indicated that less frequent assessments would not lead to changes in treatment decisions or adversely affect patient safety, particularly where the disease does not affect the vital organs.

In the next chapter, I aim to develop an alternative solution to early assessments through the development of a prognostic model to predict those patients who may require a dose delay. This proposed model could enable hospitals to prepare treatments for patients, negating the need for additional blood tests.

Chapter 7.   Exploring causes of dose delays

7.1   Overview

This chapter explores the detailed data collected for hospital 3; complete case data at this hospital made it possible to explore factors of interests with respect to dose delays. In this chapter, I also investigate the incidence of neutropenic events in patients who have been delayed from treatment, to strengthen the understanding of delay occurrence.

7.2   Background

As discussed in Chapter 1, the occurrence of dose delays can be attributable to many factors. In the UK the main cause of delays, particularly in the curative setting, is believed to be toxicity, namely neutropenic events; consequently, many service pathways rely on an early blood assessment of neutrophils to ensure that capacity is maximised. Neutropenic events are, however, not the definitive cause of dose delays. Delays can occur for scheduling reasons, i.e., bank holidays or staffing issues. Additionally, other non-haematological toxicities, such as nausea and vomiting or fatigue can result in delayed treatments (Wagland et al., 2015).

One study conducted in the US (Kogan, Davis & Brooks, 2019) determined that low neutrophils or platelets only accounted for 8% of delays. In this study, 15% of delays were defined as planned, i.e., initiated at the request of the patient. This high rate may be because in the US the patient is responsible for the cost of cancer care and affordability of treatments may be an attributing factor (Neugut et al., 2011). Nonetheless, all delays, regardless of reason, will impact the dose intensity of the treatment.

Comorbidities and polypharmacy are thought to influence chemotherapy-related toxicities (Lorimer & Simcock, 2020); however, from the systematic review conducted and detailed in Chapter 3, there were very few studies that investigated the influence of comorbidity on neutropenic events or dose delays. With data that

was collected from electronic prescribing (EP) systems, I planned to develop a prognostic model. The high volume of missing data for comorbidity (see Chapter 6) would impact methodological decisions, and, therefore, it was important to examine the influence of this factor on delays.

The data available from hospital 3 were manually collected, with full details of comorbidity and blood results from every received cycle of treatment. The data collected here would enable an understanding of delays caused by neutropenic events and allow examination of the impact of exclusion of factors, such as comorbidity, in the development of a prognostic model.

7.3   Objectives

The work presented in this chapter was guided by the following objectives:

to quantify the proportion of delays caused by neutropenia (defined by neutrophils below 1 x 10^9/L); to examine the influence of specific comorbidities on delays.

7.4   Methods

This was a cohort study using data from one single hospital. Data was collected through extraction from the EP system and also manually collected and described fully in Chapter 5. In addition, all data extracted for cycles were validated, for example, the number of cycles received was extracted and then cross-checked with the electronic record when retrieving comorbidity information. Comorbidities were manually collected using both treatment and medication histories. This was captured using notes written by pharmacists in the electronic patient record.

Pharmacy procedures at this hospital meant that upon commencing the first cycle of treatment, pharmacists were mandated to complete a medication history and document a past medical history. Upon collection of these details, comorbidities were categorised as diabetes (including type 1 and type 2 requiring medication); cardiovascular comorbidities; depression and anxiety; hypothyroidism; hyperthyroidism; ulcerative colitis or Crohn's disease; respiratory comorbidities;

rheumatoid arthritis; autoimmune disease; epilepsy; history of hepatitis B infection; and other.

7.4.1   Analysis

To understand the numbers of patients delayed from treatment with low neutrophils, I calculated the proportion of patients with a dose delay that had a neutrophil value below 1×10^9/L within 72 hours of the intended treatment; a patient with neutrophils below this level is considered to have grade 2 toxicity, warranting a dose delay (National Cancer Institute, 2017). The 72-hour period was documented within the hospital standard operating procedure as an acceptable period to assess pre-treatment neutrophils. The proportion was presented as a percentage across cycles and calculated for two levels of delay. The two levels of delay were 3 days or greater, and 7 days or greater. Delays of 7 days or greater have been defined in the literature as clinically significant (Lyman, 2003; Silber et al., 1998) but shorter delays do occur in practice and are under researched. Patient representatives on the study steering panel expressed an interest in exploring shorter delays to understand occurrence, as from a patient perspective this was of high importance. Beyond cycle 3, patients may have been delayed for other reasons, such as progression, and so delays of greater than 60 days were excluded from the analysis.

To examine the impact of comorbidity on dose delays, I used a count of comorbidity, categorizing comorbidity as 0, 1 and two or more. Using multivariable logistic regression with age and performance status as confounders, I determined the odds ratios and significance of 0, 1 and 2 or more comorbidities on the occurrence of a 7-day dose delay.

7.5   Results

The total number of patients in this analysis was 957. Table 7.1 shows the number of patients at each cycle, the proportion of delays noted at that cycle and the

proportion of delays where neutrophil values were low. Additionally, I have included the non-delays where neutrophil values were low.

Table 7-1. Each cycle and delays and neutrophils below 1<1x10⁹/L

Cycle	Delays				Total patients with ANC<1x10⁹/L and no delay	Total patients with ANC<1x10⁹/L
	3 days or greater		7 days or greater			
	Total delays	Delay with ANC<1x10⁹/L	Total delays	Delay with ANC<1x10⁹/L		
2 N=958	162 (17%)	32 (20%, 32/162)	91(9%)	19 (21%, 19/91)	64 (66%, 64/96)	96 (10%, 96/958)
3 N=907	65 (7.2%)	8 (12.3%, 8/65)	44 (5%)	5 (11.4%, 5/44)	67 (90%,67/75)	75 (8.3%, 75/907)
4 N=820	107 (13%)	19 (18%, 19/107)	45 (5%)	4 (9%,4/45)	27 (59%, 27/46)	46 (5.6%, 46/820)
5 N=732	109 (15%)	18 (17%, 18/109)	40 (5%)	5 (12.5%,5/40)	27 (60%, 27/45)	45 (6.1%, 45/732)
6 N=697	93 (13%)	20 (22%, 20/93)	33 (5%)	8 (24%, 8/33)	31 (61%, 31/51)	51 (7.3%, 51/697)

Delays defined by 3 days or greater and 7 days or greater, therefore delays appearing in 3-day or greater category included those in 7-day category. Abbreviations: ANC, absolute neutrophil count.

Note: CTCAE gradings for neutropenia: grade 2 ANC<1.5x10⁹/L, grade 3 <1x10⁹/L (National Cancer Institute, 2017).

Table 7.1 shows that the occurrence of delays are more common between cycles 1-2, compared to other cycles. Generally, there is a low proportion of patients with neutrophil values below 1 x 10⁹/L; this may be due to the tumour type investigated and the fact that all patients included were receiving first-line treatment (no prior chemotherapy exposure). It is also noted that not all neutrophils of below 1 x 10⁹/L resulted in a dose delay; however, there were no occurrences where a neutrophil value was below 0.9 x 10⁹/L. A 3-day or greater dose delay occurred more frequently than a 7-day delay; with 27% of patients delayed by 3 days or more pre-

cycle 2 and only 9% continuing to have a 7-day delay. In all cycles except pre-cycle 3, the occurrence of a 3-day dose delay was at least twice that of the 7-day delay.

7.5.1 Comorbidities

In total, 319 (33%) patients had one or more comorbidities. A total of 62% (198 out of 319) were patients with a cardiovascular comorbidity and 17% (57 out of 319) had type 1 or 2 diabetes. In Table 8.2 it can additionally be seen that 39 patients (4% of the whole population) presented with both diabetes and a cardiovascular comorbidity.

Table 7-2. Patients with comorbidities

Group	Comorbidity
0	638 (67%)
1	224 (23%)
2	81 (8%)
3	12 (1%)
4	1 (0.1%)
8	1 (0.1%)
Cardiovascular	198 (21%)
Diabetes	57 (6%)
Both cardiovascular and diabetes	39 (4%)

Multivariable logistic regressions were used to investigate the effect of comorbidity on 7-day treatment delay (Table 7.2) and although the estimated odds ratio was 1.6, indicating a 60% greater chance of a dose delay with two comorbidities, the confidence interval was 0.83-3, crossing 1, and therefore insignificant. I investigated the influence of one comorbidity with the outcome of grade 2 toxicity with respect to neutrophil count (neutrophils $<1 \times 10^9$/L). Again, here the results were insignificant with an odds ratio of 0.83 and CI 0.37-1.84.

7.6   Discussion

The findings in this chapter are important for several reasons. Firstly, for practice, I have shown that dose delays and neutropenia are most common after the first treatment cycle. It is important to understand that this may not be due to the pharmacology of the treatments received but rather the behaviours of clinicians ; for example, a clinician may increase the duration of colony stimulating factors (CSFs) or provide extra antiemetic medications to a patient that has been delayed between cycles 1-2. Showing that neutropenia is not the only cause of dose delays also influences service providers' perceptions of pathways; the blood test to guide other processes to reduce treatment waiting times is a misconception and other options should be considered. The findings were also important for the subsequent chapters. The data that I have obtained from the four hospitals allowed me only to investigate and develop a prognostic model to predict the occurrence of cycle 2 delays and I found that this is a valid decision as most occurrences of delays occur at this time. Additionally, I had limited comorbidity data and the impact of comorbidity on dose delays was unclear. Again, I have found that comorbidity does not significantly impact treatment delays.

A reason for the higher numbers of delays seen at cycle 1 could be due to the lack of evidence around stratifying colony stimulating factor (CSF) treatments. In the systematic review in Chapter 3, I demonstrated that many factors could influence neutropenic events but clinical guidelines recommend stratification by treatment only. The occurrence of a delay would prompt a clinician to prescribe CSF treatments where the cause was neutropenia-related. Patient experience is affected by any treatment delay and I found that a 3-day delay was common practice at this one hospital. The impact of this level of delay on patient experience and overall dose intensity is under-researched and it would be valuable to build on these findings to guide future practice.

Although not significant, the estimated odds ratio for two or more comorbidities was 1.56 in multivariable analysis and in line with the systematic review (Chapter

3), where I found that comorbidity did impact febrile neutropenia. Importantly, a large study included in the review separated neutropenic events and febrile neutropenia as outcomes and found that although comorbidity influences neutropenic sepsis it is not a factor that has an impact on neutropenia alone (Chao et al., 2014). My findings do however oppose a review written by Balducci, Goetz-Parten & Steinman (2013), indicating that polypharmacy was causative of dose delays. The evidence that was presented in this paper detailed problems such as drug-drug interactions and recommended that the effect of polypharmacy could be prevented through specialist pharmacy review. At hospital 3, a detailed medical and medication history are recorded by pharmacists, and this review of interactions and appropriateness of all treatments is present when commencing treatment. This may be an important factor; future research could focus on the impact of polypharmacy in two different services.

In the next chapter, I describe the methods and development of a prognostic model. The findings here are pertinent in demonstrating to clinicians within chemotherapy services that early blood tests can be replaced by such a model; this can act as a facilitator to move away from blood testing in advance of treatment. The understanding of the delays and causes can help clinicians to plan a service. It may also be an enabler to using other systems such as remote patient monitoring to reduce the numbers of patients being delayed through early identification and amelioration of any toxicity. A number of electronic resources are available allowing patients to both record any AEs suffered and communicate these to clinicians. These tools provide advice on self-management. Studies have demonstrated that these tools can reduce hospital admissions and improve treatment outcomes (Maguire et al., 2017; Basch et al., 2017).

7.7   Summary

Studies presented in this chapter were limited in that the data was only collected from a single hospital; however, the relatively large and detailed dataset allowed the exploration of factors that would guide further model development. Although

the data was detailed in some areas in my data collection, I did not capture the progression of disease or time to progression. This data would, in hindsight, have been valuable to understand the impact of a dose delay, whether it be 3 days or 7 days, on the overall patient outcome.

Having demonstrated that the majority of dose delays are found between cycle 1 and 2, it was appropriate to develop a model in this setting.

Chapter 8.   Model development

8.1   Chapter overview

In this chapter, I describe the development of a prognostic model that can be used to identify when a patient is likely to incur a chemotherapy dose delay, detailing methodological decisions made, and model performance.

8.2   Background

A significant proportion of patients due to receive chemotherapy will be inadvertently delayed. On average the percentage is thought to be around 10-15% (Xu et al., 2015) and from my data the average delay among patients with breast cancer, colorectal cancer and DLBCL was 20%. In Chapter I, I introduced prognostic research and how this can enable those working in chemotherapy to foresee a dose delay and more accurately plan treatments with this knowledge. Statistical models are often used to predict the probability that an individual with a given set of risk factors will experience a particular outcome or event (Moons et al., 2009). Figure 8.1 is a schematic diagram describing how prognostic models function.

These prognostic or risk models are developed using several risk factors, such as characteristics of a patient that are thought to be associated with the event. Given
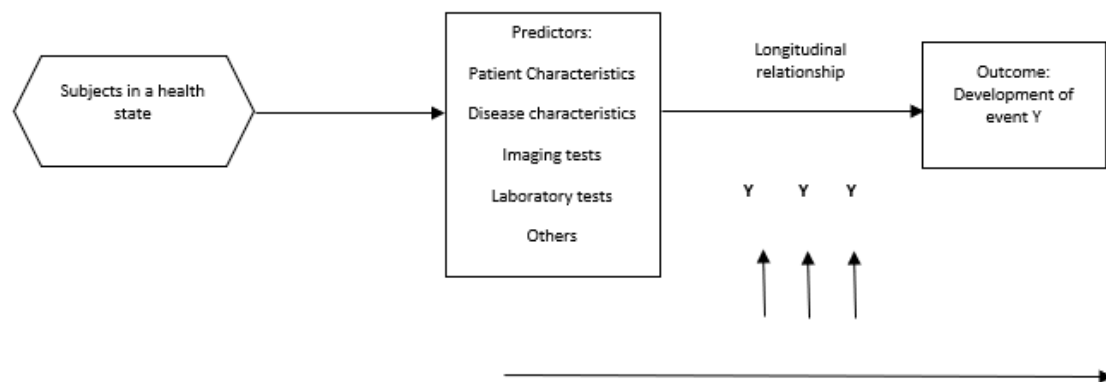
Figure 8-1. Prognostic multivariable modelling study

Types of clinical prediction models. Reproduced from Collins et al. (2015).

the characteristics of that patient, the model will yield the probability of a patient experiencing the event (Royston et al., 2009). However, before using such a model in practice the predictive ability should be ascertained. This process is referred to as model validation, and assessments of calibration (the agreement between the observed outcomes and predictions) and discrimination (the model's ability to differentiate between low and high-risk patients; Altman et al., 2009) are part of this validation process. Any prognostic model used in a clinical setting must be validated internally and then externally using patient data not used for the model development (Collins et al., 2015; Riley et al., 2016).

To improve the quality of the prognostic models used in clinical care the PROGRESS group published guidance on improving the quality and impact of prognostic studies in 2013; this was followed by the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis' (TRIPOD) statement, which is a 22-item checklist that guides the reporting of the design, conduct, analysis and interpretation of prediction modelling studies (Collins et al., 2015). The methods and findings detailed in this chapter are compliant with TRIPOD requirements.

8.3   Objectives

The objectives of this chapter are:

- to develop a prognostic model to identify those patients who are at risk of dose delays.

- to evaluate the model's performance in terms of calibration and discriminatory ability.

- to assess and adjust the model for optimism and overfitting.

8.4   Methods

A number of stages are involved in developing a prognostic model, the first being choosing the type of model with knowledge of the outcome variable. The type of

model selected is dependent on the outcome of interest, which in this case is the occurrence of a dose delay, which is binary, therefore a logistic regression was the model chosen. The equation expressed in the box below describes the derivation of a risk equation using logistic regression.

Patient's risk of a dose delay = $\dfrac{\exp(\text{patient's risk score})}{(1+\exp(\text{patient's risk score})}$

Where patient's risk score = intercept + [($b_{predictor1} \times$ predictor1) + ($b_{predictor2} \times$ predictor2) + ($b_{predictor3} \times$ predictor3) +......]

$b_{predictorx}$ are regression coefficients that describe how a patient's values of the predictor variables affect their risk.

8.4.1   Outcome events

The first step in the development of the model was to clearly define the outcome event. This definition was important to quantify the outcome and ensure an adequate sample size was available for analysis. Developed models for neutropenic sepsis (a cause of dose delays) that used dose delays as an outcome measure, as a standard a 7-day period to define delay (Julius et al., 2017; Schwenkglenks et al., 2006, 2011). However, in clinical practice delays can occur more frequently than reductions (Leonard et al., 2003). This could be 3 days, particularly if an assessment has been made several days prior to the planned administration. This type of delay is both anecdotally common and impactful to patients, as discussed in Chapter 8. Occasionally doctors will supply preventative treatments to enhance neutrophil counts (Smith et al., 2015). To decide the appropriate period over which to define dose delay, a comparison of delays at 3 days or 7 days was undertaken to appropriately choose the outcome event to take forward in my model. This was presented to patient and clinician members of the steering group and their views were also considered to make a final decision.

8.4.2   Continuous predictors

Continuous predictors are variables that can take any value within a given range. In logistic regression, it is assumed that the effect of the continuous predictors on the outcome is linear; linearity is tested using non-linear relationships between the continuous predictor and the outcome and assessing if this improves the model fit. Generally, TRIPOD (Collins et al., 2015) discourages researchers from categorising continuous predictors because details can be lost through categorisation, despite the fact that the approach could simplify the analysis and improve model usability.

The predictors of the laboratory values are all continuous data: neutrophil, platelet and haemoglobin counts, creatinine and bilirubin levels. Height, weight, BMI and age were also in a continuous format. The distributions and linear relationships to the outcome were assessed visually using scatterplots and empirically using regression coefficients. Although transformations were not required in final model development when data is skewed, transformations were considered where outliers were present and also during the multiple imputation phase; despite there not being the assumption that predictors are normally distributed when imputing data, there was a risk that a skewed distribution would yield unrealistic results when imputing missing data (Morris, White & Royston, 2014). A counter-argument to performing any transformation was that the resultant effect could be an over-fitted model and one that is uninterpretable by clinicians (Royston, 2009).

Box plots enabled the identification of outliers for continuous variables and there was an assessment of plausibility where outliers were present; an outlier was defined as any value that was 1.5 times more than the third quartile or lower than the first quartile. Any erroneous outliers were considered as missing. Where outliers were plausible, I considered the appropriate handling options, such as truncation or utilisation of splines, as both methods have been used successfully by other researchers in other areas (Riley et al., 2020; Geeson et al., 2019). A truncated sample can be thought of as being equivalent to an underlying sample with all values outside the bounds entirely omitted, with not even a count of those

omitted being kept. Splines are flexible functions; they essentially piece the data and force joins through 'knots'. The advantages of these approaches include being able to simplify the final analysis; however, use of either method could cause clinical uncertainty in the model and have downstream implications on uptake.

To balance the statistical and clinical robustness of the model I decided to categorise continuous variables for laboratory values. As already discussed, categorisation is generally not recommended (Collins et al., 2015) as it results in loss of information on predictor effects particularly when two categories are used (dichotomisation). Categorisation into more groups reduces the loss of information and is common in epidemiological studies. In this study, the continuous predictors of age and BMI were retained in their continuous form, but laboratory values were included as categorical predictors for three reasons. Firstly, the categories used are firmly established in clinical practice and therefore clinicians are well versed with them (National Cancer Institute, 2017). Secondly, in routine practice there are more than two grading categories used, meaning less loss of information in contrast to two categories. Lastly, strong evidence exists that low neutrophils and haemoglobin, or high bilirubin or creatinine are associated with dose delays, meaning truncation was inappropriate. To validate this final statement, I tabulated data from those patients with low neutrophils who incurred a treatment delay.

8.4.3   Pooling of data

A primary consideration in the decision to pool all hospitals' data was the marked difference in the outcomes described in Chapter 6. The following options were available to manage the data analysis.

1. To conduct a multilevel analysis using a random intercept model. Here each coefficient for the predictors would be derived from the hospital they were obtained for and each individual hospital would have its own intercept. This method would account for the case-mix at each hospital that would contribute to the outcome. The model produced would yield

an overall intercept; however, with only four hospitals this would not be reliable (Falconieri et al., 2020).

2. Treat each hospital as a predictor. Again, each coefficient would be adjusted for the hospital and the model would only be applicable for those hospitals that provided the development data.

3. The final approach would be to leave the hospital out altogether and conduct cross-validations, recalibrating for each hospital. If the calibration is reasonable then this would mean the hospital effect was similar. This approach was thought to be better suited to external validation rather than to develop the model (Riley et al., 2016).

The three options were considered and option 2 was decided upon the consideration of clinical understanding. Each hospital was different in its decision to delay patients and it was believed that similar hospitals would perform alike. A larger dataset per site would be required to use option 3, but this approach could be used in the external validation of the model.

8.4.4   Assessment of collinearity

Variables were collected based on clinical assessment and literature reviews. In addition, I conducted a number of statistical tests to ensure that collinearity between predictors was not present. Collinearity is when two variables are near perfect linear combinations of one another. Multicollinearity involves more than two variables. When there is multicollinearity, regression estimates are unstable and have high standard errors. The following variables were clinically understood to be correlated based on published literature:

- BMI and BSA are derived from height and weight; therefore, it was likely that it is correlated (Chambers et al., 2012).

- Vascular comorbidity: it is understood that diabetes and cardiovascular events increase with BMI and age (Savji et al., 2013).

- Serum albumin and BMI: albumin can be a marker of nutritional status and therefore BMI could correlate well.

- Platelets, neutrophils and haemoglobin are all markers of bone marrow function and these are expected to be correlated.

Correlations were assessed using scatterplots, and through linear and logistic regressions. Multicollinearity was tested by calculating variance inflation factors (VIFs), which quantify degradation caused by collinearity in terms of precision of estimate coefficients. The VIF is equal to one when there is no correlation and the number increases as variables are closely related. The command "collin" in STATA (see Appendix 6) was used to calculate the VIF (Craney et al., 2002).

Using scatterplots and simple regressions, I did not include variables that were highly correlated into the final model. I used VIFs of >10 when considering whether to exclude further variables.

8.4.5   Sample size

As discussed in Chapter 5, I needed to perform a basic sample size calculation to ensure I had adequate data available for model building. Historically, the sample size of a prognostic model development study was informed by three factors: anticipated prevalence of the outcome (treatment delays), desired sensitivity of the model to the outcome, and the precision of the 95% confidence interval around the sensitivity of the model (Riley et al., 2013), and for a binary outcome an effective sample size was dependent on the number of events and non-events present. An established rule of thumb for the required sample size is to ensure ten events per variable (EPV). The term 'variable' in this rule actually refers to each beta coefficient, and each category within a categorical variable will act as one variable. An example is the chemotherapy regimen, where each treatment regimen acts as one variable and, therefore, just to include that category would require a sample containing 80 events. When using selection techniques such as backward elimination, the sample size must represent every predictor that is considered in the model. More recently, Riley et al. (2020) developed a more accurate method

to determine the sample size that includes the overall outcome risk or mean outcome value in the target population, the number of variables, and the anticipated model performance in terms of overall model fit using a four-step approach. The authors supplemented the sample size calculation with commands on STATA to aid the calculation. The added value to the calculation defined by Riley et al. is when there are existing prognostic models available in a setting and model performance can be estimated. In my work, there were no direct comparative models where a performance benchmark could be stipulated; therefore, the 10EPV rule was applied to ensure an adequate sample of data was used, guided by the accurate understanding of numbers of predictors and outcome events in the dataset.

8.4.6   Missing data

In handling the missing values in the data, I considered three key questions: (1) why are data missing? (2) how do patients with missing and complete data differ? and (3) do the observed data help predict the missing values?

I have discussed the exclusion of comorbidity in Chapter 7. Similarly, I assessed albumin and platelets and their effect on the outcome where data were available.

If the missingness was a resultant effect of the outcome then the data would not be appropriate for imputation. I established that my data was missing at random. Missing at random (MAR) is when the probability of missing data on a variable is related to some other measured variable in the model, but not to the value of the variable with missing values itself (Horton & Kleinman, 2007). This assumption was tested statistically, firstly through a review of data points assessing extreme data values, and secondly through t-tests across variables (X_i) grouped on whether the variable X_j is missing or complete.

The following code on STATA was used to conduct the second test:

ttestX_i, by(miss X_j) and results are detailed in Appendix 6.

Multiple imputations are commonly used; the distribution of the observed data is used to estimate the missing data, incorporating the uncertainty associated with imputing unknown values. The process follows three steps: first, missing data are imputed several times, creating several new data sets of imputed data. Second, each of the new imputed data sets are analysed identically; the results will vary because different values will have been imputed for the missing data in each new data set. Third, the estimates from each of the analysed data sets are combined using Rubin's rules (White, Royston & Wood, 2011).

As more than one predictor with missing data was to be included in the model, multiple imputations by chained equations was used (MICE). MICE imputes missing values across multiple variables simultaneously. This is the only method that imputes information where the explanatory variables can have missing information. As a result, a large volume of evidence can be considered in the imputation regardless of whether there is complete or missing information for the variable. MICE can consider categorical and dichotomous data through ordinal and logit functions allowing it to be used for all forms of missing data. While this method can deal with multiple missing values there must be some complete information; otherwise, the imputation will be based on insufficient evidence and may generate poor estimates.

MICE was used to impute missing values for five variables in this study, and in the results section of this chapter, I discuss the rationale for not imputing other missing values. The data to be imputed were not all normally distributed and this could result in some erroneous imputed results, such as negative values (Morris, White & Royston, 2014); therefore, to avoid this potential problem, MICE with predictive mean matching was chosen, a method that does not carry the parametric assumption. The alternative option would be to perform a transformation and then retransform prior to model development; this was not ideal. The predictive mean matching version of MICE borrows an observed value from a donor with a similar predictive mean. Caution was taken using this method in restricting the pool of 'donors' to avoid model misspecification (Morris et al., 2014).

To give confidence that the imputed values were accurate, I reviewed the values imputed, and the models derived using imputed data were compared with the complete case model. The area of interest in this sensitivity analysis was the beta coefficients and P-values associated with them. These model coefficients were compared with those of the complete case as a sensitivity analysis.

8.4.6.1 Model performance

A good prediction model should be accurate, generalisable to settings and clinically credible. The assessment of the model's predictive performance demonstrates how well the model will perform in practice. The measures used to assess model performance are calibration and discrimination.

Discrimination is a measure of a model's ability to separate participants who have experienced an outcome compared to those who have not; I tested this using the concordance statistic (C-statistic). This is the probability of a randomly selected individual having the outcome having a higher probability than a randomly selected individual without the same outcome. Here, a value of 1 demonstrates perfect discrimination, whilst 0.5 indicates that discrimination is no better than chance. The C-statistic is related to the predictor effects and the variation in characteristics of individuals. What is considered a 'good' C-statistic differs depending on the clinical area. In the case of epilepsy it is difficult to achieve a C-statistic of 0.7 (Lamberink et al., 2017), whereas in pancreatic cancer many models have a C-statistic above 0.8, and therefore 0.7 (Boursi et al., 2017) would be regarded as a 'bad' C-statistic.

Model calibration determines performance in terms of the agreement between predicted outcome risks and those actually observed. This also tells us how accurate the model is. The Hosmer-Lemeshow test was traditionally used to test model accuracy but is no longer recommended as data are arbitrarily grouped to perform the test. I, therefore, used graphical plots to assess calibration. Calibration-in-the-large (CITL) and calibration slopes are two measures that can be used to estimate how well a prognostic model is calibrated, which quantify the systematic error in model predictions (overall agreement). CITL evaluates

calibration as an average overall individuals, using mean probabilities and mean observed values. A related measure is the expected and observed ratio (E/O), with an ideal value of 1; this gives the ratio of the mean of the predicted (expected (E)) risks against the mean of the observed risks (O). A calibration slope will also be calculated, where a value of 1 equals perfect calibration (Altman et al., 2009). It is common for a model to yield a calibration of 1 as it is fitted in the developed data. Any value other than 1 may show that model development procedures need to be revised (White et al., 2011).

Assessment of the model performance, as described, should be conducted in the imputed data set; to date, there is no method for pooling the results to obtain a discrimination value. I, therefore, planned to assess the beta coefficients for the imputed and complete case models. If there were large differences seen between the two models, I would have had to obtain the discrimination of each imputation (Phillips et al., 2012).

8.4.7   Internal validation and shrinkage

When a model is developed it is likely that our estimates are too large or optimistic, and this needs to be adjusted for. This adjustment can be achieved using a technique called shrinkage or through internal validation.

To quantify the degree of optimism, I initially undertook internal validation using bootstrap re-sampling (Altma et al., 2009). The prognostic factor variable selection procedure and model construction was repeated for 200 bootstrap samples. For each sample, the difference in bootstrap apparent performance (of the bootstrap model in the bootstrap data) and test performance (of the bootstrap model in the original data set) was averaged across the 200 samples, to obtain a single estimate of optimism for each performance statistic (Appendix 6 details the STATA commands used to perform this). I then calculated optimism-adjusted estimates of performance for the new model.

8.5 Results

In this section, I detail the results in line with TRIPOD guidelines (Collins et al., 2015). I have reported the following:

1. The descriptive statistics and exploratory analysis for each variable

2. The handling of missing data and results of imputation

3. Model development and assessment of performance

4. Any internal validation and assessments for optimism carried out

8.5.1 Baseline demographics and characteristics of the study population

Table 8.1 describes the study cohort of patients with respect to known risk factors and the factors to be included in the model. The factors described in this table include the percentage of patients on the different chemotherapy treatments with differing risks, cancer type, the median age, gender category and laboratory values previously evaluated in the literature as risk factors. Laboratory values in this table are displayed as medians and ranges as this understanding enabled me to investigate these variables further and supported the decision to categorise.

Patients of the ethnicity categorised as "white" contributed to almost 80% of patients, with all other categories falling under 5%. This would be problematic in the developed model and I made the decision to form two categories white origin and non-white origin for model development. The treatment 'FOLFOXIRI' was also of low abundance in my data; this was discussed with clinicians and senior statisticians it was decided that this should be retained.

Table 8-1. A description of patients delayed by 3 days or more and not delayed by a variable

Predictor	No delay at cycle 2	Delay to cycle 2	P-Value
Hospital 1 2 3 4	 1,409 (38%) 972 (26.3%) 796 (21.5%) 525 (14.2%)	 355 (39.4%) 313 (34.7%) 162 (18%) 72 (8%)	 <0.0005 (Chi-squared test)
Cancer Breast Colorectal DLBCL	 1,747 (47.2%) 1,372 (37.1%) 583 (15.8%)	 275 (30.5%) 532 (59%) 95 (10.5%)	 <0.0005 (Chi-squared test)
Chemotherapy FEC EC FOLFOXIRI IRMDG OXCAP OXMDG R-CHOP Doctetaxel	 1,069 (29%) 459 (12%) 12 (0.3%) 439 (12%) 321 (9%) 600 (16%) 583 (16%) 219 (6%)	 175 (19%) 61 (7%) 9 (1%) 192 (21%) 97 (11%) 234 (26%) 95 (11%) 39 (4%)	 <0.0005 (Chi-squared test)
Cycle length 14 days 21 days	 1,124 (30.4%) 2,578 (70%)	 460 (51%) 442 (49%)	 <0.0005 (Chi-squared test)
Use of CSF Yes No	 1,128 (30.5%) 2,574 (69.5%)	 173 (19.2%) 729 (81%)	 <0.0005 (Chi-squared test)
Age at start of chemotherapy (skewed)	Median 55 Range (18-90)	Median 59 Range (19-88)	N/A
Gender Female Male	 2571(69%) 1130 (31%)	 551 (61%) 351 (39%)	 <0.0005 (Chi-squared test)
Body mass index	Mean 27 SD 5.9	Mean 26 SD 5.8	N/A
Neutrophils	Median 4.6 Range (0.2-79.4)	Median 4.8 Range (0.6-76)	N/A
Haemoglobin	Median 12.7g/dl Range (5.4-59)	Median 12.5g/dl Range (5.1-45)	N/A

Predictor	No delay at cycle 2	Delay to cycle 2	P-Value
Creatinine	Median 70 Range (22-695)	Median 72 Range (16.5-560)	N/A
ALT	Median 72 Range (22-695)	Median 72 Range (16.5-560)	N/A
Albumin	Median 43 Range (24-200)	Median 43 Range (24-266)	N/A
Bilirubin	Median 7 Range (1-277)	Median 7 Range (2-72.5)	N/A
Comorbidity Yes No	 421 (18.4%) 1,872 (81.6%)	 132 (24%) 415 (76%)	P=0.52 (Chi-squared test)
Dose percentage	Median =100% Range 50-100%	Median =100% Range 50-100%	N/A
Performance status 0 1 2 3 4	 3,112 (88.4%) 346 (9.82%) 52 (1.48%) 10 (0.28%) 2 (0.06%)	 746 (85.8%) 99 (11.4%) 20 (2.3%) 4 (0.46%) 1 (0.1%)	 0.25 (Fishers-exact)
Ethnicity White Asian Black Chinese Mixed Other Unknown	 2,929 (79.14%) 177 (4.8%) 127 (3.5%) 23 (0.62%) 48 (1.3%) 179 (4.8%) 218 (5.9%)	 720 (79.8%) 43 (4.8%) 32 (3.6%) 5 (0.5%) 3 (0.3%) 56 (6.2%) 43 (4.8%)	 0.23 (Fishers-exact)

Abbreviations: DLBCL, diffuse large B-cell lymphoma; FEC, Fluorouracil, Epirubicin and Cyclophosphamide; EC, Epirubicin and cyclophosphamide; Folfoxiri, fluorouracil, irinotecan, oxaliplatin; OXMDG, Oxaliplatin modified de gramont; IRMDG irinotecan modified de gramont; R-CHOP, Rituximab, cyclophosphamide, doxorubicin and prednisolone.

8.5.2   Distributions of continuous variables

Figure 8.2 shows some continuous variables where data was missing. Using this information, I was able to investigate transformations where necessary. Distributions of continuous variables showed some skewness and outliers that needed consideration for imputation methods used. Distributions for BMI and age

were slightly skewed. Distributions of laboratory variables showed the data was highly skewed and there were many outliers.

Further analysis included the use of box plots to understand the distribution of outliers (an example is shown in Figure 8.3). I considered the use of various transformations prior to ultimately making the decision to categorise some variables for laboratory values. Age and BMI were retained in their original form to
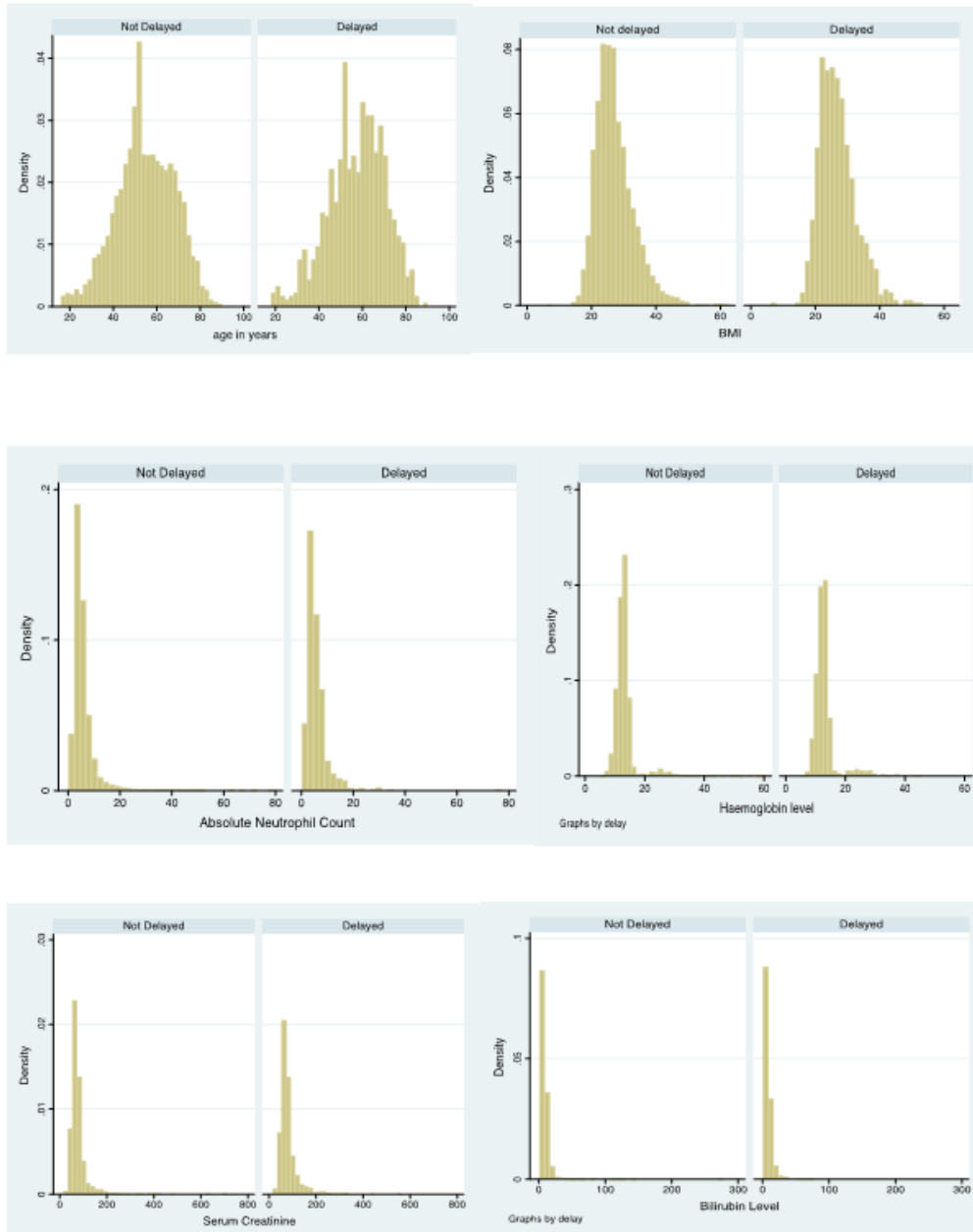
Figure 8-2. Distributions of continuous variables requiring imputation

reduce overfitting in the final prognostic model. However, I chose to categorise all laboratory values concordant with CTCAE grading (National Cancer Institute, 2017). These categories were: absolute neutrophil count $<2 \times 10^9$/L (this value is regarded as low in an individual receiving first anti-cancer treatment); ANC count between 2-7 $\times 10^9$/L (regarded as a normal count) and 7 $\times 10^9$/L (regarded as high, indicating a possible infection). A similar rationale was applied for haemoglobin, creatinine and bilirubin using values for below normal, the normal range and above normal from the CTCAE grading.
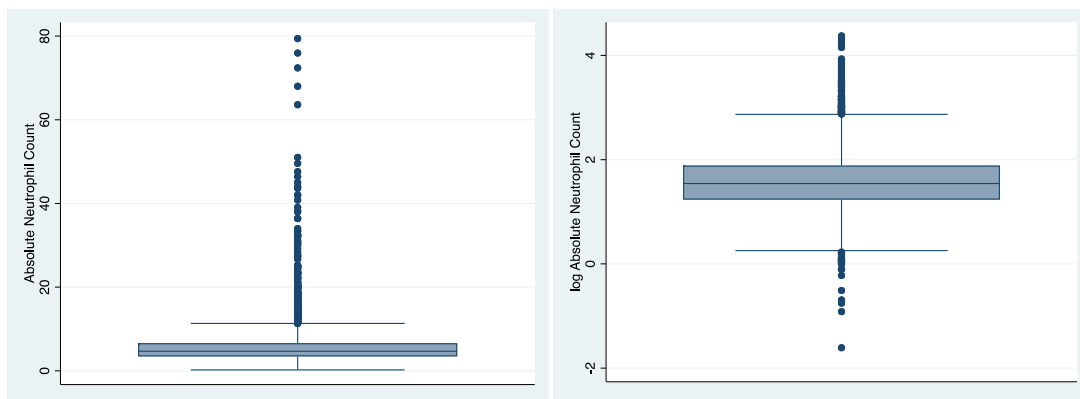
Figure 8-3. Box plot for neutrophil count value before and after log transformation

8.5.3   Outcome of interest

Investigations around the outcome of interest informed the model development methods. As I was using data from four hospitals my initial investigation was understanding the delays occurring in different hospitals. Table 8.2 shows 3-day delays or more at each hospital by cancer type. The table shows that within the DLBCL group there is little variation in the rate of delays between hospitals (range 11-16%). Interestingly, the highest rate of delay was observed at hospital 1 (16%), where DLBCL is not commonly treated and, therefore, lack of experience may cause variations in decision making (Glatzer et al., 2020). Within the colorectal cancer setting, there was a pronounced difference between hospitals' rate of delays (range 20-33%).

Table 8.3 shows that there are fewer events in the 7-day delays than 3-day delays. I discussed this data with the clinical and patient members of the steering panel.

Three days was considered as significant with patients; however, members of clinical teams highlighted that the reasons for 3-day delays may be unpredictable. Reasons for a 3-day delay occurrence may be caused by factors such as nurse capacity, scheduling and uncertainty of less experienced doctors in making decisions to treat, whereas a 7-day delay is more indicative of a toxicity-related delay. I further explored this influence in univariable analyses.

Table 8-2. Dose delays at each hospital by tumour group

Hospital /dose delay status	All	Breast	Colorectal	DLBCL
1 No delay	1,409 (80%)	592 (88%)	688 (73%)	129 (84%)
Delay	355 (20%)	80 (12%)	250 (27%)	25 (16%)
2 No delay	972 (76%)	501 (80%)	349 (67%)	122 (85%)
Delay	313 (24%)	122 (20%)	170 (33%)	21(15%)
3 No delay	796 (83%)	295 (91%)	263 (73%)	238 (87%)
Delay	162 (17%)	28 (9%)	97 (27%)	37 (13%)
4 No delay	525 (88%)	359 (89%)	72 (80%)	94 (89%)
Delay	72 (12%)	45 (11%)	15 (20%)	12 (11%)

Abbreviation: DLBCL, diffuse large B-cell lymphoma.

Table 8-3. Outcomes per disease group and cycle

Cancer Type	Delayed at 3 days	Delayed at 7 days
Breast	275 (30%)	185 (29%)
Colorectal	532 (60%)	387 (62%)
DLBCL	95 (11%)	56 (9%)
14-day cycle	460 (51%)	346 (55%)
21-day Cycle	442 (49%)	282 (45%)
Total	902	628

Abbreviation: DLBCL, diffuse large B-cell lymphoma.

Table 8-4. Univariable models for each categorical variable

Variable	Odds Ratio 3 days	95% CI 3 days	P-value 3 days	Odds Ratio 7 days	95% CI 7 days	P-value 7 days
Hospital						
1	Ref	Ref	Ref	Ref	Ref	Ref
2	1.3	1.08-1.5	0.005	0.75	0.61-0.91	0.004
3	0.8	0.65-0.99	0.04	0.48	0.38-0.62	<0.0005
4	0.54	0.41-0.7	<0.0005	0.37	0.26-0.5	<0.0005
Cancer						
DLBCL	Ref	Ref	Ref	Ref	Ref	Ref
Breast	0.97	0.75-1.24	0.75	1.1	0.82-1.52	0.48
Colorectal	2.3	1.87-3.02	<0.0005	2.8	2.1-3.8	<0.0005
Chemotherapy						
EC	Ref	Ref	Ref	Ref	Ref	Ref
FEC	1.23	0.9-1.7	0.19	0.82	0.58-1.5	0.26
Docetaxel	1.34	0.87-2.07	0.19	0.71	0.42-1.21	0.21
FOLFOXIRI	5.6	2.28-13.9	<0.0005	5.2	2.07-13.1	<0.0005
IRMDG	3.3	2.4-4.5	<0.0005	2.7	1.92-3.75	<0.0005
OXCAP	2.27	1.6-3.2	<0.0005	1.53	1.04-2.25	0.031
OXMDG	2.9	2.2-4	<0.0005	2.05	1.48-2.85	<0.0005
R-CHOP	1.22	0.86-1.73	0.25	0.76	0.51-1.13	0.17
Cycle Length						
14 days	Ref	Ref	Ref	Ref	Ref	Ref
21 days	0.42	0.36-0.42	<0.0005	0.37	0.31-0.44	<0.0005
CSF received	0.54	0.45-0.64	<0.0005	0.6	0.49-0.74	<0.0005
Vascular comorbidity present	1.41	1.13-1.77	0.002	1.3	0.99-1.74	0.053
Ethnicity white origin vs non-white origin	1.04	0.87-1.25	0.65	1.32	1.1-1.65	0.014
Performance status						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	1.19	0.94-1.5	0.14	1.4	1.07-1.81	0.013
2+	1.62	1.01-2.6	0.04	1.8	1.07-3	0.025
Neutrophil count						
<2	Ref	Ref	Ref	Ref	Ref	Ref
2-7	0.71	0.51-1	0.054	0.78	0.5-1.16	0.21
>7	0.93	0.65-1.33	0.69	1.09	0.71-1.67	0.7

Variable	Odds Ratio 3 days	95% CI 3 days	P-value 3 days	Odds Ratio 7 days	95% CI 7 days	P-value 7 days
Haemoglobin						
<8	Ref	Ref	Ref	Ref	Ref	Ref
8-10	1.09	0.43-2.8	0.9	1.62	0.47-5.5	0.44
>10	0.8	0.32-2	0.6	1.2	0.36-4	0.78
Creatinine						
<110	Ref	Ref	Ref	Ref	Ref	Ref
110-165	1.5	1.15-2.01	0.003	1.51	1.09-2.08	0.012
>165	1.44	0.99-2.1	0.059	1.85	1.24-2.8	0.003
Bilirubin						
<22	Ref	Ref	Ref	Ref	Ref	Ref
22-33	1.83	1.12-3	0.015	1.51	0.85-2.7	0.2
>33	0.96	0.44-2.07	0.912	1.04	0.44-2.5	0.09

Univariable models shown for both 3 day dose delays and 7-day dose delays as outcomes. Abbreviations: DLBCL, diffuse large B-cell lymphoma; FEC, Fluorouracil, Epirubicin and Cyclophosphamide; EC, Epirubicin and cyclophosphamide; FOLFOXIRI, fluorouracil, irinotecan, oxaliplatin; OXMDG, Oxaliplatin modified de gramont; IRMDG, irinotecan modified de gramont; R-CHOP, Rituximab, cyclophosphamide, doxorubicin and prednisolone.

In table 8.4 it can be seen that the treating hospital was found to be significantly associated with the outcome delay at 3 days. Hospital 2 has an OR of 1.3, signifying that a patient was 30% more likely to encounter a delay at this hospital compared to hospital 1; however, when the outcome was a 7-day delay, a patient treated at hospital 1 was more likely to encounter a delay. Hospital 2 had a policy of higher thresholds for neutrophils and a rule of taking blood 4 days prior to treatment that could have warranted short deferments of treatment or could be the influence of poor scheduling. Patients with colorectal cancer were, again, significantly more likely to encounter a delay in both the 3-day and 7-day delay groups with an OR of 2.3 CI (1.87-3.02) and 2.8 (2.1-3.8); this could be accounted by the fact that this group is treated more cautiously. This was also reflected in the chemotherapy treatment and the cycle length as 14-day cycles were only present for the colorectal cancer patients. Vascular comorbidity did influence the 3-day delay (OR 1.41, 95%CI 1.13-1.77) and a borderline significance of OR of 1.33 (0.99-1.74) for the 7-day delay. The effect of PS was minor (1.62) with a confidence interval of 1.01-2.6, reflecting the low number in the high PS category. Of the

laboratory tests, creatinine seemed to be the strongest influencer of a delay with narrow confidence intervals.

Following consideration of clinician and patient comments and univariable analysis conducted, I decided to proceed with a 7-day delay as my outcome variable. Irrespective of cycle length (14 or 21 days), a 7-day period is an accepted period by which to delay a patient's treatment administration due to toxicity.

8.5.4   Analysis of continuous variables and transformations

The continuous variables of age and BMI were found to have linear relationships with dose delays therefore these variables were not transformed. Linear relationships were assessed using the "predict" command in STATA (see Appendix 6).

8.5.5   Collinearity and Multicollinearity

Correlation coefficients were derived for BMI and age, with vascular comorbidity yielding values of 0.15 and 2, respectively. An interaction term of BMI and age was created to assess this correlation and this yielded the value of 0.3. From this I inferred there was a minor positive correlation between these terms and there would be minimal impact on the developed model.

VIF was used to assess for multiple collinearities and a VIF >10 indicated strong correlations. As expected, BMI, height and weight yielded values at 16,733 and 179, respectively.

Height, weight and body surface area were, therefore, not included in the final model. BMI would be included. Variables could, however, be used to impute missing values.

8.5.6   Missing data

Using data from hospital 2 to assess serum albumin at baseline, I found no significant association between albumin and the outcome of dose delays. Similar

findings were found when assessing baseline platelets and assessing the outcomes at hospitals 1 and 3.

MICE was used to impute BMI (continuous variable), baseline neutrophils, bilirubin and creatinine, all as categorical variables.

Approximately 50% of the data for vascular comorbidity was missing, all from hospital 1. Following evaluation of methodologies in imputing this data I decided against imputation. Albumin was again only available for one hospital, which was challenging; the high volume would impact the clinical credibility of the model and therefore the variable was not imputed. Baseline platelets were again missing for one hospital. The variables BMI, baseline neutrophils, baseline haemoglobin, creatinine and bilirubin had low missing data (<10%) and I, therefore, opted to impute these, using ten imputations.

Using summary tables and missingness patterns I observed that my missing data was missing at random. Table 8.5 shows that in 87% of the cases where data were missing, they were missing for all five variables to be imputed. Imputation STATA commands are detailed in Appendix 6.

Table 8-5. Patterns of missing data

Pattern (%)	BMI	ANC	HB	Cr	Bili
87	1	1	1	1	1
9	1	1	1	1	0
2	1	1	1	0	1
<1	1	0	0	1	1
<1	1	1	0	1	1
<1	1	0	1	1	1
<1	1	0	0	1	0
<1	1	1	0	0	1
<1	0	1	1	0	1
<1	0	0	0	0	1
<1	0	1	1	1	1
<1	1	0	1	0	1
<1	1	1	1	0	0
<1	0	0	1	0	1
<1	1	0	0	0	1
<1	1	0	1	1	0
<1	1	1	0	0	0

Abbreviations: BMI, Body mass index; ANC, absolute neutrophil count; HB, haemoglobin; Cr, creatinine; Bili, bilirubin. Table showing missing data patterns when data is missing, not including a complete case in the denominator for percentage.

Using multiple imputations, I imputed the variables BMI, neutrophils, haemoglobin, bilirubin and creatinine. Table 8.6 shows the numbers that were initially incomplete that were imputed.

Table 8-6. Overview of imputed data

Variable	Complete	Incomplete	Imputed	Total
BMI	4,157	447	447	4,604
ANC	4,596	8	8	4,604
Hb	4,502	102	102	4,604
Bilirubin	4,548	56	56	4,604
Creatinine	4,540	64	64	4,604

Abbreviations: BMI, Body mass index; ANC, absolute neutrophil count; HB, haemoglobin.

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I used trace plots to assess for convergence. The trace plots displayed in Figures 8.4 and 8.5 demonstrated there was no convergence.
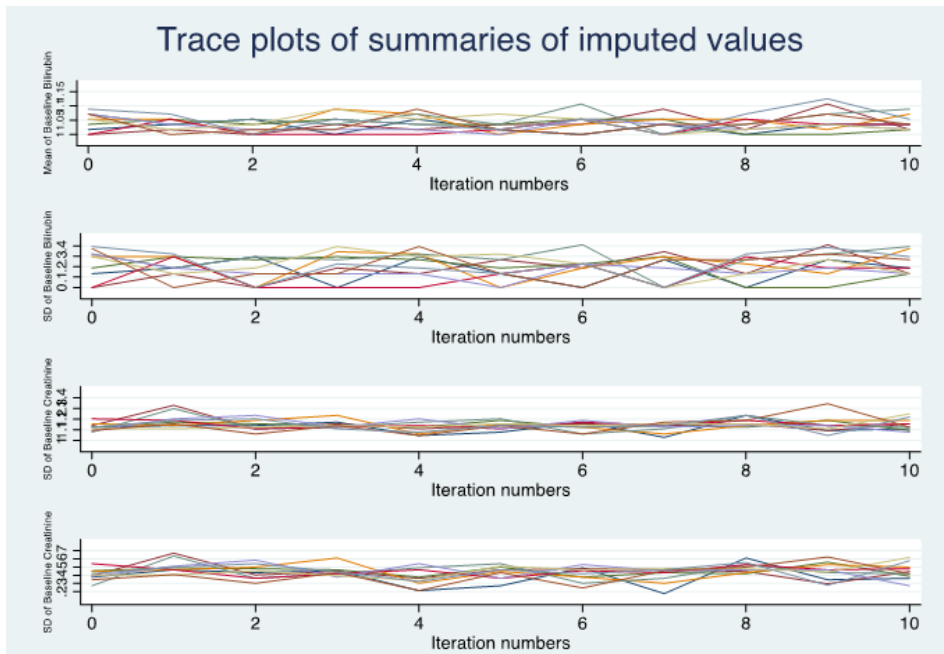
Figure 8-4. Trace plot for imputed bilirubin and creatinine showing means and standard deviations for ten imputations

Abbreviation: SD, standard deviation.
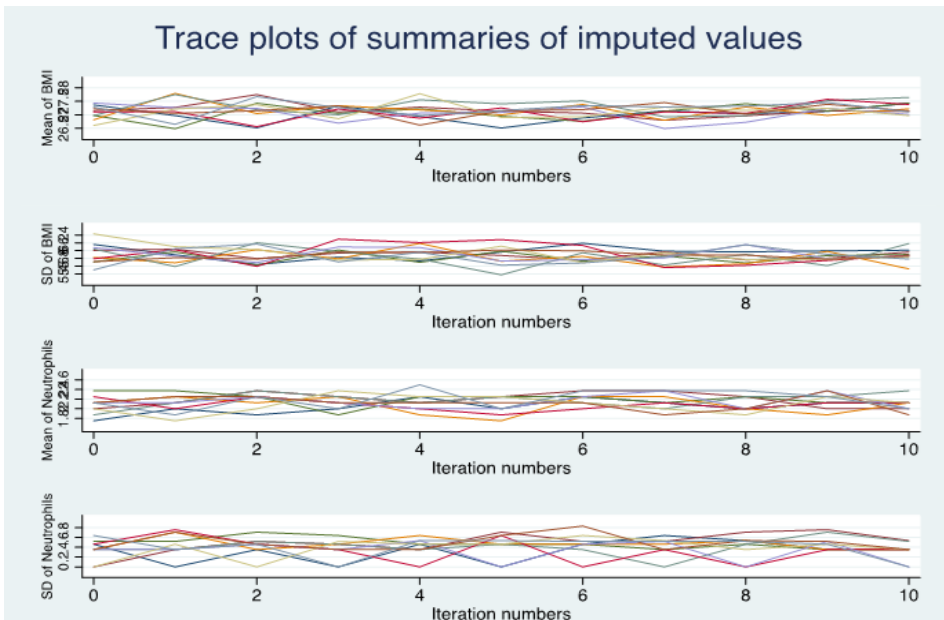
Figure 8-5. Trace plot for imputed neutrophils and body mass index showing means and standard deviations for ten imputations

Abbreviations: SD, standard deviation; BMI, body mass index.

Table 8.7 shows the beta coefficients and standard errors (SE) of the imputed model compared to the complete case. The average relative increase in variance (RVI) was 0.074 and largest fraction missing information (FMI) was 0.09. These were both low values. RVI is high when there is a large volume of missing information that is weakly correlated with other factors and a large FMI would warrant increasing the number of imputations performed.

Table 8-7. An analysis of complete cases with imputed data in a logistic regression model

Variable	Complete Case			Imputed data		
	Beta Coeff Complete case	SE Complete case	P-value	Beta Coeff	SE	P-value
Hospital 1	ref	ref	ref	Ref	Ref	Ref
2	-11.12	542.7	0.98	11.66	696.15	0.98
3	-11.64	542.7	0.98	12.15	696.15	0.98
4	-11.8	542.7	0.98	12.25	696.15	0.98
Chemotherapy EC	Ref	Ref	Ref	Ref	Ref	Ref
FEC	0.09	0.23	0.68	0.14	0.2	0.5
Docetaxel	-0.23	0.3	0.25	-0.10	0.3	0.7
FOLFOXIRI	1.57	0.69	0.023	1.84	0.6	0.03
IRMDG	0.62	0.45	0.171	0.6	0.38	0.11
OXCAP	0.43	0.3	0.152	0.5	0.27	0.26
OXMDG	0.46	0.46	0.31	0.6	0.39	0.26
R-CHOP	-0.04	0.27	0.87	0.2	0.25	0.94
Cycle Length 14 days	Ref	Ref	Ref	Ref	Ref	Ref
21 days	-.043	0.37	0.25	-0.48	0.3	0.12
Fraction of dose received	-11	542	1	-11.5	696	1
CSF received	0.05	0.17	0.8	0.003	0.16	0.9
BMI	0.05	0.08	0.5	0.02	0.07	0.07
Age	0.005	0.04	0.217	0.003	0.1	0.1
Sex Female	Ref	Ref	Ref	Ref	Ref	Ref
Male	-0.23	0.12	0.06	-0.22	1.1	0.045

Variable	Complete Case			Imputed data		
	Beta Coeff Complete case	SE Complete case	P-value	Beta Coeff	SE	P-value
Ethnicity Non White White Origin	Ref 0.14	Ref 0.12	Ref 0.26	Ref 0.14	Ref 0.12	Ref 0.27
Performance status 0 1 2+	Ref 0.16 0.59	Ref 0.15 0.29	Ref 0.28 0.041	Ref 0.12 0.46	Ref 0.14 0.27	Ref 0.3 0.09
Neutrophils <2 2-7 >7	Ref -0.61 -0.31	Ref 0.23 0.24	Ref 0.007 0.2	Ref -0.53 -0.29	Ref 0.21 0.23	Ref 0.4 0.1
Haemoglobin <8 8-10 >10	Ref 0.18 -0.01	Ref 0.65 0.64	Ref 0.787 1	Ref 0.12 0.04	Ref 067 0.66	Ref 0.86 1
Creatinine <110 110-165 >165	Ref 0.2 0.18	Ref 0.19 0.24	Re 0.3 0.46	Ref 0.62 0.16	Ref 0.17 0.22	Ref 0.72 0.46
Bilirubin <22 22-33 >33	Ref 0.4 -0.06	Ref 0.34 0.47	Ref 0.24 0.9	Ref 0.36 0.96	Ref 0.3 0.46	Ref 0.24 0.84

Abbreviations: DLBCL, diffuse large B-cell lymphoma; FEC, Fluorouracil, Epirubicin and Cyclophosphamide; EC, Epirubicin and cyclophosphamide; FOLFOXIRI, fluorouracil, irinotecan, oxaliplatin; OXMDG, oxaliplatin modified de gramont; IRMDG irinotecan modified de gramont; R-CHOP, rituximab, cyclophosphamide, doxorubicin and prednisolone.

A sensitivity analysis showed remarkable similarities in the beta coefficients and imputed model, and, therefore, I decided to use a complete case model as my final model. I calculated that by using only complete cases I would lose a total of 95 events from my data, compared to the imputed one. However, validation of the complete case model would be simpler and clinically more credible.

8.5.7 Final sample size calculation

This final sample size was calculated with the knowledge of variables taken forward to the final model. Table 8.8 shows the final 14 risk factors and details of whether these factors were categorical or continuous.

Table 8-8. Variables taken forward to the final model and categories that equate to one candidate predictor each

Variable	Continuous/categorical	Comments
Hospital	4 categories	
Chemotherapy EC FEC Docetaxel FOLFOXIRI IRMDG OXCAP OXMDG R-CHOP	8 categories	Chemotherapy specific to cancer and high level of correlation
Cycle Length 14 days 21 days	2 categories	
CSF received	2 categories	
Ethnicity	2 categories	White origin and non-white origin
Performance Status	2 categories	Small percentage in higher categories. Performance status grouped as 0-1 and 2 and over.
Age	Continuous	
BMI	Continuous	
Neutrophils	3 categories	
Haemoglobin	3 categories	
Creatinine	3 categories	
Bilirubin	3 categories	
Dose reduction	2 categories	
Sex	2 categories	Male and Female

Abbreviations: DLBCL, diffuse large B-cell lymphoma; FEC, Fluorouracil, Epirubicin and Cyclophosphamide; EC, Epirubicin and cyclophosphamide; FOLFOXIRI, fluorouracil, irinotecan, oxaliplatin; OXMDG, Oxaliplatin modified de gramont; IRMDG, irinotecan modified de gramont; R-CHOP, Rituximab, cyclophosphamide, doxorubicin and prednisolone.

The model included 38 candidate predictors (from 14 variables) as defined in Table 8.8; therefore, I needed 380 events to obtain an adequate sample. I chose to use my complete case model to bootstrap data rather than the imputed model. In total, I had 533 events in my data and an EPV of 14. An EPV >10 is necessary for a prediction model.

8.5.8 Model Development
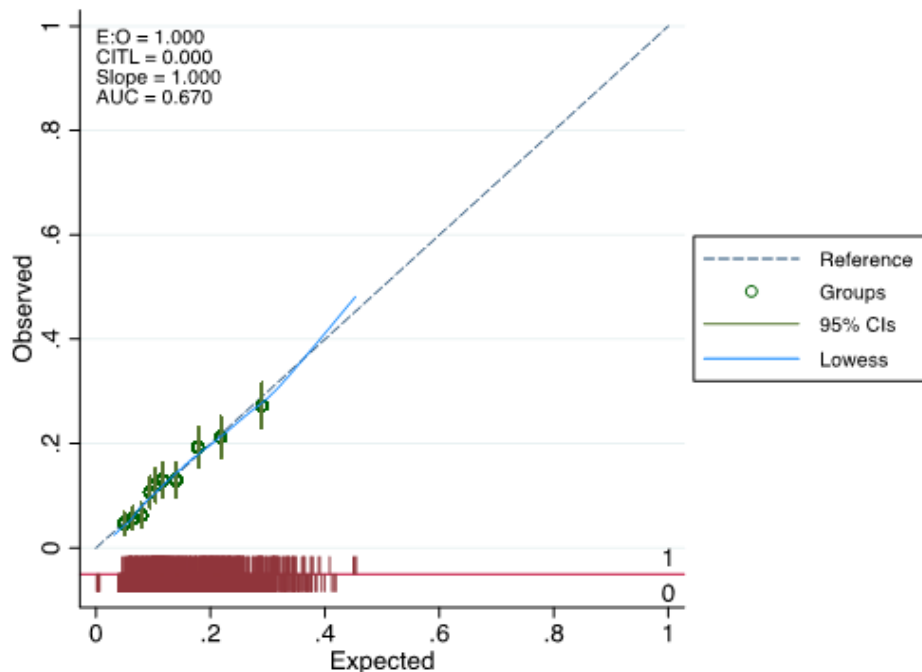
Figure 8-6. Showing a calibration plot for delay at 7 days

Notes: Calibration of the developed model is perfect and discrimination is fair.

Abbreviations: E:O, estimated to observed ratio; CITL, calibration in the large; AUC, area under the curve (or C-statistic). The model shows good calibration and fair discrimination with a C-statistic of 0.67. Spike plot shows that there are very few high probabilities >0.6.

The initial model was developed using complete cases and I compared these to the models produced using imputed data. The discrimination for the 7-day delay model was both fair with a C-statistic of 0.67 (0.65-0.71), with narrow confidence intervals.

As expected, the apparent calibration displayed in Figure 8.6 was perfect (CITL=0, Cslope=1); this is because, by definition, calibration should be perfect when fitting

E:O = 1.005
CITL = -0.006
Slope = 0.902
AUC = 0.678
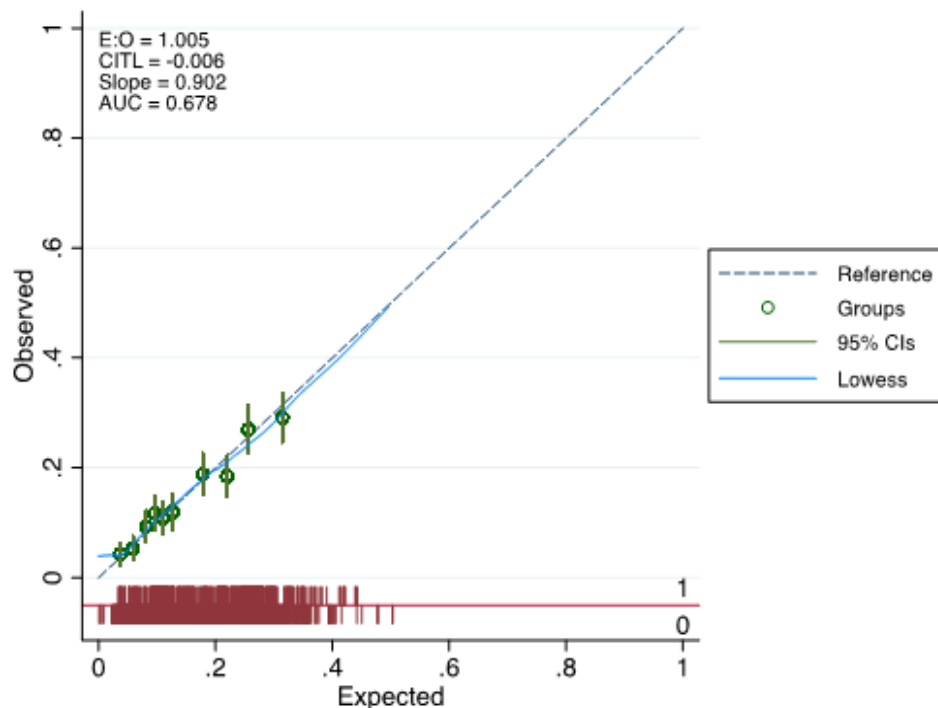
Figure 8-7. Showing a calibration plot for delay at 7 days

Notes: Following bootstrapping calibration remains strong and discrimination is similar.

Abbreviations: E:O, estimated to observed ratio; CITL, calibration in the large; AUC, area under the curve (or C-statistic).

a developed model in the developmental dataset. This step acts as a reassurance that the model has been appropriately developed. The apparent performance is good across the risk groups. Confidence intervals in groups are narrow and overlapping with the 45-degree line, indicating good calibration. Interestingly, most of the deciles are clustered left indicating that most patients have a low risk of the outcome, delay. The spike plot at the bottom of the figure shows that there are limited data for higher risk probabilities. These figures indicate that the model may not have enough data of the higher probabilities to be valuable.

Table 8-9. Evaluation of 7-day model before and after bootstrapping

	Test used	7-day model	Following bootstrapping
Overall performance	Brier Score	0.16	0.12
Discrimination	C-statistic	0.67 (0.65-0.71)	0.68 (0.66-0.7)
Calibration	Calibration in the large	0	-0.006

Abbreviations: E:O, estimated to observed ratio; CITL, calibration in the large; AUC, area under the curve (or C-statistic).

Table 8.9 details the initial model the Brier score, which is an indication of how well the model performs in terms of both discrimination and calibration. A score close to 0 would indicate a good model. It also details the overall performance, discrimination and calibration following shrinkage via bootstrapping. Surprisingly, the discrimination improved slightly, which was unexpected. This is again shown in Figure 8.7, where shrinkage has led to virtually the same model. All beta coefficients were adjusted accordingly. The lowest line indicated in blue shows that there are few probabilities above 0.6.

8.6   Discussion

In this chapter, I have developed a prediction model that would negate the need for some of the blood tests conducted. I developed a prognostic model with fair discriminatory ability (CSTAT 0.67 CI 0.65-0.71) and with similar performance to those that have been previously developed to predict chemotherapy toxicity (Brooks et al., 2015; Grant et al., 2019; Kim et al., 2018).

As I found no models developed that specifically investigated dose delays, I compared the performance of my model to those predicting grade 3-4 toxicity (a common reason for a delay). A model that is being advocated for use in the UK has been developed by the Cancer and Ageing Research Group to predict grade 3-5 toxicity in older adults (Hurria et al., 2011). Despite its wide use, the model development study did not seem to have an adequate sample size for the number of cancers, treatments and variables investigated. The discriminatory performance was reported as an AUC of 0.72 with no confidence interval reported. The tool is, however, widely used and has been translated into several languages. It is used

by clinicians to advise patients of their risk of toxicity prior to chemotherapy treatment. The model performs similarly to the 7-day model I developed, but it uses fewer risk factors in determining the risk, such as frailty. This model would, therefore, need to be used by clinicians assessing patients, whereas patient details could be inputted into my model prior to any assessment and stratify the way a patient would be treated and scheduled.

A Canadian model developed by Grant et al. (2019) that used data from 120,000 patients was shown to have benefit in patients through a net benefit analysis. The model predicted hospital admissions in patients receiving palliative chemotherapy. The C-statistic for this model was 0.61. The authors reported a C-statistic of 0.7 but this was reduced as they aimed to make the model parsimonious and increase usability at the bedside, removing variables such as income. Grant et al. concluded that their model performance may have been improved by using other variables that influence patient and clinician decision making. This is also true of my model. The decision to delay a dose can be subjective, and knowledge of the clinician prescribing and behaviours of the patient would be beneficial in the prediction.

The variables I selected were through a literature review not specific to dose delays and the selection of these may have resulted in the overall C-statistic not being strongly predictive. Model calibration was overall good and internal validation accounted for overfitting and remained similar. A prediction model assessing hospital admissions following chemotherapy (Brooks et al., 2015) found a C-statistic of 0.71 following bootstrapping. The variables found to be significant in this study were serum sodium and albumin. In the data I had available from hospital 2 on albumin, I did not find statistical a statistical significance with dose delays. Unlike Brooks et al. (2015) and Grant et al. (2019), the cohort of patients in my study were those on curative treatment, therefore, these laboratory variables may not be as predictive as in their cohorts.

I faced many methodological challenges in the development of this model. Decisions made around pooling could have contributed to the overall performance

of the model. I discovered a variability in hospitals in univariable analysis and this was not seen in the multivariable model. Snell et al. (2016) highlighted treatment centre differences in a systematic review proposing that this variation is a proxy measure for variables not collected. In my research this could be issues such as treating consultants and the variability in guidelines that influence the decisions made to delay patients. Equally, case mix in the hospital could have been important, with relatively few patients falling outside the non-white origin category. A more robust way to develop a model and take account of clustering would have been to develop a multi-level model; however, this would not have been appropriate with data from only four hospitals. With data originating from a greater number of hospitals, a random intercept model would be the model of choice, each hospital would then have its unique coefficients. Alternatively, using data from more hospitals would allow investigations of the coefficients in the current model and validate the accuracy. Another anomaly was that there was little difference seen in the performance of my model following bootstrapping. Further research and development of the model may be needed using a "Lasso or Ridge" method in shrinkage (Pavlou et al., 2015).

Usability of the model is challenging and my decision to produce a full model rather than use backward elimination to produce a parsimonious one is based on knowledge of workflows in chemotherapy services. Producing a scorecard is not practical in clinics and could be seen as a burden; however, electronic prescribing is widely used and all the data in my model is inputted into a prescribing system. This approach may not be as beneficial outside the UK, but the model could be adapted for use when externally validated. The next stages in model development will be to understand if it is beneficial to use given its discrimination and how external validation would be possible.

8.7   Summary

Using TRIPOD guidelines, I have developed and internally validated a prognostic model to predict a patient's likelihood of experiencing dose delays. This was the

first time this type of model has been developed and could potentially be used in clinical practice to improve chemotherapy services. The model has fair performance, but the true value of the model requires further investigation and I explore this in my next chapter.

Chapter 9.   Model Assessments

9.1   Overview

This chapter focuses on the benefit of the proposed developed model and the role in optimising blood testing. In this chapter, I discuss using net benefit analysis to demonstrate the advantages of my model and plans for external validation. In the introductory chapter, I discussed the chemotherapy pathways and their complexity, and how it has occurred that blood tests are duplicated: to streamline processes downstream. The previous chapter includes a model that has fair discrimination, and, in this chapter, I evaluate the benefits of the use of such a model.

9.2   Background

There are many prognostic models developed every year but very few are actually used in clinical practice (Collins et al., 2014). There are a number of reasons for this limited use: firstly, some models are discounted as their discrimination does not reach a high threshold such as 0.7; secondly, many models are not empirically evaluated in data sets that were not used in development (external data); and lastly, the model is unfeasible to use.

Considering the first problem of discriminatory ability, a number of models in different fields do not achieve a C-statistic above 0.7 but are still valuable in clinical practice. Examples are found in epilepsy (Bonnett et al., 2014) where it is very rare to find a model achieving this C-statistic. In my systematic review, presented in Chapter 3, I found prognostic models for febrile neutropenia with C-statistics that were greater than 0.8 (Lyman et al., 2005), but when exploring the overall toxicity, a C-statistic of between 0.6-0.7 (Brooks et al., 2015) was more common, and this was also true for my model. In this case, it is important to conduct a net benefit analysis. The AUC or C-statistic measuring discrimination only focuses on the predictive accuracy of the model, but it cannot tell us whether the model is worth using at all. Vickers et al. (2016) argue that this is because metrics that assess

accuracy do not incorporate information regarding consequences. An example is that a model that has a greater number of false negatives than false positives may have a higher AUC or C-statistic but it would be potentially harmful to a patient if used. Decision-curve analyses incorporate consequences and can enable decisions to be made as to whether a model is worth using (Vickers et al., 2006).

External validation is critical if a model is to be used in the clinical setting and, unfortunately, many models fail to do this (Collins et al., 2014). Reasons for assessing performance in other data sets include quantifying optimism from model overfitting or deficiencies in the statistical modelling during model development (e.g., small sample size, inappropriate handling of missing data) and evaluating the transportability of the model in different locations consisting of plausibly similar individuals (different case-mix) (Steyerberg et al., 2013).

I noted from the model that I developed that there were different case mixes seen at different hospitals and for the model to be universal this factor would need to be assessed. External validation is a way of investigating possible differences in characteristics of the cohorts (between the development and validation cohorts) and assessing how well the models perform. Ideally, external validation should also be performed by independent authors reducing inflated findings (Riley et al., 2016). It is key to replicate findings obtained during the original development of the prediction model in different data but from the same underlying target population.

The final area to explore in this chapter is the usability of the model and how I envisage the model will be used to benefit patients. In the previous chapter, I presented the model as a risk equation but in practice, this is not feasible. The ease of use is essential and, in many cases, a parsimonious model would have been optimal. Having chosen to develop a full model, it is necessary to define how this can be practically used.

9.3   Objectives

The objectives presented in this chapter were:

- To understand the net benefit of the developed model in clinical practice.

- To evaluate how the proposed model could be feasibly evaluated.

- To evaluate the way in which the risk equation could be translated into a clinical decision rule that is usable.

9.4   Methods

9.4.1   Net benefit

In developed prognostic models, probabilities are generated for each patient; from these I was able to conduct a decision-curve analysis. As previously discussed, a decision-curve analysis is a way of evaluating a prediction model. The analysis works by calculating the 'net benefit' for a prediction model compared with the default strategy of treating everyone or treating no one. This allows the model to be assessed over a range of thresholds, using the relationship between threshold probabilities. Thresholds are plotted on the x-axis, and net benefit plotted on the y-axis over a range of probabilities.

In addition, the net benefit of default policies of 'treat none' and 'treat all' are also plotted to allow comparisons to be made. The net benefit of 'treating none' is zero (as the true and false positive counts are both zero); therefore, if the net benefit of the prediction model is positive it is better to use the model than 'treat none'. The true and false positive counts for the 'treat all' strategy is the number of patients with and without the outcome, respectively; the net benefit of 'treat all' is therefore equal to the outcome prevalence at a threshold probability of zero, and equal to zero at the prevalence of the outcome. The outcomes of treating none and treating all have different meanings depending on the purpose of the model. My model aimed to aid chemotherapy pathway decisions. Treating all would, in the context of my work, mean that all patients were given an alternative pathway, taking one

blood test on the day of treatment to assess for neutrophils, having prepared treatment in advance and accept the potential drug wastage. Treating none would mean the continuation with duplicate blood tests and early assessments as a trigger to administer treatments.

The decision curve was produced on STATA and all commands can be found in Appendix 6.

9.4.2   Future model validations

To evaluate options for external validation, I considered new variables that could influence a chemotherapy dose delay. I evaluated the options of using a national data set to produce an equivalent performing model. As national data does not contain all the variables that were included in my original model, I calibrated a model only using a subset of variables found in national data sets and considered the implications.

9.4.3   Clinical use

Understanding this model and the value at low probabilities enables the consideration of firstly, who will be using the model and this influences the clinical system it should be placed in. This model was developed to assist hospital processes and I originally envisaged an electronic prescribing system to conduct the risk equation and compute a predicted probability to guide pathway discussions with patients. Other options would be the use of a nomogram and this may be used in any temporal validation that I plan. I, therefore, produced a nomogram, ranking each predictor, assigning points and then transferring this to a probability scale.

9.5   Results

9.5.1   Net benefit

Figure 9.1 shows the benefit of using the model developed over a range of predicted probabilities. As discussed in Chapter 8, this benefit is limited to those low probabilities i.e. those unlikely to have an occurrence of the event. However,

the model will have a limited impact on those with high probabilities i.e. those likely to have an occurrence of a dose delay.

Where predicted probabilities of a dose delay occurrence are between 0.1 and 0.25, the developed prediction model has the most benefit as depicted in figure 9.1. At these probabilities using the model is better than the strategies of treat none and treat all.
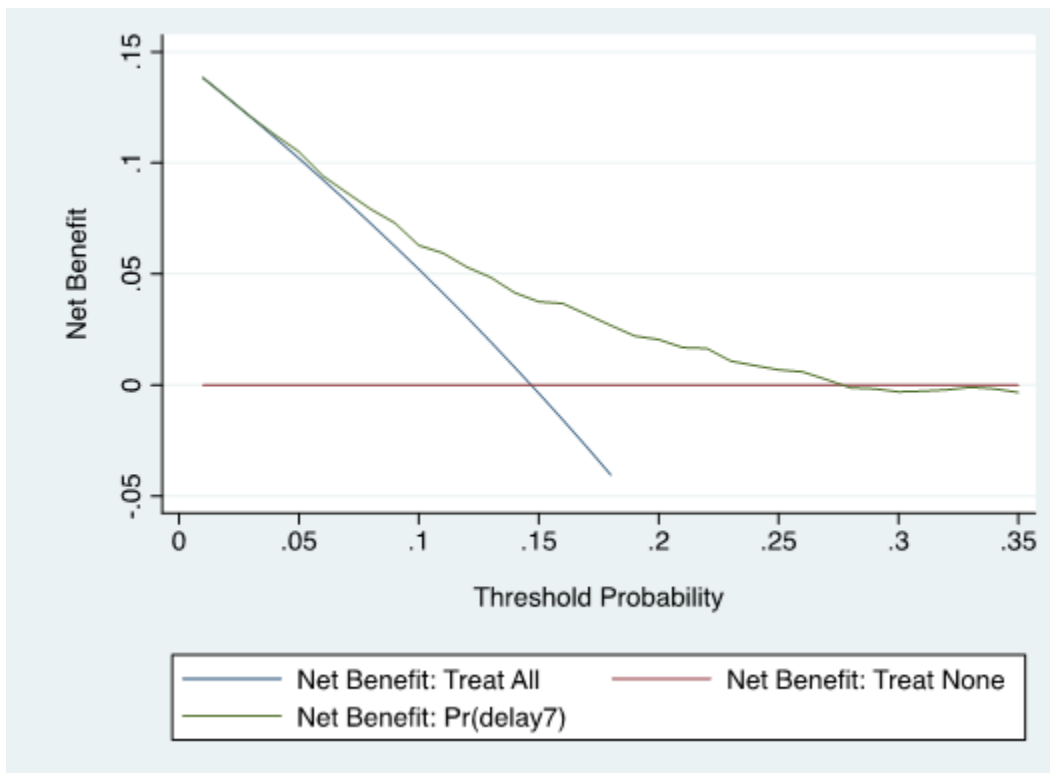
Figure 9-1. Decision curve for threshold probabilities

Table 9-1. Total Patients showing benefit in using the developed model.

Cancer type	Total patients	Total with probability 0.1-0.25	Correct prediction, i.e., patient not delayed
DLBCL	619	77 (12%)	58 (75%)
Breast	1,744	678 (39%)	597 (88%)
Colorectal	1,577	842 (53%)	842 (80%)

Abbreviations: DLBCL – Diffuse large b-cell lymphoma

From Table 9.1 it can be inferred that there is an argument to offer an alternative pathway approach to patients receiving breast and colorectal cancer treatments falling within these probabilities

9.5.2 Re-calibration of model

Figure 9.2 shows a re-calibration plot developed using all data excluding laboratory data. All this data plus additional fields can be obtained nationally through the SACT data set. These additional fields include treating consultant team, stage of disease at diagnosis, and details on socioeconomic status that can be used alone or to form part of an interaction term; as discussed in Chapter 9, these details may be valuable prognostic factors. In addition, SACT data would contain height and weight (to calculate BMI), cancer, treatment, gender, age, ethnicity, performance status and details of doses received. This model showed fair calibration C-statistic 0.665 (0.65-071), showing the exclusion of laboratory values as a feasible option.

Figure 9-2. Showing a calibration plot for delay at 7 days excluding all laboratory data

Notes – calibration and discrimination remain strong in a model including only data that can be derived nationally

Abbreviations: E:O, estimated to observed ratio; CITL, calibration in the large; AUC, area under the curve (or C-statistic). C-statistic =0.665 (0.65-071)

As the discrimination continues to be fair in this re-calibration, the validation using national data would be feasible. The addition of further factors should theoretically improve performance further.

9.5.3   Clinical use

An example of a simple nomogram that could be produced is presented in Figure 9.3. In this nomogram each predictor has been ranked and assigned probabilities. This type of schematic may be helpful for clinicians to visualise a prognostic model; however, further research is required to determine the best strategy to adopt a model in practice.
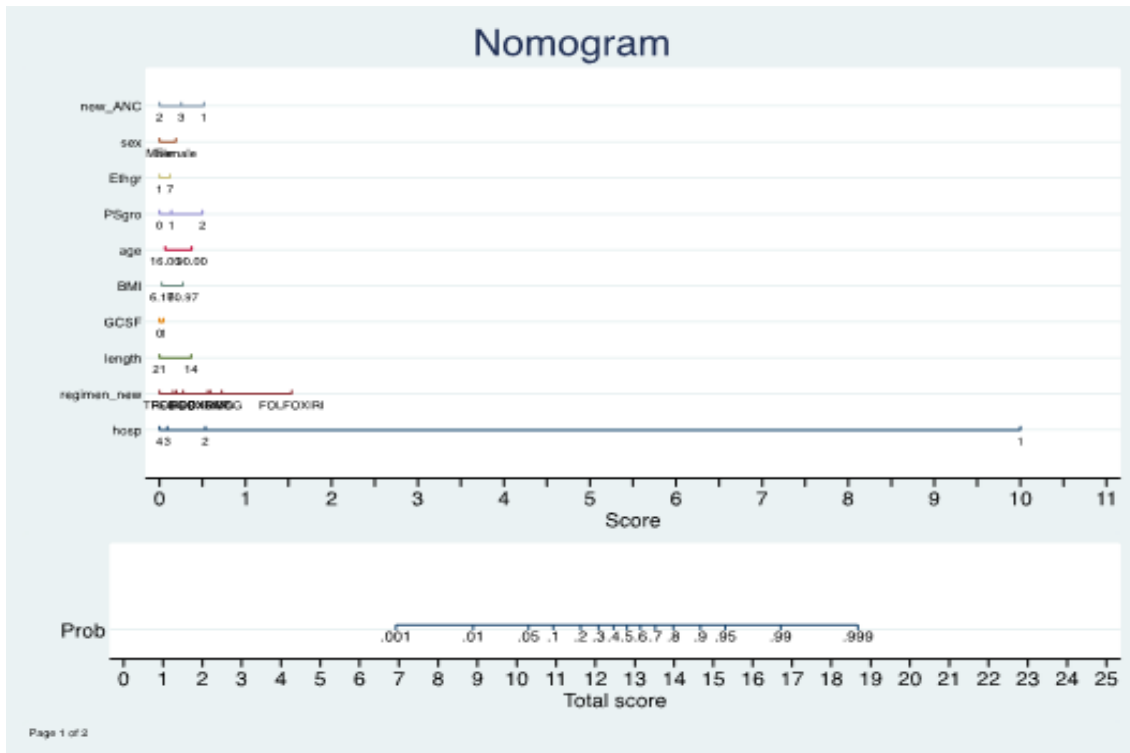

Figure 9-3. Example nomogram

9.6   Discussion

I have firstly demonstrated in this chapter the value of the prediction model I have developed and demonstrated the high volumes of patients who can be saved from unnecessary early assessments (blood tests). I have confirmed that national data can be used for external validation of the model making it a relatively low-cost

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study. Lastly, I have shown mechanisms apart from an equation that can be used during any temporal studies.

When evaluating other models available to predict toxicity, I understood two main benefits. The first is to the patient on the initiation of the treatment. Here, a patient can understand their risk of treatment-related toxicity and this information can be used with the benefits of treatment to truly give a patient-informed consent. This information is most beneficial to those receiving non-curative treatments, where the risks can sometimes outweigh the benefits. The model developed by Brooks et al. (2015) is well placed to guide treatment decisions. In the case of my model, the purpose was to offer alternative pathway options to patients without compromising safety and causing undue wastage of treatments. The population this model is intended for is the curative group who are possibly forced into a pathway that is not suited to them. The potential benefits include improvements in patient experience, during treatment, and also in saving time and reducing costs. The cost savings to the NHS are not yet understood and this is an area for further research.

A large number of prediction models are being developed, but only a small fraction of these ever get evaluated in new data (Collins et al., 2014). Systematic reviews evaluating the methodological conduct and reporting of studies developing prediction models all conclude that these studies are characterised by deficiencies in study design, inadequate statistical methodology, and poor reporting. Using nationally collected data to validate my model would provide certainty but also enable further generalisability. The evaluation of variables such as the consultant group within the hospital may also improve the model performance and extend the value to those of higher probability threshold. Demonstrating the effects in these thresholds could then guide decision making about dosing, for example in the breast cancer population where it is now desirable to reduce the time between treatments in order to improve outcomes.

A further advantage of using national data would be that it would be more feasible to develop a multi-level model. This could not be achieved using in-house data; however, national data could be used to re-develop a multilevel model with the same outcome and then validate it.

The decision-curve analysis was valuable in guiding an understanding but without further research into the economic costs and further validation, the tool cannot be adopted.

Future research needs to focus on the usability and application of prognostic models. In the case of my model, it would be valuable to understand whether clinicians would like to visualise risks by way of a nomogram or simply have the calculated probability presented at the point of deciding a patient's treatment pathway. This area of research will be valuable to ensure that the model is one day usable in the clinical setting.

9.7   Summary

In this chapter I have shown where the developed model is most beneficial in practice, proposed a mechanism by which external validation can easily be conducted and displayed an example of how the model can be visualised in practice, underlining the future work and research needed.

Chapter 10.   Overall discussion

In this chapter, I draw together the findings from previous chapters, summarising the main evidence generated and implications to practice. The main findings presented in the thesis and their immediate and long-term implications are discussed here. Additionally, this chapter evaluates the strengths and limitations of the work conducted and highlights future work needed in this area.

10.1   Timing of blood tests

Blood assessments are essential to the safe administration of SACT and are important to assure dose intensity. However, throughout this research, I found that the timing of these assessments varied depending on the treating hospital. The work that I did built on some previous work that I conducted when I was chemotherapy lead for *London Cancer* (Thwaites et al, 2017; Chambers et al., 2013). In previous work, I evaluated chemotherapy pathways across London and reported the inconsistencies in the timing of blood tests across ten different hospitals (Chambers et al., 2013). I understood that the variations were caused by an increase in service demand and the blood assessment was believed to be a primary influencer to treatment delays. The survey presented in Chapter 4 showed that not only does the timing vary, but also the threshold values employed at different hospitals, and, again, this is likely to influence the intensity of treatment received by a patient.

Treatment intensity is reduced in two ways: through dose reductions or dose delays. Inconsistencies in the absolute dose received have been investigated and highlighted by a Scottish inquiry (Scottish Government, 2019). Here, patients were receiving lower treatment doses compared to the nationally accepted standard in order to reduce toxicity to patients and national measures were implemented to prevent reoccurrence of such variation. Nonetheless, dose delays are not currently prioritised in the same way and my research is a step forward in informing future

policy around this, through demonstrating that variation in practices that impact dose delays (threshold neutrophils) do exist and should be standardised.

My findings have demonstrated that the most optimal time to assess a patient's neutrophils are as close to treatment as possible. There was a belief by chemotherapy providers that conducting assessments in advance would improve patient care (Bayliss, 2017; Thwaites et al., 2017), but I have shown that this is a misconception. In the work exploring duplication of tests, I showed that 23% of patients had a grade improvement following the initial earlier test. By testing too early, almost a quarter of the patient population would receive two blood tests rather than just one, justifying retaining the status quo of timing and not extending the window beyond 72 hours. In addition, in many cancers, cytopenias are not the crucial factor influencing a dose delay (Wagland et al., 2015; Kogan et al., 2019) but it is the clinical assessment of other toxicities. My analysis presented in Chapter 8 again demonstrates that at cycle 2 only 15% of patient delays are caused by low neutrophils. Other toxicities, such as nausea and vomiting, could be more beneficial to understand when planning a service. Additionally, patient factors such as age and comorbidity were factors that influenced some toxicities as highlighted in the systematic review presented in Chapter 3. The understanding that blood assessments are the main determinants of a dose delay could be from historic data, pre-dating the widespread use of agents such as filgrastim (Lyman, 2003). The hospital-acquired data showed that 58% of patients receiving treatment for breast cancer were receiving filgrastim as primary prophylaxis.

10.2 Development of a prognostic model

Individualisation in chemotherapy services is desperately needed to enable a balance between efficient services and patient experience. There is variation among patients and validated stratification tools could enable personalisation and in turn improve patient experience. I aimed to automate some of this by developing a prognostic model. Using the Prognostic Research Strategy Framework

(Hemingway et al., 2013) to guide the work, I ensured that future implementation would not be hindered.

Prognostic factors were found through a literature review, presented in Chapter 3, and data was collected from four hospitals in England to develop the model. A total of 4,604 patients were included in the model development study and a dose delay of 7 days was observed in 14% of patients. I chose to use all data in development rather than splitting the sample in order to improve the developed model (Steyerberg et al., 2013). The calibration was similar to other models developed to predict toxicity (Grant et al., 2019; Hurria et al., 2011) (C-statistic = 0.67), and I determined that improvement of this performance might be brought about through a collection of alternative factors.

Irrespective of the overall model performance, I showed that the model would have value in some patients through a net benefit analysis – finding that those with colorectal cancer are most likely to benefit. Here, half of the patients in the whole cohort fell into the threshold probabilities where the model worked effectively. In practice, this could mean this was a good stratification tool, guiding changes in practice in this cohort of patients, the size of which is increasing. Changes that could be applied to this tool are areas such as dose banding (Albert-Mari et al., 2018) and the use of remote assessments and reduced clinic visits (Basch et al., 2016).

I have demonstrated that existing data sets can be used for validation of my work. There is much research in improving services; however, the lack of stratification of patients to receive such interventions could be a barrier to implementation of other research in practice. This is the first model to be developed to improve processes of care for patients receiving curative SACT treatment. Other models developed to guide toxicity risk (Grant et al., 2019) are different in their intended application; these models are used to inform clinicians in the prescribing of SACT in a population where the intent is palliation and therefore they serve a different purpose. I believe my model could be adapted in the future to guide the selection

of suitable patients for more dose-dense treatments, where some patients receive two weekly treatments. This is a strategy believed to improve outcomes in early breast cancer (Gray et al., 2019); however, the model would require extensive validation for this purpose.

Before the adoption of my model, it is essential to demonstrate that the predictions it yields are valid outside of the sample. This type of validation rarely occurs and therefore very few models are implemented (Collins et al., 2014). For this reason, I believe it is important to investigate options for external validation using nationally collected data. I found that removing laboratory data as risk factors would yield a similar discrimination and the calibration of the model would remain strong. Using the SACT data set would offer other opportunities. Data would be obtained from the 220 chemotherapy delivering hospitals in England and there would be potential to develop a random intercept model or validate the use of the model in similar hospitals. Snell et al. (2016) highlighted the issues caused by the involvement of multiple hospitals and described the opportunities and challenges here.

10.2.1   Strengths and limitations

Overall, this thesis has provided evidence to guide practices around blood assessments prior to chemotherapy treatment, where there was no robust evidence in existence. Although the inclusion of data from four hospitals in England was logistically challenging at times, the result was the increased generalisability of findings. By thoroughly examining current practices, both through hospital data and survey data, I have underlined the impact of prognostic research in this area. Strengths were in model development, where I used both the PROGRESS partnership and TRIPOD statement to guide the methodology employed. Additionally, the sample size used was above the required minimum to develop such a model, thereby improving its clinical credibility. This research has paved the way for future research in terms of external validation and demonstrated benefits.

It is essential to guide future practices as numbers of treatments grow to retain a balance of patient safety and experience. To my knowledge, I have developed the first prognostic model to aid pathway decisions and save unnecessary hospital attendances for patients. This research has created knowledge that will inform many other studies in this field. The initial findings have had an impact already and a national consensus group will agree on threshold values and validity periods for blood testing in the cancers I have studied (UK Chemotherapy Board, 2020).

The main limitation of the data collected was the quality of the laboratory data in terms of the percentage of missing data beyond the baseline. Additionally, as reported in the survey, many hospitals do not hold a full record of blood results when tests are conducted locally. There may have been other factors that are more predictive that were not identified and collected, one example being socio-economic status. Although this was not identified as a predictive factor in my review, it was believed to be important by members of my patient panel. An interaction term of socio-economic status with ethnicity rather than ethnicity alone may have been worth investigating. Lastly, the absence of toxicity measures to provide ratification that the dose delay was indeed because of toxicity as opposed to scheduling would have strengthened my results. On reflection, using nationally collected data may have strengthened the performance of my developed model, but clinical concerns around the omission of detailed laboratory data may have hindered future use.

Dose delays are important to retain dose intensity and there is evidence to show that reduced dose intensity impacts the five-year progression-free survival of patients (Gray et al., 2019); however, I did not intend to nor could I evaluate survival changes. The understanding of real-world survival changes could be a lever to using prognostic research but was outside the scope of this thesis.

10.3 Implications for practice

The use of my developed prediction model cannot be advocated yet; however, other findings in this research have been directly beneficial to practice. Prior to my

work, the service benefits of advanced laboratory assessments for neutrophils were believed to be highly beneficial. Through communication of findings that the gains to the service would be counteracted by additional patient visits and increased blood tests, I have influenced hospital policies. Any changes in policy will lead to improved patient experience through the reduction of unnecessary blood tests.

I communicated findings from my systematic review, highlighting that many patient factors will influence treatment-related toxicity and clinicians should consider these when prescribing colony stimulating factors. The research questions addressed in this thesis are those that were recognised as pertinent to the safe and efficient delivery of SACT in a growing population of patients; through communication in my own clinical environment, I have demonstrated the need for more evidence with which to inform decisions. The resultant effect is the development of a research committee that will prioritise research questions around the delivery of SACT supporting research in this area.

10.3.1   Implications for future research

The work presented in this thesis has already led to a successful grant application through the NIHR Research for Patient Benefit Programme where I will be the joint chief investigator. This grant will build on findings from clinical trial data (Gray et al., 2019) that have shown that 5-year progression-free survival is hindered by delays to treatment, in a similar way to a dose reduction. I aim to investigate five-year progression-free survival in patients with early breast cancer and ovarian in the real-world population using SACT data. The prognostic model developed has the potential to influence cost-effectiveness; this is an area of future research as this knowledge will be an enabler to implementation in the future.

Finally, I have demonstrated that SACT data can be used to externally validate the model and I am driven to ensure that this research is successfully delivered. Whilst waiting for opportunities in collaboration, a temporal validation is planned in my own clinical environment and supported by clinicians, nurses and managers within

the colorectal cancer service. Following external validation, I plan to investigate whether it is preferred to integrate the model into automated prescribing systems as opposed to a nomogram. I would then plan a prospective study of the use of the model in clinical practice and evaluate benefits to the service and patients.

In disseminating my work to participating organisations and boards, the importance of blood testing for both the thresholds of neutrophils and timings has been placed on the UK Chemotherapy Board work plan. I will lead a group to develop consensus guidance in this area using the Delphi methods.

10.4 Conclusion

Overall, this thesis has highlighted the need for evidence in chemotherapy delivery and demonstrated variation and the potential impact processes can have on the dose intensity received. The work has expanded the knowledge in the stratification of patients through the development of a methodologically robust prognostic model and is the first to address dose delays in the curative intent on the chemotherapy population. Lastly, the research has the potential to inform future studies, including the impact of dose delays on progression-free survival, stratification of patients' eligibility for supportive care and stratification of patient pathways.

References

Absolom, K., Holch, P., Warrington, L., Samy, F., Hulme, C., Hewison, J., et al. (2017). Electronic patient self-reporting of adverse events: Patient Information and aDvice (eRAPID): a randomised controlled trial in systemic cancer treatment. *BMC Cancer*, 17(1), 318.

Agapinaki, E.Y.L. & Streetly, M. (2020). Full blood count review prior to bortezomib dosing at Guy's Hospital. *Journal of Oncology Pharmacy Practice*, 25(8 Suppl), 1−116.

Agiro, A., Ma, Q., Acheson, A.K., Wu, S.J., Patt, D.A., Barron, J.J., et al. (2016). Risk of neutropenia-related hospitalization in patients who received colony-stimulating factors with chemotherapy for breast cancer. *Journal of Clinical Oncology,* 19, 19.

Albert-Mari, A., Valero-Garcia, S., Fornes-Ferrer, V. & Poveda-Andres, J.L. (2018). Exploratory analysis for the implementation of antineoplastic logarithmic dose banding. *International Journal of Clinical Pharmacology,* 40(5), 1281−1291.

Alenzi, E.O. & Kelley, G.A. (2017). The association of hyperglycemia and diabetes mellitus and the risk of chemotherapy-induced neutropenia among cancer patients: A systematic review with meta-analysis. *Journal of Diabetes and its Complications*, 31(1), 267−272.

Allemani, C., Matsuda, T., Di Carlo, V., Harewood, R., Matz, M., Nikšić, M., et al. (2018). Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *The Lancet*, 391(10125), 1023−1075.

Altman, D.G., Vergouwe, Y., Royston, P. & Moons, K.G. (2009). Prognosis and prognostic research: validating a prognostic model. *BMJ*, 338, b605.

Altwairgi, A.K., Hopman, W.M. & Mates, M. (2013). Real-world impact of granulocyte-colony stimulating factor on febrile neutropenia. *Current Oncology*, 20(3), e171−179.

Arnold, M., Rutherford, M.J., Bardot, A., Ferlay, J., Andersson, T.M.L., Myklebust, T.Å., et al. (2019). Progress in cancer survival, mortality, and incidence in seven high-income countries 1995–2014 (ICBP SURVMARK-2): a population-based study. *The Lancet Oncology*, 20(11), 1493−505.

Assi, H., Murray, J., Boyle, L. & Rayson, D. (2014). Incidence of febrile neutropenia in early stage breast cancer patients receiving adjuvant FEC-D treatment. *Supportive Care in Cancer*, 22(12), 3227−3234.

Baig, H., Somlo, B., Eisen, M., Stryker, S., Bensink, M. & Morrow, P.K. (2019). Appropriateness of granulocyte colony-stimulating factor use in patients

receiving chemotherapy by febrile neutropenia risk level. *Journal of Oncology Pharmacy Practice*, 25(7), 1576−1585.

Balducci, L., Goetz-Parten, D. & Steinman, M.A. (2013). Polypharmacy and the management of the older cancer patient. *Annals of Oncology*, 24 Suppl 7, vii36−40.

Basch, E., Deal, A.M., Dueck, A.C., Scher, H.I., Kris, M.G., Hudis, C., et al. (2017). Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. *JAMA*, 318(2), 197−198.

Basch, E., Deal, A.M., Kris, M.G., Scher, H.I., Hudis, C.A., Sabbatini, P., et al. (2016). Symptom monitoring with patient-reported outcomes during routine cancer treatment: a randomized controlled trial. *Journal of Clinical Oncology*, 34(6), 557−565.

Bayliss, K. (2017). Abstract: Pilot study: Incidence of hyperbilirubinaemia in sarcoma patients receiving single agent. Journal of Oncology Pharmacy Practice, 23(8 Suppl), 1−70.

Belani, C.P. & Fossella F. (2005). Elderly subgroup analysis of a randomized phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for first-line treatment of advanced nonsmall cell lung carcinoma (TAX 326). *Cancer*, 104(12), 2766−2774.

Bonadonna, G., Valagussa, P., Moliterni, A., Zambetti, M., Brambilla, C. (1995). Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. *New England Journal of Medicine*, 332(14), 901−906.

Bonnett, L.J., Marson, A.G., Johnson, A., Kim, L., Sander, J.W., Lawn, N., et al. (2014). External validation of a prognostic model for seizure recurrence following a first unprovoked seizure and implications for driving. *PLoS One*, 9(6), e99063.

Boursi, B., Finkelman, B., Giantonio, B.J., Haynes, K., Rustgi, A.K., Rhim, A.D., et al. (2017). A clinical prediction model to assess risk for pancreatic cancer among patients with new-onset diabetes. *Gastroenterology*, 152(4), 840−850 e3.

Braun, M.S. & Seymour, M.T. (2011). Balancing the efficacy and toxicity of chemotherapy in colorectal cancer. *Therapeutic Advances in Medical Oncology*, 3(1), 43−52.

Bright, C.J., Lawton, S., Benson, S., Bomb, M., Dodwell, D., Henson, K.E., et al. (2020). Data Resource Profile: The Systemic Anti-Cancer Therapy (SACT) dataset. *International Journal of Epidemiology*, 49(1), 15-15l.

Brooks, G.A., Kansagra, A.J., Rao, S.R., Weitzman, J.I., Linden, E.A. & Jacobson, J.O. (2015). A clinical prediction model to assess risk for

chemotherapy-related hospitalization in patients initiating palliative chemotherapy. *JAMA Oncology*, 1(4), 441.

Caggiano, V., Weiss, R.V., Rickert, T.S. & Linde-Zwirble, W.T. (2005). Incidence, cost, and mortality of neutropenia hospitalization associated with chemotherapy. *Cancer*, 103(9), 1916−1924.

Calle, E.E., Rodriguez, C., Walker-Thurmond, K. & Thun, M.J. (2003). Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *New England Journal of Medicine*, 348(17), 1625−1638.

Cancer Research UK. (2017). *Breast Cancer Statistics* https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Zero.

Cardoso, F., Kyriakides, S., Ohno, S., Penault-Llorca, F., Poortmans, P., Rubio, I.T., et al. (2019). Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-updagger. *Annals of Oncology,* 30(8), 1194−1220.

Chambers, P., Daniels, S.H., Thompson, L.C. & Stephens, R.J. (2012). Chemotherapy dose reductions in obese patients with colorectal cancer. *Annals of Oncology*, 23(3), 748−753.

Chambers, P., Jani, Y., Wei, L., Kipps, E., Forster, M.D., Wong, I.C.K. (2019). Patient factors and their impact on neutropenic events: a systematic review and meta-analysis. *Supportive Care in Cancer*, 27(7), 2413−2424.

Chambers, P., Jenkinson, S. & Gallagher, C. (2013). *The London Cancer Chemotherapy Services Audit 2013*. http://www.londoncancer.org/media/84650/london-cancer-chemotherapy-audit-2013-july-2014-.pdf.

Chambers, P., Man, K.K.C., Lui, V.W.Y., Mpima, S., Nasuti, P., Forster, M.D., et al. (2020). Understanding molecular testing uptake across tumor types in eight countries: results from a multinational cross-sectional survey. *JCO Oncology Practice,* 16(8), e770−e778.

Chao, C., Page, J.H., Yang, S.J., Rodriguez, R., Huynh, J., Chia, V.M. (2014). History of chronic comorbidity and risk of chemotherapy-induced febrile neutropenia in cancer patients not receiving G-CSF prophylaxis. *Annals of Oncology*, 25(9), 1821−1829.

Chao, C., Page, J.H., Yang, S.J., Rodriguez, R., Huynh, J. & Chia, V.M. (2014). History of chronic comorbidity and risk of chemotherapy-induced febrile neutropenia in cancer patients not receiving G-CSF prophylaxis. *Annals of Oncology,* 25(9), 1821−1829.

Charlson, M., Szatrowski, T.P., Peterson, J. & Gold, J. (1994). Validation of a combined comorbidity index. *Journal of Clinical Epidemiology*, 47(11), 1245−1251.

Chemotherapy and Pharmacy Advisory Service. (2015). *Guidance on the drug related content of clinical trial protocols.* https://www.nihr.ac.uk/nihr-in-your-area/cancer/cpas.htm.

Choi, Y.W., Jeong, S.H., Ahn, M.S., Lee, H.W., Kang, S.Y., Choi, J.H., et al. (2014). Patterns of neutropenia and risk factors for febrile neutropenia of diffuse large B-cell lymphoma patients treated with rituximab-CHOP. *Journal of Korean Medical Science*, 29(11), 1493−1500.

Citron, M.L., Berry, D.A., Cirrincione, C., Hudis, C., Winer, E.P., Gradishar, W.J., et al. (2003). Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741 [Erratum appears in J Clin Oncol. 2003 21(11), 2226]. Journal of Clinical Oncology, 21(8), 1431−1439.

Collins, G.S., de Groot, J.A., Dutton, S., Omar, O., Shanyinde, M., Tajar, A., et al. (2014). External validation of multivariable prediction models: a systematic review of methodological conduct and reporting. *BMC Medical Research Methodology,* 14, 40.

Collins, G.S., Reitsma, J.B., Altman, D.G. & Moons, K.G. (2015). Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD Statement. *BMC Medicine*, 13, 1.

Craney, T.A. & Surles, J.G. (2002). Model-dependent variance inflation factor cutoff values. *Quality Engineering*, 14(3), 391−403.

Crawford, J., Glaspy, J.A., Stoller, R.G., Tomita, D.K., Vincent, M.E., McGuire, B.W., et al. (2005). Final results of a placebo-controlled study of filgrastim in small-cell lung cancer: exploration of risk factors for febrile neutropenia. *Supportive Cancer Therapy*, 3(1), 36−46.

Curigliano, G., Banerjee, S., Cervantes, A., Garassino, M.C., Garrido, P., Girard N., et al. (2020). Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. *Annals of Oncology,* 31(10), 1320−1335.

de Mendonca, B., Wield, K., Boudreau, A., Singh, S., Cheung, M.C. & Palmer, S. (2013). Optimizing patient scheduling for ambulatory chemotherapy. *Journal of Clinical Oncology*, 31(31 Suppl), 199.

Deutsch, V.R. & Tomer, A. (2006). Megakaryocyte development and platelet production. *British Journal of Haematology*, 134(5), 453−466.

Dranitsaris, G., Rayson, D., Vincent, M., Chang, J., Gelmon, K., Sandor, D., et al. (2008). Identifying patients at high risk for neutropenic complications during chemotherapy for metastatic breast cancer with doxorubicin or pegylated liposomal doxorubicin: the development of a prediction model. *American Journal of Clinical Oncology*, 31(4), 369−374.

Elamin, E.M. (2017). *Management of chemotherapy complications.* www.cccancer.com.

Elferink, M.A., Wouters, M.W., Krijnen, P., Lemmens, V.E., Jansen-Landheer, M.L., van de Velde, C.J., et al. (2010). Disparities in quality of care for colon cancer between hospitals in the Netherlands. *European Journal of Surgical Oncology*, 36(Suppl 1), S64−S73.

Falconieri, N., Van Calster, B., Timmerman, D. & Wynants, L. (2020). Developing risk models for multicenter data using standard logistic regression produced suboptimal predictions: A simulation study. *Biometrical Journal*, 62(4), 932−944.

Foukakis, T., von Minckwitz, G., Bengtsson, N.O., Brandberg, Y., Wallberg, B., Fornander, T., et al. (2016). Effect of tailored dose-dense chemotherapy vs standard 3-weekly adjuvant chemotherapy on recurrence-free survival among women with high-risk early breast cancer: a randomized clinical trial. *JAMA*, 316(18), 1888−1896.

Fujiwara, T., Kenmotsu, H., Naito, T., Kawamura, T., Mamesaya, N., Kotake, M., et al. (2017). The incidence and risk factors of febrile neutropenia in chemotherapy-naive lung cancer patients receiving etoposide plus platinum. *Cancer Chemotherapy and Pharmacology*, 79(6), 1229−1237.

Gabrilove, J.L., Jakubowski, A., Scher, H., Sternberg, C., Wong, G., Grous, J., et al. (1988). Effect of granulocyte colony-stimulating factor on neutropenia and associated morbidity due to chemotherapy for transitional-cell carcinoma of the urothelium. *New England Journal of Medicine*, 318(22), 1414−1422.

Gakwaya, A., Kigula-Mugambe, J.B., Kavuma, A., Luwaga, A., Fualal, J., Jombwe, J., et al. (2008). Cancer of the breast: 5-year survival in a tertiary hospital in Uganda. *British Journal of Cancer*, 99(1), 63−67.

Garcia-Alonso, A. (2011). Improving the chemotherapy process and service to cancer patients. *Risk Management and Healthcare Policy*, 4, 41−45.

Geeson, C., Wei, L. & Franklin, B.D. (2019). Development and performance evaluation of the Medicines Optimisation Assessment Tool (MOAT): a prognostic model to target hospital pharmacists' input to prevent medication-related problems. *BMJ Quality & Safety*, 28(8), 645−656.

Gerlier, L., Lamotte, M., Awada, A., Bosly, A., Bries, G., Cocquyt, V., et al. (2010). The use of chemotherapy regimens carrying a moderate or high risk of febrile neutropenia and the corresponding management of febrile neutropenia: an expert survey in breast cancer and non-Hodgkin's lymphoma. *BMC Cancer*, 10, 642.

Glatzer, M., Panje, C.M., Siren, C., Cihoric, N. & Putora, P.M. (2020). Decision making criteria in oncology. *Oncology*, 98(6), 370−378.

Grant, J.S. & Davis, L.L. (1997). Selection and use of content experts for instrument development. *Research in Nursing & Health*, 20(3), 269−274.

Grant, R.C., Moineddin, R., Yao, Z., Powis, M., Kukreti, V. & Krzyzanowska, M.K. (2019). Development and validation of a score to predict acute care use after initiation of systemic therapy for cancer. *JAMA Network Open*, 2(10), e1912823.

Gray, R., Bradley, R., Braybrooke, J., Liu, Z., Peto, R., Davies, L., et al. (2019). Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. *The Lancet*, 393(10179), 1440−1452.

Gupta, T., Mohanty, S., Moiyadi, A. & Jalali, R. (2013). Factors predicting temozolomide induced clinically significant acute hematologic toxicity in patients with high-grade gliomas: a clinical audit. *Clinical Neurology and Neurosurgery*, 115(9), 1814−1819.

Halek, M., Holle, D. & Bartholomeyczik, S. (2017). Development and evaluation of the content validity, practicability and feasibility of the Innovative dementia-oriented Assessment system for challenging behaviour in residents with dementia. *BMC Health Services Research*, 17(1), 554.

Hemingway, H., Croft, P., Perel, P., Hayden, J.A., Abrams, K., Timmis, A., et al. (2013). Prognosis research strategy (PROGRESS) 1: a framework for researching clinical outcomes. *BMJ*, 346, e5595.

Herbst, C., Naumann, F., Kruse, E.B., Monsef, I., Bohlius, J., Schulz, H., et al. (2009). Prophylactic antibiotics or G-CSF for the prevention of infections and improvement of survival in cancer patients undergoing chemotherapy. *Cochrane Database of Systematic Reviews*. CD007107.

Hingorani, A.D., Windt, D.A., Riley, R.D., Abrams, K., Moons, K.G., Steyerberg, E.W., et al. (2013). Prognosis research strategy (PROGRESS) 4: stratified medicine research. *BMJ*, 346, e5793.

Hippisley-Cox, J., Coupland, C., Robson, J. & Brindle, P. (2010). Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. *BMJ*, 341, c6624.

Horton, N.J. & Kleinman, K.P. (2007). Much ado about nothing. *The American Statistician*, 61(1), 79−90.

Hosmer, W., Malin, J. & Wong, M. (2011). Development and validation of a prediction model for the risk of developing febrile neutropenia in the first cycle of chemotherapy among elderly patients with breast, lung, colorectal, and prostate cancer. *Supportive Care in Cancer,* 19(3), 333−341.

Hurria, A., Brogan, K., Panageas, K.S., Pearce, C., Norton, L., Jakubowski, A., et al. (2005). Patterns of toxicity in older patients with breast cancer receiving adjuvant chemotherapy. *Breast Cancer Research and Treatment*, 92(2), 151−156.

Hurria, A., Togawa, K., Mohile, S.G., Owusu, C., Klepin, H.D., Gross, C.P., et al. (2011). Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *Journal of Clinical Oncology,* 29(25), 3457−3465.

Ichikawa, W., Uehara, K., Minamimura, K., Tanaka, C., Takii, Y., Miyauchi, H., et al. (2015). An internally and externally validated nomogram for predicting the risk of irinotecan-induced severe neutropenia in advanced colorectal cancer patients. *British Journal of Cancer,* 112(10), 1709−1716.

Ikesue, H., Watanabe, H., Hirano, M., Chikamori, A., Suetsugu, K., Ryokai, Y., et al. (2015). Risk factors for predicting severe neutropenia induced by pemetrexed plus carboplatin therapy in patients with advanced non-small cell lung cancer. *Biological Pharmaceutical Bulletin*, 38(8), 1192−1198.

Janni, W., Harbeck, N., Rack, B., Augustin, D., Jueckstock, J., Wischnik, A., et al. (2016). Randomised phase III trial of FEC120 vs EC-docetaxel in patients with high-risk node-positive primary breast cancer: final survival analysis of the ADEBAR study. *British Journal of Cancer*, 114(8), 863−871.

Jenkins, P., Scaife, J. & Freeman, S. (2012). Validation of a predictive model that identifies patients at high risk of developing febrile neutropaenia following chemotherapy for breast cancer. *Annals of Oncology*, 23(7), 1766−1771.

Jenkins, P., Scaife, J. & Freeman, S. (2012). Validation of a predictive model that identifies patients at high risk of developing febrile neutropaenia following chemotherapy for breast cancer. *Annals of Oncology*, 23(7), 1766−1771.

Jenkins, P. & Freeman, S. (2009). Pretreatment haematological laboratory values predict for excessive myelosuppression in patients receiving adjuvant FEC chemotherapy for breast cancer. *Annals of Oncology*, 20(1), 34−40.

Jiang, N., Chen, X.C. & Zhao, Y. (2013). Analysis of the risk factors for myelosuppression after concurrent chemoradiotherapy for patients with advanced non-small cell lung cancer. *Supportive Care in Cancer*, 21(3), 785−791.

Julius, J.M., Hammerstrom, A., Wei, C., Rajesh, R., Bodurka, D.C., Kurian, S., et al. (2017). Defining the impact of the use of granulocyte colony stimulating factors on the incidence of chemotherapy-induced neutropenia in patients with gynecologic malignancies. *Journal of Oncology Pharmacy Practice,* 23(2), 121−127.

Kallen, M.A., Terrell, J.A., Lewis-Patterson, P. & Hwang, J.P. (2012). Improving wait time for chemotherapy in an outpatient clinic at a comprehensive cancer center. *Journal of Oncology Practice,* 8(1), e1−e7.

Kayauchi, N., Nakagawa, Y., Oteki, T., Kagohashi, K. & Satoh, H. (2020). Change in body weight and serum albumin levels in febrile neutropenic lung cancer patients. *Asian Pacific Island Nursing Journal*, 5(3), 120−127.

Khoja, L., McGurk, A., O'Hara, C., Chow, S. & Hasan, J. (2015). Mortality within 30 days following systemic anti-cancer therapy, a review of all cases over a 4 year period in a tertiary cancer centre. *European Journal of Cancer*, 51(2), 233−240.

Kim, C.G., Sohn, J., Chon, H., Kim, J.H., Heo, S.J., Cho, H., et al. (2016). Incidence of febrile neutropenia in Korean female breast cancer patients receiving preoperative or postoperative doxorubicin/cyclophosphamide followed by docetaxel chemotherapy. *Journal of Breast Cancer*, 19(1), 76−82.

Kim, H.S., Lee, S.Y., Kim, J.W., Choi, Y.J., Park, I.H., Lee, K.S., et al. (2016). Incidence and predictors of febrile neutropenia among early-stage breast cancer patients receiving anthracycline-based chemotherapy in Korea. *Oncology*, 91(5), 274−282.

Kim, J.W., Lee, Y.-G., Hwang, I.G., Song, H.S., Koh, S.J., Ko, Y.H., et al. (2018). Predicting cumulative incidence of adverse events in older patients with cancer undergoing first-line palliative chemotherapy: Korean Cancer Study Group (KCSG) multicentre prospective study. *British Journal of Cancer*, 118(9), 1169−1175.

Kim, S.B., Sayeed, A., Villalon, A.H., Shen, Z.Z., Shah, M.A., Hou, M.F., et al. (2016). Docetaxel-based adjuvant therapy for breast cancer patients in Asia-Pacific region: Results from 5 years follow-up on Asia-Pacific Breast Initiative-I. Asia-Pacific *Journal of Clinical Oncology*, 12(2), 125−132.

Klastersky, J., de Naurois, J., Rolston, K., Rapoport, B., Maschmeyer, G., Aapro, M., et al. (2016). Management of febrile neutropaenia: ESMO Clinical Practice Guidelines. *Annals of Oncology*, 27(Suppl 5), v111−v118.

Koczwara B. (2016). *How do we measure co-morbidity*. Cancer and Chronic Conditions [Internet].

Kogan, L.G., Davis, S.L. & Brooks, G.A. (2019). Treatment delays during FOLFOX chemotherapy in patients with colorectal cancer: a multicenter retrospective analysis. *Journal of Gastrointestinal Oncology,* 10(5), 841−846.

Krens, S.D., Lassche, G., Jansman, F.G.A., Desar, I.M.E., Lankheet, N.A.G., Burger, D.M., et al. (2019). Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *The Lancet Oncology*, 20(4), e200−-e207.

Kuderer, N.M., Dale, D.C., Crawford, J. & Lyman, G.H. (2007). Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. *Journal of Clinical Oncology*, 25(21), 3158−3167.

Kwak, L.W., Halpern, J., Olshen, R.A. & Horning, S.J. (1990). Prognostic significance of actual dose intensity in diffuse large-cell lymphoma: results of a tree-structured survival analysis. *Journal of Clinical Oncology*, 8(6), 963−977.

Lalami, Y., Paesmans, M., Muanza, F., Barette, M., Plehiers, B., Dubreucq, L., et al. (2006). Can we predict the duration of chemotherapy-induced neutropenia in febrile neutropenic patients, focusing on regimen-specific risk factors? A retrospective analysis. *Annals of Oncology*, 17(3), 507−514.

Lamberink, H.J., Otte, W.M., Geerts, A.T., Pavlovic, M., Ramos-Lizana, J., Marson, A.G., et al. (2017). Individualised prediction model of seizure recurrence and long-term outcomes after withdrawal of antiepileptic drugs in seizure-free patients: a systematic review and individual participant data meta-analysis. *The Lancet Neurology*, 16(7), 523−531.

Laskey, R.A., Poniewierski, M.S., Lopez, M.A., Hanna, R.K., Secord, A.A., Gehrig, P.A., et al. (2012). Predictors of severe and febrile neutropenia during primary chemotherapy for ovarian cancer. *Gynecologic Oncology,* 125(3), 625−630.

Lau, P.K., Watson, M.J. & Hasani, A. (2014). Patients prefer chemotherapy on the same day as their medical oncology outpatient appointment. *Journal of Oncology Practice*, 10(6), e380−e384.

Leonard, R.C., Miles, D., Thomas, R., Nussey, F., Group UKBCNA. (2003). Impact of neutropenia on delivering planned adjuvant chemotherapy: UK audit of primary breast cancer patients. British Journal of Cancer, 89(11), 2062−2068.

Li, L., Kleinman, K. & Gillman, M.W. (2014). A comparison of confounding adjustment methods with an application to early life determinants of childhood obesity. *Journal of Developmental Origins of Health and Disease*, 5(6), 435−447.

Li, X., Luthra, R., Morrow, P.K., Fisher, M.D., Reiner, M., Barron, R.L., et al. (2016). Comorbidities among patients with cancer who do and do not develop febrile neutropenia during the first chemotherapy cycle. *Journal of Oncology Pharmacy Practice,* 22(5), 679−689.

Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gotzsche, P.C., Ioannidis, J.P., et al. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*, 339, b2700.

Lopez-Pousa, A., Rifa, J., Casas de Tejerina, A., Gonzalez-Larriba, J.L., Iglesias, C., Gasquet, J.A., et al. (2010). Risk assessment model for first-cycle chemotherapy-induced neutropenia in patients with solid tumours. *European Journal of Cancer Care (England)*, 19(5), 648−655.

Lorimer, C.F. & Simcock, R. (2020). Multimorbidity and cancer: the patient as a whole being. *Clinical Oncology (Royal College of Radiologists)*, 32(9), 549−550.

Luchini, C., Stubbs, B., Solmi, M. & Veronese, N. (2017). Assessing the quality of studies in meta-analyses: Advantages and limitations of the Newcastle Ottawa Scale. *World Journal of Meta-Analysis*, 5(4), 80.

Luciani, A., Bertuzzi, C., Ascione, G., Di Gennaro, E., Bozzoni, S., Zonato, S., et al. (2009). Dose intensity correlate with survival in elderly patients treated with chemotherapy for advanced non-small cell lung cancer. *Lung Cancer*, 66(1), 94−96.

Lyman, G.H., Abella, E. & Pettengell, R. (2014). Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: A systematic review. *Critical Reviews in Oncology/Hematology,* 90(3), 190−199.

Lyman, G.H., Kuderer, N.M., Crawford, J., Wolff, D.A., Culakova, E., Poniewierski, M.S., et al. (2011). Predicting individual risk of neutropenic complications in patients receiving cancer chemotherapy. *Cancer*, 117(9), 1917−1927.

Lyman, G.H., Lyman, C.H. & Agboola, O. (2005). Risk models for predicting chemotherapy-induced neutropenia. *Oncologist*, 10(6), 427−437.

Lyman, G.H., Morrison, V.A., Dale, D.C., Crawford, J., Delgado, D.J., Fridman, M., et al. (2003). Risk of febrile neutropenia among patients with intermediate-grade non-Hodgkin's lymphoma receiving CHOP chemotherapy. *Leukemia and Lymphoma,* 44(12), 2069−2076.

Lyman, G.H. (2003). Balancing the benefits and costs of colony-stimulating factors: a current perspective. *Seminars in Oncology*, 30(4 Suppl 13), 10−17.

Lyman, G.H. (2003). Introduction. Neutropenia risk models in oncology. *Oncology (Williston)*, 17(11 Suppl 11), 5−7.

Maguire, R., Fox, P.A., McCann, L., Miaskowski, C., Kotronoulas, G., Miller, M., et al. (2017). The eSMART study protocol: a randomised controlled trial to evaluate electronic symptom management using the advanced symptom management system (ASyMS) remote technology for patients with cancer. *BMJ Open*, 7(5), e015016.

McNeil, C. (2005). NCCN guidelines advocate wider use of colony-stimulating factor. *Journal of the National Cancer Institute,* 97(10), 710−711.

Merrium-Webster. (2018). Myelosuppression. (n.d.).

Meyerhardt, J.A., Kwok, A., Ratain, M.J., McGovren, J.P. & Fuchs, C.S. (2004). Relationship of baseline serum bilirubin to efficacy and toxicity of single-agent irinotecan in patients with metastatic colorectal cancer. *Journal of Clinical Oncology,* 22(8), 1439−1446.

Mezouar, S., Frere, C., Darbousset, R., Mege, D., Crescence, L., Dignat-George F., et al. (2016). Role of platelets in cancer and cancer-associated thrombosis: Experimental and clinical evidences. *Thrombosis Reseach*, 139, 65−76.

Mitani, Y., Usami, E., Kimura, M., Nakao, T., Okada, K., Matsuoka, T., et al. (2016). Risk factors for neutropenia with lenalidomide plus dexamethasone therapy for multiple myeloma. *Pharmazie*, 71(6), 349−351.

Moons, K.G., Royston, P., Vergouwe, Y., Grobbee, D.E. & Altman, D.G. (2009). Prognosis and prognostic research: what, why, and how? *BMJ,* 338, b375.

Morris, T.P., White, I.R. & Royston, P. (2014). Tuning multiple imputation by predictive mean matching and local residual draws. *BMC Medical Research Methodology*, 14, 75.

Morris, T.P., White, I.R. & Royston, P. (2014) Tuning multiple imputation by predictive mean matching and local residual draws. *BMC Medical Research Methodology*, 14(1).

Morstyn, G., Campbell, L., Lieschke, G., Layton, J.E., Maher, D., O'Connor, M., et al. (1989). Treatment of chemotherapy-induced neutropenia by subcutaneously administered granulocyte colony-stimulating factor with optimization of dose and duration of therapy. *Journal of Clinical Oncology*, 7(10), 1554−1562.

Nagel, C.I., Backes, F.J., Hade, E.M., Cohn, D.E., Eisenhauer, E.L., O'Malley, D.M., et al. (2012). Effect of chemotherapy delays and dose reductions on progression free and overall survival in the treatment of epithelial ovarian cancer. *Gynecologic Oncology*, 124(2), 221−224.

Naito, M., Yamamoto, T., Shimamoto, C. & Miwa, Y. (2017). Retrospective analysis of the risk factors for grade IV neutropenia in oesophageal cancer patients treated with a docetaxel, cisplatin, and 5-fluorouracil regimen. *Chemotherapy*, 62(4), 215−224.

National Cancer Action Team. (2009). *Chemotherapy Services in England: Ensuring quality and safety*, http://webarchive.nationalarchives.gov.uk/20130104232541/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_104501.pdf.

National Cancer Comprehensive Network. (2012). *Prevention and treatment of cancer-related infections.* https://www.nccn.org/.

National Cancer Institute. (2017). *Common Terminology Criteria for Adverse Events (CTCAE) version 5*. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50.

National Cancer Institute. (2017). *Common Terminology Criteria for Adverse Events (CTCAE) version 5* https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50.

National Cancer Registration and Analysis Service. Systemic anti-cancer therapy dataset http://www.ncin.org.uk/collecting_and_using_data/data_collection/chemotherapy.

National Institute for Health and Care Excellence. (2012). *Neutropenic sepsis: prevention and management in people with cancer*. https://www.nice.org.uk/guidance/cg151.

Neugut, A.I., Subar, M., Wilde, E.T., Stratton, S., Brouse, C.H., Hillyer, G.C., et al. (2011). Association between prescription co-payment amount and compliance with adjuvant hormonal therapy in women with early-stage breast cancer. *Journal of Clinical Oncology,* 29(18), 2534−2542.

Neuss, M.N., Gilmore, T.R., Belderson, K.M., Billett, A.L., Conti-Kalchik, T., Harvey, B.E., et al. (2016) Updated American Society of Clinical Oncology/Oncology Nursing Society Chemotherapy Administration Safety Standards, Including Standards for Pediatric Oncology. *Journal of Oncology Practice*, 12(12), 1262−1271.

Oncolink. (2018). Chemotherapy: The Basics 2018

Osmani, A.H., Jabbar, A.A., Gangwani, M.K. & Hassan B. (2017). Outcomes of high risk patients with febrile neutropenia at a tertiary care center. *Asian Pacific Journal of Cancer Prevention*, 18(10), 2741−2745.

Ozdemir, B.C., Csajka, C., Dotto, G.P. & Wagner, A.D. (2018). Sex differences in efficacy and toxicity of systemic treatments: an undervalued issue in the era of precision oncology. *Journal of Clinical Oncology,* 36(26), 2680−2683.

Ozer, H. (2003). New directions in the management of chemotherapy-induced neutropenia: Risk models, special populations, and quality of life. Seminars in Oncology, 30(4 Suppl 13), 18−23.

Page, M.J., McKenzie, J.E. & Higgins, J.P.T. (2018). Tools for assessing risk of reporting biases in studies and syntheses of studies: a systematic review. *BMJ Open*, 8(3), e019703.

Panchal, R. (2017). Systemic anticancer therapy (SACT) for lung cancer and its potential for interactions with other medicines. *Ecancermedicalscience*, 11, 764.

Pavlou, M., Ambler, G., Seaman, S.R., Guttmann, O., Elliott, P., King, M., et al. (2015). How to develop a more accurate risk prediction model when there are few events. *BMJ*, 351, h3868.

Pether, N.S., Brothwood, J.L., van Berkel, C., Dunwoodie, E.H., Blake, R.L., Price, C.P., et al. (2017). Comparative diagnostic performance of the granulocyte and neutrophil counts. *Practical Laboratory Medicine*, 9, 45−52.

Pettengell, R., Bosly, A., Szucs, T.D., Jackisch, C., Leonard, R., Paridaens, R., et al. (2009). Multivariate analysis of febrile neutropenia occurrence in patients with non-Hodgkin lymphoma: data from the INC-EU Prospective Observational European Neutropenia Study. *British Journal of Haematology*, 144(5), 677−685.

Pfeil, A.M., Vulsteke, C., Paridaens, R., Dieudonne, A.S., Pettengell, R., Hatse, S., et al. (2014). Multivariable regression analysis of febrile neutropenia occurrence in early breast cancer patients receiving chemotherapy assessing patient-related, chemotherapy-related and genetic risk factors. *BMC Cancer*, 14, 201.

Phillips, R.S., Sutton, A.J., Riley, R.D., Chisholm, J.C., Picton, S.V. & Stewart, L.A. (2012). Predicting infectious complications in neutropenic children and young people with cancer (IPD protocol). *Systematic Reviews*, 1(1).

Phippen, N.T., Lowery, W.J., Barnett, J.C., Hall, L.A., Landt, C. & Leath, C.A. III. (2011). Evaluation of the Patient-Generated Subjective Global Assessment (PG-SGA) as a predictor of febrile neutropenia in gynecologic cancer patients receiving combination chemotherapy: a pilot study. *Gynecologic Oncology,* 123(2), 360−364.

Polit, D.F., Beck, C.T. & Owen, S.V. (2007). Is the CVI an acceptable indicator of content validity? Appraisal and recommendations. *Research in Nursing and Health*, 30(4), 459−467.

Quigley, J.M., Thompson, J.C., Halfpenny, N.J. & Scott, D.A. (2018). Critical appraisal of nonrandomized studies: A review of recommended and commonly used tools. *Journal of Evaluation in Clinical Practice,* https://doi.org/10.1111/jep.12889.

Raosoft.com. (2016) *Sample Size Calculator* http://www.raosoft.com/samplesize.html.

Razai, M.S., Kankam, H.K.N., Majeed, A., Esmail, A. & Williams, D.R. (2021). Mitigating ethnic disparities in covid-19 and beyond. *BMJ*, 372, m4921.

Renehan, A.G., Lloyd, K. & Renehan, I. (2019). Awareness of the link between obesity and cancer in UK school curricula. *The Lancet*, 393(10181), 1591−1592.

Riley, R.D., Debray, T.P.A., Fisher, D., Hattle, M., Marlin, N., Hoogland, J., et al. (2020). Individual participant data meta-analysis to examine interactions

between treatment effect and participant-level covariates: Statistical recommendations for conduct and planning. *Statistics in Medicine*, 39(15), 115−2137.

Riley, R.D., Ensor, J., Snell, K.I., Debray, T.P., Altman, D.G., Moons, K.G., et al. (2016). External validation of clinical prediction models using big datasets from e-health records or IPD meta-analysis: opportunities and challenges. *BMJ*, 353, i3140.

Riley, R.D., Ensor, J., Snell, K.I.E., Harrell, F.E. Jr., Martin, G.P., Reitsma, J.B., et al. (2020). Calculating the sample size required for developing a clinical prediction model. *BMJ*, 368, m441.

Riley, R.D., Hayden, J.A., Steyerberg, E.W., Moons, K.G., Abrams, K., Kyzas, P.A., et al. (2013). Prognosis Research Strategy (PROGRESS) 2: prognostic factor research. *PLoS Medicine*, 10(2), e1001380.

Rivera, E., Erder, M.H., Moore, T.D., Shiftan, T.L., Knight, C.A., Fridman, M., et al. (2003). Targeted filgrastim support in patients with early-stage breast carcinoma: toward the implementation of a risk model. *Cancer* 98(2), 222−228.

Rivera, E., Haim Erder, M., Fridman, M., Frye, D. & Hortobagyi, G.N. (2003). First-cycle absolute neutrophil count can be used to improve chemotherapy-dose delivery and reduce the risk of febrile neutropenia in patients receiving adjuvant therapy: a validation study. *Breast Cancer Res*earch, 5(5), R114−R120.

Rosales, C. (2018). Neutrophil: a cell with many roles in inflammation or several cell types? *Frontiers in Physiology*, 9, 113.

Royston, P., Moons, K.G., Altman, D.G. & Vergouwe, Y. (2009). Prognosis and prognostic research: Developing a prognostic model. *BMJ*, 338, b604.

Salvi, F., Miller, M.D., Grilli, A., Giorgi, R., Towers, A.L., Morichi, V., et al. (2008). A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. *Journal of the American Geriatrics Society*, 56(10), 1926−1931.

Sambrook, R.J. & Girling, D.J. (2001). A national survey of the chemotherapy regimens used to treat small cell lung cancer (SCLC) in the United Kingdom. *British Journal of Cancer*, 84(11), 1447−1452.

Sandra-Petrescu, F., Herrle, F., Burkholder, I., Kienle, P. & Hofheinz, R.D. (2018). Influence of complete administration of adjuvant chemotherapy cycles on overall and disease-free survival in locally advanced rectal cancer: post hoc analysis of a randomized, multicenter, non-inferiority, phase 3 trial. *BMC Cancer*, 18(1), 369.

Sarfati, D., Koczwara, B. & Jackson, C. (2016). The impact of comorbidity on cancer and its treatment. *CA Cancer Journal for Clinicians*, 66(4), 337−350.

Savji, N., Rockman, C.B., Skolnick, A.H., Guo, Y., Adelman, M.A., Riles, T., et al. (2013). Association between advanced age and vascular disease in different arterial territories: a population database of over 3.6 million subjects. *Journal of the American College of Cardiology*, 61(16), 1736−1743.

Schwenkglenks, M., Jackisch, C., Constenla, M., Kerger, J.N., Paridaens, R., Auerbach, L., et al. (2006). Neutropenic event risk and impaired chemotherapy delivery in six European audits of breast cancer treatment. *Supportive Care in Cancer*, 14(9), 901−909.

Schwenkglenks, M., Pettengell, R., Jackisch, C., Paridaens, R., Constenla, M., Bosly, A., et al. (2011). Risk factors for chemotherapy-induced neutropenia occurrence in breast cancer patients: data from the INC-EU Prospective Observational European Neutropenia Study. *Supportive Care in Cancer*, 19(4), 483−490.

Scottish Government. (2019). *Clinical management of breast cancer in NHS Tayside: risk assessment of the Healthcare Improvement Scotland*, https://www.gov.scot/publications/clinical-risk-assessment-healthcare-improvement-scotland-report-clinical-management-breast-cancer-nhs-tayside-april-2019/.

Select Committee on Off Protocol Prescribing of Chemotherapy in New South Wales. Off-protocol prescribing of chemotherapy in New South Wales 2016 [Available from: https://www.parliament.nsw.gov.au/lcdocs/inquiries/2413/FINAL%20REPORT.pdf.

Shaikh, T., Wang, L.S., Egleston, B., Burki, M., Hoffman, J.P., Cohen, S.J., et al. (2016). Dosimetric predictors of hematologic toxicity in patients undergoing concurrent gemcitabine-based chemoradiation for localized pancreatic cancer. *Practical Radiation Oncology*, 6(4), e107−e115.

Shigeta, K., Kosaka, T., Yazawa, S., Yasumizu, Y., Mizuno, R., Nagata, H., et al. (2015). Predictive factors for severe and febrile neutropenia during docetaxel chemotherapy for castration-resistant prostate cancer. *International Journal of Clinical Oncology,* 20(3), 605−612.

Shiota, M., Yokomizo, A., Takeuchi, A., Kiyoshima, K., Inokuchi, J., Tatsugami, K., et al. (2014). Risk factors for febrile neutropenia in patients receiving docetaxel chemotherapy for castration-resistant prostate cancer. *Supportive Care in Cancer*, 22(12), 3219−3226.

Shirdel, E.A., Korenberg, M.J. & Madarnas, Y. (2011). Neutropenia prediction based on first-cycle blood counts using a FOS-3NN classifier. *Advances in Bioinformatics*, 2011, 172615.

Silber, J.H., Fridman, M., DiPaola, R.S., Erder, M.H., Pauly, M.V. & Fox, K.R. (1998). First-cycle blood counts and subsequent neutropenia, dose

reduction, or delay in early-stage breast cancer therapy. *Journal of Clinical Oncology,* 16(7), 2392−2400.

Simcock, R. & Wright, J. (2020). Beyond performance status. *Clinical Oncology (Royal College of Radiologists)*, 32(9), 553−561.

Smith, T.J., Bohlke, K., Lyman, G.H., Carson, K.R., Crawford, J., Cross, S.J., et al. (2015). Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. *Journal of Clinical Oncology,* 33(28), 3199−3212.

Smith, T.J., Bohlke, K., Lyman, G.H., Carson, K.R., Crawford, J., Cross, S.J., et al. (2015). Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice guideline update. *Journal of Clinical Oncology,* 33(28), 3199−3212.

Snell, K.I., Hua, H., Debray, T.P., Ensor, J., Look, M.P., Moons, K.G., et al. (2016). Multivariate meta-analysis of individual participant data helped externally validate the performance and implementation of a prediction model. *Journal of Clinical Epidemiology,* 69, 40−50.

Steyerberg, E.W., Moons, K.G., van der Windt, D.A., Hayden, J.A., Perel, P., Schroter, S., et al. (2013). Prognosis Research Strategy (PROGRESS) 3: prognostic model research. *PLoS Medicine*, 10(2), e1001381.

Summers, C., Rankin, S.M., Condliffe, A.M., Singh, N., Peters, A.M. & Chilvers, E.R. (2010). Neutrophil kinetics in health and disease. *Trends in Immunology,* 31(8), 318−324.

The Cochrane Collaboration. (2011). Cochrane Handbook for Systematic Reviews of Interventions https://training.cochrane.org/handbook.

Thwaites, B.M.E, Chambers, P. et al., (2017). Assessing the safety of an increase in validity of full blood counts from 72 to 96 h in our breast cancer chemotherapy patients. British Oncology Pharmacists Association Conference, Glasgow: Journal of Oncology Pharmacy Practice.

Thwaites, B.M.E., Chambers, P. & Ford, N. (2017). Editor Abstract. *Journal of Oncology Pharmacy Practice*.

Tralongo, P., Ferrau, F., Borsellino, N., Verderame, F., Caruso, M., Giuffrida, D., et al. (2011). Cancer patient-centered home care: a new model for health care in oncology. *Therapeutics and Clinical Risk Management*, 7, 387−392.

UK Chemotherapy Board. (2020). *UK Chemotherapy Board minutes October 2020*, https://4bd2316d-e45d-4e90-96b5-431f1c12dd3e.filesusr.com/ugd/638ee8_66c3bf4625ee4071bfcc2efc394228c7.pdf.

Vickers, A.J., Van Calster, B. & Steyerberg, E.W. (2016). Net benefit approaches to the evaluation of prediction models, molecular markers, and diagnostic tests. *BMJ*, 352, i6.

Vickers, A.J. & Elkin, E.B. (2006). Decision curve analysis: a novel method for evaluating prediction models. *Medical Decision Making*, 26(6), 565−574.

Vogel, C.L., Wojtukiewicz, M.Z., Carroll, R.R., Tjulandin, S.A., Barajas-Figueroa, L.J., Wiens, B.L., et al. (2005). First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: a multicenter, double-blind, placebo-controlled phase III study. *Journal of Clinical Oncology*, 23(6), 1178−1184.

Voog, E., Bienvenu, J., Warzocha, K., Moullet, I., Dumontet, C., Thieblemont, C., et al. (2000). Factors that predict chemotherapy-induced myelosuppression in lymphoma patients: role of the tumor necrosis factor ligand-receptor system. *Journal of Clinical Oncology,* 18(2), 325−331.

Wagland, R., Richardson, A., Armes, J., Hankins, M., Lennan, E. & Griffiths, P. (2015). Treatment-related problems experienced by cancer patients undergoing chemotherapy: a scoping review. *European Journal of Cancer Care (England)*, 24(5), 605−617.

Waight, C.C. & Cain, R. (2014). Authorising bortezomib treatment prior to reviewing haematology results: a step toward home administration. *Journal of Oncology Pharmacy Practice,* 20(5), 351−355.

Warr, J., Hird, A.E., DeAngelis, C., Giotis, A. & Ko, Y.J. (2013). Baseline blood work before initiation of chemotherapy: what is safe in the real world? *Journal of Oncology Practice*, 9(5), e182−185.

Warrens, M.J. (2015). Five Ways to Look at Cohen's Kappa. *Journal of Psychology & Psychotherapy*, 05(04).

Wasterlid, T., Biccler, J.L., Brown, P.N., Bogsted, M., Enblad, G., Meszaros Jorgensen, J., et al. (2018). Six cycles of R-CHOP-21 are not inferior to eight cycles for treatment of diffuse large B-cell lymphoma: a Nordic Lymphoma Group Population-based Study. *Annals of Oncology,* 29(8), 1882−1883.

Watanabe, H., Ikesue, H., Oshiro, M., Nagata, K., Mishima, K., Takada, A., et al. (2012). Risk factors for predicting severe neutropenia induced by amrubicin in patients with advanced lung cancer. *Chemotherapy*, 58(6), 419−425.

Watanabe, T. (2003). Bone marrow suppression--including guidelines for the appropriate use of G-CSF. *Gan To Kagaku Ryoho*, 30(6), 755−759.

Weycker, D., Hatfield, M., Grossman, A., Hanau, A., Lonshteyn, A., Sharma, A., et al. (2019). Risk and consequences of chemotherapy-induced thrombocytopenia in US clinical practice. *BMC Cancer*, 19(1), 151.

White, I.R., Royston, P. & Wood, A.M. (2011). Multiple imputation using chained equations: Issues and guidance for practice. *Statistics in Medicine*, 30(4), 377−399.

Wilson, B.E., Jacob, S., Yap, M.L., Ferlay, J., Bray, F. & Barton, M.B. (2019). Estimates of global chemotherapy demands and corresponding physician workforce requirements for 2018 and 2040: a population-based study. *The Lancet Oncology*, 20(6), 769−80.

World Health Organization. (2004). *ICD-10: international statistical classification of diseases and related health problems: tenth revision*, https://apps.who.int/iris/handle/10665/42980.

World Health Organization. (2020) *Cancer Today* http://gco.iarc.fr/today/home.

Wu, Y., Aravind, S., Ranganathan, G., Martin, A. & Nalysnyk, L. (2009). Anemia and thrombocytopenia in patients undergoing chemotherapy for solid tumors: a descriptive study of a large outpatient oncology practice database, 2000-2007. *Clinical Therapeutics*, 31 Pt 2, 2416−2432.

Xiao, A.T., Tong, Y.X., Xu, X.S., Zhou, Y. & Zhang, S. (2020). Preoperative nutritional status contributes to the development of neutropenia event in patients with gastric cancer receiving CAPEOX adjuvant chemotherapy. *Frontiers in Oncology*, 10, 692.

Xu, H., Chao, C., Xu, L., Cannavale, K., Sattiyapiwat, O., Page, J., et al. (2015). Pattern of dose delay and dose reduction among cancer patients treated with chemotherapy. *Journal of Clinical Oncology*, 33(15 Suppl), e20705.

Yang, L.L., Zhang, X.C., Yang, X.N., Yang, J.J., Wang, Z., Chen, H.J., et al. (2014). Lung cancer treatment disparities in China: a question in need of an answer. *Oncologist*, 19(10), 1084−1090.

Appendices

Appendix 1 – Letters of Approval

NHS
Health Research Authority

Professor Ian CK Wong
Chair of Pharmacy Practice, Head of Practice and Policy
UCL School of Pharmacy
Brunswick Square
London
WC1N 1AX

Email: hra.approval@nhs.net

24 November 2017

Dear Professor Wong,

Letter of HRA Approval

Study title:	The development and Validation of the Validity Blood Assessment (VBA) Risk Model to Optimise the Blood Testing Schedules for Chemotherapy Patients
IRAS project ID:	226078
Sponsor	University College London

I am pleased to confirm that HRA Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. Please read *Appendix B* carefully, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

Page 1 of 8

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from the HRA website.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators"*, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found through IRAS.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application

procedure. If you wish to make your views known please use the feedback form available on the HRA website.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details on the HRA website.

Your IRAS project ID is **226078**. Please quote this on all correspondence.

Yours sincerely

Thomas Fairman
HRA Assessor

Email: hra.approval@nhs.net

Copy to: *Miss Misha Ladva, UCL/UCLH Joint Research Office,*
                   (Sponsor Contact and Lead NHS R&D Contact)

NHS
The Leeds
Teaching Hospitals
NHS Trust

Dr Dunwoodie
Registrar in Medical Oncology
Leeds Cancer Centre
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Re: The development and validation of the Validity Blood Assessment (VBA) Risk model to optimise the blood testing schedules for chemotherapy patients.

Dear Dr Dunwoodie

Thank you for your application for Leeds Teaching Hospitals NHS Trust regarding the development and validation of the VBA Risk model to optimise the blood testing schedules for chemotherapy patients.

Chemotherapy numbers have grown over the past decade, this has led to many NHS services to change their patient pathways, in order to reduce patient waiting times and maximise capacity. A 72 hour period is currently considered an appropriate time period between having a blood test and receiving chemotherapy. It is not well understood if this 72 hour period (validity period) is an ideal window or not between a patient having a blood test and then receiving chemotherapy.

LTHTrust will collaborate with the University College London Hospitals (UCLH) to evaluate how far in advance of delivery of chemotherapy blood tests can be measured to ensure safe delivery of the chemotherapy.

The achievable objectives are:

- To retrospectively analyse data, where duplicate blood test have been performed (exceeding validity period). The proportion of patients that received an unnecessary blood test will be calculated from this.
- To develop and externally validate a risk model for five chemotherapy regimens, enabling clinicians to confidently extend validity periods as appropriate.
- To undertake a small pilot study to evaluate the use of the risk model for one tumour group.

Data for this project will be extracted from the Chemocare electronic prescribing system by an LTHTrust analyst. The information being used will be completely de-identified and no other new or additional information will be requested from patients; consent will not be required due to this. The data will be stored within the LTHTrust systems and data will be shared with UCLH via an NHS.net email account to an NHS.net email account.

Chair Dr Linda Pollard CBE DL   Chief Executive Julian Hartley

Dr Dunwoodie has demonstrated a clear understanding of the Data Protection legislation and Caldicott guidelines, understanding her duties to comply fully with the legislation during the collection and processing of Trust data/other organisations data.

I am happy to express my support for the development and evaluation of VBA Risk model to optimise the blood testing schedules for chemotherapy patients and wish Dr Dunwoodie well with her project.

Yours sincerely
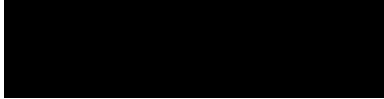
Dr John McElwaine
Deputy Caldicott Guardian
Leeds Teaching Hospitals NHS

R&D Governance Office   University Hospitals Birmingham **NHS**

NHS Foundation Trust

(Nov17)

Notice of No Objection

Project reference: RRK 6382

Nick Duncan
Pharmacy Dept
Queen Elizabeth Hospital Birmingham
Mindelsohn Way
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Birmingham B15 2WB

UHB Research Governance Office
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Heritage Building
Queen Elizabeth Hospital Birmingham
Mindelsohn Way
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Tel. 0121 371 4185

Trust Reference RRK6382

IRAS Project ID   226078

19 June 2018
Dear Mr Duncan
The development and Validation of the Validity Blood Assessment (VBA) Risk Model to Optimise the Blood Testing Schedules for Chemotherapy Patients

This approval applies to the following site(s) only: **Queen Elizabeth Hospital Birmingham**

Thank you for providing details of this study. I understand that the study only involves analysing clinical information that is routinely collected and will be fully anonymised before leaving the Trust. On this basis I am happy to confirm that there are no objections to the study and you may proceed with it.

If circumstances change, in particular if you wish to obtain non-routine information, wish to collect data prospectively, or require patient identifiable information, then you must let the R&D office know of the changes and you many need to submit a fresh application for a full review of the study

Please be sure to inform the R&D office at University Hospitals Birmingham of any amendments to the study.

Sponsorship
University College London has agreed to act as sponsor for this study.

Annual Reports
We may ask you to provide an annual update of progress with this study.

Dr Christopher Counsell
Head of R&D Governance

Copies to:

     Service Departments
     Division A Manager, Yma Choudhury

R&D Office
Head of R&D Governance: Dr Christopher Counsell
Head of R&D Operations: Joanne Plumb
R&D Office, 1st Floor, ITM, Heritage Building, Queen Elizabeth Hospital Birmingham, Edgbaston Birmingham B15 2WG
Tel: 0121 371 4185 Fax:0121 371 4204 Email: R&D@uhb.nhs.uk
Website: www.research.uhb.nhs.uk
Projects database: //uhb\userdata/R & D/R&D database/distributed database 2002.mdb

Appendix 2 – Data extraction form

Table A2.1 Study overview fields

Study ID	Year	Title	Authors	Extractor	Retrospective/Prospective	Study Design	Author description of design	Age range	Tumour groups	Country

Table A2.2 Statistical methods' fields

Study ID	No Patients included	How factors were selected	Events per variable	Dichotomisation	Assessment methods	other

Table A2.3 Extraction of variables

Study ID	Age	Weight/BSA	Gender	Treatment	Comorbidity	PS	Cancer Type	Stage	Liver	Renal	myelosuppression	other

Each heading was populated with odds ratios or relative risks associated with each variable for each study. Where categories were formed these odds or risks were separated per category.

Appendix 3 – Survey

Evaluation of Pre-Chemotherapy blood assessments within the United Kingdom

Purpose

Anecdotally, it is understood that many hospitals in the United Kingdom have differing guidelines on pre chemotherapy blood assessments. Differences may exist in both the timing that blood assessments are taken and the threshold values that should be achieved prior to receiving treatment. This quick 5-minute survey is to capture the differences between hospitals delivering chemotherapy for commonly used treatments, in three cancers.

The survey has been developed at University College London and University College London NHS Foundation Trust. For more information about this collaboration please contact Pinkie Chambers (p.chambers@ucl.ac.uk).

Findings will enable a better understanding of differences between hospitals. This information will be important to guide future practice and policy.

Why have I been asked to take part?

We wish to capture a wide range of views from the people in charge of designing, implementing and interacting with the delivery of cancer care. We believe you have a valuable perspective.

What does taking part involve?

The survey will include questions about your current role and your experience followed by questions directly related to chemotherapy regimens used in breast and colorectal cancers and diffuse large b cell lymphomas.

Do I have to take part?

No, it is up to you to decide whether or not to take part. If you decide to take part and click on the link to complete the survey, this will be taken as consent.

Is what I say confidential?

Yes, we will not inform anyone outside the research team that you have participated in the evaluation. All information will be stored securely and will only be accessed by members of the research team. Your data will be archived securely for 20 years after completion, before its eventual destruction.

What if I change my mind?

You are free to withdraw from the survey at any time. Even if you start the survey, you can stop it at any point if you wish to.

What are the risks of taking part?

There are no risks. Helping us with this evaluation will take up a little of your time. You can also contact the study team to discuss any concerns you have before or after agreeing to take part.

What are the benefits of taking part?

There may be limited personal benefits emerging from the evaluation, but there may be future benefits to improving patient care and experience. We aim to disseminate findings of any differences as soon as possible. This will be important to guide any local policies. The final results from the study will be shared across participating societies

10. What will happen to the results of the evaluation

We will aim to present findings at national and meetings and conferences.

11. What happens if something goes wrong?

If you wish to complain or have any concerns about any aspect of the way you have been approached or treated through your participation in the research, you may wish to contact the investigator (details below).

12. Local Data Protection Privacy Notice

The information that is required to be provided to participants under data protection legislation (GDPR and DPA 2018) is provided across both the 'local' and 'general' privacy notices. We will be collecting data on your hospital; type of institution and professional role. The lawful basis that will be used to process your personal data are: 'Public task' for personal data. Your personal data will be processed so long as it is required for the research project. If we are able to anonymise or pseudonymise the personal data you provide we will undertake this, and will endeavour to minimise the processing of personal data wherever possible.

If you are concerned about how your personal data is being processed, or if you would like to contact us about your rights, please contact UCL in the first instance at data-protection@ucl.ac.uk.

Investigators

Investigators:

Pinkie Chambers (p.chambers@ucl.ac.uk)

Dr.Yogini Jani (y.jani@ucl.ac.uk)

Professor Li Wei (l.wei@ucl.ac.uk)

Professor Ian Wong (i.wong@ucl.ac.uk)

Thank you for taking the time to read this information and for considering helping with our study.

Participation is voluntary, and continuing will be taken as consent.

Demographics

What hospital do you work at?

_____

What type of health professional are you?

○ Clinical Oncologist (8)

○ Medical Oncologist (9)

○ Pharmacist (1)

○ Chemotherapy Nurse (2)

○ Other (11) _____

Page Break

Q1 Please indicate the minimum neutrophil level that is accepted for the following protocols at your hospital before administration can proceed without dose amendments. NB -units 109cells/L

	<1 (1)	1 (2)	between 1.1-1.5 (4)	>1.5 (3)	Unknown (5)	Not used regimen (7)
Adjuvant breast - FEC (1)	○	○	○	○	○	○
Adjuvant breast-EC (2)	○	○	○	○	○	○
Adjuvant breast-docetaxel (3)	○	○	○	○	○	○
Palliative Colorectal –IrMDG (4)	○	○	○	○	○	○
Adjuvant Colorectal-OXMDG (5)	○	○	○	○	○	○

	<50 (1)	between 50-75 (2)	between 76-99 (4)	100 (3)	Other value>100 (6)	Unknown (7)	Not used regimen (9)
Palliative Colorectal-OXMDG (10)	○	○	○	○	○	○	
Adjuvant Colorectal-OXCAP21 day (6)	○	○	○	○	○	○	
Adjuvant Colorectal-OXCAP14 day (8)	○	○	○	○	○	○	
DLBCL -R-CHOP (9)	○	○	○	○	○	○	

Q2 Please indicate the platelet level cut off for the following protocols at your hospital before administration can proceed without dose amendments. Nb units 109cells/L

Adjuvant breast-FEC (1)	○	○	○	○	○	○	○
Adjuvant breast-EC (2)	○	○	○	○	○	○	○
Adjuvant breast-docetaxel (3)	○	○	○	○	○	○	○
Palliative colorectal –IrMDG (4)	○	○	○	○	○	○	○
Palliative Colorectal-OXMDG (10)	○	○	○	○	○	○	○
Adjuvant Colorectal-OXMDG (5)	○	○	○	○	○	○	○
Adjuvant Colorectal:	○	○	○	○	○	○	○

OXCAP21 day (6)								
Adjuvant Colorectal-OXCAP 14day (8)	○	○	○	○	○	○	○	
DLBCL -R-CHOP (9)	○	○	○	○	○	○	○	

Q3 Please indicate how far in advance of treatment a blood assessment for neutrophils and platelets can be undertaken at your hospital for the following protocols (second cycle onwards)

	No guidance (1)	within 7 days (2)	within 5 days (4)	within 4 days (3)	within 3 days (6)	within 2 days (7)	within 24 hours (8)	Unknown (9)	Not used regimen (10)
Adjuvant breast-FEC (1)	○	○	○	○	○	○	○	○	○
Adjuvant breast-EC (2)	○	○	○	○	○	○	○	○	○

Adjuvant breast-docetaxel (3)	○	○	○	○	○	○	○	○	○
Palliative colorectal – IrMDG (4)	○	○	○	○	○	○	○	○	○
Palliative Colorectal-OXMDG (5)	○	○	○	○	○	○	○	○	○
Adjuvant Colorectal-OXMDG (11)	○	○	○	○	○	○	○	○	○
Adjuvant Colorectal-OXCAP	○	○	○	○	○	○	○	○	○

21 day (6)									
Adjuvant Colorectal- OXCAP 14 day (8)	◯	◯	◯	◯	◯	◯	◯	◯	◯
DLBCL - R-CHOP (9)	◯	◯	◯	◯	◯	◯	◯	◯	◯

Page Break

Do you have any further comments relating to cut off thresholds and blood assessments pre-treatment?

_____

_____

_____

_____

_____

End of Block: Part 1 – Time to Recognition of AE by Patient

Examples answers to open question.

Do you have any further comments relating to cut off thresholds and blood assessments pre-treatment?

"The thresholds are stated in the treatment protocol but there is an unwritten rule that doctors can exercise their discretion with borderline values especially in patients receiving adjuvant treatment."

"We would accept lower counts for patients with DLBL and known marrow involvement"

"It would help if this was standardised across all trusts and the names of the proforma's were identical"

"Historically different Oncologists like different thresholds and take into account WBC as well as neutrophils. Currently looking at composing in house guidelines to have more of a streamlined approach, therefore the results from this survey would be very interesting."

"It also may vary between the 8 consultants!"

"Peripheral hospitals (less access to medics) will tend to defer on results less than threshold. Centre will refer to medic (or prescribing non-medic). May decide to re-check (i.e. deciding to proceed on a 3 day old result != Deciding to delay). Some would treat palliative patients if > 1.0 and rising, or PLT 75+ and rising. Possibly, arbitrary, 0.9 risen to 1.2 might not be treated, 1.1 to 1.3 probably would. The individual patient would be a factor in this both in terms of where traveling from AND PS/frailty. Have answered 50-75 on platelets as threshold is >= 75. Feels like a misleading answer".

Examples of open ended answers provides

Appendix 4 – Specification for Data Extraction, Chemotherapy Mapping and Cycle Lengths.

Chemotherapy Regimen / Disease groups :

SACT approved names

FEC or FEC+Docetaxel or FEC+Docetaxel +Trastuzumab (Breast)

Epirubicin + Cyclophosphamide – (Breast Cancer)

CHOP- R or CHOP (indication Diffuse large B cell lymphoma)

Irinotecan + Fluorouracil (Colorectal)

Oxaliplatin + Fluorouracil (Colorectal)

Oxaliplatin+ Capecitabine (Colorectal)

Baseline Information

Date of birth

Gender

Ethnicity

Weight (baseline)

Height (baseline)

Stage

Performance Status (if available)

Comorbidity

Dates of Chemotherapy and doses administered

Cycle number

If filgrastim or Lenograstim was included

Blood test Results

Cycle 1 Creatinine bilirubin , ALT, Albumin, absolute neutrophil count, platelet count, Haemoglobin level – dates and results (-14 days) prior to 1st chemotherapy.

Cycle 2+ Creatinine (assay method), bili, ALT, Albumin, absolute neutrophil count, platelet count, Haemoglobin level – dates and results (-7 days) prior to each cycle and including the day of chemotherapy. There may be more than 1 result.

It may actually be easier for you to extract all bloods and dates within a 6 month period of cycle 1 as I have done at UCLH (see attached script). If you add a generic identifier so that I can link the records with cycle.

Appendix 5 – Data handling Template

The Health Research Authority (HRA) have granted approval for the study (IRAS 226078). Data is required in an anonymised format from (insert hospital name). This data will be aggregated with data from other NHS trusts in England, to understand the blood testing schedules for chemotherapy patients. As the data required will not require identifiers the HRA has classified the study exempt from Ethical Committee review.

Required data fields:

Data will be extracted for patients who meet the following criteria:

- Age 18 years or older
- Received any of the chemotherapy regimens for the named diagnoses listed below
- Met the above 2 criteria from 01.01.2013 to present
1. Chemotherapy Regimen / Disease groups :

Using National SACT audit approved regimen nomenclature

FEC or FEC+Docetaxel or FEC+Docetaxel +Trastuzumab (Breast)

Epirubicin + Cyclophosphamide – (Breast Cancer)

CHOP- R or CHOP (Diffuse large B cell lymphoma)

Irinotecan + Fluorouracil (Colorectal)

Oxaliplatin + Fluorouracil (Colorectal)

Oxaliplatin+ Capecitabine (Colorectal)

2. Baseline Information for each patient

Age

Gender

Ethnicity

Weight (baseline)

Height (baseline)

Stage

Performance Status (if available)

Comorbidity if available

Dates of Chemotherapy and doses administered

Cycle number

If filgrastim or lenograstim was included

3. Blood test Results

Cycle 1. Creatinine, bilirubin, ALT, albumin, absolute neutrophil count, platelet count, haemoglobin level – dates and results (-14 days) prior to 1st chemotherapy.

Cycle 2+. Creatinine (assay method), bilirubin, ALT, albumin, absolute neutrophil count, platelet count, haemoglobin level – dates and results (-7 days) prior to each cycle and including the day of chemotherapy delivery. There may be more than 1 result.

Data Handing

Data will be extracted from the Chemocare electronic prescribing system for the following fields by an analyst working at the trust. NHS numbers will be used within (hospital name) to exclude data from patients who have requested that their data is not used for research purposes. The patient identifiers (NHS number, name, DOB) will be removed after this process.

Data Transfer

Data can be transferred to the research team via the following methods.

The Excel data sheet can be password protected and emailed via nhs.net account to another nhs.net account.

An encrypted device can be brought to the trust by the researcher where password protected files can be transferred.

Access can be granted to the UCL data safe haven aiding the transfer of files.

Data Storage

Data will be analysed and stored on a single NHS laptop which will be stored securely in a dedicated locked cabinet at UCLH NHS Foundation trust all times when not in use. Data on encrypted devices used for transfer will be appropriately destroyed.

Appendix 6 – Data grouping and STATA commands used for Development of Prognostic model

Chemotherapy treatments lengths and drugs

Disease	Treatment	Length (days)	Cycle 1 -2 coding of regimen
Breast	FEC-T	21	FEC
	EC	21	EC
	FEC	21	FEC
	T-FEC	21	Docetaxel
Colorectal	IRMDG	14	IRMDG
	OXMDG	14	OXMDG
	OXCAP	14 or 21	OXCAP
	FOLFOXIRI	14	FOLFOXIRI
DLBCL	RCHOP	21	RCHOP
	Mini RCHOP	21	Mini RCHOP

Commands used to describe data

tab sex delay, col

tab hosp delay, col

tab regimen_new delay, col

tab GCSF delay, col

hosp delay, col

cancer_new delay, col

regimen_new

regimen_new delay, col

length delay, col

length delay, col

tab vcomorbidity delay, col

tab EthnicGroup_new delay, col

EthnicGroup_new

tab PS delay, col

Distributions of continuous variables

hist age, by(delay)

hist height, by(delay)

hist weight1, by(delay)

hist BMI, by(delay)

hist DR, by(delay)

hist baseANC, by(delay)

hist basehb, by(delay)

hist basecreat, by(delay)

hist basebili, by(delay)

hist DR2, by(delay)

bysort delay: summ age, detail

bysort delay: summ height, detail

bysort delay: summ weight1, detail

bysort delay: summ BMI, detail

bysort delay: summ baseANC, detail

bysort delay: summ basehb, detail

bysort delay: summ basecreat, detail

bysort delay: summ weight1, detail

bysort delay: summ BMI, detail

bysort delay: summ basealt, detail

bysort delay: summ basealb, detail

bysort delay: summ basebili, detail

bysort delay: summ DI, detail

list basebili if basebili<2

Univariable models for categorical variables

logistic delay i.hosp

logistic delay i.cancer_new

logistic delay i.length

logistic delay i.GCSF

logistic delay i.vcomorbidity

logistic delay i.PSgro

logistic delay i.Ethgr

logistic delay i.regimen_new

Checking linear relationships

predict lp_age_lin, xb

Checking collinearility

Collins: BMI

logistic delay i.hosp i.regimen_new i.PSgro i.Ethgr age basebili BMI basecreat i.GCSF DI i.sex baseANC basehb

Imputation Commands

mi misstable patterns BMI new_ANC new_hb new_cr new_bili

mi misstable patterns, all

mi register imputed BMI new_ANC new_hb new_cr new_bili

mi register regular delay7 hosp regimen_new length GCSF age PSgro Ethgr sex DI

mi register passive height weight1

check for convergence

regress BMI i.new_ANC i.new_hb i.new_cr i.new_bili delay7 i.hosp i.regimen_new i.length i.GCSF age i.PSgro i. Ethgr i.sex i.DI

mlogit new_ANC BMI i.new_hb i.new_cr i.new_bili delay7 i.hosp i.regimen_new i.length i.GCSF age i.PSgro i. Ethgr i.sex i.DI

mi impute chained (regress) BMI (pmm,knn(3)) new_ANC (pmm,knn(3))new_hb (pmm,knn(3))new_cr (pmm,knn(3))new_bili= delay7 sex height weight1 ,force add(5) rseed(4409) savetrace(extrace, replace) burnin(100)

use extrace, replace

mi impute chained (regress) BMI basebili basecreat basehb baseANC=height weight1 delay sex, add(10) rseed (53421) savetrace(trace1,replace)

mi estimate: logit delay BMI basebili basecreat basehb baseANC

mi impute,chained (regress) BMI basebili basecreat basehb baseANC = delay weight1, add(20) replace rseed(1234) savetrace(trace1,replace), force

mi estimate: logit delay BMI basebili basecreat basehb baseANC

logit delay BMI basebili basecreat basehb baseANC

mi register imputed BMI baseANC basehb basecreat basebili

mi register imputed new_ANC new_hb new_bili new_cr BMI

mi register regular delay age sex height weight1

mi register imputed weight height

mi impute chained (regress) BMI (mlogit) new_ANC new_hb new_bili new_cr = delay age sex, add(10) replace rseed(1234) savetrace(trace1,replace)

mi estimate logit delay7 i.hosp i.regimen_new length GCSF age i.PSgro i.Ethgr i.sex DI i.new_ANC i.new_hb i.new_bili i.new_cr

describe

reshape wide *mean *sd, i(iter) j(m)

tsset iter

tsline BMI_mean1, name(mice1,replace)legend(off) ytitle("Mean of BMI")

tsline new_bili_mean*, name(mice1,replace)legend(off) ytitle("Mean of Baseline Bilirubin")

tsline new_bili_sd*, name(mice2, replace) legend(off) ytitle("SD of Baseline Bilirubin")

tsline new_cr_mean*, name(mice3,replace)legend(off) ytitle("SD of Baseline Creatinine")

tsline new_cr_sd*, name(mice4, replace) legend(off) ytitle("SD of Baseline Creatinine")

graph combine mice1 mice2 mice3 mice4, xcommon cols(1) title(Trace plots of summaries of imputed values)

tsline BMI_mean*, name(mice1,replace)legend(off) ytitle("Mean of BMI")

tsline BMI_sd*, name(mice2, replace) legend(off) ytitle("SD of BMI")

tsline new_ANC_mean*, name(mice3,replace)legend(off) ytitle("Mean of Neutrophils")

tsline new_ANC_sd*, name(mice4, replace) legend(off) ytitle("SD of Neutrophils")

graph combine mice1 mice2 mice3 mice4, xcommon cols(1) title(Trace plots of summaries of imputed values)

graph combine mice1 mice2, xcommon cols(1) title(Trace plots of summaries of imputed values - Body Mass Index)

tsline basecreat_mean*, name(mice3,replace)legend(off) ytitle("SD of Baseline Creatinine")

tsline basecreat_sd*, name(mice4, replace) legend(off) ytitle("SD of Baseline Creatinine")

graph combine mice1 mice2, xcommon cols(1) title(Trace plots of summaries of imputed values -Creatinine)

tsline basehb_mean*, name(mice1,replace)legend(off) ytitle("Mean of Baseline Haemoglobin")

tsline basehb_sd*, name(mice2, replace) legend(off) ytitle("SD of Baseline Haemoglobin")

graph combine mice1 mice2, xcommon cols(1) title(Trace plots of summaries of imputed values- Haemoglobin)

tsline new_ANC_mean*, name(mice1,replace)legend(off) ytitle("Mean of Neutrophils")

tsline new_ANC_sd*, name(mice2, replace) legend(off) ytitle("SD of Neutrophils")

graph combine mice1 mice2, xcommon cols(1) title(Trace plots of summaries of imputed values -Absolute Neutrophil Count)

histogram BSA, normal

histogram baseANC, normal

tab baseANC,missing

mi describe

mi estimate: histogram basebili, normal

histogram basecreat, normal

mi set wide

asdoc mi misstable summarize BMI new_ANC new_hb new_bili new_cr

misstable patterns BMI

mi sum: BMI, detail

** checks

logit delay age BMI i.hosp i.regimen_new i.new_ANC i.new_hb i.new_bili i.new_cr

mi estimate:logit delay age BMI i.hosp i.regimen_new i.new_ANC i.new_hb i.new_bili i.new_cr

mi xeq: summ BMI

mi estimate: logistic delay7 i.hosp i.regimen_new i.length i.GCSF BMI age i.PSgro i. Ethgr i.sex i.new_ANC i.new_hb i.new_cr i.new_bili i.DI

calculate apparent discrimination peformance

* obtain the predicted probabilities for each patient

predict pr

* obtain the linear predictor/PI for each patient

predict lp, xb

* summarise the distribution of linear predictor

summarize lp

* obtaining c statistic / AUC

roctab delay7 pr

global cstat_orig = r(area)

drop pr lp

Commands for Bootstrap

matrix results = J(400,6,.)

set seed 635432

qui forvalues i=1/200 {

* then load the original sample data

use   "/Users/pinkiechambers/Documents/ALL   hosp   MASTER   imputed
data.dta",clear

bsample

nois _dots `i' 0

*Fit model to the bootstrap sample

logistic delay7 i.hosp i.regimen_new i.length i.GCSF BMI age i.PSgro i. Ethgr i.sex
i.new_ANC i.new_hb i.new_cr i.new_bili i.DI

* predict probabilities & lp from the bootstrap model in the bs sample

predict pr

predict lp, xb

roctab delay7 pr

matrix results[`i',1] = r(area)

*apparent slope

logistic delay7 lp, coef

```
matrix results[`i',2] = _b[lp]

* bootstrap apparent CITL

logistic delay7, offset(lp) coef

matrix results[`i',3] = _b[_cons]

logistic delay7 i.hosp i.regimen_new i.length i.GCSF BMI age i.PSgro i. Ethgr i.sex
i.new_ANC i.new_hb i.new_cr i.new_bili i.DI

load the original sample data

use      "/Users/pinkiechambers/Documents/ALL      hosp      MASTER      imputed
data.dta",clear

* predict probabilities & lp from the bs model in the original dataset

predict pr

predict lp, xb

* calculate the test performance in original data C-slope

logistic delay7 lp, coef

matrix results[`i',5] = _b[lp]

* calculate the test performance in original data CITL

logistic delay7, offset(lp) coef

matrix results[`i',6] = _b[_cons]

* calculate the test performance in original data C-statistic

roctab delay7 pr

matrix results[`i',4] = r(area)

}
```
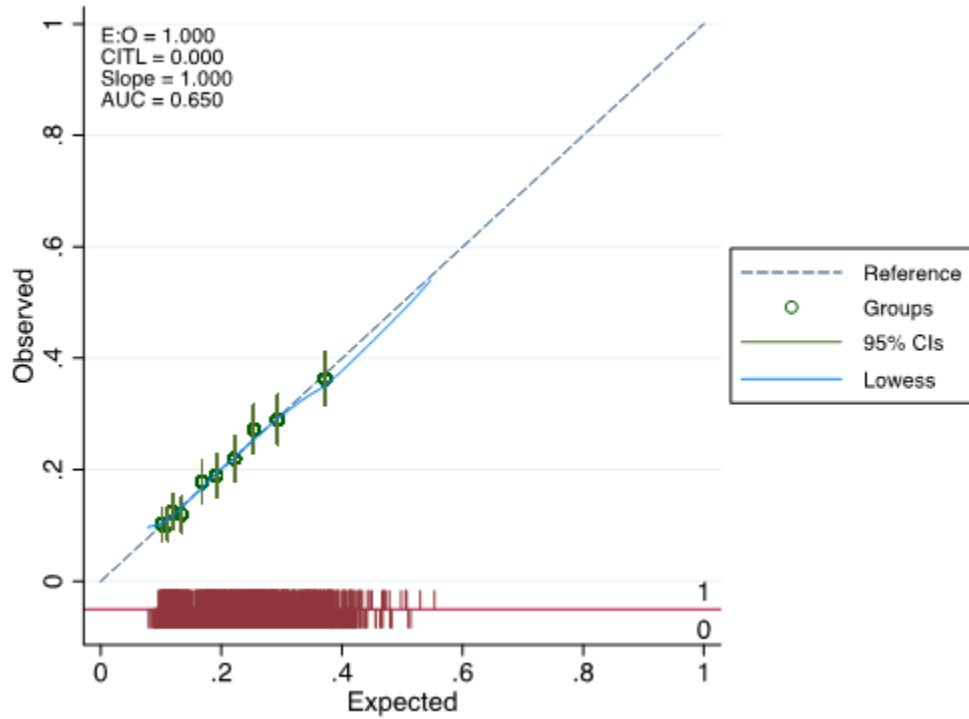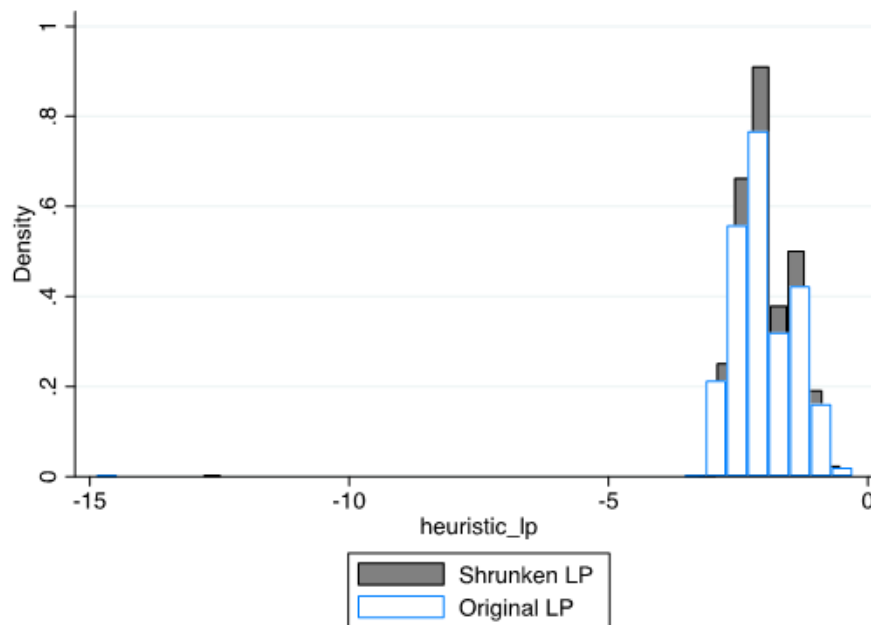
Appendix 7 – Additional Model development Figures

A7- Figure 1. 3-day model developed

E:O = 1.000
CITL = 0.000
Slope = 1.000
AUC = 0.650

Reference
Groups
95% CIs
Lowess

Observed

Expected

A7 Figure 2. Linear shrinkage following model

Density

heuristic_lp

Shrunken LP
Original LP

development

Appendix 8 – UK Chemotherapy board Paper

Validity Periods of bloods: Question for the UK Chemotherapy Board should be have a Consensus statement.

Pinkie Chambers and Dr Martin Forster.

Background

Many hospitals are changing processes of care for cancer patients whilst we are amidst the SARS-CoV-2 pandemic, with the aim to minimise healthcare interactions for those patients that require treatment. One of these interactions being pre-treatment blood tests. Additionally, duplication of blood tests causes wastage of laboratory capacity. We would like to discuss with the board the possibility of a consensus statement on the correct validity period.

Part 1: Analysis of results from 4 hospitals in England

Using electronic prescribing record data from hospitals in England of repeated blood tests for neutrophils, creatinine and bilirubin we aimed to determine whether the time window for assessing pre-chemotherapy blood levels could be extended without compromising patient safety. Data were collected from e-prescribing systems following HRA approvals and local governance agreements.

Table 1. Grade Changes in Neutrophils, Bilirubin and Creatinine values.

	Neutrophils	Bilirubin	Creatinine
Total patients with more than 1 result within a defined period*	616	3973	3828
Result worsened by 10% or more	246 (40%)	725 (18%)	721 (19%)
Grade Worsened by 1 grade	16 (2.6%)	6 (0.15%)	24 (0.6%)
Grade Worsened by 2 or more grades	5 (0.8%)	12 (0.3%)	25 (0.7%)
Grade improved	142 (23%)		

*Neutrophil grade changes between two levels taken within seven days; both prior to the second chemotherapy administration. Creatinine and bilirubin changes prior to first and second chemotherapy cycles. Grade improvements in creatinine and bilirubin not reported as only applicable where values were initially abnormal. Grade used CTCAE grades to assess changes. Implications of grade improvement would be a potential duplicate test impacting patient experience.

Table 2.Showing those eligible for treatment at test 1 and test 2 using ANC1 as a threshold value.

	Test 2: ANC>=1 x 10^9 /L	Test 2: ANC<1 x 10^9 /L
Test 1: ANC>=1 x 10^9 /L	498 (81%)	**5 (0.8%)**
Test 1:ANC<1 x 10^9 /L	**111 (18%)**	2 (0.3%)

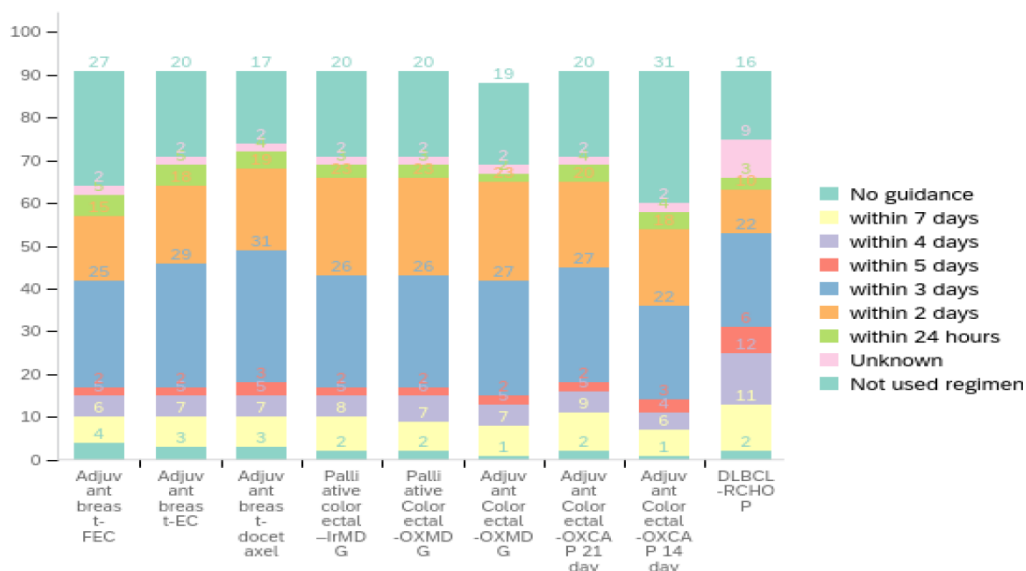Abbreviations ANC – absolute neutrophil count.

Here it can be seen where test 1 is taken 7 -4 days pre-chemotherapy and ANC>1 0.8% will have dropped below 1 when tested again within 72 hours of treatment. 18% of patients will have been understood not to be eligible at test 1 and retested.

Out of the five patients that dropped neutrophils late, three patients fell marginally short of the threshold of 1 X10^9 /L, but with neutrophils greater than 0.9X10^9 /L. These three patients had a record of receiving chemotherapy without delay or future delay. One further patient had a record of receiving treatment (EC) but subsequent cycles were not recorded.   The final patient, receiving FEC, received a dose reduction of 25% at cycle 2 and no further cycles were recorded in their treatment record.

Part 2: What is the Variation Nationally for regimens included?

A questionnaire was sent to BOPA and ACP members.

Total results from 91 participants. From these 88 completed the hospital they worked at. In total this data is from 77 independent hospitals. Where there were duplicate responses from the same hospital different cancer types were reported upon.

Acknowledgements

Appendix 9 – Steering Committee membership and affiliations

Academic membership	Dr Yogini Jani, Professor Li Wei and Professor Ian Wong. UCL School of Pharmacy
Clinical Membership	Dr Martin Forster. Medical Oncologist and Chemotherapy Lead. UCLH NHS Foundation Trust. Dr Emma Kipps. Medical oncologist. The Royal Marsden Hospital. Dr Jaimal Kothari. Haematologist. Oxford University Hospitals. Professor Nicola Stoner. Consultant Pharmacist. Oxford University Hospitals. Alkesh Patel. Lead Research Pharmacist, The Christie Hospital. Nick Duncan. Consultant Pharmacist. Birmingham University Hospitals.
Lay Members	Ms Edna Young Mr Raj Metha Ms Katie Ruane
Managerial membership	Dr Donna Chung – NCL Centre for Cancer Outcomes

Appendix 10 – Research Collaborations and fellowship support

In conducting this research work, I have personally learned a great deal and the experiences I have gained during this time will influence both my clinical and future academic roles. I feel privileged to have been awarded a doctoral research fellowship and have guided other clinical colleagues nationally to achieve their ambitions. Collaborations were formed during this PhD both with stakeholders directly involved and also by those that recognise my ambitions to improve cancer patient care.

Collaborations formed

The Cancer Medicines Outcomes Programme, Strathclyde University. This is a Scottish government funded study investigating linkages of chemotherapy data. In November 2017, I advised them on the data that was held in England and also presented at their workshop. The group paid for my travel and accommodation to attend the workshop.

The International Society of Oncology Pharmacist Practitioners (ISOPP). In 2019, I helped organise the ISOPP conference in London. I gave many delegates tours of our clinical sites from low-middle income countries and learnt about the challenges they face. I discussed my research in depth with many Canadian pharmacists and understood them to face similar challenges as the United Kingdom. I am still in touch with colleagues from Australia, Canada and Kenya and we hope to work together soon.

Pharmalliance – UCL, Monash and The University of North Carolina is a strategic partnership between three pharmacy schools. In 2019, I was able to present early findings from my research. Through this, I was contacted by investigators at Monash to learn more. We remain in touch and hope to collaborate in the future.

Professor Anita Wagner at Harvard University, USA was introduced to me via my mentor as a future collaborator. A site visit was planned to understand her research

and data in the US; however, this has been postponed. I meet with Anita monthly to discuss ways in which we can collaborate and have given an online seminar to her research group.

Dr Cecilia Vindrola is an anthropologist and was an embedded researcher at UCLH. We have to date collaborated on one successful manuscript, one unsuccessful cancer research UK grant and a manuscript on the global impact of COVID-19 that is being drafted. Working with Cecilia has enabled me to appreciate and understand qualitative research.

Chromadose study. This is an invention that enables point of care drug monitoring for chemotherapy. I am a named collaborator on the successful NIHR invention for improvement grant (£980,000), to develop this work.

Fellowship Support

In 2019, I developed a successful project for the Royal Marsden Partners PAN London fellowship scheme. The project was worth £55,000 and enabled a pharmacist to complete a 1-year pre-doctoral fellowship to understand depression and anxiety in patients receiving chemotherapy.

In 2019, I developed a further in-house UCLH fellowship to enable a pharmacist to work for 2 days a week in the research environment, undertaking a number of research activities.

In 2020, I was co-applicant to a research capacity and capability award at Newcastle Hospital NHS Foundation trust. This award allowed a pharmacist 30 days of paid research time to undertake a systematic review.