

Home Testing of Blood Counts in Patients with Cancer

Dr Elaine Dunwoodie

Submitted in accordance with requirements for the degree of
Doctor of Medicine

The University of Leeds, School of Medicine

July 2018

Intellectual Property and Publication Statements

The candidate confirms that the work submitted is her own, except where work which has formed part of jointly-authored publications has been included. The contributions of the candidate and the other authors to this work have been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Details of work from jointly-authored publications

1. Part of chapter 2 formed work in a jointly-authored publication.

Baker K and Dunwoodie E (joint first authors), Jones R, Newsham A, Johnson O, Price C, Wolstenholme J, Leal J, McGinley P, Twelves C, Hall G. Process mining routinely collected electronic health records to define real-life clinical pathways during chemotherapy. *International Journal of Medical Informatics*. 2017, 103, p.32-41.

Elaine Dunwoodie defined clinical parameters underlying the model, and worked with Karl Baker to develop and refine the model. Karl Baker translated the clinical definitions into C# language and developed software to support the model. There was methodological support and critical review of the manuscript in an advisory capacity from the remaining authors.

2. Part of chapter 4 formed work in a jointly-authored publication.

Pether S, Brothwood J, van Berkel C, Dunwoodie E, Blake R, Price C, Jones R, Baker K, Hall G. Comparative diagnostic performance of the granulocyte and neutrophil counts. *Practical Laboratory Medicine*. 2017, 9, p.45-52.

Elaine Dunwoodie identified clinical perspectives and definitions for the data extraction and statistical analysis, and included these in the manuscript preparation. Nicola Pether and Jess Brothwood analysed the data and drafted the manuscript. Karl Baker extracted and pseudonymised the data. Cees van Berkel provided statistical support. Rob Blake developed the research question and approved the manuscript. Chris Price developed the research question and provided critical review of the analysis and manuscript. Geoff Hall provided clinical perspectives and critical review of the manuscript.

This copy has been supplied on the understanding that it is copyright material and that no quotation from the thesis may be published without proper acknowledgement.

Acknowledgments

I would like to thank my supervisors, Dr Geoff Hall and Professor Chris Twelves. I have been very fortunate to work with them in the set up and during this project and I have valued their expertise and guidance throughout. The clinical research nurses, Suzanne Rogerson and Elizabeth Wright, also deserve a special mention for their work and support. In particular, Suzanne's contribution to data collection and running the profiling trial was invaluable. In addition, the data analyst Karl Baker was instrumental in the practical aspects of data extraction and handling.

This work came about through the enthusiasm and engagement of Professor Christopher Price, Dr Malcolm Luker and Dr Alison Sundset. They were all instrumental in developing the project prior to and during the stage where it was funded by Innovate UK (Technology Strategy Board) through a Small Business Research Initiative (SBRI) Grant. This was awarded to Philips Home Clinical Monitoring, which forwarded an unrestricted educational grant to the University of Leeds. The work was hosted by Leeds Teaching Hospitals NHS Trust.

There was support for this work on an advisory capacity from a number of other people from Leeds Teaching Hospitals NHS Trust, the University of Leeds, the University of Oxford, and Philips Home Clinical Monitoring.

I would also like to say a particular thank you to my family for their support during the past four years.

Abstract

Background: Neutropenia is a dose-limiting toxicity of chemotherapy administered to patients with cancer. Neutrophil counts are usually measured using venous samples on centralised analysers. The aim of this work was to explore the feasibility and potential of home neutrophil count monitoring during chemotherapy.

Methods: The prevalence of febrile neutropenia was defined in an unselected population using routine electronic health records of patients receiving chemotherapy for cancer. Patient and professional attitudes to home blood count monitoring were explored through questionnaires. Performance of the Hemocue WBC DIFF analyser in measuring capillary neutrophil counts was evaluated in the neutropenic range. Daily neutrophil counts were measured for the duration of a cycle of chemotherapy.

Results: Baseline pathways were quantified in a Markov model using data from 28,919 patients receiving chemotherapy for cancer. Ten percent of all cancer site and chemotherapy combinations had a prevalence of febrile neutropenia of >10% (highest prevalence was 66.7%).

The majority (86.9%) of patients surveyed would use home neutrophil count monitoring. Correlation of capillary Hemocue WBC DIFF measured neutrophil counts in the neutropenic range to venous ADVIA 2120 measured counts was $r = 0.867$, $y = 0.95x + 0.01$. The capillary neutrophil threshold $<1.1 \times 10^9/L$ performed best in identifying both patients at risk of febrile neutropenia and patients whose neutrophil count had not recovered prior to subsequent chemotherapy.

The 21 daily neutrophil count profiles recorded during chemotherapy were heterogeneous. Four out of 10 patients with a neutrophil nadir $<0.5 \times 10^9/L$ were admitted with febrile neutropenia. Four out of 21 patients had insufficient neutrophil count recovery by day 21 for subsequent chemotherapy.

Conclusion: Home neutrophil count monitoring during chemotherapy is feasible. Electronic health records can be utilised to quantify patient pathways. This work generated much evidence in support of adoption of home neutrophil count monitoring during chemotherapy, and informs future work defining the true potential.

Contents

Chapter 1 Introduction	1
1.1 Neutrophils	1
1.2 Neutropenic complications of chemotherapy.....	2
1.2.1 Febrile Neutropenia	3
1.2.2 Neutropenic sepsis.....	4
1.2.3 Incidence of febrile neutropenia.....	7
1.2.4 Consequences of febrile neutropenia.....	8
1.2.5 Interventions	9
1.3 Diagnostics.....	12
1.3.1 Point of care testing	12
1.3.2 The devices.....	19
1.4 The innovation.....	23
1.5 Objectives	25
Chapter 2 Characterising clinical pathways during chemotherapy to define the incidence of neutropenic complications.....	27
2.1 Introduction.....	27
2.2 Objectives	30
2.2.1 Primary objectives:.....	30
2.2.2 Secondary objectives:	30
2.3 Methods	30
2.3.1 Resources	30
2.3.2 Processes.....	32
2.3.3 Quantification of clinical pathways.....	37
2.3.4 Neutropenic complications and comparisons with previously published data	38
2.3.5 Approvals.....	39
2.4 Results	39
2.4.1 Defining clinical pathways as a Markov model	40
2.4.2 Quantification of clinical pathways.....	44
2.4.3 Comparison of neutropenic complications to published data.....	51
2.5 Discussion	54
2.5.1 Main Findings	54
2.5.2 Strengths & Weaknesses.....	56
2.5.3 Implications	58
2.5.4 Conclusion	60

5.2.2	Secondary objectives	112
5.3	Materials and Methods	113
5.3.1	Methods of neutrophil count measurement	113
5.3.2	Neutropenic range evaluation	114
5.3.3	Patient self-test evaluation	115
5.3.4	Statistical analysis	116
5.4	Results	117
5.4.1	Neutropenic range evaluation	117
5.4.2	Patient self-test evaluation	135
5.5	Discussion	141
5.5.1	Main findings.....	141
5.5.2	Strengths and weaknesses	144
5.5.3	Implications	145
5.5.4	Conclusion	146
Chapter 6 Profiling neutrophil counts during chemotherapy.....		148
6.1	Introduction.....	148
6.2	Objectives	152
6.2.1	Primary	152
6.2.2	Secondary.....	152
6.3	Methods	153
6.3.1	Patient population.....	153
6.3.2	Approvals and Funding.....	153
6.3.3	Procedures followed	154
6.3.4	Data analyses	156
6.4	Results	157
6.4.1	Descriptive.....	157
6.4.2	The profiles.....	159
6.5	Discussion	172
6.5.1	Main findings.....	172
6.5.2	Strengths and weaknesses	174
6.5.3	Implications	175
6.5.4	Conclusion	177
Chapter 7 Overall discussion.....		178
Appendices.....		185
Appendix 1 – Patient questionnaire		187
Appendix 2 – Consultant questionnaire		190

VIII

Appendix 3 – Tables of free-text comments from questionnaire respondents.....	193
Appendix 4 - Summary of the performance analysis of the Philips XBC blood count analyser.....	199
References.....	204

Abbreviations

5-FU	5-fluorouracil
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AP	alkaline phosphatase
APTT	activated partial thromboplastin time
ASCO	American Society Clinical Oncology
AUC	area under the curve
BEP	bleomycin, etoposide, cisplatin
BP	blood pressure
CAP	cyclophosphamide, doxorubicin, cisplatin
CAV	cyclophosphamide, doxorubicin, vincristine
CBC	complete blood count
CDS	Commissioning Data Sets
CE	Conformité Européene
CI	confidence interval
CMF	cyclophosphamide, methotrexate, fluorouracil
CNS	central nervous system
COSD	Cancer Outcomes and Services dataset
CRP	c-reactive protein
CSV	comma separated value
CTCAE	common toxicity criteria of adverse events
CTG	clinical trials group
CTRAB	Clinical Trials Research Approvals Board
CV	co-efficient of variation
CWT	cancer waiting times
DEC	Diagnostics Evidence Co-operative
DI	deviation index
DUKE2011	a neutropenic risk prediction tool
EC	epirubicin and cyclophosphamide
ECX	epirubicin, cisplatin, capecitabine
EDTA	ethylenediaminetetraacetic acid
EHRs	electronic health records
EORTC	European Organisation for Research and Treatment of Cancer
EOX	epirubicin, oxaliplatin, capecitabine
ESMO	European Society of Medical Oncology
EWS	Early Warning Score
FEC	fluorouracil, epirubicin, cyclophosphamide
FN	febrile neutropenia
FNR	false negative rate
FP	false positives
FPR	false positive rate
GCSF	granulocyte colony stimulating factor
GFR	glomerular filtration rate
GI	gastrointestinal

GP	general practitioner
GPRS	General Packet Radio Services
HDU	high dependency unit
HRGs	Healthcare Resource Groups
ICD	International Classification of Diseases
ICU	intensive care unit
IDSA	Infectious Diseases Society of America
INR	international normalised ratio
IV	intravenous
IVD	in vitro diagnostic
KTP	Knowledge Transfer Partnership
LCD	Local Care Direct
LLN	lower limit of normal
LTHT	Leeds Teaching Hospitals NHS Trust
MASCC	Multinational Association for Supportive Care in Cancer
Mdn	median
MDT	mutli-disciplinary team
MHRA	Medicines and Healthcare products Regulatory Agency
MIC	Medtech and In Vitro Diagnostics Co-operative
MRC	Medical Research Council
NCAG	National Chemotherapy Advisory Group
NCCN	National Comprehensive Cancer Network
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NCWTMD	National Cancer Waiting Times Monitoring Dataset
NEQAS	National External Quality Assessment Service
NETIMIS	Network Tools for Intelligent Simulation
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NPV	negative predictive value
NS	neutropenic sepsis
OR	odds ratio
OxMdG	oxaliplatin and infusional 5-fluorouracil
PAS	patient administration system
PEG	pegylated
PICC	peripherally inserted central catheter
POC	point of care
POCT	point of care team
PPM	Patient Pathway Manager
PPV	positive predictive value
QC	quality control
r	correlation co-efficient
R & D	Research & Development
r ²	co-efficient of determination
REC	Research Ethics Committee
RMSE	root mean square error
ROC	receiver operator characteristic

RR	risk ratio
RSE	residual standard error
SACT	systemic anti-cancer therapy
SBRI	Small Business Research Initiative
SD	standard deviation
SKUP	Scandinavian evaluation of laboratory equipment for primary health care
Sn	sensitivity
Sp	specificity
STARD	Standards for Reporting Diagnostic Accuracy
T10	top 10% risk
TN	true negatives
TP	true positives
UK	United Kingdom
US	United States of America
USB	universal serial bus
VAMP	vincristine, methotrexate, 6-mercaptopurine and prednisolone
WBC	white blood cell count
XBC	name of iteration of device prior to Minicare H-2000
XELOX	capecitabine, oxaliplatin
YI	Youden index

List of Figures

Figure 1: Neutrophil count diagnostic of neutropenia in “neutropenic sepsis” guidelines in use in England and Wales.	4
Figure 2: Example extract from a UK NEQAS performance report for a laboratory using automated differential leucocyte analysers.	16
Figure 3: Bulls eye visual demonstration of accuracy and precision.	18
Figure 4: Images of the three point of care devices with capabilities of measuring finger-prick white cell counts.	21
Figure 5: Overview of data entered into PPM.	31
Figure 6: The Markov state model at the end of iteration eight.	41
Figure 7: An example of the improved pathway Markov model of patient pathways during chemotherapy which captures 0 day and ≥ 1 day admissions.	42
Figure 8: Bar charts displaying demographics of patient questionnaire respondents.	68
Figure 9: Bar graph showing the scenario chosen by respondents in question 2 according to age group and gender.	71
Figure 10: Bar graph displaying the maximum risk of becoming seriously unwell that respondents would accept to reduce unnecessary trips to hospital.	72
Figure 11: Bar graph showing maximum risk of becoming dangerously unwell that.....	74
Figure 12: Bar graph showing grouped maximum risk of becoming dangerously unwell that respondents were willing to accept to avoid unnecessary trips to hospital, by duration of travel to Cancer Centre. Analysis by all categories of travel duration, $p = 0.750$. When split into travel duration < 60 mins or ≥ 60 mins, $p = 0.183$	75
Figure 13: Frequency of responses to question 1a asking if clinicians would be willing for their patients to measure their blood count at home when they feel unwell and require neutropenia to be excluded.	77
Figure 14: Percentage of responses to question 2a, which asked for the neutrophil threshold to recommend urgent clinical assessment when a patient on chemotherapy is at home, has a fever and is otherwise well.	79
Figure 15: Frequency of responses to question 2b, which asked the maximum risk of incorrectly advising a patient to stay at home, which the respondent considered acceptable.	80
Figure 16: Scatterplots showing the relationship of neutrophil and granulocyte counts.	94
Figure 17: Bland-Altman plots showing the agreement between neutrophil and granulocyte counts.	94
Figure 18: Line graph of frequency of isolated thrombocytopenia according to neutrophil thresholds.	100
Figure 19: Consort diagram of study participants and sets of blood samples with paired neutrophil counts available for analysis.	119
Figure 20: Scatter plot showing the relationship of venous ADVIA 2120 and venous Hemocue WBC DIFF neutrophil counts in the neutropenic range.	123

Figure 21: Agreement analysis between venous ADVIA 2120 and venous Hemocue WBC DIFF neutrophil counts in the neutropenic range.....	124
Figure 22: Scatter plot showing the relationship of venous Hemocue WBC DIFF and capillary Hemocue WBC DIFF neutrophil counts in the neutropenic range.	125
Figure 23: Agreement analysis between venous Hemocue and capillary Hemocue WBC DIFF neutrophil counts in the neutropenic range.....	126
Figure 24: Scatter plot showing the relationship of venous ADVIA 2120 and capillary Hemocue WBC DIFF neutrophil counts in the neutropenic range.	127
Figure 25: Agreement analysis between venous ADVIA and capillary Hemocue WBC DIFF neutrophil counts in the neutropenic range.	128
Figure 26: Receiver operator characteristic (ROC) curve evaluating the performance of capillary Hemocue WBC DIFF neutrophil count as a surrogate of venous ADVIA 2120 neutrophil count threshold of $<1.0 \times 10^9/L$	130
Figure 27: Receiver operator characteristic (ROC) curve evaluating the performance of capillary Hemocue WBC DIFF neutrophil count as a surrogate of venous ADVIA 2120 neutrophil count threshold of $<1.5 \times 10^9/L$	132
Figure 28: Consort diagram of study participants and sets of blood samples with paired neutrophil counts available for analysis.	137
Figure 29: Scatter plot showing the relationship of capillary nurse-obtained Hemocue WBC DIFF and capillary patient-obtained Hemocue WBC DIFF neutrophil counts.	139
Figure 30: Agreement analysis between capillary nurse-obtained and capillary patient-obtained Hemocue WBC DIFF neutrophil counts.	140
Figure 31: Line graph showing potential neutrophil count profiles during chemotherapy.	152
Figure 32: Neutrophil profiles of the patients who were admitted and treated for febrile neutropenia.....	160
Figure 33: Neutrophil profiles of the patients with a neutrophil nadir $<0.5 \times 10^9/L$ who were not admitted to hospital for febrile neutropenia.	161
Figure 34: Profiles of the neutrophil counts where the neutrophils had not recovered sufficiently for delivery of the subsequent cycle of chemotherapy.....	164
Figure 35: The six neutrophil profiles where the neutrophil count never fell below the threshold for delivery of the subsequent cycle of chemotherapy.....	165
Figure 36: The neutrophil profiles for epirubicin and cyclophosphamide chemotherapy regimen.	167
Figure 37: The neutrophil profiles for bleomycin, etoposide and cisplatin (BEP) chemotherapy regimens.....	168
Figure 38: The neutrophil profiles from patients by chemotherapy regimen received, excluding epirubicin and cyclophosphamide (EC) and bleomycin, etoposide and cisplatin (BEP).	170
Figure 39: Flow diagram of the unplanned patient-initiated telephone consultations during chemotherapy with the nurse practitioner manning the acute assessment line.	171

List of Tables

Table 1: Common Terminology Criteria for Adverse Events (CTCAE) neutropenia grades (17).....	3
Table 2: Definitions and evidence supporting the definitions of febrile neutropenia in published local, national and international guidelines.....	5
Table 3: Diagnostic criteria for sepsis.	6
Table 4: Tables explaining parameters used to describe the performance of a test.....	20
Table 5: Description of rules and methods used to define patient clinical characteristics.	33
Table 6: Description of rules and methods used to define health states within the pathway.	34
Table 7: Table of clinical descriptions of all the health states within the improved Markov model.	43
Table 8: Counts of the main pathways traversed for the first cycle of chemotherapy for epirubicin and cyclophosphamide (EC) and oxaliplatin and modified de Gramont (OxMdG).....	45
Table 9: Prevalence of health states by cycle of chemotherapy for epirubicin and cyclophosphamide (EC) and oxaliplatin and modified de Gramont (OxMdG).....	46
Table 10: The top 20 chemotherapy regimen and diagnosis site combinations ordered by patient number (largest to smallest).....	47
Table 11: The top 20 chemotherapy regimen and diagnosis site combinations ordered by number of chemotherapy cycles (largest to smallest).....	48
Table 12: The chemotherapy regimen and diagnosis site combinations with a high and intermediate risk of combined rate of febrile neutropenia and neutropenic sepsis.	49
Table 13: Table showing the breakdown of chemotherapy regimen and diagnosis site combinations which include either concomitant GCSF or targeted therapies or both.	50
Table 14: Table showing Leeds regimen and diagnosis site combination rates of febrile neutropenia and uncomplicated neutropenia in comparison to published figures.....	53
Table 15: Risk thresholds of becoming dangerously unwell used in the questionnaires.	65
Table 16: Demographics of patients who completed the questionnaires.	67
Table 17: Table showing the scenario chosen in question 2 according to the respondent's demographic information.....	70
Table 18: Comments associated with Question 1a regarding consultant attitudes towards patients measuring their own blood count at home when they feel unwell and neutropenia is required to be excluded.	76
Table 19: Frequency table combining neutrophil threshold chosen to recommend urgent clinical assessment in a patient who is at home, has a fever and is otherwise well, with the maximum risk of incorrectly advising a patient to stay at home.....	81

Table 20: The distribution of cell counts for (a) granulocytes and the 3-part differential counts, and for (b) neutropenic counts ($<2.0 \times 10^9/L$).	93
Table 21: Table showing classification of the validation dataset into CTCAE neutrophil grades using the equivalent granulocyte count.	96
Table 22: Classification of neutropenic results using various granulocyte count thresholds.	97
Table 23: Performance of absolute neutrophil count thresholds in identifying clinically significant thrombocytopenia (platelets $<10 \times 10^9/L$).	99
Table 24: Common Terminology Criteria for Adverse Events (CTCAE) neutropenia grades and equivalent granulocyte counts.	102
Table 25: Table displaying the accuracy of the Hemocue WBC DIFF analyser as reported by the manufacturer in the Operating Manual (200).	109
Table 26: Table displaying the precision of the Hemocue WBC DIFF analyser as reported by the manufacturer in the Operating Manual.	109
Table 27: Table summarising accuracy of the Hemocue WBC DIFF as available in published articles.	109
Table 28: Summary of published comparisons of capillary and venous sample white cells counts.	111
Table 29: Frequency table of reason patients who were screened did then not participate in the study.	118
Table 30: Characteristics of venous and capillary sample neutrophil measurements from the Siemens ADVIA 2120, and the Hemocue WBC DIFF.	120
Table 31: Table explaining the Hemocue WBC DIFF error codes which occurred during the analysis, and suggested actions to resolve them.	121
Table 32: Performance analysis of capillary Hemocue WBC DIFF neutrophil count thresholds as surrogate indicators of the venous ADVIA 2120 neutrophil count threshold of $1.0 \times 10^9/L$.	131
Table 33: Performance analysis of capillary Hemocue WBC DIFF neutrophil count thresholds as surrogate indicators of the venous ADVIA 2120	133
Table 34: Table showing within and between Hemocue WBC DIFF device co-efficient of variations (CV).	134
Table 35: Table summarising the time differences between collection and measurements of the 3 different samples.	138
Table 36: Table summarising the neutrophil results according to the sample and device used to measure the neutrophil count.	138
Table 37: Table showing correlation between the 3 blood sample neutrophil counts (nurse and patient finger-prick Hemocue samples and venous ADVIA 2120 samples).	139
Table 38: Table of chemotherapy parameters and frequency of regimens for which the neutrophil profiles were obtained.	158
Table 39: Table showing the proportion of each cycle the neutrophil count is $<0.5 \times 10^9/L$ and $<1.0 \times 10^9/L$ by chemotherapy regimen.	163

Chapter 1 Introduction

Chemotherapy is commonly given on its own or as part of multi-modality anti-cancer treatment in the curative and palliative settings. Administration is limited by toxicities, one of the most common of which is myelosuppression resulting in reduced haemoglobin, leukocytes and platelets. Leukopenia, and more specifically neutropenia, can be life-threatening when complicated by infection, and recovery needs to occur prior to safe delivery of subsequent chemotherapy cycles. This thesis explores the principle of home neutrophil count monitoring in patients during chemotherapy. It concentrates on the feasibility and potential of home blood count monitoring in the management of severe neutropenia and its complications, whilst acknowledging home blood count monitoring may have further reaching roles which are explored in the profiling trial described in the final chapter.

1.1 Neutrophils

Neutrophils are one of three types of white cells in circulating blood that are classified as granulocytes. Eosinophils and basophils constitute the remaining granulocytes, all of which are distinguished morphologically from other differential white cells by the presence of multi-lobular nuclei and granules in the cytoplasm. In a healthy individual, neutrophils are the most abundant white cell, forming 40 to 80% of the total white blood cell count (1). All types of granulocyte are involved in the immune defence against invading pathogenic organisms, with neutrophils performing the main anti-bacterial function through phagocytosis.

Neutrophils are present in three compartments; bone marrow, peripheral blood and intra-cellular. Within the bone marrow there are three stages of development;

- (i) committed multipotent haematopoietic stem cells, which differentiate into progenitor cells
- (ii) mitotic compartment consisting of promyelocytes, myelocytes and myeloblasts
- (iii) maturation compartment consisting of metamyelocytes, band and polymorphonuclear neutrophils.

The transit time is approximately six days through the bone marrow mitotic compartment and an additional six to nine days through the maturation compartment except in patients with infection where maturation can be as short as two days (2-5). The half-life of neutrophils in circulating blood is six to eight hours before sequestration into tissue for either cellular action

or death. It can be informative to analyse the type of neutrophils in the circulating blood as immature neutrophils such as bands are increased (often referred to as a shift to the left) in association with acute infections and inflammation (6). An increase in mean neutrophil lobe count (shift to the right) can be associated with vitamin B12 or folic acid deficiency, congenital hypersegmentation of neutrophils or renal disease (7). Within the circulating blood, neutrophils are divided approximately evenly between circulating and marginated pools, the latter being neutrophils that are adhered to the vascular endothelium (8). They move from the marginated to circulating pool in scenarios such as sepsis, high dose steroid use and immediately after vigorous exercise (9). In contrast, use of granulocyte colony stimulating factor increases the mitotic pool of granulocytes in bone marrow and decreases the maturation department transit time (10), but does not promote demargination.

Circulating neutrophils are activated by soluble chemotactic factors produced by bacteria themselves, interaction of bacteria with other blood components e.g. antibodies and complement system and interaction of bacteria with the host cells (1). Chemotactic factors such as platelet-activating factor and leukotrienes bind receptors on neutrophils and this receptor-ligand interaction activates neutrophils in seconds. The first response is that the neutrophils adhere to the vascular endothelial cells near the site of bacterial invasion, a process facilitated by cytokine-mediated presentation of adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1). Once adhered, neutrophils follow a further gradient of chemotactic factors which guide them through the vascular endothelium. This involves binding of molecules such as cleavage product component (C5a), leukotriene B4 and platelet-activating factor to specific neutrophil membrane receptors. Neutrophils may then move beneath the vascular endothelium until they can pass through the basement membrane into the adjacent connective tissue. The passage through the vessel wall tends to be irreversible (11, 12), but moves the activated neutrophils to the proximity of the invading organism, facilitating destruction through phagocytosis and release of anti-bacterial granules into the phagocytic vesicle. The process from neutrophil activation to reaching the site of invading bacteria takes approximately thirty minutes (13).

1.2 Neutropenic complications of chemotherapy

Within the bone marrow, chemotherapy initiates apoptosis largely of the haematopoietic progenitor cells in the bone marrow (14, 15). After standard 3 or 4-weekly chemotherapy administration, patients are expected to become neutropenic at days 7 to 10, with the nadir at days 10 to 14, when the previously affected progenitor cells would otherwise have matured

and entered the circulation. Neutropenic toxicities of chemotherapy include asymptomatic neutropenia, febrile neutropenia and neutropenic sepsis. The grade and duration of neutropenia is directly proportional to the risk of infective bacterial complications (16), albeit that the evidence for quantitative relationship between differential white cell counts and the risk of infective consequences is now quite dated.

By definition, neutropenia is an absolute neutrophil count less than the lower limit of the specified “normal” range on the reference analyser. At Leeds Teaching Hospitals NHS Trust the neutrophil lower limit of normal is $2.0 \times 10^9/L$. Neutropenia is categorised into grades 0 to 4 (Table 1) in the Common Terminology Criteria for Adverse Events (CTCAE) (17).

Version	Adverse Event	Grade				
		0	1	2	3	4
4.0	Neutrophil count decreased	Within normal limits	< LLN to $1.5 \times 10^9/L$	<1.5 to $1.0 \times 10^9/L$	<1.0 to $0.5 \times 10^9/L$	<0.5 $\times 10^9/L$
		Definition: A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen				

Table 1: Common Terminology Criteria for Adverse Events (CTCAE) neutropenia grades (17). LLN – lower limit of normal.

1.2.1 Febrile Neutropenia

Febrile neutropenia is neutropenia in the presence of a fever. Neutropenic sepsis is neutropenia with systemic signs of infection (see 1.2.2). However, in clinical practice, the terms febrile neutropenia and neutropenic sepsis tend to be used interchangeably. For the purposes of clarity in this thesis, they are defined separately, but referred to as “febrile neutropenia or worse” when incorporated together in one group.

The National Institute for Health and Care Excellence (NICE) carried out a survey of definitions of febrile neutropenia in use across all acute trusts in England and Wales (Figure 1). Eighty valid questionnaires were returned from 51 centres. Some centres had separate policies for specific patient groups. The majority used a neutrophil count threshold of $\leq 1.0 \times 10^9/L$ in conjunction with a fever to be diagnostic of complicated neutropenia requiring change in management. However, the consensus neutrophil count threshold below which patients with

fever or suspected infection warrant management with antibiotics in published guidelines is $0.5 \times 10^9/L$. This has not changed since early guidelines published in 1994 (18).

Table 2 summarises the definitions of febrile neutropenia and evidence supporting these in published guidelines. Four of these guidelines qualify the use of neutrophil count $<0.5 \times 10^9/L$ as the threshold to change management by also including “predicted or expected” to fall to $<0.5 \times 10^9/L$ within a certain timeframe. In a patient presenting acutely, clinical management decisions frequently need to be made without a trend in neutrophil counts, but based on a single reading, so this is the likely explanation for the threshold of $<1.0 \times 10^9/L$ neutrophil count being used in NHS Trusts in England and Wales.

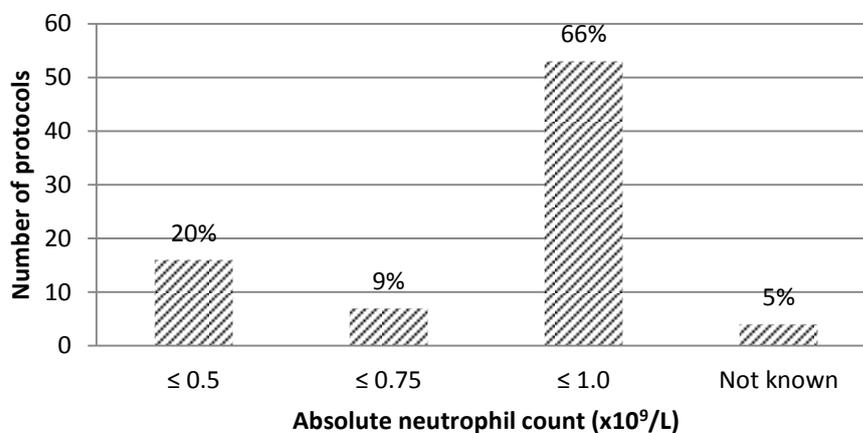


Figure 1: Neutrophil count diagnostic of neutropenia in “neutropenic sepsis” guidelines in use in England and Wales.

n = 80, reproduced from NICE Neutropenic Sepsis Clinical Guidelines (19).

1.2.2 Neutropenic sepsis

Neutropenic sepsis is neutropenia in the presence of systemic manifestations of infection.

Table 3 lists some of the diagnostic criteria for sepsis endorsed by the “Surviving Sepsis Campaign” (20, 21). However, some of the parameters listed in

Table 3 could be present in patients with cancer on chemotherapy in the absence of sepsis, such as significant oedema, elevated C-reactive protein and thrombocytopenia. Therefore this has to be interpreted with caution and each parameter considered in relation to an individual patient’s baseline and clinical context. It should also be noted that much of the evidence around neutropenic sepsis pre-dates this sepsis guideline, and so should be evaluated with that in mind.

Guidelines (Year of publication)	ANC (x10 ⁹ /L)	Temperature	Evidence informing ANC threshold
MASCC Scoring System (2000) (22)	<0.5	1 x >38°C	Link not made to evidence. Introduction cites 1 publication which refers to granulocyte count and risk of infection (number of patients = 52) (16).
CTCAE version 4.03 (2009) (17)	<1.0	1 x >38.3°C or ≥38°C sustained over 1 hour	Evidence not discussed.
ESMO (2010) (23)	≤0.5 or expected to fall below 0.5	1 x >38.5°C or 2 x >38°C for 2 hours	Link not made to evidence or indication of level of evidence to inform decision values.
EORTC (2011) (24)	<0.5 or <1.0 and predicted to fall below 0.5 within 48 hours	Fever No specific temperature specified	Referenced a definition in which the link is not made to evidence (25). Studies included in analysis not limited to a specific definition of neutropenia.
IDSA (2011) (26)	<0.5 or expected to decrease to <0.5 during the next 48 hours	1 x ≥38.3°C (101°F) or ≥38°C sustained over 1 hour	Link not made to evidence, but introduction cites 2 studies showing ANC <0.1 x10 ⁹ /L and prolonged neutropenia increases risk of bacteraemia (number of patients = 52 and 403) (16, 27).
NICE (2012) (19)	≤0.5	1 x >38°C	Carried out own systematic review, reported within guideline, included 11 eligible studies, found quality of evidence to be low.
NCCN (2012) (28)	<0.5 or <1.0 and a predicted decline to ≤0.5 over the next 48 hours	1 x ≥38.3°C or ≥38.0°C over 1 hour	Link not made to evidence but described as based on low-level evidence and uniform NCCN consensus. Introduction cites 2 studies showing decrease in neutrophils leads to increased infections (16, 29).
ASCO (2013) (30)	<1.0 (severe <0.5, profound <0.1)	≥38.3°C	Link not made to evidence. Recommendations refer to 2 studies from >35 years ago (number of patients = 52 and 494) (16, 31).
LTHT (2014) Guidelines for the management of suspected neutropenic sepsis	≤0.5	1 x >38.5°C or >38°C for ≥1 hour or 2 x >38°C in 12 hours	Local expert consensus indicating either no guidance found or wide disagreement in expert consensus.

Table 2: Definitions and evidence supporting the definitions of febrile neutropenia in published local, national and international guidelines.

ANC, Absolute neutrophil count; MASCC, Multinational Association for Supportive care in Cancer; NICE, National Institute for Health and Care Excellence; ESMO, European Society of Medical Oncology; ASCO, American Society Clinical Oncology; EORTC, European Organisation for Research and Treatment of Cancer; LTHT, Leeds Teaching Hospitals NHS Trust; NCCN, National Comprehensive Cancer Network; IDSA, Infectious Diseases Society of America; CTCAE, Common toxicity criteria of adverse events.

Infection, documented or suspected, and some of the following:
<p>General variables</p> <p>Fever (>38.3°C)</p> <p>Hypothermia (<36°C)</p> <p>Heart rate >90 /min</p> <p>Tachypnoea</p> <p>Altered mental status</p> <p>Significant oedema or positive fluid balance (>20mL/kg over 24 hours)</p> <p>Hyperglycaemia (plasma glucose >7.7mmol/L) in the absence of diabetes</p>
<p>Inflammatory variables</p> <p>Elevated CRP</p> <p>Elevated procalcitonin</p>
<p>Haemodynamic variables</p> <p>Hypotension (systolic BP <90mmHg or systolic BP decrease >40mmHg)</p> <p>Organ dysfunction variables</p> <p>Arterial hypoxaemia</p> <p>Oliguria (urine output <0.5mL/kg/hour)</p> <p>Creatinine increase (>44.2µmol/L)</p> <p>Coagulation abnormalities (INR>1.5 or APTT >60 seconds)</p> <p>Ileus</p> <p>Thrombocytopenia (platelet count <100 x10⁹/µL)</p> <p>Hyperbilirubinaemia (plasma total bilirubin >70µmol/L)</p>
<p>Tissue perfusion variables</p> <p>Raised lactate (>1mmol/L)</p> <p>Decreased capillary refill or mottling</p>

Table 3: Diagnostic criteria for sepsis.

WBC, white blood cell. CRP, C-reactive protein. BP, blood pressure. INR, international normalised ratio. APTT, activated partial thromboplastin time. Adapted from Levy et al., 2001 (20).

1.2.3 Incidence of febrile neutropenia

The incidence rates of all cancers combined are projected to increase by 2% in the United Kingdom between 2014 and 2035, to 742 cases per 100,000 people by 2035 (32), with the number of patients living with and beyond cancer also increasing. Despite the recent advances in the use of targeted and immunotherapies (33, 34), chemotherapy is likely to remain the backbone of systemic treatment for most patients with cancer, and thus the absolute number of patients experiencing neutropenic complications is expected to increase. The risk of febrile neutropenia after chemotherapy has been categorised into low (<10%), medium (10-20%) and high (>20%) according to primary cancer site and chemotherapy regimen received (24). In addition, uncomplicated neutropenia following certain targeted therapies has been described as >10%, but the risk of febrile neutropenia is <10% (35). However, the reported incidence of febrile neutropenia after common chemotherapy regimens varies considerably between randomised controlled trials; trial patient cohorts usually do not reflect the more unselected patients of routine practice who may be at greater risk of febrile neutropenia and other toxicities. Certainly uncomplicated neutropenia as a toxicity of chemotherapy is under-estimated, because routine blood counts during chemotherapy cycles are done more often in trials than in routine clinical practice (36).

Individual patient characteristics increase the risk of febrile neutropenia including prior chemotherapy, age >65 years, co-morbidities, low estimated glomerular filtration rate, low baseline white cell count, low haemoglobin level, elevated bilirubin, elevated alkaline phosphatase and elevated transaminases (37-43). For example, in a study including patients with solid tumours or lymphoma, where a predictive model was trained on a derivation cohort (n=2425 patients) and validated on a different cohort (n=1213 patients), multivariate analysis showed an elevated bilirubin at the start of cycle 1 chemotherapy to increase the odds ratio for either uncomplicated severe neutropenia (neutrophil count $<0.5 \times 10^9/L$) or febrile neutropenia to 2.152 (95% confidence interval (CI) was 1.235-3.747, $p=0.007$) (37). The risk of febrile neutropenia is greatest within the first cycle of chemotherapy as patients generally receive the full dose intensity of chemotherapy (44), usually without prophylactic measures such as granulocyte colony stimulating factor (37, 43, 45). There are assessment models for predicting risk of infective neutropenic complications (37, 46), but these were developed on data from the United States and are currently not embedded within routine clinical practice in the United Kingdom. There is, therefore, a need to collect comprehensive, country-specific, clinical data on the incidence of neutropenia and neutropenic complications in routine clinical

practice, thus minimising the potential for bias with a view to optimising treatment and maintaining patient safety.

1.2.4 Consequences of febrile neutropenia

Infective neutropenic complications are associated with reduced quality of life, and increased morbidity, mortality and cost (47). In a robust study of 41,779 patients who were admitted with chemotherapy-induced febrile neutropenia across 115 US medical centres between 1995 and 2000, the mean duration of admission was 11.5 days, median duration was 6 days, with 35% of patients admitted for ≥ 10 days (47). However, there were outliers with prolonged admissions, and the 35% of hospitalisations for ≥ 10 days accounted for 74% of overall hospital days. In addition, this study included patients with haematological malignancies and since the data were collected, there has been a trend towards using risk stratification to down-scale antibiotics early in low-risk patients (22), and may facilitate earlier discharge. Moreover, it was carried out in the US medical system where care is often paid for through insurance schemes, which have the potential to prolong duration of admission (48). However, the duration of admission for chemotherapy-induced febrile neutropenia from an audit of care in the NHS at the South West London Chemotherapy Network in 2006 was comparable (49). It included a considerably smaller number of patients, but 64 patients were admitted 71 times over a 4 month period, with the median admission duration being 5 days, the mean 9 days and the range 1-60 days. Again, the data distribution is not normal, as with the US data.

In the absence of preventive measures, between 48 and 60% of febrile neutropenic patients have an established or occult infection, and around 16 to 20% of patients with neutrophil counts less than $0.1 \times 10^9/L$ have bacteraemia (16, 29, 50). Consequently, neutropenic sepsis can be life-threatening, with studies showing inpatient mortality rates of 4.2% to 12.5% (49, 51, 52). Individual patient risk factors should be considered with respect to risk of death for patients admitted with neutropenic sepsis. For example, mortality has been reported in relation to the number of co-morbidities; in a trial of adult patients with a range of tumour types and chemotherapy regimens who were admitted to hospital in the United states with febrile neutropenia ($n=41,779$), having no co-morbidities was associated with 2.6% risk of death, 1 co-morbidity was associated with 10.3% risk of death and >1 co-morbidity was associated with 21.4% risk of death (47).

1.2.5 Interventions

In addition to reducing mortality, prevention of febrile neutropenia reduces hospital admissions and associated costs, antibiotic usage and dose reductions or delays in subsequent chemotherapy cycles, which are associated with worse cancer outcomes (53-59). Where phase III trials show chemotherapy as the best available treatment for a cancer, particularly in the curative setting, it may be desirable to consider prevention of complicated neutropenia in order to maintain dose intensity and/or density (59). Historically, two approaches have been used to prevent febrile neutropenia; prophylactic granulocyte colony stimulating factor and prophylactic antibiotics. Both are briefly discussed below.

1.2.5.1 Prophylactic granulocyte colony stimulating factor

Granulocyte colony stimulating factor is an endogenous cytokine produced by monocytes, fibroblasts and endothelial cells, which stimulates the production, maturation and activation of granulocytes (neutrophils, basophils, eosinophils). Filgrastim is the generic drug name of a synthetic analogue of granulocyte colony stimulating factor which can be administered subcutaneously or intravenously. Another preparation of filgrastim has polyethylene glycol (PEG) attached and is known as PEG filgrastim. The polyethylene glycol attachment slows degradation and elimination of filgrastim from the body, hence enabling a single injection compared to the recommended single dose of 5 consecutive days for unpegylated filgrastim.

Much work has been done evaluating the effectiveness of primary and secondary prophylactic granulocyte colony stimulating factor in the setting of chemotherapy-induced neutropenia. The majority of this supports the use of filgrastim to decrease the severity and duration of neutropenia (60-64). Current guidelines recommend primary prophylactic use of GCSF when the risk of febrile neutropenia is approximately 20% or higher. These recommendations are based largely on two phase III clinical trials (65, 66) and a systematic review of primary prophylaxis (67):

1. The Vogel et al. trial reported administration of primary prophylactic PEG-filgrastim at 6mg subcutaneously on day 2 following docetaxel chemotherapy at 100mg/m² for breast cancer as superior to placebo at preventing febrile neutropenia (1% versus 17%, p<0.001), febrile neutropenia-related hospitalisation (1% versus 14%, p<0.001), and intravenous antibiotic use (2% versus 10%, p<0.001) (65). The methodology was strong with a large sample size (n=920), multi-centre recruitment and it was placebo controlled. However, the definition of febrile neutropenia had stricter boundaries than used in current practice

(it used temperature $>38.2^{\circ}\text{C}$ and neutrophil count $<0.5 \times 10^9/\text{L}$), meaning it may have underestimated the benefits, and although it recorded some patient factors, it did not include co-morbidity, a characteristic previously linked to poor outcome (47).

2. In the Timmer-Bonte et al. trial (66), primary prophylactic granulocyte colony stimulating factor administered along with prophylactic antibiotics was found to be superior to prophylactic antibiotics alone at preventing febrile neutropenia in cycle one of cyclophosphamide, doxorubicin and etoposide for patients with small-cell lung cancer (incidence of febrile neutropenia was 10% versus 24%, $p=0.01$). There were 175 patients randomised in this trial, where the primary outcome measure was difference between the 2 arms in proportion of patients with febrile neutropenia in the first cycle of chemotherapy. Exploratory analyses of length of febrile neutropenia, length of hospital admission for febrile neutropenia, or death secondary to infection (cycle 1, death secondary to infection was 2% (antibiotic + GCSF arm) versus 5% (antibiotic only arm), $p = 0.37$) found the difference between the arms to be not statistically significant.
3. In the systematic review, granulocyte colony stimulating factor was effective at reducing incidence of febrile neutropenia compared to the controls receiving placebo or no prophylactic therapy (relative reduction = 0.54, 95% CI 0.43-0.67, $p<0.001$), infection-related mortality (relative reduction = 0.55, 95% CI 0.33-0.90, $p=0.018$) and all-cause mortality (relative reduction = 0.60, 95% CI 0.43-0.83, $p=0.002$), independent of age, secondary GSCF prophylaxis and antibiotic prophylaxis. Seventeen randomised controlled trials were analysed, but only 15 of these (including the two randomised controlled trials mentioned above), totalling 3182 patients, reported febrile neutropenia as an outcome. Strengths include robust methodology as the strategy recommended by Cochrane Collaboration was followed and studies ($n=3$) were permitted where both the experimental and control arms received prophylactic antibiotics. The analysis did not, however, include patients receiving dose-dense chemotherapy regimens, and only one study used PEG filgrastim whereas the others used filgrastim.

As with all treatment, the advantages should be offset against the disadvantages. With filgrastim these are most commonly reported as bone pain (35% PEG-filgrastim, 36% filgrastim) (68), which sometimes requires opiate analgesia, and drug costs including administration (65, 69, 70). In 1998, Lyman et al. reported a risk of 20-25% of febrile neutropenia to justify the cost of prophylactic granulocyte colony stimulating factor (69, 70).

However, a more recent study in 2006 found that the addition of granulocyte colony stimulating factor to prophylactic antibiotics, was only cost saving if the probability of febrile neutropenia was greater than 84%, the cost of granulocyte colony stimulating factor was less than €469 per patient, and the cost of an episode of febrile neutropenia was greater than Euro(€)11,552 (70). Given that the mean cost of an episode of febrile neutropenia in this trial was €3,300, it would seem likely that most patients would not qualify to receive prophylactic granulocyte colony stimulating factor. Moreover, a study conducted in the United States only two years earlier reported a mean cost of an episode of febrile neutropenia of US\$12,302 (71). Both trials used robust methods of cost calculation and adjusted the cost to year-specific price levels. The main difference in costs was for hospitalisation. For example, antibiotics cost less in the Netherlands, there was more frequent use of intensive care in the US, and definitions of febrile neutropenia varied. These differences highlight the need for country and population-specific economic analyses, in order to inform routine practice, in which primary prophylactic granulocyte colony stimulating factor is not currently embedded as standard.

1.2.5.2 Prophylactic antibiotics

Much work has also been done evaluating prophylactic antibiotic use. There was a meta-analysis in 2006 with 3440 patients (72), including a large randomised controlled trial of 1565 patients of whom 72.3% had a diagnosis of breast, testis or lung cancer (73). The meta-analysis concluded that prophylactic fluoroquinolone antibiotics reduced all-cause mortality during the first cycle of chemotherapy in patients with solid tumours or lymphomas (patients receiving prophylactic antibiotics versus either placebo or not antibiotics, relative risk 0.51, 95% CI 0.27-0.97) (72). Given concerns regarding the use of prophylactic antibiotics in patients on chemotherapy such as selection of resistant strains of bacteria and the use of quinolones resulting in a resurgence of Gram positive bacteraemia, Cullen et al. addressed the issue of selective application of prophylactic quinolones to prevent fever and hospitalisation from infection amongst patients with a range of characteristics, including diagnoses of breast, testis and small cell lung cancer (74). They found antibiotic prophylaxis to be most effective during the first cycle of chemotherapy, during subsequent cycles after an episode of fever, and they reported the efficacy to be consistent across age, gender, performance status, treatment context and disease type.

Cochrane published a systematic review on antibiotic prophylaxis during chemotherapy in 2012 (75). The relative risk reductions in main endpoints were quite persuasive; antibiotic prophylaxis significantly reduced the risk of death from all causes (risk ratio (RR) 0.66, 95% CI

0.55 to 0.79), the risk of infection-related death (RR 0.61, 95% CI 0.48 to 0.77), the occurrence of fever (RR 0.80, 95% CI 0.74 to 0.87), clinically documented infection (RR 0.65, 95%CI 0.56 to 0.76) and microbiologically documented infection (RR 0.51, 95% CI 0.42 to 0.62). This included a large number of patients (13,579), but 70 out of the 109 studies included only patients with haematological malignancies and only 13 studies comprised >80% patients with solid tumours, making the conclusions from this more applicable to haematological practice than solid tumour oncology. Other anomalies are that 22 studies were included that started antibiotic prophylaxis when the patient became neutropenic rather than at initiation of chemotherapy; the majority of studies did not report antibiotic compliance and in many the follow-up was too short to assess bacterial resistance. This review has not resolved the subjectivity reflected in international guidelines, recommending quinolone prophylaxis for intermediate and high risk patients with solid tumours determined by the expected extent and duration of neutropenia (19, 26, 28, 30). Despite this, use of primary prophylactic antibiotics is not common practice in the United Kingdom for low or intermediate risk chemotherapies. This may be because of the changing landscape brought about by initiatives such as use of the MASCC score to identify patients at low risk of complications of febrile neutropenia (22). This presented the opportunity to select patients for novel pathways, such as early downscaling of intravenous antibiotics to oral and subsequently earlier discharge, thus reducing the burden and therefore opportunity costs of febrile neutropenia. There are other methods with potential to be used to select patients according to their risk of neutropenic complications, including use of diagnostics to monitor neutrophils at different stages of a chemotherapy cycle.

1.3 Diagnostics

Diagnostics are defined as instruments or techniques used in medical diagnosis. Diagnostics are used routinely in medical practice, for example, blood test measurement in the laboratory, X-rays, blood pressure measurement, temperature measurement. The key aspect when considering diagnostic tests is to establish whether the patient is likely to benefit from the test and whether the potential of the benefits out-weigh the associated risks.

1.3.1 Point of care testing

Point of care testing refers to diagnostics carried out at or near the patient. It is sometimes known as “near patient testing”. It is in contrast, for example, to a routine venous laboratory

blood sample, where the tube of blood is transported to the laboratory analyser, and is not measured at the time or place of the patient. The benefit of point of care testing is assumed to be convenience of bringing the test to the patient, often with expedition of speed of the result in comparison to traditional methods. The “point of care” test may be by a professional within a primary or secondary care environment, but to maximise benefit to the patient, it may be in their home, or even a self-test in their home. The challenge is delivering the quality of measurement in a cost effective manner that does not result in inferior care for the patient in comparison to standard practice.

A successful example of using in vitro device testing at the point of care has been the introduction of self-management of International Normalised Ratio (INR) in patients on warfarin in reducing further thrombotic events (76). This has gone a step further than many point of care testing devices in use, by being proven to be effective in the hands of patients, thus making “point of care” the patient’s home rather than an NHS care provider.

Desktop laboratory haematology analysers can be used in oncology departments, but these still require operation by a professional and therefore do not negate the need for the patient to travel to hospital. A major burden and limiting factor in measuring blood counts in patients on chemotherapy is that usually the patient is required to visit a hospital or their local general practitioner’s surgery. Patient-led home blood count monitoring may be possible using patient-obtained capillary samples and this has the potential to improve clinical pathways by reducing patient journeys to hospital. It is currently common practice to routinely measure capillary blood counts in neonates, but not adults. Another advantage of testing capillary samples in adult patients on chemotherapy is that it requires a smaller volume of blood than venous samples and is less invasive in patients who require preservation of veins for the delivery of chemotherapy and frequent blood tests.

1.3.1.1 Evaluation of point of care testing

The evaluation of diagnostics has historically been given less attention than, for example, pharmaceutical interventions (77). This may be in part because pharmaceutical interventions often have a more direct impact on patient outcome, whereas the link to outcome with medical tests depends on how the result is used to guide clinical management. Therefore, evaluation of diagnostics should include;

- Analytical performance: a measure of how reliably results correspond to the true value.

- Clinical performance: a measure of whether the diagnostic distinguishes disease from the non-diseased state.
- Clinical effectiveness: a measure of whether the diagnostic guides management better than not relying on that test (includes costs to the patient and service provider).

As such, evaluation of diagnostics is complex and may require a multi-disciplinary approach. In the context of using an in vitro-diagnostic device to measure neutrophil counts, this requires involvement from haematology laboratory professionals and clinicians.

There are national and international guidelines and standards to ensure that point of care testing is conducted to high standards and minimises risk to patients (78-81). These provide a framework for local arrangements for point of care haematology tests within NHS hospitals, and are prescriptive regarding requirements for point of care tests to be comparable to those of local reference laboratory analysers, including how flagged results should be managed.

The gold standard for testing white cell differential counts is manual counting (82). However, this method of differential counting is not feasible in a time frame required in acute hospitals such as in Leeds Teaching Hospitals NHS Trust, due to the number of tests being done and the fact that white cells degrade in vitro. Moreover, manual counting is unlikely to be precise in the extreme neutropenic range as the number of white cells can be insufficient to reach the minimum required to standardise the count (83). Therefore it has been suggested that flow cytometry using monoclonal antibodies may be a more suitable reference for neutropenic samples (84).

Leeds Teaching Hospitals NHS Trust haematology laboratories currently use the Siemens ADVIA 2120 automated haematology cell counter to measure total blood counts. There are four of these machines within the St James's site haematology laboratory alone. These are subject to both internal and external quality assurance processes. The internal processes involve daily quality control checks using samples bought from the manufacturer with three levels of control covering the normal and both extremes of range. The values are set by the manufacturer and +/- 10% of the value is indicated as acceptable performance. The external process uses the UK National External Quality Assessment Service (NEQAS), which is an independent service aiming to ensure the optimal quality in testing for the benefit of patients. This distributes commercially-prepared whole blood samples to registered laboratories to be tested on analysers, and performance across the country is independently compared and statistical calculations applied. The performance is reported in comparison to the mean of the

anonymised analysers in all other registered laboratories across the UK. The limits of acceptance for neutrophil counts are ± 2 standard deviation (SD) indices from the overall mean count, which is a measure of how close an individual laboratory analyser performed in relation to the mean value. Leeds Teaching Hospitals NHS Trust haematology laboratories receive and test a full blood count sample that includes total white cell count every month, and they receive a sample for differential white cell count testing including neutrophils every other month. The reference neutrophil value of the sample varies from neutropenic, through the normal range to neutrophilic. Figure 2 shows an example NEQAS performance report for a laboratory measuring neutrophil counts.

For all analyses in this thesis, the neutrophil count from the Siemens ADVIA 2120 automated analysers used by Leeds Teaching Hospitals NHS Trust were taken as the reference counts. This is because the overarching important clinical question is regarding whether a point of care white cell differential analyser can be safely used in place of the current standard of care laboratory generated results. Published independent performance analyses of the ADVIA 2120 in comparison to both manual counting and flow cytometry indicate high accuracy and precision, with the warning of imprecision in cell counts with low numbers. In a study of 106 patients with a neutrophil count $<2.0 \times 10^9/L$, the correlation of the ADVIA 2120 with flow cytometry reference counts reported the correlation as $r^2=0.968$, $y=0.99x + 0.02$, and the precision was reported as co-efficient of variation (CV) 5.7% (85). In another study where the neutrophil count was measured in 593 venous blood samples across the full range of neutrophil counts by both manual counting and on the automated ADVIA 2120, r was 0.948, with the line of best fit being $y = 0.90x + 0.73$ (86). Given the Leeds Teaching Hospitals NHS Trust ADVIA 2120 machines report within 10% of the reference value in internal quality control procedures, this is the limit of error around what is used as the reference value in the forthcoming performance analyses.

1.3.1.1.1 Relevant statistical terms

There are a number of statistical terms or methods that are of paramount importance in analysing and discussing the performance of point of care devices in measuring neutrophil counts in comparison to the laboratory automated ADVIA 2120 neutrophil counts. These are:

(i) Accuracy

Defined as deviation of measurements from the standard or true value, and tends to be expressed as;

- Correlation – degree of association between two variables.

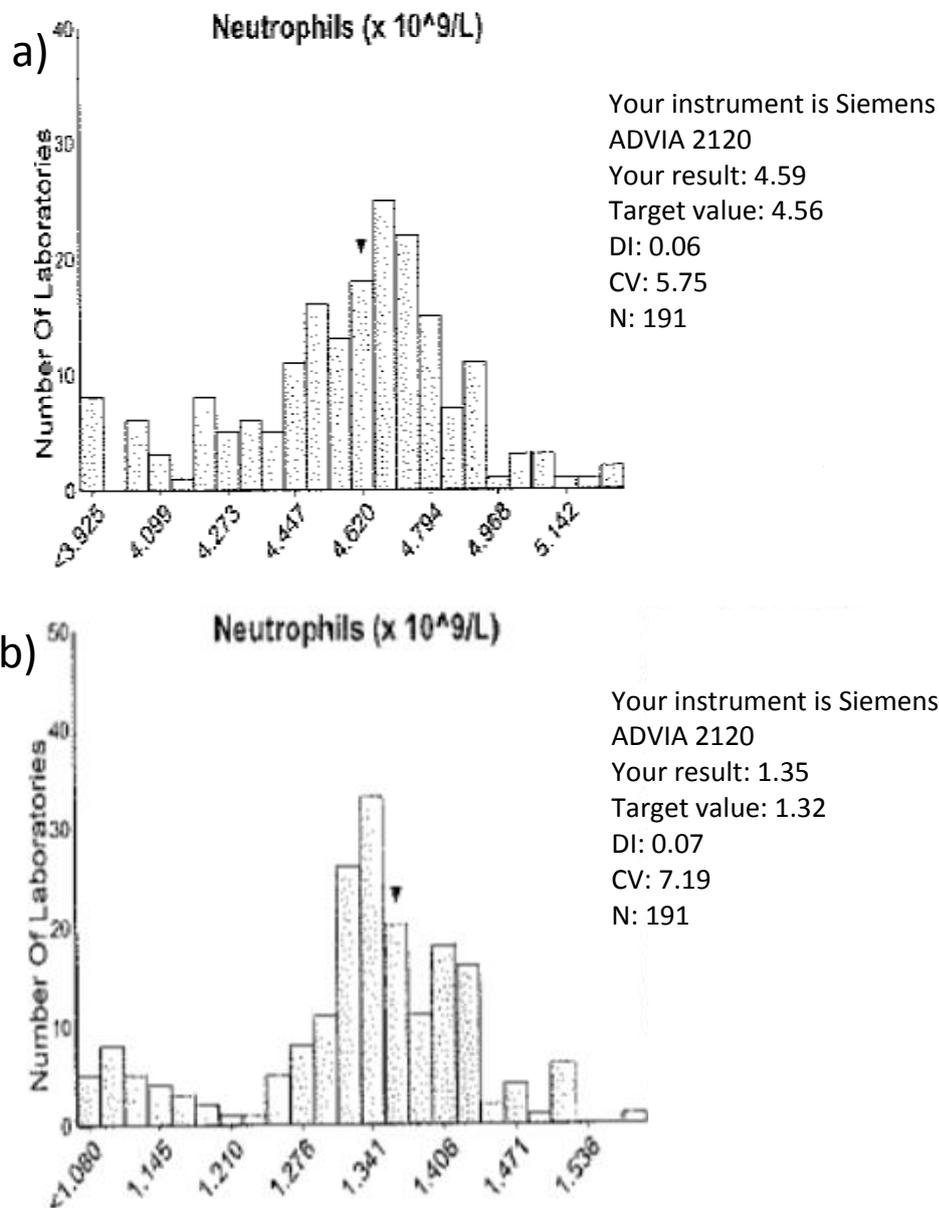


Figure 2: Example extract from a UK NEQAS performance report for a laboratory using automated differential leucocyte analysers.

This is reproduced from a paper copy of a monthly report of the performance of one of the Leeds Teaching Hospitals NHS Trust, Siemens ADVIA 2120 analysers, with permission from Leeds Teaching Hospital NHS Trust pathology department. This shows the performance of the neutrophil counts only, on 2 different test samples; a) target neutrophil count within “normal” range, and b) target neutrophil count within neutropenic range. DI, deviation index. CV, coefficient of variation (%). The performance score is also plotted on a distribution graph, comparing to all other participating laboratories.

- Correlation co-efficient (r) – a measure of how close observations are to the straight line which best describes the linear relationship within the range of measurements plotted. If $r = \pm 1.0$ then there is perfect correlation.
- Co-efficient of determination (r^2) – a measure of how well the line of best fit approximates the data.
- Bland-Altman plots - demonstrate the agreement between the two assays, including identifying bias and outlying measurements (87). In these plots, each of the samples is represented by assigning the mean of both measurements as the x-axis value, and the difference between the two values as the y-axis value. The mean difference is the estimated bias, and the SD of the differences measures the random fluctuations around this mean. Good concordance tends to be represented by 95% of the differences falling within 1.96 SDs from the mean difference, and the mean difference being close to zero. The first example of a Bland-Altman plot in this thesis is in Figure 17, chapter 3.
- Receiver operator characteristic (ROC) curves – assess the ability of a test to correctly classify patients into diseased or non-diseased groups. In these curves, false positive rate (1-specificity) is plotted on the x axis, versus true positive rate (sensitivity) on the y axis, for different cut-off values of a parameter (neutrophil count in the context of this thesis). These performance terms are explained in Table 4. Each observation plotted represents a sensitivity/specificity pair corresponding to a particular decision threshold. The area under the curve (AUC) is calculated and is a measure of how well the parameter (neutrophil threshold) can distinguish between two groups (neutropenic and not neutropenic). The closer to 1.0 the AUC is, the more accurate the test. The first example of a ROC curve in this thesis is in Figure 26, chapter 4.

(ii) Precision

Defined as how close a group of measurements are to one another, and tends to be expressed as co-efficient of variation ($CV = \frac{\text{standard deviation}}{\text{mean}}$). The closer the data is clustered, the smaller the coefficient of variation.

The larger the number of paired and repeated measurements, the tighter the CIs are around the accuracy and precision.

There is a diagrammatic representation of accuracy and precision in Figure 3.

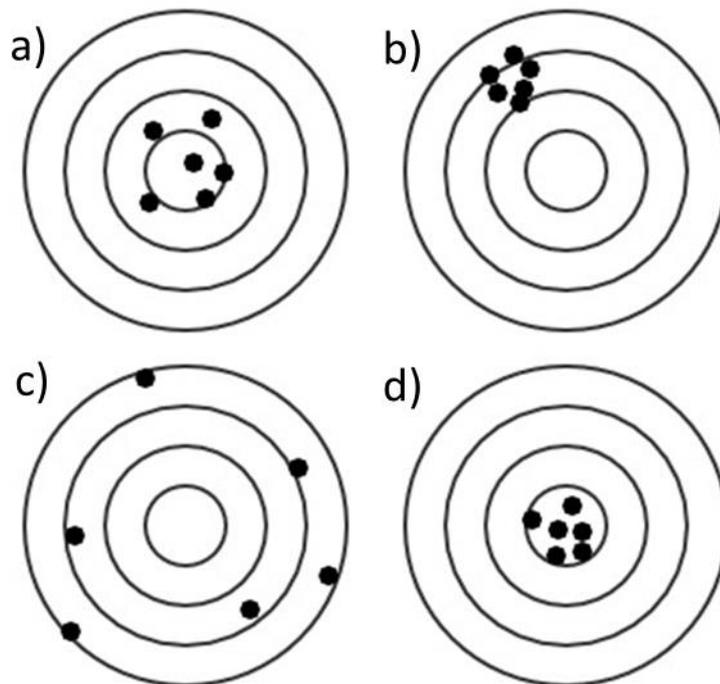


Figure 3: Bulls eye visual demonstration of accuracy and precision.

The circular grids represent the target measurement, where the central circle indicates the true or comparator value. The larger circles indicate values successively further from the comparator value. The black dots represent theoretical values indicated by the test device. a) The black dots close to the comparator value, but spread in different directions represent accurate, but not precise measurements. b) The black dots clustered together far away from the comparator value represent precise, but not accurate measurements. c) The black dots spread far from the comparator value and each other in all directions represent neither accurate or precise measurements. d) The black dots clustered close together and to the comparator value represent both accurate and precise measurements. Use of the “bull’s eye” diagram to explain accuracy and precision is common practice. This diagram has been adapted from multiple freely available sources.

It is also useful to understand the measures of performance of tests in identifying disease, which is neutropenia in the context of this thesis. Table 4 is used to explain the terms. For example, in a situation where a point of care device is being used to identify patients who are neutropenic in those with suspected febrile neutropenia, sensitivity is the statistical term which corresponds to the proportion of patients out of all those who are neutropenic on the reference analyser who are correctly identified using the point of care device. Again in the situation where a point of care device is being used to identify patients who are neutropenic in those with suspected febrile neutropenia, the important clinical question is “what proportion of patients who are identified as not neutropenic by the point of care device, are

in fact incorrectly identified as they are truly neutropenic?”. The statistical term which correlates with this patient group is 1 – negative predictive value.

1.3.2 The devices

There are three devices discussed in this section;

1. Philips XBC
2. Philips Minicare H-2000
3. Hemocue WBC DIFF

These devices measure either finger-prick granulocyte or neutrophil counts and there are photographs of each in Figure 4. This project progresses from investigating the XBC, to the Minicare H-2000 through to the Hemocue WBC DIFF, as support for the former two devices was withdrawn during the time-period of this work. This is why chapter 4 addresses the role of granulocytes being used as a surrogate for neutrophil counts, but subsequently, the performance analysis in chapter 5 uses the Hemocue WBC DIFF and specifically neutrophil counts.

1.3.2.1 XBC

Horizon scanning of the international market identified three devices and one technology in development capable of being used to measure either granulocyte or neutrophil counts at point of care (87). One of these was ChempaQ XBC which was “Conformité Européenne” (CE) marked for professional use and was capable of measuring haemoglobin and 3-part differential white cell counts via a finger-prick capillary blood sample. Philips Healthcare bought this device, and re-packaged it as the XBC. It used the Beckman-Coulter counter principle to measure the granulocyte count in which cell counting and sizing is based on the detection and measurement of changes in electrical impedance (resistance) produced by a particle as it passes through a small aperture. Generation of the granulocyte count required finger-prick blood sampling by a health-care professional using a lancet, such that a blood droplet was formed. This droplet was then placed in a cartridge, which was introduced to the device which then took three minutes to display and print the result.

a)

Laboratory venous ADVIA 2120 neutrophil count			
POC neutrophil count	Neutropenic	Not neutropenic	Total
Neutropenic	a	b	a+b
Not neutropenic	c	d	c+d
Total	a+c	b+d	n=a+b+c+d

b)

Measure of performance	Equation	Description
Sensitivity	$\frac{a}{(a + c)}$	Proportion of individuals who are neutropenic and are correctly identified by the point of care device.
Specificity	$\frac{d}{(b + d)}$	Proportion of individuals who are not neutropenic and are correctly identified by the point of care device.
True positive	a	Individuals who are neutropenic and are correctly identified by the point of care device.
True negative	d	Individuals who are not neutropenic and are correctly identified by the point of care device.
False positive	b	Individuals who are not neutropenic and are incorrectly identified as neutropenic by the point of care device.
False negative	c	Individuals who are neutropenic and are incorrectly identified as not neutropenic by the point of care device.
Positive predictive value	$\frac{a}{(a + b)}$	Proportion of individuals who are truly neutropenic of all those identified as neutropenic by the point of care device.
Negative predictive value	$\frac{d}{(c + d)}$	Proportion of individuals who are truly not neutropenic of all those identified as not neutropenic by the point of care device.
False negative rate	$\frac{c}{(a + c)}$	Proportion of individuals identified as not neutropenic by the point of care device of all those who are truly neutropenic.
False positive rate	$\frac{b}{(b + d)}$	Proportion of individuals who are identified as neutropenic by the point of care device of all those who are truly not neutropenic.

Table 4: Tables explaining parameters used to describe the performance of a test.

a) 2 x 2 table demonstrating identification of neutropenia by the reference and point of care methods, and b) Table explaining measures of performance. POC – point of care.



Figure 4: Images of the three point of care devices with capabilities of measuring finger-prick white cell counts.

a) Philips XBC – for professional use to generate haemoglobin, total white cell count and 3-part white cell differential count. b) Philips Minicare H-2000 – intended for patient self-test use to generate haemoglobin, total white cell count, 3-part white cell differential count using the finger-prick blood sample, and to measure tympanic membrane temperature using the Bluetooth-linked thermometer, and to transmit these results electronically to the health-care provider through the 3G, 4G or GPRS network. c) Hemocue WBC DIFF – for professional self-test use to generate haemoglobin, total white cell count, 5-part white cell differential count.

1.3.2.2 Minicare H-2000

The Minicare H-2000 was developed to facilitate patient self-test home monitoring of haemoglobin, total white cell count and granulocyte count, temperature recordings and symptoms. The blood count measuring technology was as described for the XBC. As it was intended for patient self-test use, the method of ascertaining sufficient blood sample within the cartridge and the way in which the cartridge was received into the reader were more patient-appropriate. The four integral components facilitating home self-test use were;

- i) blood count measuring technology for use with a capillary sample
- ii) a Bluetooth connected thermometer
- iii) a tele-hub with touchscreen allowing pre-defined two-way communication between patient and health-care provider
- iv) secure communication technology allowing linkage to a server within the secondary care provider via the 3G, 4G or general packet radio services (GPRS) networks or internet.

Manufacture of the Minicare H-2000 on a larger scale than the early prototypes was fraught with complications which were not overcome by the manufacturing quality control team in a time scale or resource use that was acceptable to Philips. Most of the complications were directly related to materials being used, but in some cases they affected the performance of the device, and as such were critical hurdles. Philips Healthcare withdrew support for this device in October 2016.

1.3.2.3 Hemocue WBC DIFF

The Hemocue WBC DIFF System is “Conformité Européene” (CE) marked for professional use and measures total white cell count, neutrophils, lymphocytes, monocytes, basophils and eosinophils. It therefore has the advantage over the other devices of generating a neutrophil count, thus negating the need to incorporate a margin to account for using the granulocyte count in oncology practice that now tends to use the neutrophil count for safe delivery and management of toxicities of chemotherapy.

The device uses image analysis techniques to count the white blood cells and perform a 5-part differentiation. Ten microlitres of blood from a droplet obtained via a finger-prick skin puncture is drawn by capillary action into the microcuvette, which is preloaded with reagent and serves as a pipette, sample container and reaction chamber. The erythrocytes are

haemolysed and the leukocytes are stained with methylene blue within the microcuvette. A camera repeatedly moves through the cavity of the microcuvette to capture images of the stained white cells. It takes more than 30 images of each cell, merging these into one final image. More than 30 different features, such as size, shape, texture, granules etc, have been identified for each cell type and translated into a mathematical algorithm which is implemented in the device. It is capable of using this state-of-the-art imaging technology to count total white cells in the range $0.4 - 30 \times 10^9/L$. It has an inbuilt Quality Control system which checks for problems such as incorrect filling of the microcuvette, improper light, blurred cells, reagent stability and it displays an error code without the result if the QC check fails.

1.4 The innovation

The National Chemotherapy Advisory Board Good Practice guideline promotes patient empowerment and pro-active monitoring of patients on chemotherapy to improve quality of care of patients on chemotherapy (88). A device suitable for patient self-test home blood count monitoring has the potential to facilitate both of these approaches and to personalise patient care. This could initially be in collaboration with health-care professionals co-ordinating the care, but subsequently could be through clinician pre-defined parameters stored on the device. We hypothesized that there are four time points during a cycle of chemotherapy where there is scope to explore the potential role of home neutrophil count monitoring in individualising patient care:

1. After chemotherapy delivery to identify if early changes in neutrophil counts are predictive of neutropenic complications.
2. Any time during the cycle to exclude neutropenia in those with suspected febrile neutropenia.
3. At intervals during the cycle to quantify neutrophil nadir.
4. Prior to delivery of the subsequent chemotherapy cycle to confirm sufficient neutrophil recovery.

In an NHS under ever-increasing financial constraints, this personalised medicine approach has the potential to be used to risk stratify patients on chemotherapy and hence streamline the service and clinical pathways according to the greatest need. Clinical pathways could be defined according to risk of febrile neutropenia, thus focusing resource on those that are most likely to benefit. Interestingly, there is convincing evidence of prognostic value in attaining neutropenia during chemotherapy (89-93), and of progression-free survival benefit using the

neutrophil nadir to tailor chemotherapy dosing (94). For example, a retrospective review of routine practice in the adjuvant breast cancer setting reported a 10% absolute survival advantage for those with a grade 2 or 3 neutropenia (89). However, most data supporting prognostic value is in the adjuvant breast cancer setting only and is retrospective. Moreover, the prospective trial only collected the neutrophil count at day 10 during the chemotherapy cycle, and therefore may also underestimate the true nadir and its prognostic value. Thus there is a potential to use home blood count monitoring to guide chemotherapy dose intensity and density to improve outcomes. This is discussed further in the introduction to chapter 6.

This thesis explores the potential of home blood count monitoring to individualise chemotherapy delivery and supportive management through prediction of neutropenia, its duration and complications, early detection of neutropenia and monitoring of recovery. The ambition in the long-term would be to evaluate a self-test device in high risk patient groups at all points in the pathway stated above. The potential gains envisaged with a successful test and treat risk stratified strategy using home neutrophil count testing in patients during chemotherapy could include:

- (i) Reduction in frequency and severity of chemotherapy-induced neutropenic adverse events, achieved by;
 - a. more intense testing schedule in high risk patients to provide an early alert of severe neutropenia.
 - b. intervention such as prophylactic use of antibiotics or granulocyte colony stimulating factor in high-risk groups.

- (ii) Reduction in patient hospital attendances through;
 - a. advising the patient to stay at home if mildly unwell mid chemotherapy cycle, and they are not neutropenic.
 - b. developing novel pathways of care such as delivery of antibiotics in the community for well patients with febrile neutropenia.
 - c. advising the patient to stay at home if the neutrophil count on the day subsequent chemotherapy is due has not recovered sufficiently for safe delivery.

- (iii) Improve patient outcomes through;
 - a. reduction in frequency and severity of neutropenic complications.
 - b. potential to improve cancer outcomes through personalising dose intensity and density of chemotherapy based on neutrophil nadir, and early re-treatment once the neutrophil threshold for treatment is crossed.

- (iv) Improved patient experience through;
 - a. any of 1, 2 and 3 above.
 - b. reducing anxiety and inconvenience through retrieving prompt neutrophil results.

- (v) Financial savings through;
 - a. reduction in number and length of inpatient admissions and outpatient attendances.
 - b. reduction in laboratory investigations.
 - c. reduction in transport costs.
 - d. reduction in wasted chemotherapy.

1.5 Objectives

This thesis aims to explore the feasibility of home neutrophil count monitoring in patients with cancer on chemotherapy. It forms the necessary early work in a longer-term vision that is to use home blood count monitoring to change treatment pathways of patients with cancer by individualising chemotherapy delivery and supportive management, through prediction of neutropenic complications, early detection of these, quantifying the neutrophil nadir and monitoring of neutrophil recovery. The objectives of this thesis are re-defined through progression of the project due to the challenges and limited functionality of the available devices. The primary objectives are addressed throughout each chapter, and the secondary objectives align with individual chapters.

The final objectives are;

- Primary
 1. To explore the feasibility of self-test home neutrophil count monitoring in patients on chemotherapy.

2. To generate sufficient evidence to justify a test and treat pilot study using patient self-test home neutrophil count testing to improve patient experience and neutropenic complication outcomes.
- Secondary
 1. To explore patient and professional views on the acceptability of home blood count monitoring.
 2. To define error and risk associated with using haematological parameters available on point of care devices as surrogate markers of laboratory-generated results.
 3. To assess performance of the Hemocue WBC DIFF device in the neutropenic range clinically relevant to oncological practices.
 4. To define the extent of neutropenic complications in current practice.
 5. To profile neutrophil counts during chemotherapy to identify points in the clinical pathways where there is potential for use of home testing to improve patient experience and outcomes.

Chapter 2 Characterising clinical pathways during chemotherapy to define the incidence of neutropenic complications

2.1 Introduction

In an NHS under ever-increasing financial and performance pressures, the need for change to current practice in order to find efficiency savings whilst maintaining clinical standards has never been greater. This is true in oncological practice where the number of patients living with cancer is increasing and forecast to continue in this way, in addition to the increasing cost of new treatments. Importantly, although many new treatments are either molecularly targeted agents or immunotherapies, these are often given in combination with cytotoxic chemotherapy which will remain central to the treatment of patients with cancer for the foreseeable future.

Challenges within oncological practice were identified by the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) in 2008, which reported that 42% of patients who died within thirty days of systemic anticancer therapy were admitted with a treatment-related complication to a general medical ward, rather than to a ward with oncology-specific expertise (95). This identified problems at a high level with limited amount of detail. The NCEPOD and the National Chemotherapy Advisory Group highlighted the incompleteness of patient records, many of which were paper-based at the time, along with shortcomings of conventional real-life data collection (96). At LTHT, electronic health records (EHRs) have been used in routine practice to collect comprehensive clinical data on oncology patients since 2004, and this chapter realises some of the benefits of this data collection by processing it in such a way that it can be used to characterise clinical pathways of patients on chemotherapy.

Existing clinical pathways establish the expected standard of care, which in turn guides the processes and procedures required to meet those standards (97). These pathways are increasingly more evidence-based (98, 99), but such evidence is generally derived from carefully structured clinical trials rather than learning directly from routine clinical practice which can be very different to the trial situation. For example, the reported incidence of febrile neutropenia after common chemotherapy regimens varies considerably between randomised controlled trials, and trial patient cohorts usually do not reflect the more unselected patients of routine practice; consequently, uncomplicated neutropenia as a toxicity of chemotherapy may be under-estimated (36). Thus, it is important to question whether perceived patterns of existing care are accurate and meaningful.

In oncology, there is increasing attention on the use of large datasets (100), with much of the focus being on applications of next generation sequencing genomics (101). Process mining is one emerging “big data” approach for discovering and analysing process models based on the very large event logs contained within information systems (102) and there is a growing body of literature on process mining in healthcare (103). A review of the process mining literature identified thirty-seven peer reviewed papers using electronic health record (EHR) data to map pathways in oncology (104). This review was hindered by there being no standard medical subject heading (MeSH) term for “process mining” and therefore may not be comprehensive. None of the thirty-seven papers specifically reported mapping neutropenic complications. Challenges included the difficulty of capturing outpatient events (105), the use of data collected for non-clinical purposes, missing data or unstructured data and clinically inaccurate time-stamps (106). This issue of data quality in electronic health records, and therefore suitability for research, has been acknowledged (107, 108). An example is the discrepancy in quality associated with structured and unstructured data fields. A structured data field allows only a finite list of possible data entries chosen from a list, whereas unstructured can be free-text, meaning similar content can be entered in a number of different ways, hence making it difficult to group these for audit or research purposes.

The Leeds Teaching Hospitals NHS Trust has developed and uses Patient Pathway Manager (PPM) as the Trust-wide electronic health record (EHR). It is a mature EHR that is used to capture comprehensive clinical data on all patients undergoing treatment for cancer at the Leeds Cancer Centre. It was initially developed in 2003 to support collection and reporting of the National Cancer Outcomes Services Dataset (109). It has extended further more recently to collate data on all patients whose care has been delivered at LTHT since the year 2000. In this chapter, PPM is the data source used to map patient pathways during chemotherapy. These pathways are comprehensive and patient-centred, addressing issues in published oncology process mining by reporting most contacts the patient has with the hospital including in- and out-patient events and pathology results. A novel iterative approach is used to address data quality through clinical review to refine the model. The results are reported through formulation of a Markov model (see following paragraph), quantification of pathways followed within two exemplar chemotherapy regimen and diagnosis combinations and compared across all chemotherapy regimen and cancer diagnosis site combinations. The reported febrile neutropenia rates are compared to existing published rates.

Markov models are often used to aid health care decision making. They are suited to decisions where the timing of events is important and when events may happen more than once,

appropriate when the strategies being evaluated are of sequential or repetitive nature. The principles of Markov modelling are briefly described here as they are comprehensively discussed in the literature (110, 111). A cluster of clinical events are simplified by defining them as clinically important health states or Markov states. For example, in the model described in this chapter during chemotherapy, a patient in the health state of febrile neutropenia, has;

- (i) an entry in the hospital admissions table.
- (ii) a neutropenic blood count.
- (iii) blood cultures analysed that did not grow a pathogenic organism.

Markov models assume that the health states are mutually exclusive as a patient cannot be in more than one state at any one time. The transition of a patient from one health state to another is assigned a probability, known as the transition probability. Markov models represent repetitive processes over time whereby the patient passes through the same health state on more than one occasion, represented in this model by the delivery of chemotherapy. Patients can therefore, only exit the repetitive model via defined exit states, which in this model exist as one of only three states; complete chemotherapy, stop chemotherapy prematurely, death. There is also an assumption that transition to future states depend only on the current state, and not on any events that occurred before the current state. This is known as the Markov assumption.

The work described in this chapter defines the baseline patient pathways during chemotherapy and quantifies the real-life extent of neutropenic complications, with the potential to identify where in the pathway there is scope to use home blood count monitoring. Understanding the real-life starting point early is well characterised as an essential step in the process of change management; “dissatisfaction with the status quo is not enough to create change on its own – there needs to be a vision of the future and the first few steps mapped on the path to get there” (112). This has been expressed mathematically as;

$$\text{Change} = \text{current pain} \times \text{vision} \times \text{easy first steps}$$

This chapter deals with understanding the “current pain”, in other words, the real-life prevalence of neutropenic complications in an unselected population of patients served by Leeds Cancer Centre. It determines the value of establishing the local baseline pathways over

and above the information which is available from published trials, in order to inform patient selection for the trial described in chapter 6.

2.2 Objectives

2.2.1 Primary objectives:

1. To understand the prevalence of febrile neutropenia or neutropenic sepsis in the unselected patient population on chemotherapy served by LTHT.
2. To map clinical pathways of unselected patients on chemotherapy, thus defining and quantifying the baseline patient pathways.
3. To compare the prevalence of neutropenic complications to published data in order to identify the value in establishing institution specific prevalence.

2.2.2 Secondary objectives:

1. To inform patient selection criteria for the subsequent trial aiming to profile neutrophil counts during chemotherapy.
2. To inform clinical and health economic modelling processes of where in clinical pathways the use of home blood count testing has the potential to be of benefit.

2.3 Methods

2.3.1 Resources

2.3.1.1 Patient Pathway Manager

PPM integrates electronic data held within multiple disparate systems within the Trust into a single EHR database including data on patient admissions and out-patient events from the Patient Administration System (PAS), chemotherapy data from Chemocare (113), radiotherapy data from Mosaiq (114), blood, pathology and microbiology results from laboratory systems and data entered directly into PPM including surgery, cancer waiting times and multi-disciplinary team meetings. Figure 5 illustrates how components of PPM are entered. In PPM, each event is recorded with a patient identification and date time stamp, enabling a historical pathway to be extracted for every patient.

2.3.1.2 Computing facilities and expertise

An information technology data analyst, Karl Baker, developed the datamining software with capabilities to develop the pathway model of patients on chemotherapy. The data mining software created a warehouse database by extracting and transforming data from PPM. The warehouse database is used to generate Comma Separated Value (CSV) exports of aggregate figures. This software was written in C# and was run on a machine with an Intel Core i7 processor with 16GB of memory.

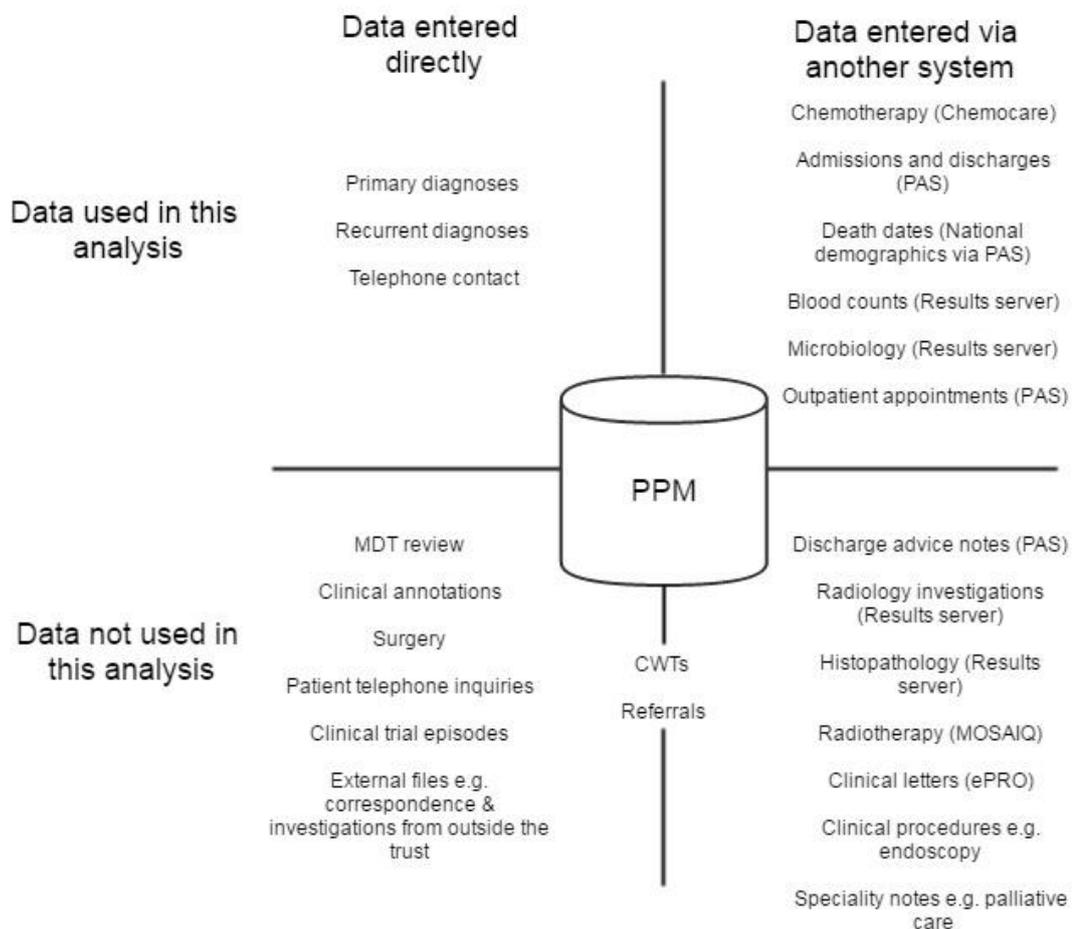


Figure 5: Overview of data entered into PPM.

MDT, multi-disciplinary team. Chemocare, chemotherapy electronic prescribing system. PAS, patient administration system. Results server, LHT software importing all patient investigation results from multiple disciplines. CWT, cancer waiting times. MOSAIC, radiation oncology software. ePRO, clinical information management system working with Winscribe's digital dictation system. Telephone contact, hospital staff telephone patient. Patient telephone enquiries, patient rings hospital with a clinical enquiry. Some of the data in PPM was not used in this analysis as it either was not a result of direct patient contact with the hospital (i.e. it was generated by previous contact, such as MDT review), it was unstructured (for example, clinical letters), or it did not form part of the pathway during a cycle of chemotherapy.

2.3.2 Processes

2.3.2.1 Defining the Markov Model

The steps followed to construct a Markov model are described below and were; define the patient inclusion criteria, defined the relevant health/Markov states, defined acceptable transitions between health states, identified transition probabilities, identified health outcomes, then ran the model over repeated Markov cycles. The transition probabilities were calculated by patient data from PPM, in contrast to estimations where such a comprehensive dataset is not available to inform the process.

All clinical parameters underlying the model were defined, with a data analyst (KB) translating these into C# language and developing the software to support the model. With KB a model was developed and refined through the iterative process described below.

2.3.2.1.1 Clinical Definitions

Patient characteristics

Patient data were included in the dataset if they had a diagnosis of cancer and received either cytotoxic chemotherapy or targeted therapy for this diagnosis at Leeds Cancer Centre on or between 1st April 2004 to 1st January 2016. Table 5 shows the rules used to define the clinical characteristics.

Patients receiving single agent hormones or bisphosphonates were excluded. The recorded treatment intent was not used as a selection criterion, as this was considered to be unreliable after manually reviewing a random selection of approximately 100 records. Patients receiving prophylactic granulocyte colony stimulating factor during the cycle of chemotherapy were included. The period before (7 days) and after chemotherapy administration (5 days) accounts for the fact that the date held electronically for granulocyte colony stimulating factor was the date of dispensing from pharmacy, and not the date of administration to the patient. Prophylactic granulocyte colony stimulating factor is most commonly dispensed at either the chemotherapy pre-assessment visit or chemotherapy delivery. Granulocyte colony stimulating factor used therapeutically in an acutely unwell patient is not recorded electronically as it is dispensed from ward stock and is therefore not included in this analysis.

Health states

Clinical rules were defined and applied to the data to create the model health states. All events had to occur between the start and end date of chemotherapy. Day 1 was considered

to be the day chemotherapy was delivered. Table 6 shows the rules used to define the model health states.

Clinical characteristic	Defining rules and methods
Diagnosis of cancer	Used ICD-10 codes for cancer (begin with C or D), which is automatically generated in PPM when malignancy, primary site and morphology is manually entered into PPM. In the 13.9% which did not have an ICD-10 code, the manually entered primary site diagnosis code(CDS) was used. Overall 1.1% of records had neither an ICD-10 or CDS code.
Received chemotherapy	Used an entry marked as “delivered” in the PPM chemotherapy drugs table, if it was between the specified dates, and the primary treating institution was Leeds.* Data in this table is imported from Chemocare, and “delivered” indicates generation of the prescription.
Linking diagnosis with chemotherapy	The CWT table in PPM linked the diagnosis to chemotherapy in 75% of records. In the remaining 25%, if there was only 1 cancer diagnosis it was linked to the chemotherapy. If ≥ 1 cancer diagnosis, a link was made if the same chemotherapy was given for one of the diagnoses in $\geq 95\%$ of cases. Otherwise, the diagnosis date closest to and before the delivery of chemotherapy was used.
Regimen nomenclature	Chemotherapy regimens were obtained from the “regimens” table in PPM and labelled according to the national SACT dataset mapping. Non-cytotoxic anti-cancer drugs were identified by labels in the SACT mapping. Identifiable regimens delivered as part of a trial were included, but records where the drug could not be identified such as receiving treatment in a trial with a placebo arm were excluded.
Regimen cycle length	Cycle length was defined by the modal cycle length of that regimen in the dataset.
Regimen cycle number	Cycles were numbered continuously whilst the regimen and diagnosis remained the same. The numbering restarted at “1” if the diagnosis or regimen changed or the same regimen was delivered ≥ 95 days after the start of the previous cycle.
Prophylactic GCSF	Used pharmacy dispensing record of GCSF. Considered prophylactic GCSF was used if dispensed up to 7 days before and 5 days after delivery of chemotherapy. It was indicated by adding GCSF to regimen name.

Table 5: Description of rules and methods used to define patient clinical characteristics.

ICD, International Classification of Diseases. PPM, Patient Pathway Manager. CDS, Commissioning Data Sets site diagnosis code. CWT, Cancer Waiting Time. SACT, Systemic Anti-cancer Therapy. GCSF, granulocyte colony stimulating factor. *Patients managed in other hospitals can be discussed at Leeds MDTs as it is a tertiary referral centre. These patients’ records are in PPM, but as they receive chemotherapy at their referring institution, PPM does not hold the records of their care during chemotherapy.

Health state	Defining rules and methods
≥1 day admission	Entry in admissions table that was recorded as starting before and ending after midnight of the day it started.
0 day admission	Entry in admissions table, with a “non-elective” label that was recorded as starting before and ending before midnight of the day it started.
Neutropenic	A full blood count result on results server during a cycle length, where the neutrophil count is $<1.0 \times 10^9/L$. (Neutropenia at time chemotherapy is due is considered to be $<1.5 \times 10^9/L$ for 3-weekly regimens)
Blood cultures taken	Presence of a microbiology report of blood culture on results server.
Bacteraemia	Used microbiology free-text reports. Searched approximately 500 manually to identify commonly used phrases that indicate or exclude culture of pathogenic organisms. Then automated the searching of the full dataset of blood culture results on results server taken within the cycle of chemotherapy using the phrases.
Other positive microbiology	As above, except samples from sites other than blood.
Urgent outpatient appointment	Entry in the outpatient appointment table, labelled as “emergency”.
Elective ward review	Entry in the admissions table, with a “non-urgent” label and duration of admission <1 day.
GP contact with neutropenia	Blood count result on results server with no simultaneous record of activity in PPM.
Hospital attendance but no chemotherapy due to neutropenia	Entry in admissions table labelled as elective, between 3 days before or 3 days after the date subsequent chemotherapy is due, but blood count in results server in same period showing neutropenia, and chemotherapy is not delivered.
Hospital attendance but no chemotherapy due to other reasons	As above, but blood counts do not show neutropenia.
Reschedule chemotherapy (prior to hospital attendance) due to neutropenia.	No entry in admissions table (elective), between 3 days before or 3 days after the date subsequent chemotherapy is due, and the blood count in results server in same period shows neutropenia, and chemotherapy is not delivered.
Reschedule chemotherapy (prior to hospital attendance) due to other reasons.	As above, but blood counts do not show neutropenia.

Table 6: Description of rules and methods used to define health states within the pathway.
GP, general practitioner.

Neutropenic sepsis is defined as neutropenic and bacteraemic. Febrile neutropenia is defined as one of two health states, which are necessarily mutually exclusive from neutropenic sepsis on the model;

- Neutropenic, blood cultures taken and no bacteraemia.
- Neutropenic, no blood cultures taken, but other positive microbiology.

The presence of blood culture reports on results server were used as a surrogate for fever, as recording of temperature was not held electronically at the time of this analysis.

The Markov state definitions used to define the clinically relevant situations are described below (the bracket contents refer to how the states are labelled in

Figure 7);

a) Acute Events

1. Neutropenic Sepsis

Neutropenic and bacteraemic, either admitted (A3,S5, M1,S6) or not (A2,S5,M1,S6)

OR

Neutropenic, no bacteraemia (A3,S5,M1,S8 or A2,S5,M1,S8)), but go to intensive care or high dependency unit (ICU/HDU) or die.

OR

Progress to either of the above scenarios (A3,S9,M1,S6 or A3,S9,M1,S6 and go to ICU/HDU or die).

2. Febrile Neutropenia

Excluded from this definition if included in Neutropenic Sepsis.

Neutropenic, blood cultures taken, no bacteraemia, either admitted (A3,S5,M1,S8) or not (A2,S5,M1,S8).

OR

Neutropenic, no blood cultures taken, other microbiology positive, either admitted (A3,S5,M2,M3) or not (A2,S5,M2,M3).

OR

Progress to either of the above scenarios (A3,S9,M1,S8 or A3,S9,M2,M3).

3. At Risk Group (attend acute assessment and blood cultures taken)

Excluded from this definition if included in Neutropenic Sepsis or Febrile Neutropenia.

Blood cultures taken, not neutropenic, either admitted (A3,S4,M1) or not (A2,S4,M1). Those who are neutropenic are already captured in Neutropenic Sepsis or Febrile Neutropenia groups.

b) Elective Events

1. Late Chemotherapy Delay

Chemotherapy delayed on day of delivery secondary to neutropenia (S2)

2.3.2.1.2 Allocation of patients to model states

A brief description of the computer processes followed to define the model are described below, and in more detail elsewhere (115).

Allocation of patients to model states required applying a data mining process to the data in two main stages;

1. Extracting events for each patient from the many tables in PPM and transforming the events into a single table, ordered by date and time, thus creating an event log for each patient.
2. Matching this pathway of events to a pathway of clinically pre-defined states in the model, using the repetitive event as chemotherapy delivery.

Data modelling followed an iterative process (116). The initial data mining software was sufficient to extract only the parts of the patient pathway defined by the initial model, which was schematic of the patient pathway based on expert opinion and work with a small focus group of doctors and nurses involved in chemotherapy delivery. Subsequent model iterations involved redefinition, accounting for complexity revealed by the data that was not previously foreseen. For example, a number of patients had blood test results present outside episodes of hospital care due to them attending their General Practitioner. In addition, there were validation checks, ensuring that transitions between health states found in the data were represented by pre-defined paths between the states.

As the model cannot accommodate transition between all health states, when patients experienced more than one state within a cycle of chemotherapy they were prioritised by the most severe event, but counts were kept of the frequency of all health states. For example, if a patient received chemotherapy, then had an urgent outpatient review and was admitted 2 days later, they were represented in the model in the most severe pathway(admission), but are also counted in the other health state (urgent outpatient appointment). So where there were 2 numbers in brackets after the proportion figure attached to each pathway, the first represents the number of patients where this health state was the most severe experience during that cycle of chemotherapy, the second number represents the total number of patients who experienced that health state. The severity was ranked from most to least severe using expert consensus agreement, which was (contents of brackets refer to labels in Figure 7);

- Death without hospital contact (D5).
- Emergency admission to hospital with neutropenia (A3, S5).
- Emergency admission without neutropenia, progressing to neutropenia whilst in hospital (A3,S9).
- Emergency admission to hospital without neutropenia (A3, S4).
- Day case review (D4).
- Urgent outpatient review (D3).
- Contacted GP and tested positive for neutropenia (D7).
- No contact (D1) (planned pathway).

2.3.3 Quantification of clinical pathways

The Markov model underpins this work. The patients were grouped by combinations of chemotherapy regimens and cancer diagnosis site. A high level cancer diagnosis site was used, such as thoracic, gynaecological, gastrointestinal, in an attempt to reduce the number of permutations, thus making the results more widely applicable and interpretable. Patients were allocated to health states as described in 2.3.2.1.2 by regimen and site combinations. Health states were recorded per patient across all cycles of chemotherapy delivered, as is common reporting practice in clinical trials. For example, if the rate of febrile neutropenia is reported as 20%, this means 20% of patients will experience febrile neutropenia at least once during all six planned cycles, and not that 20% of patients will experience it per cycle.

Aggregated numbers for each health state, representing a specific pathway, were extracted into a file of comma separated value (csv) format for analysis.

Epirubicin and cyclophosphamide (EC) for breast cancer and oxaliplatin and modified de Gramont (OxMdG) for colorectal cancer were used to compare and contrast patient pathways because these combinations have the greatest number of patients in the dataset (Table 10) and are most often used for different intents; EC as adjuvant therapy and OxMdG as palliative therapy. This analysis of EC and OxMdG, included only cycle 1 of the first exposure a patient had to the same regimen where no concurrent targeted systemic anti-cancer therapy was delivered.

Where chemotherapy was delivered with either granulocyte colony stimulating factor or other systemic anti-cancer therapy with potential to impact the proportion of patients experiencing neutropenia, subset analyses were performed

2.3.4 Neutropenic complications and comparisons with previously published data

The prevalence of febrile neutropenia or neutropenic sepsis was compared to febrile neutropenic rates reported in published phase III clinical trials. Most published phase III trials report the definition of febrile neutropenia as a neutrophil and temperature threshold being surpassed. Such a definition incorporates patients with neutropenic sepsis.

Regimen and diagnosis site combinations were selected to compare to published data if they were in the top 10 counts of febrile neutropenia or neutropenic sepsis in the Leeds data, or had >20% risk of febrile neutropenia or neutropenic sepsis in the Leeds data. In addition, carboplatin AUC 2-5 and sunitinib were included as these combinations had the highest count of patients with the outcome of febrile neutropenia or neutropenic sepsis in the Leeds data, which were not already included. The combined febrile neutropenia and neutropenic sepsis rates calculated from the Leeds population data did not include those of chemotherapy regimens given concurrently with other systemic anticancer therapies, in order to improve comparability of data. For example, data for docetaxel given concurrently with trastuzumab were not included.

Published trials were searched for which met the following criteria; phase III chemotherapy intervention in cancer patients, >50 patients received the intervention, reported worst neutrophil count nadir, reported the definition and prevalence of febrile neutropenia. The

aim was to include two comparable published trials in each chemotherapy and site diagnosis combinations, with contrasting treatment intents where possible, such as adjuvant/palliative or good/poor prognosis disease. Pubmed database was searched using terms for the chemotherapy regimen and site diagnosis in Title and Abstract. Where two publications meeting the criteria could not be found, reference lists were scoured in the European Organisation for Research and Treatment of Cancer (EORTC) GCSF guidelines (lists regimens with >20% risk of febrile neutropenia) and in the Textbook of Cancer by de Vita, Hellman and Rosenberg (117). Where more than 2 trials for each category were identified, those included either had the most equivalent patient population or the largest number of patients.

2.3.5 Approvals

This work was carried out with approvals from the LTH Director of Research and Innovations and Director of the Clinical Commissioning Support Unit (CSU), with strict information governance procedures, where data were extracted, anonymised and analysed by aggregated pathways, not at an individual patient level. This work pre-dates the publication of the Caldicott report on “Review of data security, consent, and opt-outs” (118), which recommends a process for patients to opt-out of their data being included in population-wide analyses. It is acknowledged that there was no opt out process for patients for whom data were included.

2.4 Results

The total number of patients with a diagnosis of cancer who received either cytotoxic chemotherapy or targeted therapy for these diagnoses at Leeds Cancer Centre on or between 1st April 2004 to 1st January 2016 was 33,371. Data were excluded from the analysis if ≤ 25 patients were in a diagnosis and chemotherapy regimen combination, meaning 4452 patients with 1222 diagnosis and chemotherapy regimen combinations were excluded. Data were extracted for 28,919 patients receiving cytotoxic chemotherapy or targeted therapy for a solid tumour. Within this there were 162 different diagnosis and chemotherapy regimen combinations and 84,668 cycles of chemotherapy delivered. The total number of raw events analysed was 1,333,187, giving a mean number of 46 raw events per patient. Raw events were clustered as described in the methods to form a health state in the model, such as an admission with neutropenia. In total 255,156 health state events occurred in the 28,919 patients, giving a mean number of 9 health states per patient.

2.4.1 Defining clinical pathways as a Markov model

The data extracted from the LTHT electronic health records, PPM, were structured into a Markov model, representing the pathway of clinical contacts followed during cycles of chemotherapy. Figure 6 represents the first model considered to be an accurate representation of patient-centred clinical pathways. The model includes a number of health states, each with a code. S1 is the point at which the patient receives chemotherapy; states clustered near the bottom right corner represent admissions, whereas those clustered in the bottom left represent events when the patient is not admitted, and states clustered in the upper half of Figure 6 represent events that occur when the patient is due the next cycle of chemotherapy. An uncomplicated case would be represented by a patient traversing through chemotherapy delivery (S1), followed by no contact (D1), then by patient review (R1) and back to chemotherapy delivery (S1). By contrast, an emergency admission to hospital and a blood test result within 24 hours indicating neutropenia would represent state S5 in the model. Attendance for chemotherapy that was not delivered on the expected date and a blood test result within 24 hours indicating neutropenia would represent state S2 in the model. For 3 weekly chemotherapy regimens, neutropenia delaying subsequent chemotherapy cycle delivery was defined as neutrophil count $<1.5 \times 10^9/L$. For weekly regimens, neutropenia delaying subsequent chemotherapy cycle delivery was defined as neutrophil count $<1.0 \times 10^9/L$.

The Markov model in Figure 6 was improved to capture differentiation between 0 day and ≥ 1 day admissions, which clinically translate into patients who attend for an acute assessment and then go home the same day compared to those who are admitted and have an overnight stay in a bed. The improved Markov model also excluded telephone contacts as these were identified as representing telephone calls from clinical nurse specialists to patients only. They underrepresent the workload of the acute team fielding symptom-driven telephone calls as they did not include unplanned telephone calls from patients to the hospital. An example of this improved Markov model is shown in Figure 7, in which an uncomplicated cycle of chemotherapy is highlighted by the red dotted line. Both models can be accessed electronically for easier viewing via the links at the end of the legends. Table 7 gives clinical explanations of every coded health state in the model in Figure 7.

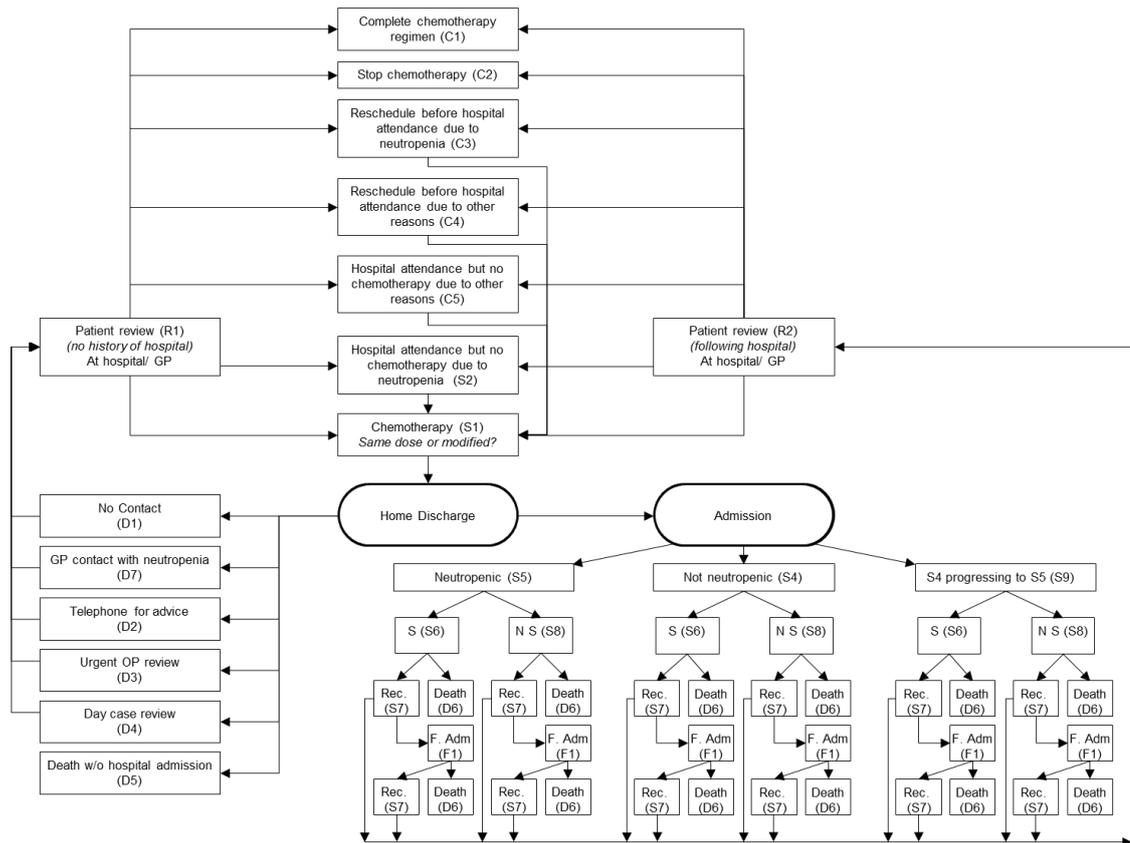


Figure 6: The Markov state model at the end of iteration eight.

S1, patient presents and the chemotherapy goes ahead as normal. D0, home discharge following chemotherapy. D1, patient makes no contact with the hospital. D2, telephone contact between hospital and patient. D3, patient has an urgent outpatient review. D4, patient has an urgent outpatient appointment. D5, death without hospital admission. D7, GP attendance with neutropenia. S2, patient attends hospital for chemotherapy but it is re-scheduled/delayed due to neutropenia. S4, patient is admitted acutely to hospital with no evidence of neutropenia. S5, patient is admitted acutely to hospital with evidence of neutropenia. S6, patient develops bacteraemia. S8, patient does not develop bacteraemia. S9, patient is admitted without neutropenia but develops it during admission. D6, patient dies in hospital. S7, patient fully recovers from acute event. F1, patient undergoes further hospital admissions. R1, review before the day of planned chemotherapy for patients without hospital admission (in that cycle). R2, review before the day of planned chemotherapy for patients with hospital admission (in that cycle). C1, complete all planned chemotherapy. C2, stop planned chemotherapy prematurely. C3, re-schedule before hospital attendance to undergo chemotherapy due to neutropenia. C4, re-schedule before hospital attendance to undergo chemotherapy due to reasons other than neutropenia. C5, patient attends hospital for chemotherapy but it is re-scheduled due to reasons other than neutropenia. Bacteraemia is defined as a positive blood culture. S, septic defined by positive blood cultures. NS, not septic defined by no positive blood cultures. Rec., recovered. An electronic version of this Figure that can be enlarged is accessible via the following link into a web-browser:

<https://tinyurl.com/EDThesisFigure6>

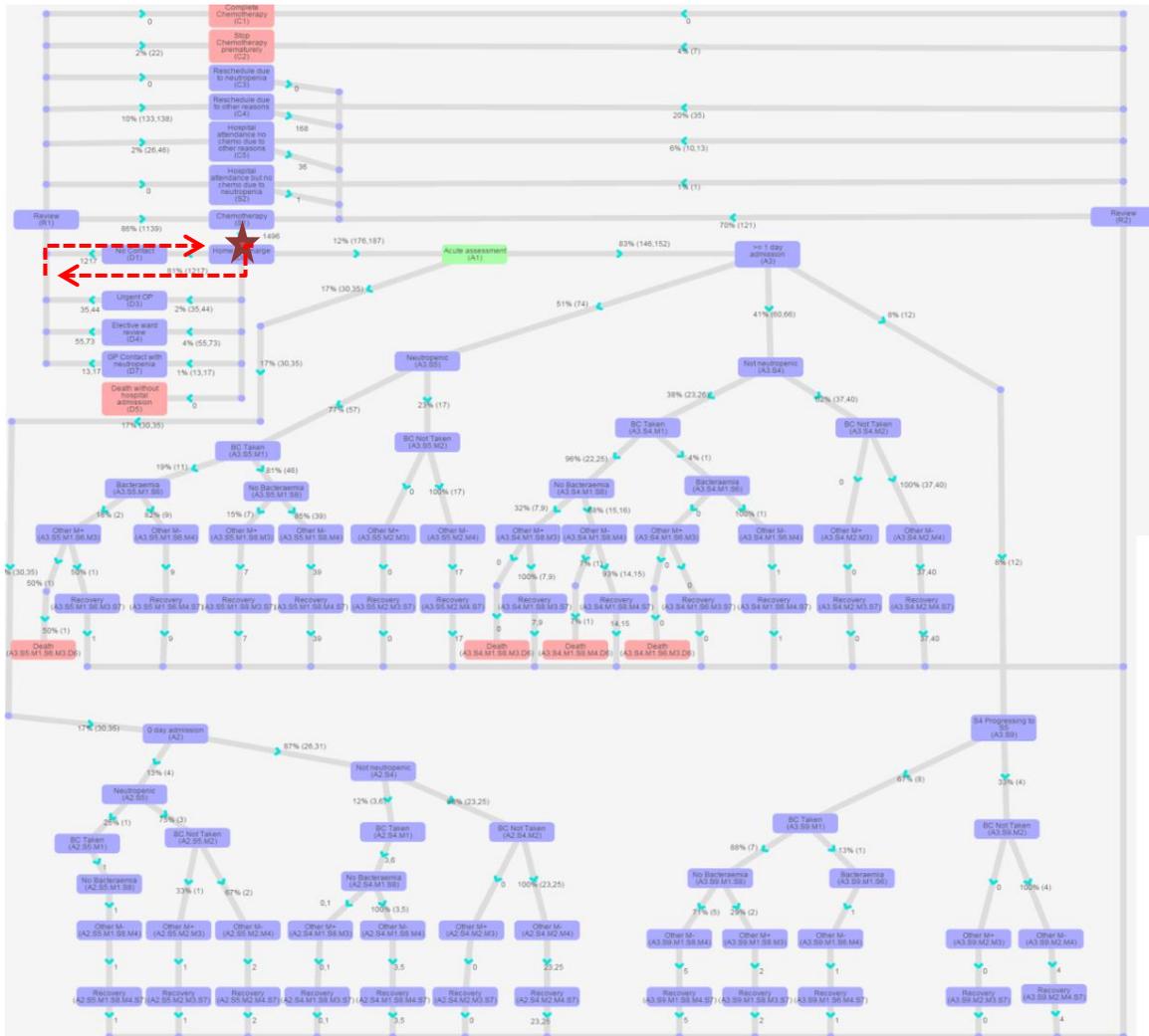


Figure 7: An example of the improved pathway Markov model of patient pathways during chemotherapy which captures 0 day and ≥ 1 day admissions.

This shows additional clusters of health states not displayed on Figure 6. Blue box, Markov health state. Red box, exit box of pathway represented by death, completion of planned chemotherapy or premature stopping of chemotherapy. Green box, for data processing purposes only, labelled acute assessment. Grey lines with green arrow, direction of transition from one health state to another. Where there are 2 numbers in brackets after the proportion figure attached to each pathway, the first represents the number of patients where this health state was the most severe during the chemotherapy cycle, the second number represents the total number of patients who experienced that health state. Red star, chemotherapy delivered which is the entry point for all patients to the pathway. Broken red line, represents patient pathway between chemotherapy cycles where there is no unplanned contact with the hospital between chemotherapy cycles. Boxes clustered in the centre beyond the green box and the bottom right corner represent pathways of patients who are admitted to hospital. Boxes clustered in the bottom left corner represent pathways of patients who attend hospital for an acute assessment and are discharged the same day (0 day admissions). The three blue boxes in the left centre area bounded by the red broken arrow above and the red box below represent an urgent outpatient appointment, elective ward review and GP contact with neutropenia. The four blue boxes at the top bounded by the 2 red boxes above and the red starred box below represent scenarios where the patient does not receive their subsequent cycle of chemotherapy at the planned time. An electronic version of this Figure can be accessed and enlarged via a web-browser: <https://tinyurl.com/EDThesisFigure7>. A paper version printed on A3 paper is slotted inside the back cover.

Health states	Description
S1	Chemotherapy delivered.
D0	Home discharge following chemotherapy.
D1	No clinical contact with hospital, as defined by other health states.
D3	Urgent outpatient review.
D4	Elective ward review.
D5	Death without hospital admission.
D7	GP contact with neutropenia. *
S2	Patient attends hospital for chemotherapy but it is re-scheduled/delayed due to neutropenia.**
A1	Acute assessment.
A2	0 day admission, meaning acute assessment and discharge the same day.
A2, S4 [§]	0 day admission, not neutropenic, discharge the same day.
A2, S5 [§]	0 day admission, neutropenic, discharge the same day.
A3	≥ 1 day admission, meaning acute admission to a bed at least overnight.
A3, S4 [§]	≥ 1 day admission, not neutropenic.
A3, S5 [§]	≥ 1 day admission, neutropenic.
A3, S9 [§]	≥ 1 day admission, initially not neutropenic, but then develops neutropenia during admission.
M1	Blood cultures taken.
M2	No blood cultures taken.
S6	Bacteraemia, defined as blood cultures positive for a pathogenic organism.
S8	No bacteraemia, defined as blood cultures negative for pathogenic organisms.
M3	Cultures, from any site other than blood, positive for a pathogenic organism.
M4	Cultures, from any site other than blood, negative for pathogenic organisms.
D6	Death in hospital.
S7	Recovery from acute event.
R1	Review before subsequent chemotherapy cycle for patients without admissions in the cycle.
R2	Review before subsequent chemotherapy cycle for patients with admission in the cycle.
C1	Completed planned chemotherapy.
C2	Stop chemotherapy before completing the planned regimen. ***
C3	Re-schedule chemotherapy before hospital attendance due to neutropenia. †
C4	Re-schedule before hospital attendance to undergo chemotherapy due to reasons other than neutropenia. ††
C5	Patient attends hospital for chemotherapy but it is re-scheduled/delayed due to reasons other than neutropenia. ††

Table 7: Table of clinical descriptions of all the health states within the improved Markov model.

* Indicated by neutropenic blood count result on Leeds Teaching Hospitals NHS Trust Results server, but no other hospital contact recorded within 3 days. ** Neutropenia is defined as a neutrophil count of $<1.5 \times 10^9/L$ for 3 weekly regimens and $<1.0 \times 10^9/L$ for weekly regimens. *** Planned regimen defined by modal cycle length in dataset. † Had chemotherapy more than 3 days late and was neutropenic up to 7 days before the scheduled cycle date and 3 days after. †† Had chemotherapy more than 3 days late but was not neutropenic. § These model states are all first branches of pathways in the model which continue to be further defined into M1/M2, S6/s8, M3/M4, D6/S7.

2.4.2 Quantification of clinical pathways

2.4.2.1 Within chemotherapy regimen and diagnosis combinations

During the first cycle of the first exposure to the chemotherapy regimen, 78.6% and 76.6% of patients receiving EC and OxMdG chemotherapy, respectively, traversed the “planned pathway” (Table 8) i.e. without encountering deviation caused either by treatment toxicity, other health complications or personal events unrelated to health such as holidays. Patients receiving the first cycle of EC chemotherapy experienced a higher percentage of urgent outpatient review and GP contact with positive test for neutropenia; none of these patients died without hospital contact. Conversely, of the patients receiving first cycle of OxMdG chemotherapy, 1.1% (n=10) died without hospital contact, and they experienced a higher percentage of elective ward reviews. During cycle 1 of chemotherapy, 5.0% (n=70) of those patients receiving EC chemotherapy experienced febrile neutropenia or neutropenic sepsis, and 0.2% (n=2) of those receiving OxMdG experienced the same.

Table 9 compares and contrasts the prevalence of health states by cycle of chemotherapy for EC and OxMdG. In patients receiving EC chemotherapy, the biggest drop-out rate is between cycles 3 to 4 when 24.2% stop chemotherapy. In those receiving OxMdG, the biggest drop-out rate is between cycles 6 to 7 (37.7%). With both regimens, the proportion of patients per cycle with no unplanned contact fluctuates, but remains high for each cycle. Despite this, over all the cycles less than one quarter (23.6% EC and 22.0% OxMdG) of patients received the scheduled six or nine cycles of chemotherapy on the planned pathway. Of those receiving EC, the highest proportion of patients were admitted to hospital during cycle 1; although this is also the case for OxMdG, the admission rate for OxMdG during cycle 2 and 3 remained high. Over all cycles, the patients receiving EC had a lower rate of admission (13.3% EC and 28.0% OxMdG), meaning that the risk per patient of being admitted at least once during a course of chemotherapy is smaller whilst receiving EC than OxMdG. The proportion of patients who experience either febrile neutropenia or neutropenic sepsis during EC chemotherapy is largest in cycle 1, being at least double the rate of any of cycles 2 to 6. This is not the pattern during OxMdG chemotherapy, where the rate of febrile neutropenia or neutropenic sepsis remains relatively low and stable through successive cycles, with the exception of cycle 3. The rate of febrile neutropenia or neutropenic sepsis across all cycles during EC and OxMdG is notably larger than single cycles at 11.0% and 4.8%.

Across all cycles of EC chemotherapy a higher proportion of patients experienced febrile neutropenia or neutropenic sepsis than had it excluded at assessment (11.0% vs 6.4%). In

contrast, across all cycles of OxMdG chemotherapy a lower proportion of patients experienced febrile neutropenia or neutropenic sepsis than had it excluded at assessment (4.8% vs 16.4%). The number of patients who experienced neutropenic sepsis and died was 1 of 154 patients during EC and 2 of 45 patients during OxMdG.

Event	EC			OxMdG		
	Count	Percent	Cumulative (%)	Count	Percent	Cumulative (%)
Death without hospital contact (D5)	0	0	0	10	1.1	1.1
Emergency admission \geq 1 day duration (A3)	149	10.6	10.6	77	8.2	9.3
Emergency acute assessment (0 day admission) (A2)	28	2.0	12.6	24	2.5	11.8
Elective ward review (D4)	54	3.9	16.5	105	11.1	22.9
Urgent outpatient review (D3)	40	2.9	19.4	5	0.5	23.4
GP contact with neutropenia (D7)	29	2.0	21.4	0	0	23.4
No contact (minimum pathway) (D1)	1102	78.6	100.0	723	76.6	100.0
Total	1402			944		

Table 8: Counts of the main pathways traversed for the first cycle of chemotherapy for epirubicin and cyclophosphamide (EC) and oxaliplatin and modified de Gramont (OxMdG). Ordered from most severe event type (D5) to least severe (D1).

Cycle	EC				OxMdG					
	Patient count starting cycle	No contact (D1)	Admission ≥1 day (A3)	Febrile neutropenia or neutropenic sepsis	Assessed and febrile neutropenia excluded	Patient count starting cycle	No contact (D1)	Admission ≥1 day (A3)	Febrile neutropenia or neutropenic sepsis	Assessed and febrile neutropenia excluded
	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
1	1402	78.6 (1102)	10.6 (149)	5.0 (70)	1.8 (25)	944	76.6 (723)	8.2 (77)	0.2 (2)	3.6 (34)
2	1369	80.4 (1101)	5.0 (68)	2.0 (27)	1.2 (17)	881	79.8 (703)	6.2 (55)	0.9 (8)	2.8 (25)
3	1209	72.2 (873)	4.5 (55)	2.3 (28)	1.1 (13)	834	78.4 (654)	7.7 (64)	1.9 (16)	3.0 (25)
4	916	74.7 (684)	6.0 (55)	2.5 (23)	2.2 (20)	770	80.9 (623)	5.6 (43)	0.6 (5)	3.1 (26)
5	713	83.5 (595)	4.6 (33)	2.1 (15)	1.4 (10)	724	79.1 (573)	4.3 (31)	0.8 (6)	2.8 (20)
6	675	85.5 (577)	3.9 (26)	1.3 (9)	1.2 (8)	669	79.8 (534)	4.5 (30)	0.6 (4)	3.1 (21)
7						417	83.0 (346)	4.1 (17)	0.3 (2)	1.6 (11)
8						376	82.2 (309)	1.9 (7)	0.5 (2)	0.3 (1)
9						338	80.4 (271)	5.6 (19)	0.3 (1)	3.0 (10)
All	1402	23.6 (332)	13.3 (187)	11.0 (154)	6.4 (90)	944	22.0 (208)	28.0 (264)	4.8 (45)	16.4 (155)

Table 9: Prevalence of health states by cycle of chemotherapy for epirubicin and cyclophosphamide (EC) and oxaliplatin and modified de Gramont (OxMdG).

D1 and A3 refer to health states represented in Figure 7

Figure 7.

2.4.2.2 Between chemotherapy regimen and diagnosis combinations

The chemotherapy regimen and diagnosis site combination given to the highest number of patients was epirubicin and cyclophosphamide given for breast cancer, closely followed by oxaliplatin and modified de Gramont for gastrointestinal cancers. However, more cycles of the latter were delivered than the former. Table 10 and Table 11 display the chemotherapy regimen and diagnosis site combinations ordered by number of patients and number of cycles delivered. Of note, the regimen and diagnosis site differ in several cases according to whether listed by patient numbers or number of cycles. In the whole dataset, chemotherapy was given to the most number of patients for gastrointestinal cancers (n=8491), followed by breast (n=3823), gynaecological (n=3646), thoracic (n=3268), urological (n=2738), head and neck (n=1760), central nervous system (n=933), skin (n=444) and soft tissue cancers (n=255).

Chemotherapy Regimen	Diagnosis Site	Number Patients	Number Cycles
Epirubicin and Cyclophosphamide (EC)	Breast	1586	6907
Oxaliplatin & modified de Gramont (OxMdG)	Gastrointestinal	1226	7007
Carboplatin + paclitaxel (3 weekly)	Gynaecological	1116	4679
Carboplatin AUC 2 - 5	Gynaecological	907	3486
Capecitabine 35days + RT	Gastrointestinal	907	910
Cisplatin	Head & neck	847	1507
Carboplatin + etoposide IV 3 day	Thoracic	740	2099
Sunitinib	Urological	677	2555
Carboplatin & Gemcitabine days 1+8	Thoracic	612	1660
Capecitabine	Gastrointestinal	583	2530
Cisplatin	Gynaecological	557	2548
Gemcitabine weekly	Gastrointestinal	549	1588
Epirubicin, oxaliplatin & Capecitabine (EOX)	Gastrointestinal	495	1793
Epirubicin, cisplatin & Capecitabine (ECX)	Gastrointestinal	480	1747
Capecitabine + oxaliplatin 21day	Gastrointestinal	457	1841
Erlotinib	Thoracic	441	1037
Bleomycin, etoposide & cisplatin (BEP) 3 & 5 day	Urological	406	989
Docetaxel 100mg/m ² (21 day)	Breast	399	1309
Temozolomide	CNS	369	1886
Fluorouracil + folinic acid weekly	Gastrointestinal	368	1007

Table 10: The top 20 chemotherapy regimen and diagnosis site combinations ordered by patient number (largest to smallest).

The names used for chemotherapy regimens map onto the national systemic anticancer therapy audit nomenclature. Carboplatin AUC 2-5 incorporates weekly and 3-weekly regimens. The regimen docetaxel 100mg/m² (21 day) includes primary prophylactic granulocyte colony stimulating factor. AUC, area under the curve. RT, radiotherapy. IV, intravenous. CNS, central nervous system.

Chemotherapy Regimen	Diagnosis Site	Number Cycles	Number Patients	Combined Febrile Neutropenia & Neutropenic Sepsis Rate % (patient count)
Oxaliplatin & modified de Gramont (OxMdG)	Gastrointestinal	7007	1226	4.8 (59)
Epirubicin and Cyclophosphamide (EC)	Breast	6907	1586	10.5 (167)
Carboplatin + paclitaxel (3 weekly)	Gynaecological	4679	1116	4.5 (50)
Carboplatin AUC 2 - 5	Gynaecological	3486	907	1.3 (12)
Sunitinib	Urological	2555	677	0.9 (6)
Cisplatin	Gynaecological	2548	557	2.9 (16)
Capecitabine	Gastrointestinal	2530	583	0.2 (1)
Carboplatin + etoposide iv 3 day	Thoracic	2099	740	8.8 (65)
Temozolomide	CNS	1886	369	0.5 (2)
Capecitabine + oxaliplatin 21day	Gastrointestinal	1841	457	0.7 (3)
Irinotecan + modified de gramont (IrMdG)	Gastrointestinal	1796	320	8.1 (26)
Epirubicin, oxaliplatin & Capecitabine (EOX)	Gastrointestinal	1793	495	7.1 (35)
All capecitabine	Breast	1778	316	1.3 (4)
Epirubicin, cisplatin & Capecitabine (ECX)	Gastrointestinal	1747	480	3.8 (18)
Carboplatin & Gemcitabine days 1+8	Thoracic	1660	612	5.6 (34)
Gemcitabine weekly	Gastrointestinal	1588	549	2.2 (12)
Cisplatin	Head & neck	1507	847	9.1 (77)
Docetaxel 75mg/m ² (21 day)	Urological	1496	258	5.4 (14)
Docetaxel 100mg/m ² (21 day)	Breast	1309	399	4.8 (19)
Docetaxel (75mg/m ²)	Breast	1295	343	16.3 (56)

Table 11: The top 20 chemotherapy regimen and diagnosis site combinations ordered by number of chemotherapy cycles (largest to smallest).

The names used for chemotherapy regimens map onto the national systemic anticancer therapy audit nomenclature. Carboplatin AUC 2-5 incorporates weekly and 3-weekly regimens. The regimen docetaxel 100mg/m² (21 day) includes primary prophylactic granulocyte colony stimulating factor. AUC, area under the curve. IV, intravenous. CNS, central nervous system.

Four chemotherapy regimen and diagnosis site combinations had a high combined risk of febrile neutropenia or neutropenic sepsis according to the definition of febrile neutropenia specified in international guidelines which is >20% (24). Thirteen combinations were within the limits of the intermediate risk group (10 to ≤20% risk), but notably, many of these had low numbers experiencing the neutropenic infective complication. Table 12 displays the high and intermediate risk chemotherapy regimen and diagnosis site combinations. All remaining combinations were low risk, representing the greatest proportion of chemotherapy delivered. Overall, 87.3% (n=117) chemotherapy regimen and diagnosis site combinations had a combined risk of febrile neutropenia or neutropenic sepsis less than 10%, and 64.9% (n=87) had a combined risk less than 5%.

Chemotherapy Regimen	Diagnosis Site	Combined Febrile Neutropenia & Neutropenic Sepsis Rate % (patient count)
Doxorubicin + ifosfamide	Soft tissues	66.7 (18)
Bleomycin, etoposide + cisplatin (BEP) 3 & 5 day	Urological	24.4 (99)
Doxorubicin 75mg/m ²	Soft tissues	23.9 (28)
Doxorubicin 75mg/m ²	Gynaecological	23.3 (7)
Docetaxel (75mg/m ²)	Breast	16.3 (56)
Carboplatin + paclitaxel (3 weekly)	Head & neck	15.4 (4)
Cisplatin + doxorubicin	Gynaecological	15.2 (5)
Vinorelbine IV	Thoracic	14.7 (5)
Cyclophosphamide, doxorubicin + vincristine (CAV)	Thoracic	14.3 (5)
Cisplatin + etoposide (3 day)	Urological	13.8 (4)
Cisplatin + etoposide (3 day)	Thoracic	13.3 (32)
Bevacizumab + carboplatin + gemcitabine	Gynaecological	13.2 (5)
Carboplatin + etoposide IV 3 day	Gastrointestinal	12.5 (7)
Folfinirox	Gastrointestinal	11.5 (7)
Fluorouracil, epirubicin + cyclophosphamide (FEC) 60 or 75	Breast	11.3 (22)
Cisplatin + docetaxel + fluorouracil	Head & neck	11.2 (14)
Epirubicin and Cyclophosphamide (EC)	Breast	10.5 (167)

Table 12: The chemotherapy regimen and diagnosis site combinations with a high and intermediate risk of combined rate of febrile neutropenia and neutropenic sepsis.

The horizontal line demarcates the combined risk of febrile neutropenia and neutropenic sepsis into high risk (>20%), intermediate risk (10 to ≤20%).

2.4.2.3 Chemotherapy given concurrently with monoclonal antibodies or granulocyte colony stimulating factor

Four chemotherapy regimen and diagnosis combinations were given both on their own and with a subset of patients given either primary or secondary prophylactic granulocyte colony stimulating factor concurrently with the cytotoxic drugs. Three of the same chemotherapy regimens were also given in combination with trastuzumab. In total, there were 6 chemotherapy regimen and diagnosis combinations given concurrently with targeted agents, namely either trastuzumab or bevacizumab. The breakdown of these regimens is displayed in Table 13 along with the neutropenic complication risks by all patients receiving the regimen and diagnosis combination and the subsets of patients receiving the concurrent therapies.

Chemotherapy Regimen	Diagnosis Site	Number Cycles	Number Patients	Neutropenic Sepsis Rate (patient count)	Febrile Neutropenia Rate (patient count)	Combined Febrile Neutropenia & Neutropenic Sepsis Rate % (patient count)
Bep 3 day		747	292	2.1 (6)	22.9 (67)	25.0 (73)
Bep 3 day + GCSF	Urological	49	30	10 (3)	30 (9)	40.0 (12)
All BEP 3 day		796	322	2.8 (9)	23.6 (76)	26.3 (85)
EC		4914	1034	1.6 (17)	5.6 (58)	7.3 (75)
EC + GCSF		1381	383	1.3 (5)	19.3 (74)	20.6 (79)
EC + Trastuzumab + GCSF	Breast	382	116	0 (0)	9.5 (11)	9.5 (11)
EC + Trastuzumab		230	53	0 (0)	3.8 (2)	3.8 (2)
All EC		6907	1586	1.4 (22)	9.1 (145)	10.5 (167)
Docetaxel 100mg/m2 + GCSF		825	254	0.4 (1)	3.5 (9)	3.9 (10)
Docetaxel 100mg/m2 + Trastuzumab + GCSF	Breast	484	145	0 (0)	6.2 (9)	6.2 (9)
All Docetaxel 100mg/m2 (21 day)		1309	399	0.3 (1)	4.5 (18)	4.8 (19)
Docetaxel		644	167	4.2 (7)	9.6 (16)	13.8 (23)
Docetaxel + GCSF		300	82	1.2 (1)	24.4 (20)	25.6 (21)
Docetaxel + Trastuzumab	Breast	196	48	0 (0)	8.3 (4)	8.3 (4)
Docetaxel + Trastuzumab + GCSF		155	46	2.2 (1)	15.2 (7)	17.4 (8)
All Docetaxel (75mg/m²)		1295	343	2.6 (9)	13.7 (47)	16.3 (56)
Carboplatin + paclitaxel (3 weekly)		4491	1071	0.3 (3)	4.2 (45)	4.5 (48)
Carboplatin + paclitaxel (3 weekly) + Bevacizumab	Gynaecological	188	45	0 (0)	4.4 (2)	4.4 (2)
All Carboplatin + paclitaxel (3 weekly)		4679	1116	0.3 (3)	4.2 (47)	4.5 (50)
Oxaliplatin + modified de Gramont		6784	1190	1 (12)	3.9 (46)	4.9 (58)
Oxaliplatin + modified de Gramont + bevacizumab	Gastrointestinal	223	36	0 (0)	2.8 (1)	2.8 (1)
All oxaliplatin and modified de Gramont		7007	1226	1.0 (12)	3.8 (47)	4.8 (59)
Capecitabine		1604	285	0.7 (2)	0.7 (2)	1.4 (4)
Capecitabine + Trastuzumab	Breast	174	31	0 (0)	0 (0)	0.0 (0)
All capecitabine		1778	316	0.6 (2)	0.6 (2)	1.3 (4)

Table 13: Table showing the breakdown of chemotherapy regimen and diagnosis site combinations which include either concomitant GCSF or targeted therapies or both.

The three chemotherapy regimen and diagnosis combinations which are sometimes given concomitantly with granulocyte colony stimulating factor all show that the subset of patients who receive granulocyte colony stimulating factor are at greater risk of either febrile neutropenia or neutropenic sepsis, than their counterparts who do not receive granulocyte colony stimulating factor. In the patients who receive bleomycin, etoposide + cisplatin (BEP) over 3 days for urological cancer, this is a reflection of approximately 5 times greater risk of neutropenic sepsis, rather than an increased risk of febrile neutropenia. In the other two chemotherapy regimen and diagnosis combinations (epirubicin and cyclophosphamide for breast cancer and docetaxel 75mg/m² for breast cancer), the combined increased risk of febrile neutropenia or neutropenic sepsis is due to increased risk of febrile neutropenia.

Three out of the 4 chemotherapy regimen and diagnosis combinations given concurrently with trastuzumab had a lower rate of combined febrile neutropenia and neutropenic sepsis than when compared to the same populations when chemotherapy was delivered without the trastuzumab. The prevalence of febrile neutropenia and neutropenic sepsis in the populations receiving bevacizumab was so small that conclusions regarding the influence of bevacizumab on the neutropenic complication rate cannot be drawn.

2.4.3 Comparison of neutropenic complications to published data

Table 14 displays the comparison to published data. The febrile neutropenia or neutropenic sepsis rates identified in the Leeds population data were underestimated by more than 10% in 66.7% of the published trials, overestimated by more than 10% in 13.3% of the published trials, and within 10% of the Leeds population data rates in 13.3% of the trials. In contrast, the rates of uncomplicated neutropenia identified in the Leeds population data were overestimated by more than 10% in 60.0% of the published trials, underestimated by more than 10% in 26.7% of the published trials, and within 10% of the Leeds population data in 14.3% of the published trials. For example, with epirubicin and cyclophosphamide given for breast cancer the combined febrile neutropenia and neutropenic sepsis rate of 10.5% in the Leeds population data compares to 6.0% in both the reported trials; the Leeds population data uncomplicated neutropenic rate of 34.7% compares to 34.0% and 43.0% in the published trials.

Of the 4 chemotherapy regimens where at least one of the published trials reported a noticeably higher uncomplicated rate of neutropenia, 3 were for thoracic cancers (carboplatin and etoposide (trial 1), carboplatin and gemcitabine (trial 1), cisplatin and etoposide (trial 2)).

Table 14: Continued on next page

Regimen (comparator trials)		Site	FN/NS rate (%) (Number in dataset)	Leeds population data	Published trials	Neutropenic rate	Neutropenic rate	Variances in the published data
				Neutropenic rate	FN rate (%) (Number in trial arm)	Neutropenic rate		
Epirubicin and Cyclophosphamide (EC) (119, 120)	Breast		10.5 (1417)	34.7	1. 6.0 (751)	2. 6.0 (104)	43	1. Changed to 2 weekly chemotherapy after 284 patients. 2. Reports grade 4 neutropenic rate and FN definition is not specified.
					1. Not reported (58)*	2. <1.2 (83)	24.1	2. Leukopenia <1.5 x10 ⁹ /L reported.
Cisplatin (121, 122)	Head & Neck		9.1 (847)	20.2	1. 14.0 (339)	2. 2.5 (398)	10.0 [†]	1. Use of GCSF was allowed, definition of FN used leukocytes <2.0 x10 ⁹ /L. 2. If episode of FN, use of GCSF mandatory for subsequent cycles.
					1. 7.0 (110)	2. 4.5 (447)	60.0 [†]	
Carboplatin + etoposide IV 3 day (125, 126)	Thoracic		8.8 (740)	38.4	1. 1.7 (1321)	2. 1.0 (209)	32.6	2. 600mg/m ² IV infusion of 5-FU used compared to 1200mg/m ² at Leeds.
					1. 8.0 (388)	2. 4.2 (501)	41.7	
Bleomycin, etoposide + cisplatin (BEP) 3 & 5 day (123, 124)	Urological		24.4 (406)	83.7	1. 14.0 (339)	2. 2.5 (398)	10.0 [†]	1. Use of GCSF was allowed, definition of FN used leukocytes <2.0 x10 ⁹ /L. 2. If episode of FN, use of GCSF mandatory for subsequent cycles.
					1. 7.0 (110)	2. 4.5 (447)	60.0 [†]	
Carboplatin + Oxaliplatin & modified de Gramont (OxMdG)	GI		4.9 (1190)	25.9	1. 1.7 (1321)	2. 1.0 (209)	32.6	2. 600mg/m ² IV infusion of 5-FU used compared to 1200mg/m ² at Leeds.
					1. 8.0 (388)	2. 4.2 (501)	41.7	
Carboplatin + paclitaxel (3 weekly) (129, 130)	Gynae		4.5 (1071)	25.4	1. 8.0 (388)	2. 4.2 (501)	37.0 [†]	
					1. 21.0 (255)	2. 4.2 (501)	45.7	
Docetaxel (75mg/m ²) (131, 132)	Breast		17.7 (249)	25.4	1. 21.0 (255)	2. 7.4 (190)	83.7	1. Used 100mg/m ² docetaxel, but 36% received dose reduction. 2. Given GCSF if developed grade 4 uncomplicated neutropenia, FN, or documented infection (17.9% in total).
					1. 21.0 (255)	2. 7.4 (190)	83.7	

Epirubicin, oxaliplatin & Capecitabine (EOX) (133, 134)	GI	7.1 (495)	21.6	1. 7.8 (232) 2. 3.5 (112)	27.6 23.2	2. Prospective observational study using modified EOX (capecitabine days 1-14 instead of 1-21).
Carboplatin & Gemcitabine days 1+8 (135, 136)	Thoracic	5.6 (612)	26.3	1. 9.0 (217) 2. 6.0 (219)	51.0[‡] 29.4	
Cisplatin + etoposide (3 day) (137, 138)	Thoracic	13.3 (241)	46.1	1. 6.0 (324) 2. 12.0 (378)	68.0 84.0^f	
Doxorubicin + ifosfamide (139, 140)	Soft tissues	66.7 (27)	77.8	1. 4.6 (149) 2. 46.0 (224)	92.0 42.0	1. Uses doxorubicin 50mg/m ² and ifosfamide 5g/m ² compared to doxorubicin 60mg/m ² and ifosfamide 9g/m ² at Leeds. 2. Uses doxorubicin 75mg/m ² and ifosfamide 10g/m ² with primary prophylactic GCSF.
Doxorubicin 75mg/m² (140, 141)	Soft tissues	23.9 (117)	43.6	1. 9.1 (110) 2. 13.0 (223)	53.6[‡] 37.0	
Doxorubicin 75mg/m² (142, 143)	Gynae	23.3 (30)	43.3	1. 5.0 (171) 2. 4.9 (82)	43.0 30.5^f	1 & 2. Use doxorubicin 60mg/m ² compared to 75mg/m ² at Leeds. 1. Reports grade 4 neutropenia only.
Carboplatin AUC 2-5 (144, 145)	Gynae	1.3 (907)	11.5	1. 0.6 (174) 2. Not reported (455)**	12.0^f 10.0[†]	
Sunitinib (146, 147)	Urology	0.9 (677)	5	1. 0.5 (375) 2. ≤1.0 (548)	12.0 20.0	

Table 14: Table showing Leeds regimen and diagnosis site combination rates of febrile neutropenia and uncomplicated neutropenia in comparison to published figures.

Table continues from page 52 to 53.

FN, febrile neutropenia. NS, neutropenic sepsis. IV, intravenous. AUC, area under the curve. Numbers in red are >10% higher than the Leeds population data output. Numbers in green are >10% lower than the Leeds data output. *A study with only n=40 receiving single agent cisplatin reported a febrile neutropenia rate of 2.5%. ** A study with only n=30 receiving single agent carboplatin reported a febrile neutropenia rate of 0.0%.

^f Denotes trial data where the full blood count is prospectively measured more frequently than the standard length of the chemotherapy regimen cycle.

[†] Denotes where leukocytes are reported and not neutrophils. [‡] Denotes where granulocytes are reported and not neutrophils.

The 4th regimen was docetaxel for breast cancer (trial 2), where 17.9% of the trial patients received granulocyte colony stimulating factor compared to 32.9% of patients in the Leeds population data set. Similar differences were not seen in the febrile neutropenia or neutropenic sepsis rates for these regimen and diagnosis combinations.

2.5 Discussion

2.5.1 Main Findings

The key methodology underpinning this work was successful construction of the Markov model that was representative of the most severe events and frequency of events experienced by patients during a cycle of chemotherapy. This enabled both visualisation and quantification of the pathways, identifying many pathway variants and most importantly, establishing the prevalence of febrile neutropenia in all chemotherapy regimens given to the unselected patient population served by Leeds Cancer Centre. This was the first time this methodology has been applied to pathways of patients on chemotherapy, thus documenting the baseline pathways for modelling of interventions and to inform further work.

Using the Markov model to look at subsets of patients receiving EC and OxMdG chemotherapy, over 75% of patients had no unplanned hospital contact during the first cycle of chemotherapy, but this reduced to less than 25% over all the planned cycles of both regimens, indicating that it is common place for patients to require some form of urgent care during a course of chemotherapy, regardless of the intent of treatment. It is of concern that there are patients who have no contact with the hospital, but are neutropenic on bloods taken at their GP practice. This in itself does not prove they have febrile neutropenia, but it is reasonable to assume there is an indication for the blood test, which may include symptoms compatible with febrile neutropenia. The all cause emergency admission rate is high at 13.3% and 28.0% for EC and OxMdG respectively, not surprisingly higher in the regimen given most commonly for palliative intent (OxMdG), reflecting complications associated with burden of disease. However, without formal statistical analysis, the all cause emergency admission rate during cycle 1 only, appears higher in those receiving EC than it is in those receiving OxMdG and in subsequent cycles, perhaps reflecting the higher doses and associated side effects of an adjuvant chemotherapy regimen and the “unknown” of the first cycle.

The proportion of patients at Leeds who were admitted with febrile neutropenia or worse and subsequently died during the same admission was low (EC 0.8% and OxMdG 4.0%), but confirms that neutropenic sepsis remains a life-threatening complication of both adjuvant and

palliative chemotherapy. With this in mind, and the fact that patients are strongly advised to seek advice from the cancer centre if they have any symptoms suggestive of febrile neutropenia, it is somewhat surprising that the proportion of patients receiving EC chemotherapy in whom febrile neutropenia was excluded is lower than the proportion who were diagnosed with febrile neutropenia or worse in each of the 6 cycles and across all cycles. It might be expected that patients in whom febrile neutropenia was excluded were included in a different health state, but this does not appear to be the case. However, a proportion of those receiving EC had contact with the GP whilst neutropenic, which was not true in the OxMdG group. Perhaps there was a higher attendance at GP practices with complications during EC chemotherapy than was captured by this data, such as consultations where no full blood count was sent to the central laboratory.

As expected, the highest rate of febrile neutropenia or neutropenic sepsis in the EC group was in cycle 1, where it was approximately double the rate of subsequent cycles. This supports the use of cycle 1 chemotherapy regimens in selection of patients for the study profiling neutrophil counts during chemotherapy (45). The rate of febrile neutropenia or neutropenic sepsis across all cycles during EC and OxMdG was notably larger than single cycles at 11.0% and 4.8%, indicating that it was mostly different patients who experienced the complication in each cycle.

As discussed in 2.5.2, the Leeds population data captures prophylactic granulocyte colony stimulating factor use. The only regimen at Leeds Cancer Centre where granulocyte colony stimulating factor was given routinely as primary prophylaxis was adjuvant docetaxel for breast cancer. In each of the other three regimens where granulocyte colony stimulating factor was captured (BEP, EC and palliative docetaxel ($75\text{mg}/\text{m}^2$), the rate of febrile neutropenia or neutropenic sepsis was higher where granulocyte colony stimulating factor was used. This reflects it being used as secondary prophylactic granulocyte colony stimulating factor, hence only those patients with high risk characteristics, such as febrile neutropenia in the previous cycle, received it. Other concurrent therapy delivered during the time limits of the data capture included targeted therapy. In the Leeds population data, the concurrent use of trastuzumab with docetaxel $100\text{mg}/\text{m}^2$ in the adjuvant setting led to a higher rate of febrile neutropenia or neutropenic sepsis than compared to the chemotherapy alone. This concurs with reports of this combination of systemic anticancer therapy in the literature (148, 149). However, in the Leeds population data the concurrent use of trastuzumab with the palliative dose of docetaxel ($75\text{mg}/\text{m}^2$) resulted in a lower rate of febrile neutropenia or neutropenic sepsis, which contrasts with the literature which reports an increase, as in the adjuvant setting

(150). The reasons for this are unclear, but may be because patients receiving the adjuvant dose have often been given a course of EC chemotherapy prior to the docetaxel.

When comparing the Leeds population data outputs to comparable published trial data, the Leeds data tended to underestimate the uncomplicated neutropenic rates and overestimate the febrile neutropenic rates. As the Leeds population data were collected retrospectively, full blood counts were only measured mid chemotherapy cycle as a result of symptom-led assessments or pre-planned procedures, whereas the trials tended to prospectively measure blood counts. For example, in one of the cisplatin and etoposide trials for thoracic cancers, the full blood count was measured on day 8, 9, 10 and 15, and in one of the doxorubicin and ifosfamide trials, it was measured on day 1, 8, 11, 15, 18 and 21 (138, 139). Therefore this could explain why these published data tended to report uncomplicated neutropenia to be so much higher than the Leeds population data, except in the example of carboplatin and gemcitabine for thoracic cancer, where both the trials and in the Leeds practice, a full blood count is measured on day 8, yet trial 1 (Table 14) still reports a noticeably higher uncomplicated neutropenic rate. Moreover, if the higher rate of uncomplicated neutropenia was solely due to the prospective collection of neutrophil counts, one might expect the rate of febrile neutropenia in the published trial to be similar or higher than the Leeds population data, as the knowledge of neutropenia may change patient behaviour in recognition of symptoms and seeking clinical assessment. However, this is not the case; the higher rate of febrile neutropenia in the Leeds population data could, therefore, be attributable more to the inclusion of an unselected patient population, hence justifying the need to map patient-centred real-life baseline clinical pathways.

2.5.2 Strengths & Weaknesses

The key strengths of this work were the volume of Leeds population data and that it was collected for routine clinical care purposes in a mature and detailed electronic health record. The data were from a large and diverse unselected patient population collected over more than ten years, enabling representation of real-life pathways of all comers, in comparison to those identified during selective clinical trials. Close collaboration between the data analyst and the clinician facilitated identification of deficiencies in the methods, idiosyncrasies in the pathways and the generation of successively more accurate model iterations. Using PPM enabled quality assurance through electronic criteria adherence reporting, computation of quality indicators and facilitated identification and checking of anomalies. The use of a Markov model enabled visual representation of the pathways described, aided

comprehensible dissemination of the findings and facilitated the on-going health economic analysis of the aggregated patient numbers traversing each pathway.

In terms of weaknesses, this was a retrospective analysis and as such, was limited by the data available. For example, temperature recordings were not held electronically during the period from which data were extracted, so the presence of blood culture results was used as a surrogate marker for fever. Granulocyte colony stimulating factor administered to inpatients was not captured in the dataset, and therefore only the use of prophylactic granulocyte colony stimulating factor was included. Moreover, uncomplicated neutropenia is assumed to be under-reported in this dataset. It is reasonable to surmise that the prevalence of uncomplicated neutropenia recorded for patients on weekly chemotherapy regimens, may be more accurate than for chemotherapy regimens given at longer intervals, due to the frequency of blood tests.

A second limitation was the long interval of data collection. Although it enabled larger patient numbers to be included, it introduced the problem of inconsistency of chemotherapy nomenclature over time due to changing prescription and recording systems. The regimens were mapped to the National Systemic Anticancer Therapy (SACT) audit in order to group them in a standardised way, however, in some instances, this resulted in loss of granularity of data. For example, single agent carboplatin was represented in the Leeds raw data as carboplatin weekly and carboplatin 3-weekly. The SACT dataset merges this to carboplatin AUC 2-5, so the delivery interval is not distinguished by the name.

Finally, whilst efforts were made during the literature search to select publications with characteristics comparable to those of the Leeds population dataset, some variances could not be eliminated. For example, both trials of bleomycin, etoposide and cisplatin for urological tumours used granulocyte colony stimulating factor that was not standard practice at Leeds, and one of these trials recruited good prognosis patients only, meaning they received three cycles of chemotherapy, whereas the reported Leeds population data included patients who received either 3 or 4 cycles. Six trials reported either granulocytopenia or leukopenia rather than neutropenia and although many broke the neutropenia down into grades 3 and 4, two only reported grade 4, reducing the comparative proportion of uncomplicated and febrile neutropenia. It is, however, the overall patterns identified in the difference between reported rates of uncomplicated and complicated neutropenia which are of particular value.

2.5.3 Implications

In October 2016, the Department of Health published the “Accelerated Access Review” which was intended to be the guiding principal for introducing innovation into healthcare and is suitable for medical technologies and diagnostics (151). Chapter 4 in the review addresses the importance of digital infrastructure to capture information on the use of innovations and associated outcomes. The pathway modelling work described herein is an example of how the digital infrastructure at LTHT is detailed and robust enough to capture clinically useful information and represents a means through which data can be meaningfully shared and used in the first steps towards informing practice change. It also identified the current unselected patient pathways, in line with the review which recommends “develop evidence of performance in real-world settings”. One of the focuses of this project as a whole has been to develop evidence in the real-world setting, as shown by this pathway mapping and comparing it to published trial data, and the assessment of performance of the device specifically in neutropenic patients (Chapter 5). However, this mapping provides a high-level view of the clinical pathways for large numbers of patients, aggregating patients within specific pathways. This does not give the whole view of individual patient experience, which may be better captured on a limited number of patients, but in extensive detail through lean pathway mapping of patients’ journey during chemotherapy, the methodology of which has been described (152). This could serve as another measure of how accurately the data collection and generated pathways reflect what actually happens in the patient journey.

This pathway mapping provides data on the real-life risk of neutropenic complications, which cannot be obtained through published data from clinical trials in carefully selected patient populations. In addition, it provides data not always present in national cancer datasets in the UK such as the National Cancer Waiting Times Monitoring Dataset (NCWTMD), Cancer Outcomes and Services Dataset, Systemic Anticancer Therapy Dataset and cancer registries. Some aspects of care are not well represented in the national datasets such as suspected cancer diagnoses not referred by a general practitioner, care prior to a 2-week wait referral and care post referral to community palliative care teams. These specific care elements were not captured here due to time boundaries implemented either side of the delivery of chemotherapy. However, patients crossing the boundaries of primary and secondary care were captured, facilitated by the UK model of central rather than peripheral laboratories analysing samples from primary care.

The most tangible value of this work for the purposes of this thesis was to inform selection of patients at high risk of neutropenic complications for the clinical trial aiming to profile neutrophil counts during chemotherapy (Chapter 6). It provides information above and beyond that available through other sources, and it both accurately represents the local population and is available on a large scale. It has done this through identification of the rates and counts of neutropenic complications by chemotherapy regimen and diagnosis combination. This was considered alongside individual patient characteristics and recruitment logistics for trial approach.

The value of this work for the wider project was to quantify the baseline patient pathways so as to be able to model potential practice changes and later to be able to quantify these changes both in terms of clinical and health economic benefits or otherwise. The Markov model enables estimates of cost and outcomes by assigning estimates of resource usage (using Healthcare Resource groups (HRGs)) and health outcomes to health states and transitions between states, then running the model over a large number of the repeated Markov cycles. HRGs are standard groupings of clinically similar treatments, which are used to charge for treatment delivered within the NHS and are used to help institutions understand the clinical activity they deliver. A finished consultant episode is a number of activities grouped together to indicate one episode of care such as an admission. HRGs contain an “average” payment for finished consultant episodes, therefore, do not account for high costs sometimes associated with variant pathways such as admission to intensive care (153). As such, the frequency and cost of variant pathways may negatively impact provider institution finances, making understanding the baseline pathways of paramount importance to quantify the true impact of new innovations within the NHS.

The intention is for the Markov model to be developed into a dynamic visual representation of patients traversing the defined pathways. Attempts to do this have started using the software tool “Network Tools for Intelligent Simulation” (NETIMIS) (154), and have been well received whilst embedded within presentations at National conferences (155-157). This will enable visual recognition of unmet needs in the patient pathway such as bottle-necks, common variant pathways and process delays contributing to delayed targets such as those mandated by the National Cancer Waiting Time Monitoring Dataset. Dynamic visualisation of the pathways will be invaluable in communicating benefits to changing patient pathways to the wide range of stakeholders which includes patients, clinical staff, laboratory staff, NHS managers, finance staff, commissioners. Moreover, the formatted dataset alone is a rich source of information which will be shared with clinical staff within LTH in order that it can

be used to better inform clinical practice and patients of the risks associated with chemotherapy delivery.

2.5.4 Conclusion

This chapter serves as an exemplar of advantageous secondary use of data collected primarily for routine care purposes in electronic health records. It has demonstrated that a surprisingly high proportion of real-life care pathways during chemotherapy differ from those which represent the expected standard of care. It also suggests the prevalence of febrile neutropenia in the unselected patient population served by Leeds Cancer Centre is frequently different to the reported rates in the carefully selected populations of phase III clinical trials. Hence it shows there is value to be gained through establishing real-life patient-centred clinical pathways prior to introducing innovation within healthcare. One potential advantage is the provision of a platform through which true benefits can go on to be quantified at a local level in a complex health system. In addition to using this work to inform patient selection for the neutrophil profiling trial reported in a subsequent chapter of this thesis, collaborative work with health economists and a data analyst continues using the established pathways to model the potential impact on clinical outcomes and cost benefits of home blood count monitoring.

Chapter 3 Patient and professional perceptions of home blood count monitoring

3.1 Introduction

The availability of advancing technology makes the use of point of care testing (POCT) attractive in a health-care system such as the National Health Service, which is required to continually improve efficiency and patient satisfaction. Testing for glucose in urine is often referred to as one of the first examples of POCT. This evolved to patient capillary blood self-testing, which is now such a familiar concept that it is impossible to conceive modern management of diabetes mellitus without patient self-testing of capillary blood samples. Frequent finger-prick blood glucose monitoring in most patients with type-I diabetes mellitus along with self-management using behavioural changes and glucose-lowering medications, is widely accepted as standard practice (158). A phobia of skin prick testing has a negative influence on compliance with blood glucose management (159), but those who tolerate finger-pricks do so with the advantage of achieving tighter HBA1c control (160). This field continues to develop with the ability to self-test glycated protein as an indicator of better longer term glucose control and considerable research directed towards non-invasive methods of blood glucose monitoring (161-163).

A more recent example of successful introduction of testing at the point of care has been patient self-management of International Normalised Ratio (INR) in reducing further thrombotic events in those anticoagulated with warfarin (76). Such practices have been successful as point of care self-testing necessitates patient education, enables patient empowerment and control over their own care, as well as offering convenience, piece of mind and efficiency of care with early indication of poor control (in the case of diabetes and warfarin treatment) and in some cases, a reduction in dependency on the health-care profession. In order for such benefits to be realised, it is paramount that patient self-test point of care monitoring is accompanied by professional support and patient education and training (164-166).

In the scenario of patients with cancer receiving chemotherapy using home blood count monitoring, there is the potential for the capillary tests to be used in a more acute context in comparison to the majority of uncomplicated patients with diabetes mellitus, where it tends to be used for a more chronic indication. The patients with cancer on chemotherapy would only be expected to use the home blood count monitoring for a finite period of time (the duration of chemotherapy) and there may be urgent action required dependent on multiple

factors, one of which is the neutrophil result. The consequence of poor decisions in this patient population can be immediately life-threatening. To counteract the risks of delayed reporting of serious chemotherapy side effects, the next generation of the finger-prick blood count monitoring device is expected to have alerts set at clinician-defined thresholds or time-points to prompt patients to test or contact their cancer care provider. It is also expected to transfer results wirelessly to the care provider, so they can initiate a change in management based on incoming results, if appropriate to do so. This approach is very topical given the recently published National Chemotherapy Board guidelines on “Promoting Early Identification of Systemic Anti-Cancer Therapies Side Effects”, which focuses on empowering patients and proactive monitoring (88).

Technology has been used to enable patients on chemotherapy to report new symptoms and receive management advice or contact from a healthcare professional (167, 168). Some web-based tools used for patient reported outcome measures have a high rate of adherence (169). However, the proposed home blood count monitoring goes a step further by asking patients to perform a procedure (finger-prick) on themselves. An unpublished study carried out in Dundee during the early stages of development of the home blood count testing device, required volunteer patients to finger-prick themselves and put the blood drop in the cartridge required to use the XBC (Prof N. Kearney, Nine-wells Hospital, 2012). Out of 49 patients who tested themselves, 42 reported the finger-prick as painless, 49 indicated they would be happy to test themselves at least weekly, and 39 would be prepared to test daily. This suggests there is potential for patients to be willing to use such a system.

The proposed home blood count monitoring should be classed as a complex intervention, as defined by Medical Research Council (MRC) “Developing and evaluating complex interventions” guidelines (170). This is because implementation will require significant behavioural change by those delivering and receiving the intervention, and there are a number of interacting outcomes. The recognition of the concept of complex interventions, outside of drug development, has been in a state of development (170, 171). The updated MRC guidance expands to non-drug related interventions, but acknowledges on-going debate on the issues surrounding evaluations of such interventions and refers to their guidance as a reference source, not prescriptive rules.

Challenges involved in developing a complex intervention include; identifying existing evidence, identifying and developing the theory, assessing feasibility, modelling process and outcomes, assessing effectiveness, measuring outcomes. Within the remit of assessing

feasibility of home blood count monitoring, and in an attempt to predict and minimise problems of acceptability, compliance, recruitment and retention, this chapter addresses end-user views on willingness to use and methods of using a home blood count monitoring system. The end-users are both patients on chemotherapy and clinicians with responsibility for care of such patients; without the support of both, development, evaluation and ultimately the uptake of home blood count monitoring will be unsuccessful.

This chapter describes the development, conduct and results of two questionnaires, one distributed to patients with cancer and experience of chemotherapy and the other to consultant oncologists. The aim was to establish attitudes of oncology patients and consultants towards the use of patient self-test home neutrophil count monitoring during chemotherapy.

3.2 Objectives

1. a) To establish patient acceptability of using home blood count monitoring to guide management of neutropenic complications.
b) To ascertain acceptability to oncology consultants of their patients on chemotherapy measuring their own blood counts at home, in each of the following three clinical scenarios;
 - i. In patients who are at home, have a fever and require neutropenia to be excluded.
 - ii. Prior to delivery of subsequent chemotherapy cycles to avoid hospital attendance in patients whose neutrophil count has not recovered sufficiently.
 - iii. In the days following chemotherapy delivery to identify those patients potentially at high risk of neutropenic complications.
2. To establish whether patients at risk of neutropenic infections who have a fever would prefer to be inconvenienced by trips to hospital where they are assessed and sent home with no management changes, or to minimise such trips at the expense of a small risk of delaying treatment for a neutropenic infection.
3. Establish the oncology consultant consensus neutrophil threshold to use to recommend urgent clinical assessment in patients on chemotherapy who are at home, have a fever but are otherwise well.

4. Establish if a degree of clinical risk is acceptable to consultants to gain the benefits of reducing unnecessary hospital visits.

3.3 Methods

3.3.1 Oncology patient questionnaire

A questionnaire was developed through an iterative process involving review by;

- members of the Psychosocial Oncology Group at Leeds Institute of Cancer and Pathology (University of Leeds) and Leeds Cancer Centre.
- a patient and public involvement group.
- a focused interview with 10 patients.

Feedback included making the link with neutropenia and infection clearer in the introduction, improving flow of wording, defining start point of travel to hospital i.e. work or home. Due to concerns raised about patient understanding of the risk referred to in question 3, much consideration was given to the presentation of this question, including use of visual analogue scales, Likert scales, and a decision choice experiment. The final questionnaire used a version of pairwise comparison to gather information on respondent choice of current standard care compared to using home blood count monitoring and visual infographic to represent risk. Appendix 1 is a copy of the final questionnaire. The questionnaire was piloted on 15 experienced chemotherapy patients, before distributing to the wider population described. The results of these 15 patients are reported together with all the responses.

The intention was to collect 100 completed questionnaires, a pragmatically chosen sample size. Patients were invited to complete a questionnaire if they were attending an oncology outpatient clinic, were receiving or had previously received cytotoxic chemotherapy and were in one of the following diagnostic categories; breast cancer, gynaecological cancer, prostate cancer, gastrointestinal cancer, germ cell tumours, teenage and young adult cancer.

Statistical analyses were performed using Stata STRS. The Sign test was applied to proportional data to return a p value. The Chi² test was applied to categorical data with more than one category to return a p value. The p value was regarded as statistically significant at <0.05, with a corresponding confidence interval of 95%. Risk thresholds used to categorise clinical risk correspond to percentage risk and negative predictive values (NPV) shown in Table 15. The treating clinical team identified appropriate patients and approved approach for this

questionnaire. As this was a questionnaire exploring attitudes towards service development, formal ethical approval was not sought.

Risk	% risk	NPV
1 in 5	20	80
1 in 7.5	15	85
1 in 10	10	90
1 in 20	5	95
1 in 50	2	98
1 in 100	1	99
1 in 1000	0.1	99.9

Table 15: Risk thresholds of becoming dangerously unwell used in the questionnaires. These were used in the patient questionnaire, question 3, and the consultant questionnaire, question 2b. The corresponding percentage risk and negative predictive value (NPV) are shown.

3.3.2 Oncology consultant questionnaire

A questionnaire was developed to explore consultant attitudes towards their patients on chemotherapy measuring their own blood counts at home using capillary finger-prick blood samples (Appendix 2). This involved first a focused interview with an independent clinical registrar to ensure clarity of meaning of text and questions. Responses were identifiable by respondent name, but there was the option for the response to be anonymous by removal of the front sheet. Responses that were identifiable, were categorised by gender, year of primary medical qualification (either 1990 and earlier or after 1990) using information obtained from the General Medical Council register, and subspecialty (medical or clinical oncology).

All medical and clinical oncology consultants at Leeds Teaching Hospitals NHS Trust, who were not in a period of absence from work, were invited to complete a paper questionnaire. The questionnaire was distributed via the named consultant secretaries. Formal statistical analyses were not planned. A reminder email was sent 3 weeks after distribution of the questionnaire.

Neutrophil thresholds used in the questionnaire correspond either to national and local guidelines for management of febrile neutropenia or higher neutrophil thresholds. The percentage risk used in the questionnaire correspond to specific negative predictive values (NPV) as shown in Table 15. As this was a review of clinical attitudes, prior approval was not sought.

3.4 Results

3.4.1 Oncology patient questionnaire

Question 1

- Question 1 sought to collect demographical information on the respondents.

107 patients completed the questionnaire. No record was kept of numbers of patients that declined to complete it. Table 16 displays demographic details of patients who completed the questionnaire. The age category and length of time taken to travel to Leeds Cancer Centre are shown in Figure 8. The minimum age of respondents was 20 years (n=1) and the maximum was 85 years (n=1). The median age category was 60-69 years and the mode was ≥ 70 years.

Demographic		Percentage (n)
Gender		
Female		51 (55)
Male		49 (52)
Living arrangements		
Lives on own		21 (22)
Lives with others		77 (82)
No answer		3 (3)
Time since most recent chemotherapy		
Within 6 weeks		54 (58)
Greater than 6 weeks ago		46 (49)
Previous experience of febrile neutropenia		
Attended hospital with suspected infection during chemotherapy and been discharged the same day	Yes	20 (21)
	No	77 (82)
	No answer	4 (4)
Admitted to hospital with an infection during chemotherapy	Yes	34 (36)
	No	66 (71)
Experienced both of these scenarios		8 (9)
Experienced neither of these scenarios		55 (59)

Table 16: Demographics of patients who completed the questionnaires.
(n=107)

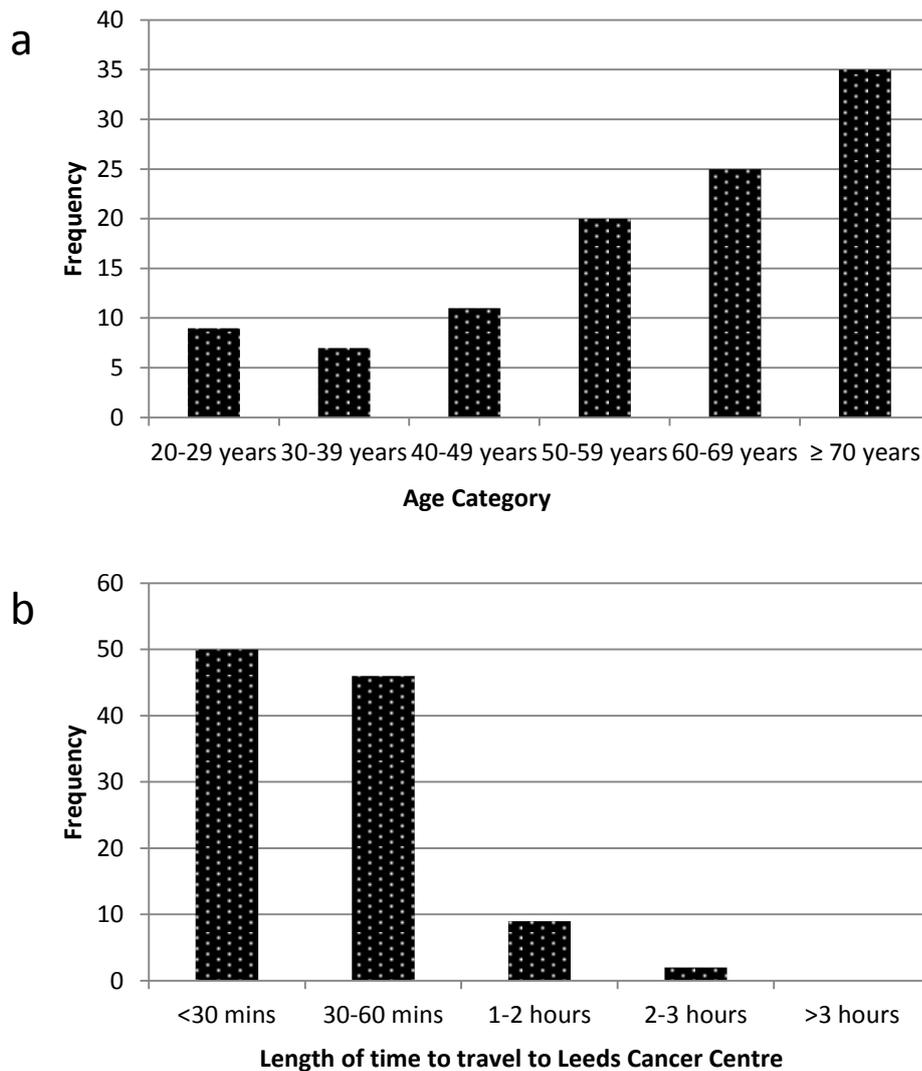


Figure 8: Bar charts displaying demographics of patient questionnaire respondents.

a) Bar chart displaying age distribution. b) Bar chart displaying length of time taken to travel to Leeds Cancer Centre.

Question 2

- Question 2 described a situation where the patient had chemotherapy a week ago, felt tired, but otherwise alright. It sought to assess whether the respondent would prefer the current practice of in hospital assessment including venous blood test and face-to-face reassurance (scenario A), or to use self-test home blood count monitoring and be reassured by the blood result and advice delivered on the device screen (scenario B).

Thirteen (12.1%) respondents chose scenario A and 93 (86.9%) chose scenario B. One respondent did not provide an answer. There were 8 free-text comments from those who chose scenario A which are displayed in Appendix 3, Table 1 and 40 free-text comments from

those who chose scenario B which are displayed in Appendix 3, Table 2. Six out of the 8 comments from those who chose scenario A were related to preferring reassurance from interaction either on the telephone or face-to-face with a healthcare professional. One of the eight comments referred to lack of confidence in doing the blood test, and 1 of the 8 was referring to carer anxiety likely to be caused by having responsibility for the home testing process.

Of the 40 free-text comments by those who chose scenario B, 21 mentioned choosing to use home blood count monitoring due to time saved. Fourteen mentioned reassurance in their answers, but 5 of these were suggesting they would be reassured by the device, 4 indicated some doubt as to whether they would be reassured by the device alone and 7 specifically indicated they would like to be able to telephone to interact with a healthcare professional if necessary. Eleven of the 40 free-text comments specified avoiding travelling a distance as a reason for choosing scenario B and 8 of the 40 specified avoiding hospital attendance as a reason. Two raised concerns regarding the ease of use of the device and 1 mentioned being afraid of finger-pricking, stating it is painful compared to venepuncture.

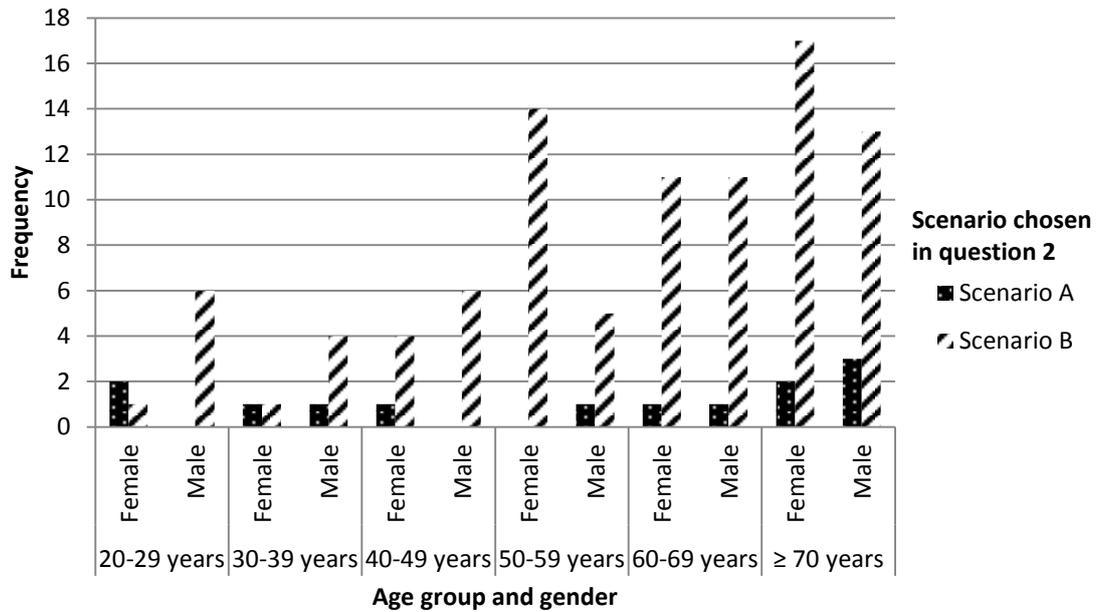
Table 17 shows the scenario chosen according to the demographic information. None of gender, living arrangements, duration of travel to hospital, time since most recent chemotherapy or experience of febrile neutropenia influenced the choice of scenario in question 2 (all p values >0.05). Some of those living within 60 minutes travel duration of the hospital chose scenario A, compared to 100% of those living 1 hour away or longer choosing scenario B. However, even when travel duration was split into this dichotomous variable, it did not reach statistical significance ($p = 0.397$).

Figure 9 displays the scenario chosen in question 2 according to age group. There are small numbers in the lower age categories. There is no statistical difference in the scenario chosen by age category ($p=0.682$). There remains no statistical difference when age categories are split into the dichotomous variables of <40 years and ≥ 40 years ($p=0.219$) or <60 years and ≥ 60 years ($p=0.667$).

Demographic	Choice of scenario in % (n)		p value	
	A	B		
All respondents	12 (13)	88 (93)	<0.001	
Gender				
Female	13 (7)	87 (48)	0.580	
Male	12 (6)	87 (45)		
Living arrangements				
Lives on own	14 (3)	86 (19)	0.942	
Lives with others	12 (10)	87 (71)		
Duration of travel to hospital				
<30 minutes	18 (9)	82 (41)	0.556	
30-60 minutes	9 (4)	89 (41)		
1-2 hours	0 (0)	100 (9)		
2-3 hours	0 (0)	100 (2)		
Time since most recent chemotherapy				
Within 6 weeks	10 (6)	90 (52)	0.442	
Greater than 6 weeks ago	14 (7)	84 (41)		
Experience of febrile neutropenia				
Previously attended hospital with suspected infection during chemotherapy and been discharged the same day	Yes	19 (4)	81 (17)	0.758
	No	11 (9)		
Previously admitted to hospital with an infection during chemotherapy	Yes	14 (5)	86 (31)	0.724
	No	11 (8)		

Table 17: Table showing the scenario chosen in question 2 according to the respondent's demographic information.

Scenario A is the current practice of telephoning the hospital and attending for assessment. Scenario B is using the home blood count monitoring system.



Age group (years)	20-29		30-39		40-49		50-59		60-69		≥ 70	
Gender	F	M	F	M	F	M	F	M	F	M	F	M
Scenario A	2	0	1	1	1	0	0	1	1	1	2	3
Scenario B	0	6	1	4	4	6	14	5	11	11	17	13

Figure 9: Bar graph showing the scenario chosen by respondents in question 2 according to age group and gender.

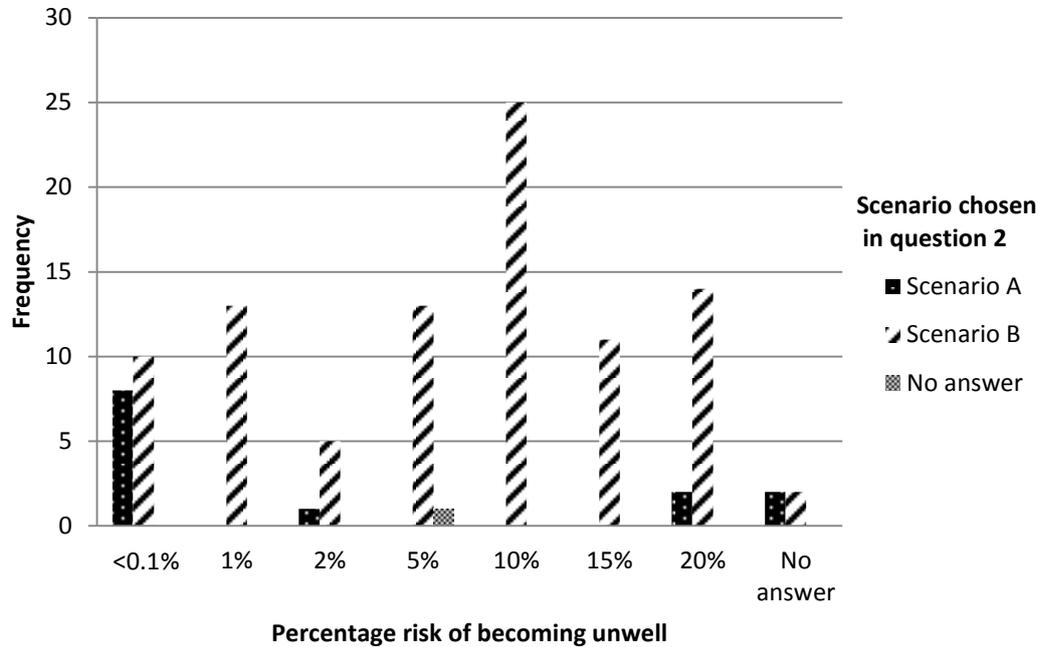
Scenario chosen by age group, $p = 0.682$

Question 3

- Question 3 sought to ascertain what risk of becoming dangerously unwell respondents would accept, to gain the benefits of preventing unnecessary trips to hospital.

Of the 107 respondents, 4 did not answer this question. Only one of these indicated why, and that was because they had selected hospital attendance and face-to-face reassurance in question 2 and therefore felt this was not relevant to them. Where more than one option was marked ($n=9$), the highest risk indicated was used for the analyses as this reflected the boundary of acceptance.

Figure 10 displays the degree of risk respondents indicated they were willing to take. Those who chose scenario A (not home blood count testing) also tended to choose the lowest risk of



	Maximum risk							No answer
	<0.1%	1%	2%	5%	10%	15%	20%	
Scenario A	8	0	1	0	0	0	2	2
Scenario B	10	13	5	13	25	11	14	2
No answer	0	0	0	1	0	0	0	0

Figure 10: Bar graph displaying the maximum risk of becoming seriously unwell that respondents would accept to reduce unnecessary trips to hospital.

Scenario A is the current practice of telephoning the hospital and attending for assessment. Scenario B is using the home blood count monitoring system. Scenario chosen by risk group, $p < 0.001$.

becoming unwell ($p < 0.001$). Appendix 3, Table 3 contains the free-text comments associated with this question. Eight out of the 25 responses explicitly stated they would not want to take any risk of becoming dangerously unwell. Five responses were very positive statements towards using the device, three commented on difficulties answering this question and 1 respondent indicated they would not mind having a trip to hospital as they live within 10 minutes journey.

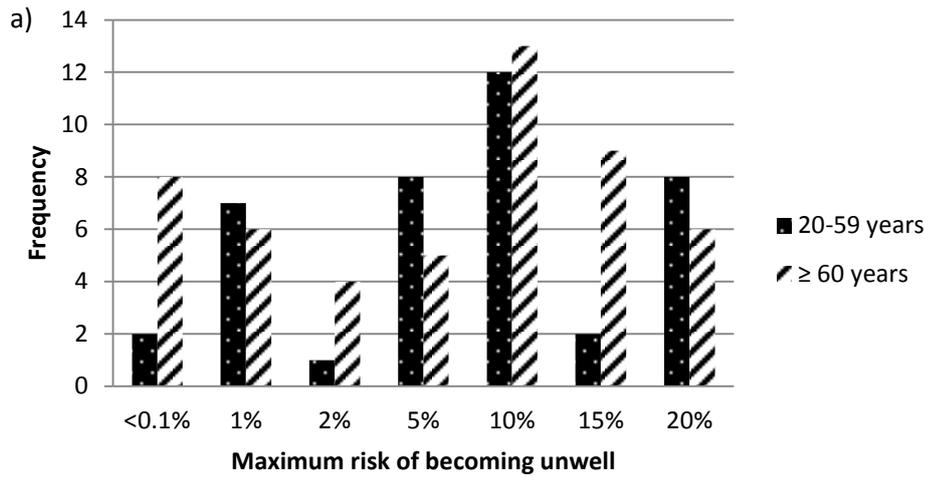
The nurses who interacted with the patients during conduction of this questionnaire had the opportunity to add free-text comments regarding their involvement/discussions with the respondents. There were 6 comments indicating the respondent found the concept of risk very difficult to understand and needed extra explanation. In one instance the respondent had said "It puts the patient in more control. I like it".

All three patient age groups incorporating those 50 years and older, spanned the full range of maximum risk respondents were willing to take to avoid unnecessary trips to hospital (minimum of $< 0.1\%$ to maximum of 20%). The youngest patient group (20-29 years) had the smallest range of risk, with no respondents choosing either the maximum or minimum risk.

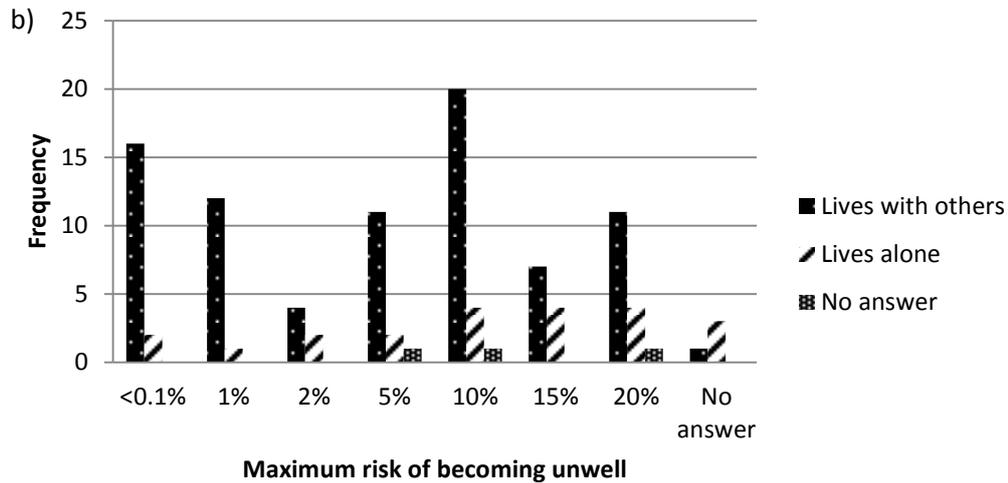
Figure 11a shows that the risk respondents were willing to take was not influenced by age when split into above and below 60 years. Figure 11b shows that the risk respondents were willing to take was not influenced by whether they lived alone or not.

Travel time to get to Leeds Cancer Centre did not influence the risk chosen of becoming dangerously unwell to avoid unnecessary trips to hospital, as shown in Figure 12.

There were no trends between any of the following demographic details and risk respondents were willing to accept; gender ($p = 0.138$), time since last chemotherapy ($p = 0.412$), whether or not the respondents had previously been assessed for febrile neutropenia and sent home ($p = 0.533$), or admitted to hospital with an infective complication ($p = 0.678$).



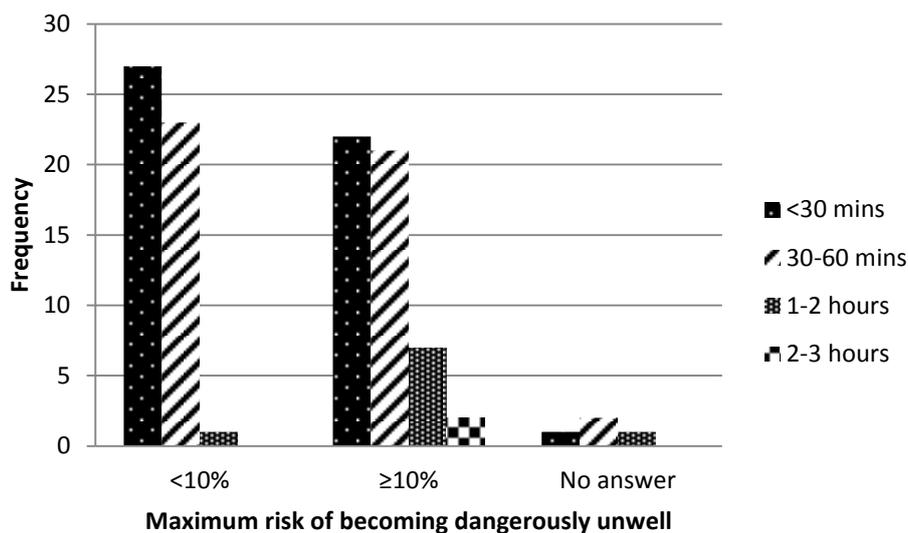
	Maximum risk						
	<0.1%	1%	2%	5%	10%	15%	20%
20-59 years	2	7	1	8	12	2	8
≥ 60 years	8	6	4	5	13	9	6



	Maximum risk							
	<0.1%	1%	2%	5%	10%	15%	20%	No answer
Lives with others	16	12	4	11	20	7	11	1
Lives alone	2	1	2	2	4	4	4	3
No answer	0	0	0	1	1	0	1	0

Figure 11: Bar graph showing maximum risk of becoming dangerously unwell that respondents were willing to accept to avoid unnecessary trips to hospital, by age and living arrangements.

a) Bar graph by age either side of 60 years, $p = 0.398$ and b) Bar graph by living arrangements, $p = 0.317$.



Risk	<30 mins	30-60 mins	1-2 hours	2-3 hours
<10%	27	23	1	0
≥10%	22	21	7	2
No answer	1	2	1	0

Figure 12: Bar graph showing grouped maximum risk of becoming dangerously unwell that respondents were willing to accept to avoid unnecessary trips to hospital, by duration of travel to Cancer Centre. Analysis by all categories of travel duration, $p = 0.750$. When split into travel duration < 60 mins or ≥60 mins, $p = 0.183$.

3.4.2 Oncology consultant questionnaire

Thirty-four of 49 consultants (16 Medical and 33 clinical Oncologists) returned the questionnaires; the response rate was 69.4%. Of the 49, 16 went to Medical Oncologists and 33 went to Clinical Oncologists. Of the 34 returned, 1 was not completed as the consultant no longer gives chemotherapy, and 1 answered the first question only.

Of the 33 completed questionnaires, 10 were from Medical Oncologists, 17 were from Clinical Oncologists and 6 were anonymous. Of the 27 identified respondents, 11 (41%) achieved their primary medical qualification in 1990 or earlier, 16 (59%) achieved this after 1990, 13 (48%) were female and 14 (52%) were male. Amongst either non-responders ($n=15$) or the anonymous group ($n=6$), 6 were Medical Oncologists and 15 were Clinical Oncologists.

Question 1

- Question 1 described 3 scenarios in which patient self-test home blood count monitoring could be used. It sought to assess the acceptability of using it.

Thirteen of the 32 respondents who answered all three parts of question 1, answered “Yes” to all 3 parts. No respondents answered “No” to all three parts of the question.

Q1a: In patients who feel unwell at home and require neutropenia to be excluded.

Of the 33 respondents, 20 (60.6%) indicated “Yes”, 6 (18.2%) indicated “No” and 7 (21.2%) indicated “Not sure”, $p = 0.004$.

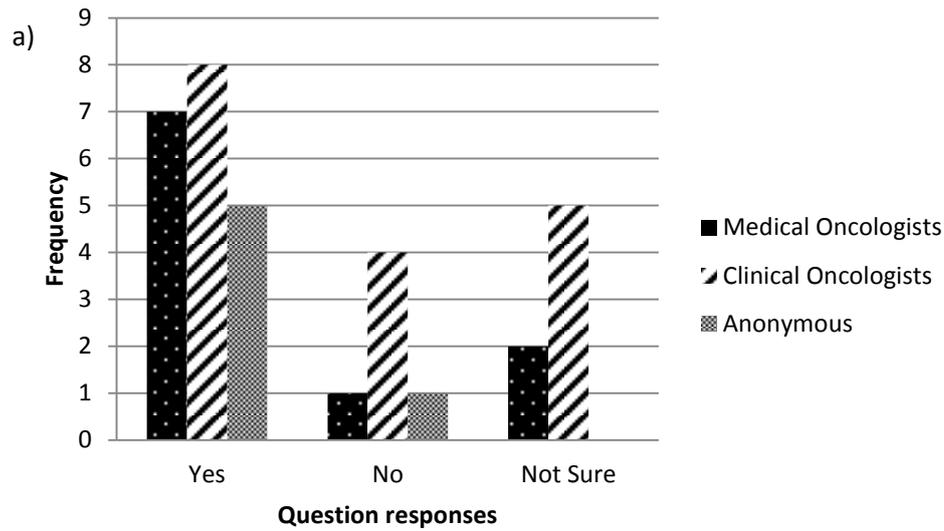
Figure 13 shows these numbers with the breakdown of oncological speciality and year of primary medical qualification. Gender was represented proportionally in each of the three categories. The comments associated with this question are listed in Table 18.

Answer to Q1A	Comment
Yes	<ul style="list-style-type: none"> • “With a pathway for non-neutropenic illnesses”
No	<ul style="list-style-type: none"> • “Yes with telephone consultation” • “Need to be seen if unwell”
Not sure	<ul style="list-style-type: none"> • “Would still want them to come in for assessment” • “I may ask them to come to hosp. if they are unwell” • “Most of my lung cancer patients who are unwell would need to be seen” • “Depends on definition. Would not want to delay attendance”

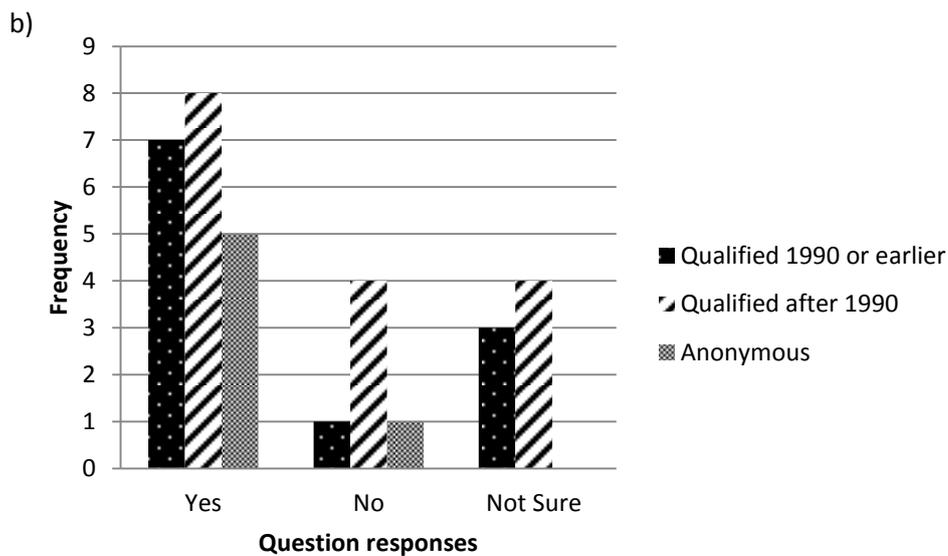
Table 18: Comments associated with Question 1a regarding consultant attitudes towards patients measuring their own blood count at home when they feel unwell and neutropenia is required to be excluded.

Q1b: Prior to delivery of subsequent chemotherapy cycles to avoid hospital attendance in patients whose neutrophil count has not recovered sufficiently.

Of the 32 respondents, 28 (87.5%) indicated “Yes”, 4 (12.5%) indicated “Not sure” and none indicated “No”. Of the 28 who indicated “Yes”, 5 were anonymous. There was no difference in responses according to subspecialty ($p = 0.286$), year of primary medical qualification ($p = 0.846$) or gender ($p = 0.088$). There were no comments associated with this question.



Question response	Yes	No	Not Sure
Medical Oncologists	7	1	2
Clinical Oncologists	8	4	5
Anonymous	5	1	0



Question response	Yes	No	Not Sure
Qualified 1990 or earlier	7	1	3
Qualified after 1990	8	4	4
Anonymous	5	1	0

Figure 13: Frequency of responses to question 1a asking if clinicians would be willing for their patients to measure their blood count at home when they feel unwell and require neutropenia to be excluded.

a) demonstrates the proportion of each response answered by oncological speciality, $p = 0.488$ b) demonstrates the proportion of each response answered according to year of primary medical qualification, $p = 0.571$.

Q1c: In the days following chemotherapy delivery to identify patients at high risk of neutropenic complications, based on the changes in the neutrophil count.

Of the 32 respondents, 24 (75.0%) indicated “Yes”, 8 (25.0%) indicated “Not sure” and none indicated “No”. There was no difference in responses according to subspecialty ($p = 0.286$), year of primary medical qualification ($p = 0.740$) or gender ($p=0.088$).

There were only 2 comments associated with this question. One respondent answered “yes” and commented “For sure!”. The other respondent answered “Not sure” and commented “I'd like to see the data first. How frequently will the tests be done? Daily? For X days? May be a burden to patients and hospital staff”.

Question 2

- Question 2 considers the neutrophil threshold to be used and the acceptable associated risk when a patient on chemotherapy has a fever and is otherwise well and has a neutrophil count measured at home.

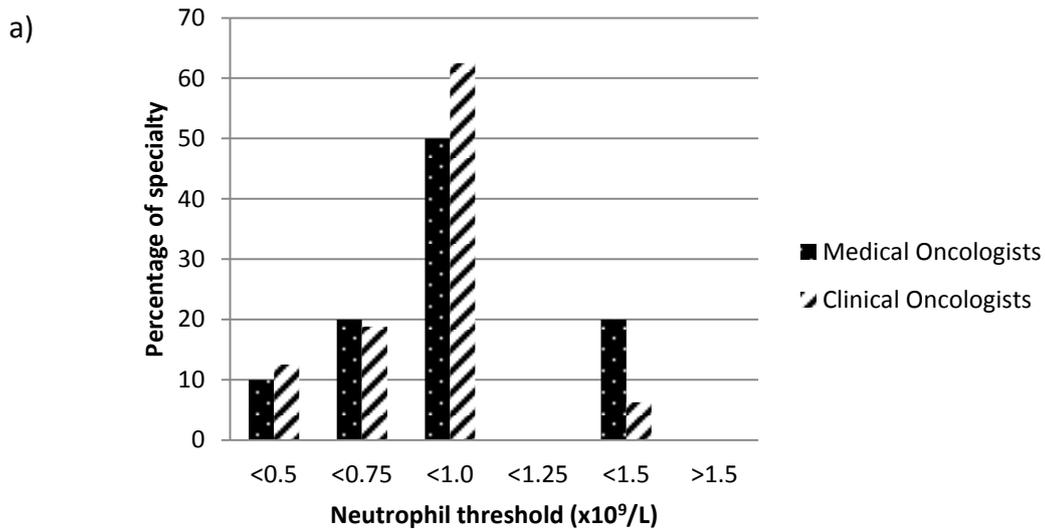
Q2a: Please tick the neutrophil threshold you suggest we use in this scenario to recommend urgent clinical assessment (units are $\times 10^9/L$).

Of the 32 respondents, none indicated a neutrophil count threshold greater than $1.5 \times 10^9/L$. The modal and median threshold was a neutrophil count of $<1.0 \times 10^9/L$, with the range being <0.5 to $<1.5 \times 10^9/L$.

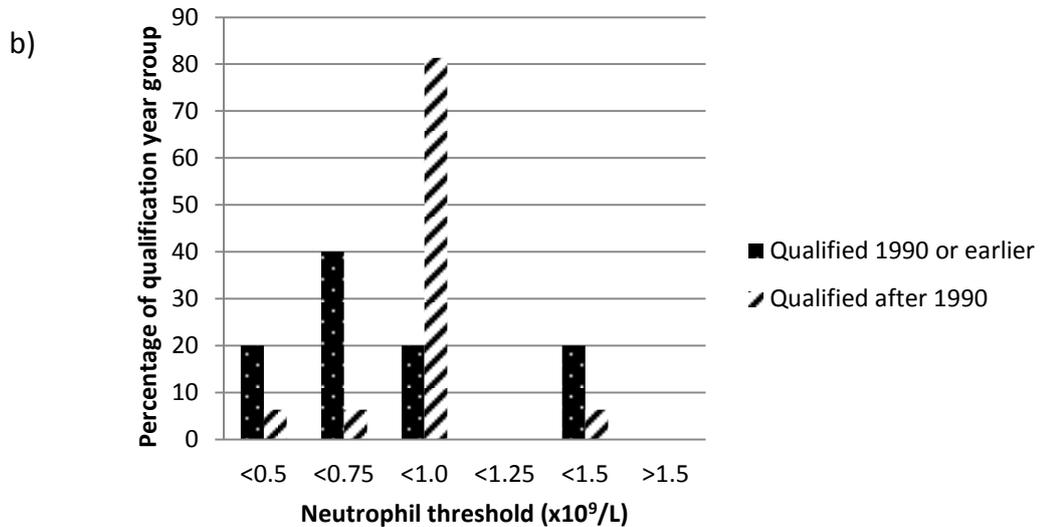
Figure 14 shows the percentage of oncological speciality and year of primary medical qualification choosing each threshold. All the respondents who indicated a neutrophil threshold of $<0.5 \times 10^9/L$ were male ($n=3$).

Q2b: Using the threshold you've selected, please tick the maximum risk of incorrectly advising a patient to stay at home, which you consider to be acceptable.

The median risk option chosen was 2%. The responses are distributed with 2 modes of 1% and 2%. 29 (90.6%) respondents chose a risk between and including 0.1% to 10%, with 23 (71%) choosing 1%, 2% or 5%. Figure 15 shows the frequency of risk options chosen by oncological speciality and year of primary medical qualification. The minimum ($<0.1\%$) and maximum (20%) risk options given were chosen by 2 respondents and 1 respondent respectively.



Neutrophil threshold ($\times 10^9/L$)	<math><0.5</math>	<math><0.75</math>	<math><1.0</math>	<math><1.25</math>	<math><1.5</math>	>1.5
Frequency Medical Oncologists (% of specialty)	1 (10)	2 (20)	5 (50)	0 (0)	2 (20)	0 (0)
Frequency of Clinical Oncologists (% of specialty)	2 (13)	3 (19)	10 (63)	0 (0)	1 (6)	0 (0)
Unknown specialty (% of group)	0 (0)	1 (17)	2 (33)	1 (17)	2 (33)	0 (0)



Neutrophil threshold ($\times 10^9/L$)	<math><0.5</math>	<math><0.75</math>	<math><1.0</math>	<math><1.25</math>	<math><1.5</math>	>1.5
Qualified 1990 or earlier (%)	2 (20)	4 (40)	2 (20)	0 (0)	2 (20)	0 (0)
Qualified after 1990 (%)	1 (6)	1 (6)	13 (81)	0 (0)	1 (6)	0 (0)
Anonymous (%)	0 (0)	1 (17)	2 (33)	1 (17)	2 (33)	0 (0)

Figure 14: Percentage of responses to question 2a, which asked for the neutrophil threshold to recommend urgent clinical assessment when a patient on chemotherapy is at home, has a fever and is otherwise well.

a) demonstrates the response by percentage of each oncological speciality, $p = 0.750$ b)

demonstrates the response by percentage of year of primary medical qualification, $p = 0.022$.

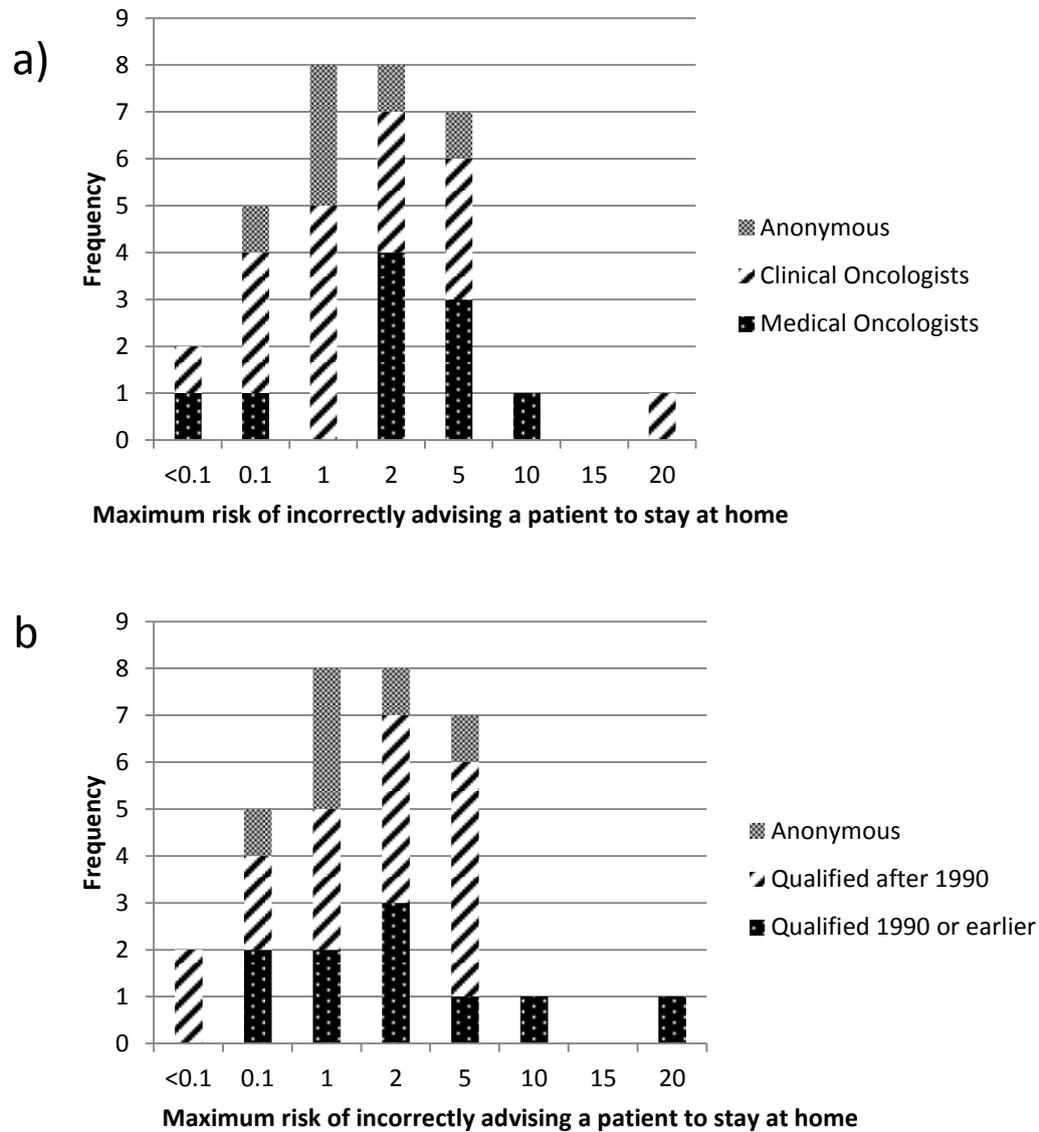


Figure 15: Frequency of responses to question 2b, which asked the maximum risk of incorrectly advising a patient to stay at home, which the respondent considered acceptable. a) demonstrates the proportion of each response answered by oncological speciality, $p = 0.308$ b) demonstrates the proportion of each response answered according to year of primary medical qualification, $p = 0.430$.

The comments associated with this question are listed;

- “Ideally no risk”.
- “Depends on risk of chemotherapy”.
- “As threshold is high” (indicated <1.0 neutrophil threshold and 2% risk).

- “Death as a complication of management of suspected febrile neutropenia should be a never event. The test does not replace clinical assessment. I am more confident in scenarios b and c”.

Q2a and b combined

Table 19 shows the frequency of neutrophil threshold chosen in combination with maximum risk of incorrectly advising the patient to stay at home. For example, it shows that of the three respondents choosing a neutrophil threshold of $<0.5 \times 10^9/L$, the associated risk they would be willing to accept is diverse (1.0, 2.0 and 20.0%). It also shows that $<1.0 \times 10^9/L$ is the neutrophil threshold most commonly chosen ($n=17$), but there is a large range of risk that respondents who chose this are willing to accept (<0.1 to 10.0%), with the maximum risk of 1.0% being the modal value.

Neutrophil Threshold ($\times 10^9/L$)	Maximum risk (percent)							Total
	<0.1	0.1	1.0	2.0	5.0	10.0	20.0	
<0.5	-	-	1	1	-	-	1	3
<0.75	1	2	1	2	-	-	-	6
<1.0	1	2	5	4	4	1	-	17
<1.25	-	1	-	-	-	-	-	1
<1.5	-	-	1	1	3	-	-	5
Total	2	5	8	8	7	1	1	32

Table 19: Frequency table combining neutrophil threshold chosen to recommend urgent clinical assessment in a patient who is at home, has a fever and is otherwise well, with the maximum risk of incorrectly advising a patient to stay at home.

The respondent who indicated using a $<0.5 \times 10^9/L$ neutrophil threshold with a 20% risk of incorrectly advising the patient to stay at home, clarified these answers by saying the patient would “need a clinical assessment if high risk” and low risk patients would need a “repeat blood count the next day and be advised to have a clinical assessment if unwell”.

Five of the 6 respondents who indicated they would not use the self-test home blood count monitoring in patients who feel unwell at home and require neutropenia to be excluded in question 1a, completed question 2 a and b about threshold they would use and acceptable risk associated with this. Of these 5, 4 indicated they would use a neutrophil threshold of <1.0

$\times 10^9/L$, each with a different maximum risk of incorrectly advising the patient to stay at home, namely 0.1%, 1%, 2% and 5%. The respondents who indicated 0.1 and 1% risk clarified their responses with the comments “Need to be seen if unwell” and indicated they would have answered question 1a as “Yes with telephone consultation”. The remaining 1 of these 5, indicated a neutrophil threshold of $<0.75 \times 10^9/L$ with a 2% risk of incorrect advise.

General Comments

Nine respondents entered free text comments in the space to do so at the end of the questionnaire. These are shown in Appendix 3, Table 4.

3.5 Discussion

3.5.1 Main findings

The vast majority of patients and consultants would be willing to use patient self-test capillary blood count monitoring. Some of the most valuable learning points from these questionnaires were raised via the free-text comments. For patients, the most frequent incentive was to save time, but the importance of patient choice, education and training also recurred on multiple occasions. For the consultants, there were repeated references to the need for neutropenic risk stratification to define the clinical management pathway and the use of successive blood counts to monitor the neutrophil count trend.

3.5.1.1 Patient questionnaire

The key finding from this questionnaire was that a clear majority (86.9%) of the respondents indicated they would prefer to use home blood count monitoring over the current system of attending the hospital for assessment and reassurance by a health-care professional. This is from a population where almost half (48/107) had experience of being assessed for infection during chemotherapy, whether they were discharged the same day or admitted for treatment, meaning they could reasonably be expected to have some understanding of the scenarios being described. There was a greater number of respondents in higher age categories than younger, as might be expected, and the majority of patients lived within an hour’s travel time of the hospital, as Leeds Cancer Centre is based in a city. Of those who preferred home blood count monitoring, the most common reason was to save time; of those,

on the other hand, who chose the current system of in hospital assessment, the most common reason was for reassurance by a healthcare professional.

The demographics which appeared to influence choice of method of assessment (scenario A or B) when febrile neutropenia needs to be excluded, were time taken to travel to hospital being greater than or equal to one hour, experience of either assessment for febrile neutropenia or admission for treatment of an infection during chemotherapy, and age <40 years. All of those living at least one hour from the hospital chose home blood count monitoring as the preferred method of assessment. This fits with the most popular reason being to save time, as these patients have the most potential time to save. It appears that previous experience of febrile neutropenia, whether that be an assessment at the hospital alone or admission to hospital, may have inclined respondents to prefer hospital assessment rather than home blood count monitoring. Accepting the limited numbers, it is difficult to ignore that a higher proportion of those less than 40 years old preferred in hospital assessment, compared to those over 40 years or older. However, this may be multifactorial such as teenage and young adult patients receiving more intensive chemotherapy and hence being more likely to have experienced febrile neutropenia in the past.

The most important message from the patient questionnaire assessment about risk is that respondents were willing to accept some risk to gain the benefits of using home blood count monitoring. Risk is a difficult concept to portray and to understand, and definite conclusions cannot be drawn about the “acceptable” level of risk. Seven out of the 10 respondents who preferred the current system of in-hospital assessment indicated they would be willing to take only the lowest risk (0.1%) of becoming dangerously unwell. This indicates these respondents understood the question. Of those who accepted the highest percentage risk categories, a larger proportion of these respondents lived alone and a larger proportion lived an hour or more travel time from the hospital, when compared to the other risk categories chosen, suggesting there may be confounding factors influencing their decision-making process.

3.5.1.2 Consultant questionnaire

The important message from this questionnaire was that generally there is enthusiasm from consultants for patients to use home blood count monitoring during chemotherapy in all three scenarios described, but with some trepidation in the patient who requires febrile neutropenia to be excluded (60.6% answered “yes”, 18.2% answered “no” for use in this scenario). Of those who indicated “no”, clinical oncologists and those who qualified after 1990 appeared disproportionately represented. It is difficult to comment on the

proportionate representation in those who indicated “yes”, as one quarter were anonymous. No consultant indicated “no” to use both before delivery of chemotherapy or after chemotherapy to predict risk of neutropenic complications.

The modal and median neutrophil threshold chosen to be used in the scenario where a patient requires neutropenia to be excluded was $<1.0 \times 10^9/L$. Respondents who qualified in 1990 or earlier were disproportionately represented in those who chose the lowest neutrophil thresholds (0.5 and $0.75 \times 10^9/L$) and also in those who would accept the highest risk of incorrectly advising a patient to stay at home (10% and 20%). Oncological sub-specialty did not appear to influence the neutrophil threshold chosen or maximum risk they would accept. It was expected that the neutrophil threshold to exclude febrile neutropenia would correlate with the maximum risk of incorrectly advising a patient to stay at home, such that those who chose the lowest neutrophil threshold would also choose the lowest acceptable risk. This was not the case. This is possibly a reflection of the difficulty in measuring risk and indicates that the risks and benefits reasoning should be considered on an individual basis and in conjunction with the patient. Themes that repeatedly arose in the free-text comments support this explanation; the desire to stratify patients according to their risk of febrile neutropenia and using the trend of the blood count result, rather than a one-off reading, to use home blood count monitoring as part of pre-defined pathway-led care.

3.5.2 Strengths and weaknesses

Strengths of this work include the relatively large number of completed patient and consultant questionnaires and the demographics of respondents. There was a wide range of patient ages, and a high proportion of patients (45%) having had previous experience of assessment or admission to hospital for an infection during chemotherapy, thus with some knowledge of the problem being addressed. The proportion of oncology consultants who returned the questionnaire (69.4%) was much better than published work examining response rates (172, 173).

Free-text answers provided respondents with the opportunity to expand and reason, highlighting important issues such as the value patients place upon interaction with healthcare professionals. Despite this, it proved very difficult to structure short questionnaires to accurately assess attitudes towards trading off the benefits of one practice for those of another. The iterations of the patient questionnaire progressed through using a visual analogue scale, Likert scale and a discrete choice experiment, before settling on a

version of paired comparison. Discrete choice experiment methods have been used successfully in medicine to establish patient preferences, and would have been the preferred design as they can demonstrate reasons behind a preference, but there were too few attributes in the scenarios to use this (174-177).

Portrayal of implications of risk and representation of risk are complicated, but an essential part of assessing acceptability of using patient self-test home blood count monitoring. Exploration of risk should be approached by assessing the perceived risk, prior to assessing attitudes towards the risk(178). Given that the consultant questionnaire was only distributed to oncologists, knowledge of the perceived risk was assumed. Assessment of consultant attitudes towards the risk were limited by the questionnaire design not allowing for differing risk in an individual's practice to be accounted for. It was clear that despite the patient involvement in developing and piloting the questionnaire, some still had difficulties answering the question about risk, mostly due to difficulty trading off the attributes of each scenario. Notably, 2 respondents indicated they would not want to use the home blood count monitoring, then indicated they would accept a 20% risk of becoming dangerously unwell. Interestingly, 20% was the maximum risk option available, but still respondents of both questionnaires chose this. In hindsight, perhaps the maximum risk preferred should have been higher.

3.5.3 Implications

The risk of febrile neutropenia ranges from low (<10%) to high (>20%)(24), and is dependent upon the chemotherapy regimen given and other parameters such as baseline haematology, age greater than 65 years and co-morbidities (37, 38). This is why results of the consultant questionnaire indicated a desire to consider use of patient self-test capillary blood count monitoring as part of a formalised pathway of triage and assessment, defined by clinical characteristics of the individual and chemotherapy regimen proposed to be used. For example, some patients, such as those at low risk of infective neutropenic complications whose count falls within a "grey" area either side of the chosen threshold, could be advised to repeat the blood test after a specified period of time, giving information on the trend of the neutrophil count. In contrast, those known to be at high risk of neutropenic complications could be advised to have a clinical assessment in this scenario.

Within this stratified personalised medicine model, there could be scope for methods of clinical assessment other than the current advice to attend the acute assessment unit. For

example, in some circumstances a telephone review may suffice, with the patient self-test capillary blood count results built into the triage methods. Another option may be to use the home blood count testing device to intensively monitor those at high risk of neutropenic complications, in order to identify signs of infection as early as possible. Use of such a device in the above ways, would require re-structuring of current clinical pathways and resource allocation or re-allocation, dependent upon the true effects of such a device in clinical practice. With this in mind, it is prudent to consider the final sentence of the penultimate comment in Appendix 3, Table 4, which was made by a clinician with experience of introducing change to clinical practice across a department, highlighting the merits of a step-wise approach.

Through the progression of this project, it is important, as highlighted in the patient free-text comments, that a structured education and training plan for use of home blood count monitoring be developed both for patients and professionals. This will contribute to the empowerment of patients, which has been a recurring beneficial theme raised in patient focus groups during the development of the patient questionnaire and other aspects of this project. Secondary gains of this work are in focusing attentions on where there is patient satisfaction and dissatisfaction with the current service. The positive attributes can continue to be incorporated in home blood count monitoring proposals, and improvements can be made in the acute assessment service such as introducing a point of care device in the acute oncology unit.

3.5.4 Conclusion

The questionnaires show that there is considerable support and enthusiasm from patients and oncology consultants to explore ways of using patient self-test home blood count monitoring to improve the care of patients on chemotherapy. There is some scepticism regarding use in the scenario of patients who are acutely at risk of febrile neutropenia. However, this is only one of three potential time points in the pathway of a patient on chemotherapy, where it could be used.

Chapter 4 Evaluation of point of care results as surrogate indicators of haematological parameters

4.1 Introduction

Point of care technology exists to test a wide range of haematological parameters, including haemoglobin, glycosylated haemoglobin, glucose, white cell counts and international normalised ratio (INR). However they do not measure platelet count. This is limited to desktop and larger analysers (179). Evaluation and reporting of analyses of point of care devices has been fraught with inconsistencies, resulting in the publication of the Standards for Reporting of Diagnostic Accuracy (STARD) statement in an attempt to standardise the approach to evaluations (77, 180). One criticism of work on diagnostic test performance in the 1990s was apparent thinking in silos, often with the analytical performance and clinical performance evaluations of medical tests being disconnected (181, 182). Work in this area has greatly improved, and the need to continue to do so was recognised by the National Institute for Health Research (NIHR), which funded four Diagnostic Evaluation Co-operatives (DECs) in England for four years in 2013, with the aim of helping to generate information on clinical and cost-effectiveness of in-vitro diagnostic devices. With this in mind, we sought to consider the purpose of haematological tests in patients with cancer on chemotherapy, looking at which parameters are currently used to change patient pathways and how the blood count results generated by point of care devices may guide management decisions.

Blood counts are carried out in patients with cancer on chemotherapy for a variety of reasons including (i) before starting a new cycle of chemotherapy to ensure adequate recovery from previous treatment, (ii) during a chemotherapy cycle to identify haematological toxicities of chemotherapy, and (iii) to investigate possible haematological consequences of the underlying malignancy due, for example, to infiltration of the bone marrow. Blood counts performed on patients during chemotherapy may reveal bone marrow suppression, which can include pancytopenia or isolated suppression of individual haematopoietic cell lines. In the management of patient with solid tumours, suppression of haemoglobin production, neutrophil or platelet counts may require intervention either prophylactically or in response to symptoms or complications. Anaemia can be a consequence of either disease or can be treatment-related. Treatment-related anaemia tends not to be an acute issue.

In contrast, patients on chemotherapy can experience acute falls in platelet counts. This may present with a bleed or they can develop severe thrombocytopenia without indicative signs or symptoms. It is, therefore, relevant to consider that point of care devices measuring blood

counts do not measure platelets. The British Society for Haematology guidelines on the use of platelet transfusions, recommend giving prophylactic platelet transfusions to asymptomatic patients with reversible bone marrow failure to maintain a platelet count at or above $10 \times 10^9/L$ (183). There is a risk of isolated thrombocytopenia with chemotherapy for solid tumours, and as such, it is important to investigate the likelihood of failing to identify such a thrombocytopenia whilst using the point of care home blood count monitoring devices during chemotherapy.

Historically, granulocytopenia was used to identify patients at risk of severe or life-threatening infections during chemotherapy (16). Despite the fifty year time lapse since publication of this paper and the terminology in guidelines and published evidence changing to neutrophils rather than granulocytes in the early 1990s, this remains the most consistently cited work in current international guidelines and the most relevant to date on quantitative relationship of leukopenia to infection (22, 26, 28, 30). The change from granulocytes to neutrophils probably occurred, at least in part, as a result of laboratory analysers being able to measure five-part differentials becoming common place in healthcare provider laboratories.

Although desktop and laboratory analysers usually report five-part differential white blood cell counts, some hand-held point of care devices, including the XBC and others, generate three-part differential white cell counts comprising lymphocytes, monocytes and granulocytes (184, 185). The three component cells of granulocytes (neutrophils, eosinophils and basophils), are distinguished morphologically by multilobular nuclei, but have different immunological functions. The absolute values of differential counts in reference ranges depend on the specific measuring laboratory and population it serves, but neutrophils usually form by far the greatest proportion. Suggested ranges are neutrophils $2.0\text{--}7.0 \times 10^9/L$ (40–80% of total white cell count), eosinophils $0.02\text{--}0.5 \times 10^9/L$ (1–6% total white cell count) and basophils $0.02\text{--}0.1 \times 10^9/L$ (< 1–2% total white cell count) (1).

Due to the potential advantages and increasing availability of point of care devices that measure three-part differential white cell counts, but routine oncological practice being based on neutrophil counts, it is important to determine the confidence with which a granulocyte count can be used as an indicator of absolute neutrophil count. A previous study aiming to correlate granulocyte counts from 3-part analysers to laboratory measured neutrophil counts found no disadvantage to using the 3-part differential analyser granulocyte count in the absence of a neutrophil count (185). In the 133 samples processed, the correlation between 3-part analyser granulocyte count and 5-part analyser neutrophil count or manual neutrophil

count produced an R^2 greater than or equal to 0.98. This study used robust methodology such as ensuring all measurements occurred within four hours of the venepuncture, that the samples were processed by two 3-part differential analysers (ABX Micros ES 60, Horiba Medical and PochH-100i, Sysmex), and that the 3-part analyser results were compared to both the routine laboratory analyser but also to a manual differential neutrophil count. The method of determining the granulocyte count in the 3-part differential analyser was impedance, which is also used in the XBC. However, this study used blood samples from patients whose diagnosis was not reported and compared the results to a 5-part haematology analyser (ABX Pentra 80, Horiba Medical) different to that used in routine practice in Leeds Teaching Hospitals NHS Trust haematology laboratories (ADVIA 2120, Siemens). The report describes the accuracy of the 3-part analyser granulocyte counts in indicating neutrophil counts, but does not address the precision. Moreover, there was no attempt to quantify the absolute differences between granulocytes and neutrophils in ranges relevant to oncological practice, nor apply this to clinical decision thresholds.

In a further study evaluating the accuracy and precision of point of care analysers in the neutropenic range, the accuracy of the Siemens ADVIA-60 3-part differential analyser granulocyte count in determining the neutrophil count was reported to be satisfactory with R^2 of 0.850 and coefficient of variation of 6.0% (85). The methodology of this study was strong and relevant with a sample size of 106, and blood results in the neutropenic range (neutrophil count $<2.0 \times 10^9/L$); both accuracy and precision were reported conventionally for such a study (using correlation, logistic regression and coefficient of variation). However, the Siemens ADVIA 60 used was not subject to the same quality assurance checks as the other haematology analysers reported in the same study, the time lapse between venepuncture and analysis was long at eight hours, and the diagnosis of patients from whom the blood samples were obtained was not reported. The results showed the regression line to have a large positive intercept ($y=1.26x + 0.25$), indicating that the ADVIA-60 overestimated the neutrophil count in samples with few neutrophils. This, and the fact that the study again does not report on misclassification of samples either side of clinically relevant thresholds, emphasizes the need for further work comparing the appropriateness of using granulocytes as an indicator of neutrophils in neutropenic ranges.

This chapter addresses how the results available from point of care analysers can be used appropriately in oncological practice. The point of care device used in this project changed as it progressed. The first one, the XBC, gave a 3-part white cell differential count, so the majority of work here focused on using granulocytes as a surrogate for neutrophils. The later

device, the Haemocue WBC DIFF, gave a 5-part white cell differential count, so a lesser part of this chapter focused on use of neutrophils to predict thrombocytopenia.

4.2 Objectives

1. To determine if granulocyte counts can be used as an indicator of absolute neutrophil counts in the neutropenic range
2. To determine limits of granulocyte grades that are equivalent to Common Terminology Criteria for Adverse Event (CTCAE) grades of neutropenia.
3. Analyse the performance of absolute neutrophil count thresholds in identifying clinically significant thrombocytopenia

4.3 Methods

4.3.1 Granulocyte count thresholds predicting clinically significant neutropenia

Venous full blood count results were extracted from the Leeds Teaching Hospitals NHS Trust electronic results server if they were from a patient who had received chemotherapy for a solid tumour, and the blood test was dated between 1st January 2004 and 1st January 2016. These results were all obtained using the Siemens ADVIA 2120 automated 5-part differential analyser, which is the Leeds Teaching Hospitals NHS Trust reference analyser. The results of interest were the absolute neutrophil count and total granulocyte count, which was derived from the sum of basophils, eosinophils and neutrophils. The patient group was defined as those with a solid tumour (excluding lymphoma) International Classification of Diseases 10th revision code (ICD-10) (186), with an entry indicating “delivered” in the electronic chemotherapy drugs table. The data were limited to one blood count result per patient per day. The extracted data were anonymised.

Correlation between the neutrophil and granulocyte counts was determined using Pearson’s correlation co-efficient (r), the co-efficient of determination (R^2) and linear regression, where the neutrophil counts were $\geq 1.5 \times 10^9/L$ to $7.5 \times 10^9/L$ (CTCAE neutropenia grade 1 and normal) and also where neutrophil counts were $< 1.5 \times 10^9/L$ (CTCAE neutropenia grade ≥ 2). Bland-Altman plots were performed to analyse the agreement between the two assays, including identifying bias and outlying measurements, as described in the introduction chapter (187).

To investigate the ability to classify neutropenic CTCAE grades using granulocyte counts, the dataset was randomly split (1:2) into derivation and validation datasets. Granulocyte ranges equivalent to the CTCAE neutropenic grades were derived by multinomial logistic regression classification, which was trained on the derivation dataset and tested on the validation dataset. Multinomial logistic regression classification is a method used to apply logistic regression where there are ≥ 2 categorical outcomes. It is used to predict probabilities of different categories of a categorically distributed dependent variable, which are the grades of granulocytopenia in this analysis.

The relationship of granulocytes to neutrophils was additionally explored in 2 subsets of blood samples; (i) where counts from patients with eosinophilia or basophilia were excluded (defined as counts above the upper limit of normal), and (ii) where the samples were obtained within 6 weeks of chemotherapy delivery. This was to aid understanding of how such conditions may be influence the utility of home blood count monitoring in clinical practice.

Descriptive analyses were performed using Microsoft Excel 2010 and statistical analyses were mostly performed using Stata STRS, but Figure 16 and Figure 17 were drawn using the R programming language package(188-190). The reference system used to determine grade of neutropenia was the Common Toxicity Criteria of Adverse Events version 4.03 (CTCAE) (17).

This work was sanctioned under the information governance procedures of Leeds Teaching Hospitals NHS Trust.

4.3.2 Neutrophil count thresholds predicting clinically significant thrombocytopenia

The same rules were applied as in 4.3.1 to extract venous full blood count results from PPM, except there was a restriction to have received chemotherapy within 42 days of the full blood count result. Again, the blood results were all measured using the Siemens ADVIA 2120 automated 5-part differential analyser. The results of interest were the absolute neutrophil count and the platelet count. The patient group was also defined using ICD-10 as in 4.3.1, with an entry indicating “delivered” in the electronic chemotherapy drugs table within 42 days prior to the date of the blood test. There was no limit on the frequency of inclusion of blood tests from a single patient. The extracted data were anonymised. For the purposes of this analysis, clinically significant thrombocytopenia was defined as a platelet count $<10 \times 10^9/L$. Descriptive analyses were performed using Microsoft Excel 2010 and statistical analyses using Stata STRS(188, 189).

The data were extracted, anonymised and placed in a research database by a data analyst. This work was sanctioned under the information governance procedures of Leeds Teaching Hospitals NHS Trust.

4.4 Results

4.4.1 Granulocyte count thresholds predicting clinically significant neutropenia

There were 508,646 full blood count results meeting the inclusion criteria. Of these, 134,119 (26.4%) had CTCAE v4.03 grade ≥ 1 neutropenia (neutrophils $< 2.0 \times 10^9/L$), 296,510 (58.3%) had neutrophils within the normal range ($2.0 - 7.5 \times 10^9/L$), and 78,017 (15.3%) had neutrophils above the normal range ($> 7.5 \times 10^9/L$). Table 20 a and b show the distribution of cell counts for the 3-part differential counts, and for neutropenic counts ($< 2.0 \times 10^9/L$).

The extent of the relationship between neutrophils and granulocytes was investigated with a view to using granulocytes to predict the neutrophil count. Pearson's correlation co-efficient for the full range of neutrophils versus granulocytes was 0.997, R^2 was 0.995. Figure 16 shows the relationship of neutrophils versus granulocytes when analysed in two groups; results with either grade 1 neutropenia or a neutrophil count within normal range, and neutrophil results categorised as grade ≥ 2 neutropenia. Investigation of the relationship by individual grades of neutropenia fluctuated, and was better for grade 4, than grades 2 and 3;

- grade 1 neutropenia gave an R^2 of 0.848 and residual standard error of 0.112
- grade 2 gave an R^2 of 0.699 and residual standard error of 0.079
- grade 3 gave an R^2 of 0.743 and residual standard error of 0.074
- grade 4 gave an R^2 of 0.891 and residual standard error of 0.048

Taken together, when there was a grade ≥ 2 neutropenia, the R^2 was 0.964 indicating better accuracy at distinguishing either side of this threshold than identifying those samples falling within the boundaries of a specific grade.

Bland-Altman plots, performed to visualise the agreement between the two parameters, are shown; results with either a grade 1 neutropenia or a neutrophil count within normal range are shown in Figure 17a, and neutrophil results categorised as grade ≥ 2 neutropenia are shown in Figure 17b. The total agreement shown indicates the percentage of results which

(a)

Differential cell count	Minimum (x10 ⁹ /L)	Maximum (x10 ⁹ /L)	Median (x10 ⁹ /L)	Mean (x10 ⁹ /L)	SD
Granulocytes	0.00	213.42	3.73	4.65	4.31
Neutrophils	0.00	180.58	3.55	4.49	4.21
Eosinophils	0.00	53.69	0.07	0.12	0.26
Basophils	0.00	51.43	0.03	0.04	0.15

(b)

CTCAE v4.03 neutrophil grade (count x10 ⁹ /L)	Frequency (%)
1 (<2.0 to ≥1.5)	35,467 (26.4)
2 (<1.5 to ≥1.0)	29,770 (22.2)
3 (<1.0 to ≥0.5)	24,118 (18.0)
4 (<0.5)	44,764 (33.4)
Totals	134,119 (100)

Table 20: The distribution of cell counts for (a) granulocytes and the 3-part differential counts, and for (b) neutropenic counts (<2.0 x10⁹/L).

fall within 1.96 x SD. For example, 97.6% of granulocyte results were within 0.265 x10⁹/L of the neutrophil count (Figure 17b). Therefore, if a threshold of <1.5 x10⁹/L neutrophil count was applied, using an equivalent granulocyte threshold of <1.765 would correctly identify 97.6% of patients with a neutrophil count <1.5 x10⁹/L.

Analysis of CTCAE neutropenic grades individually showed that 97.0% of grade 1 neutropenic counts had a difference of less than 0.358 x10⁹/L and a mean difference of 0.111 x10⁹/L, 96.6% of grade 2 neutropenic counts were <0.278 x10⁹/L with a mean of 0.086 x10⁹/L, 97.2% of grade 3 neutropenic counts were <0.242 x10⁹/L with a mean of 0.066 and 97.5% of grade 4 neutropenic counts were <0.140 x10⁹/L with a mean of 0.026 x10⁹/L.

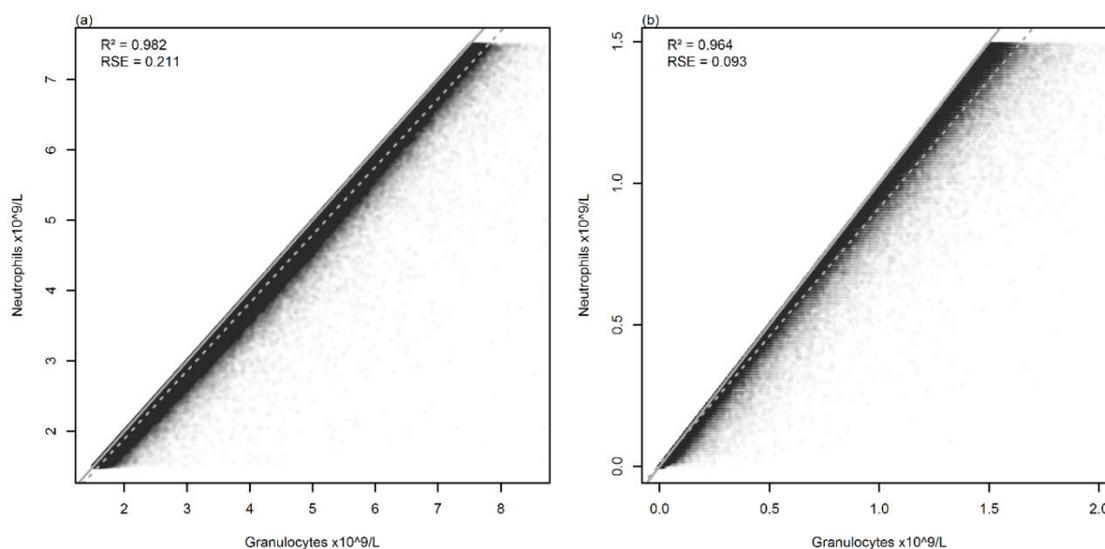


Figure 16: Scatterplots showing the relationship of neutrophil and granulocyte counts. (a) neutrophil counts $\geq 1.5 \times 10^9/L$ to $7.5 \times 10^9/L$ (CTCAE neutropenia grade 1 and normal range) and, (b) neutrophil counts $< 1.5 \times 10^9/L$ (CTCAE neutropenia grade 2 or worse). In (a) $n=331,977$ and $y = 0.9659x - 0.03453$, and in (b) $n=98,652$ and $y = 0.9074x + 0.00671$. RSE is residual standard error, solid grey line is $x=y$, dashed grey line is line of best fit.

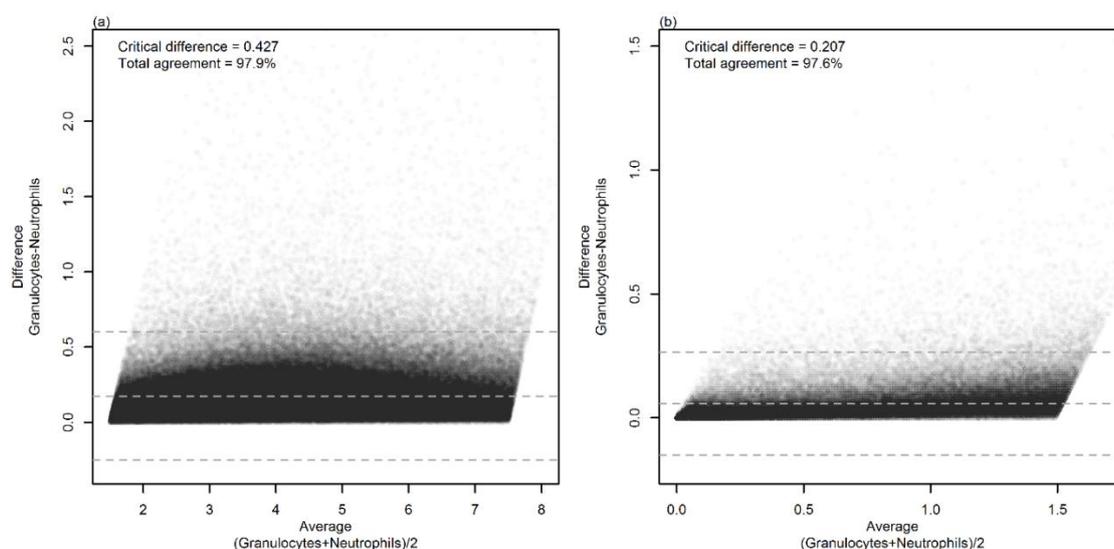


Figure 17: Bland-Altman plots showing the agreement between neutrophil and granulocyte counts.

(a) Neutrophil counts $\geq 1.5 \times 10^9/L$ to $7.5 \times 10^9/L$ (CTCAE neutropenia grade 1 and normal range, $n=331,977$) and, (b) neutrophil counts $< 1.5 \times 10^9/L$ (CTCAE neutropenia grade 2 or worse, $n=98,652$). Outer grey dashed lines represent upper and lower limits of agreement ($\pm 1.96 \times SD$) and the middle dashed line is the mean difference. In (a) from top to bottom, the value of the lines are 0.600, 0.174, -0.252, and in (b) 0.265, 0.058, -0.149. As difference cannot be less than zero, the lower limits are irrelevant.

The split data comprised derivation (n=167,853) and validation (n=340,793) datasets. The granulocyte ranges equivalent to the CTCAE neutropenic grades were derived by the multinomial logistic regression classifier and then tested on the validation dataset, achieving an accuracy of 96.4%.

Table 21 displays the performance of the equivalent granulocyte count ranges in identifying the neutrophil grade. The proportion of correct predictions of the granulocyte count equivalent range improved as the severity of CTCAE grade neutropenia increased, with 87.3% of grade 1 being correct, 88.5% of grade 2, 90.5% of grade 3 and 97.5% of grade 4. The worst performing equivalent granulocyte range was grade 1 where there was a 5.3% chance of classifying the neutropenia as grade 1 where it was truly a worse grade than this, with 0.07% chance of truly being grade 3 or worse. Using the granulocyte equivalent range for grade 2, there was a 4.2% chance of misclassifying as grade 2, when the true neutrophil count was grade 3 or worse.

Three different grade thresholds and the use of different equivalent granulocyte boundaries for each of these thresholds were investigated. The thresholds were neutrophil count of $<1.5 \times 10^9/L$ (CTCAE 2 or worse), $<1.0 \times 10^9/L$ (CTCAE grade 3 or worse) and $<0.5 \times 10^9/L$ (CTCAE grade 4). Table 22 displays these results. Using a threshold of $1.5 \times 10^9/L$ neutrophil count, the equivalent granulocyte count of $<1.69 \times 10^9/L$ performed best in terms of maximising the product of sensitivity and specificity, but the equivalent granulocyte threshold had to be $<2.39 \times 10^9/L$ to reach 100% sensitivity (when rounded up); even using this threshold, 49 results out of the 98,652 (0.05%) results with neutrophil count $<1.5 \times 10^9/L$ were false negatives. Using a threshold of $1.0 \times 10^9/L$ neutrophil count, equivalent granulocyte count of <1.13 performed the best in terms of maximising the product of sensitivity and specificity, but again even using the higher boundary of $<1.71 \times 10^9/L$, there were still 34 false negatives out of the 68,882 results with neutrophil count $<1.0 \times 10^9/L$.

When results were excluded if eosinophils were $\geq 0.4 \times 10^9/L$ or basophils were $\geq 0.1 \times 10^9/L$, the dataset reduced to 469,433 results. Correlation of granulocytes to neutrophils improved with R^2 of 0.996 when the neutrophil count was ≤ 7.5 to $\geq 1.5 \times 10^9/L$, and also when the neutrophil count was $<1.5 \times 10^9/L$ with R^2 of 0.988. Correlation of granulocytes to neutrophils also improved for the categories mentioned respectively, R^2 0.989 and R^2 0.978, when the dataset was restricted to include only patient who had received chemotherapy within 6 weeks (42 days).

Granulocyte count ($\times 10^9/L$)	CTCAE Neutropenia Grade (Neutrophil Count ($\times 10^9/L$))					Performance (%)				
	>7.5	Normal ≤ 7.5 to ≥ 2.0	Grade 1 < 2.0 to ≥ 1.5	Grade 2 < 1.5 to ≥ 1.0	Grade 3 < 1.0 to ≥ 0.5	Grade 4 < 0.5	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Neutrophilia	51,014	970	5	1	0	0	97.8 (97.6-97.9)	99.7 (99.6-99.7)	98.1 (98.0-98.2)	99.6 (99.6-99.6)
≥ 7.73										
Normal	1167	195,963	1746	52	3	2	98.6 (98.6-98.7)	97.9 (97.8-98.0)	98.5 (98.5-98.6)	98.1 (98.0-98.2)
< 7.73 to ≥ 2.12										
Grade 1	0	1754	20,512	1226	16	1	86.5 (86.1-86.9)	99.1 (99.0-99.1)	87.3 (86.8-87.7)	99 (99.0-99.0)
< 2.12 to ≥ 1.60										
Grade 2	0	0	1452	17,751	834	13	88.7 (88.3-89.1)	99.3 (99.3-99.3)	88.5 (88.1-89.0)	99.3 (99.3-99.3)
< 1.60 to ≥ 1.08										
Grade 3	0	0	0	984	14,589	548	90 (89.6-90.5)	99.5 (99.5-99.6)	90.5 (90.0-91.0)	99.5 (99.5-99.5)
< 1.08 to ≥ 0.56										
Grade 4	0	0	0	0	760	29,430	98.1 (98.0-98.3)	99.8 (99.7-99.8)	97.5 (97.3-97.7)	99.8 (99.8-99.8)
< 0.56										

Table 21: Table showing classification of the validation dataset into CTCAE neutrophil grades using the equivalent granulocyte count. grades using the equivalent granulocyte count.

$n = 340,793$. PPV is positive predictive value, NPV is negative predictive value, CI is CI. Grey boxes indicate correctly identified results

Granulocyte Threshold (x10 ⁹ /L)		Performance							
		Frequency				Percentage (%)			
		True positive	False positive	True negative	False negative	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Grade 2-4	i) <1.53	94,250	129	409,865	4,402	95.5 (95.4-95.7)	100.0 (100.0-100.0)	99.9 (99.8-99.0)	98.9 (98.9-99.0)
	ii) <1.69	97,790	6,849	403,145	862	99.1 (99.1-99.2)	98.3 (98.3-98.4)	93.5 (93.3-93.6)	99.8 (99.8-99.8)
	iii) <2.39	98,603	55,164	354,830	49	100.0 (99.9-100.0)	86.6 (86.4-86.7)	64.1 (63.9-64.4)	100.0 (100.0-100.0)
Grade 3-4	i) <1.03	66,281	195	439,569	2,601	96.2 (96.1-96.4)	100.0 (100.0-100.0)	99.7 (99.7-99.8)	99.4 (99.4-99.4)
	ii) <1.13	68,155	3,436	436,328	727	98.9 (98.9-99.0)	99.2 (99.2-99.2)	95.2 (95.0-95.4)	99.8 (99.8-99.9)
	iii) <1.71	68,848	37,051	402,713	34	100.0 (99.9-100.0)	91.6 (91.5-91.7)	65.0 (64.7-65.3)	100.0 (100.0-100.0)
Grade 4	i) <0.51	42,703	38	463,844	2,061	95.4 (95.2-95.6)	100.0 (100.0-100.0)	99.9 (99.9-99.9)	99.6 (99.5-99.6)
	ii) <0.62	44,361	3,359	460,523	403	99.1 (99.0-99.2)	99.3 (99.3-99.3)	93.0 (92.7-93.2)	99.9 (99.9-99.9)
	iii) <1.15	44,742	28,437	435,445	22	100.0 (99.9-100.0)	93.9 (93.8-93.9)	61.1 (60.8-61.5)	100.0 (100.0-100.0)

Table 22: Classification of neutropenic results using various granulocyte count thresholds.

Decision thresholds represented maximise i) specificity, ii) the product of sensitivity and specificity and iii) sensitivity. n=508,646.

4.4.2 Neutrophil count thresholds predicting clinically significant thrombocytopenia

There were 279,059 full blood count results from 24,935 patients which contained a neutrophil count meeting the criteria. Of these, 96 results had no platelet count result, leaving a total of 278,963 results with both a platelet and neutrophil count result. The mean neutrophil count was $5.42 \times 10^9/L$ (range 0.00 to $199.98 \times 10^9/L$). The mean platelet count was $297 \times 10^9/L$ (range 1 to $2163 \times 10^9/L$). The highest absolute neutrophil count in a blood result when the platelet count was simultaneously recorded as $<10 \times 10^9/L$ was $33.41 \times 10^9/L$.

Table 23 shows the frequency and statistical performance of absolute neutrophil count thresholds in identifying thrombocytopenia. Using the neutrophil threshold of $<0.5 \times 10^9/L$ as an example; 316 samples were correctly identified as having a platelet count of $<10 \times 10^9/L$, 12,031 samples with a neutrophil count $<0.5 \times 10^9/L$ had a platelet count $\geq 10 \times 10^9/L$, 266,330 samples with a neutrophil count $\geq 0.5 \times 10^9/L$ were correctly identified as also having a platelet count $\geq 10 \times 10^9/L$ and 286 samples had a neutrophil count $\geq 0.5 \times 10^9/L$, but a platelet count of $<10 \times 10^9/L$ and so the thrombocytopenia was missed by using the neutrophil count alone.

Of the thresholds analysed, the absolute neutrophil count threshold of $<1.25 \times 10^9/L$ performed best in terms of maximising the product of sensitivity and specificity, closely followed by the threshold of $<1.5 \times 10^9/L$. Figure 18 shows the percentage of samples where there was an isolated thrombocytopenia by neutrophil threshold. Based on this data, if a neutrophil count were to be used to indicate a patient requires an urgent assessment during chemotherapy, approximately 0.1% or 1 in 1000 of those who tested above the neutrophil threshold, would have simultaneously had a clinically significant isolated thrombocytopenia missed (platelets $<10 \times 10^9/L$).

Neutrophil threshold (x10 ⁹ /L)	Performance in predicting platelets <10 x10 ⁹ /L							
	Frequency				Percentage (%)			
	True positive	False positive	True negative	False negative	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
<0.5	316	12,031	266,330	286	52.5 (48.4-56.6)	95.7 (95.6-95.8)	2.6 (2.3-2.9)	99.9 (99.9-99.9)
<0.75	342	17,517	260,844	260	56.8 (52.8-60.8)	93.7 (93.6-93.8)	1.9 (1.7-2.1)	99.9 (99.9-99.9)
<1.0	372	24,417	253,944	230	61.8 (57.8-65.7)	91.2 (91.1-91.3)	1.5 (1.4-1.7)	99.9 (99.9-99.9)
<1.25	400	32,900	245,461	202	66.5 (62.5-70.2)	88.2 (88.1-88.3)	1.2 (1.1-1.3)	99.9 (99.9-99.9)
<1.5	412	43,184	235,177	190	68.5 (64.6-72.1)	84.5 (84.4-84.6)	1.0 (0.9-1.0)	99.9 (99.9-99.9)
<1.75	423	54,754	223,607	179	70.3 (66.4-73.9)	80.3 (80.2-80.5)	0.8 (0.7-0.8)	99.9 (99.9-99.9)
<2.0	440	67,137	211,224	162	73.1 (69.4-76.6)	75.9 (75.7-76.0)	0.7 (0.6-0.7)	99.9 (99.9-99.9)
<2.25	444	79,990	198,371	158	73.8 (70.1-77.2)	71.3 (71.1-71.4)	0.6 (0.5-0.6)	99.9 (99.9-99.9)

Table 23: Performance of absolute neutrophil count thresholds in identifying clinically significant thrombocytopenia (platelets <10 x10⁹/L). (n = 278,963)

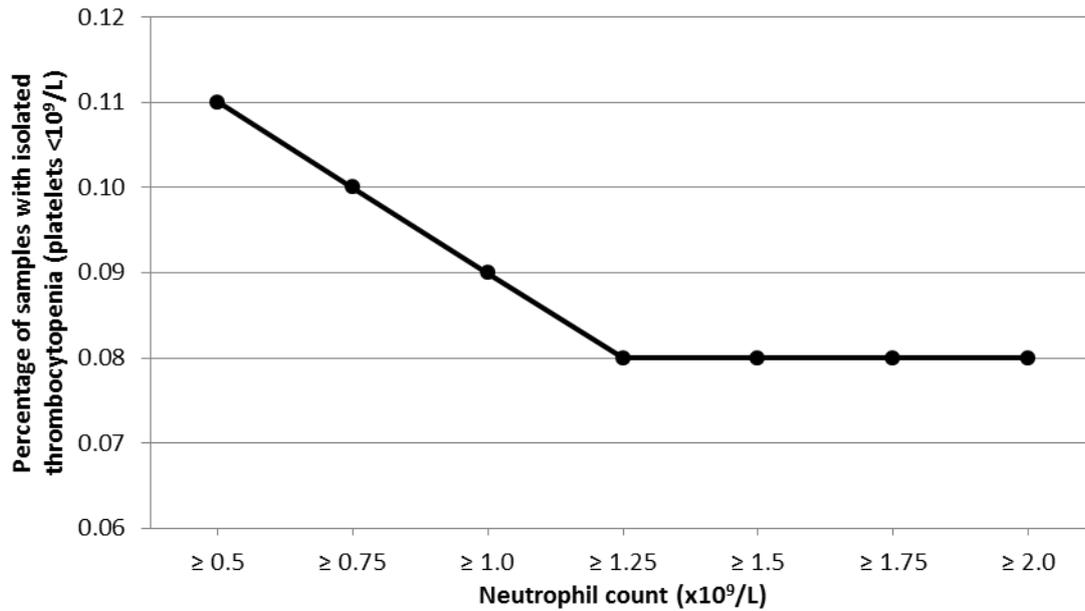


Figure 18: Line graph of frequency of isolated thrombocytopenia according to neutrophil thresholds.

The percentage represents a proportion of all samples where the neutrophil count was above the threshold indicated, in which the platelet count was also $<10^9/L$. Using the terms in Table 23, this translates as $\left(\frac{\text{false negative}}{\text{false negative} + \text{true negative}}\right)$.

4.5 Discussion

4.5.1 Main findings

This analysis quantified the relationship between both granulocyte and neutrophil counts, and neutrophil and platelet counts. The key finding is that neutrophils and granulocytes can be used as surrogate indicators of platelets and neutrophils respectively in a controlled manner, under defined clinical circumstances. They are not, however, a substitute for direct laboratory reference analyser results outside of controlled scenarios or where there is any clinical doubt.

4.5.1.1 Granulocyte count thresholds predicting clinically significant neutropenia

There is a very strong correlation between granulocyte and neutrophil counts, which is maintained even when the absolute neutrophil count reduces to less than $1.5 \times 10^9/L$, and improves further when excluding those with eosinophilia or basophilia. The correlation is,

however, less satisfactory in the direct comparison of granulocytes to neutrophils when broken down into individual grades of neutropenia, with the R^2 dropping as low as 0.743 for grade 3. However, the difference analyses reassuringly showed good agreement with 97.6% of granulocytes being within $0.265 \times 10^9/L$ of the neutrophil count where all neutrophils counts were less than $1.5 \times 10^9/L$. This gives an indicator as to the margin which needs to be introduced to raise a specified threshold from that appropriate for neutrophil counts to that appropriate for granulocyte counts.

One of the main outputs of this work is the first definition of granulocyte counts equivalent to the CTCAE v4.03 neutropenia grades, which has not been identified elsewhere. These are clearly defined in Table 24, and perform considerably better (96.4% accuracy) than the direct comparison of granulocytes and neutrophils broken down into grades. Given these definitions proposed to use the granulocyte count as a surrogate for neutrophil count, there are always uncertainties around extremes of thresholds due to pre-analytical, analytical and post analytical variables, which result in misclassification of some results. This may become clinically significant at thresholds that are used to change patient management. So for example, using the defined equivalent granulocyte grades, a patient could be predicted as having grade 1 neutropenia (neutrophil count <2.0 to $\geq 1.5 \times 10^9/L$), but truly have an absolute neutrophil count of less than $1.0 \times 10^9/L$. If the neutrophil count were known to be less than $1.0 \times 10^9/L$ in a patient at home, management may be changed. In the data analysed, this scenario would occur 1 in every 1429 patients. However, it should also be remembered that international guidelines advocate the use of $<0.5 \times 10^9/L$ to start antibiotics in a patient with suspected febrile neutropenia during chemotherapy, and misclassification of a granulocyte result as grade 1 neutropenia when it was truly a grade 4 (neutrophil count $<0.5 \times 10^9/L$), only occurred 1 in 23,509 results.

In clinical practice there would be little need to change management decisions based on the specific grade of neutropenia, but more likely which side of a specified threshold, the patient neutrophil count falls. Therefore the boundaries of clinically relevant thresholds were investigated, identifying that if neutrophils $<1.5 \times 10^9/L$ were used, the best performing granulocyte count would be $<1.69 \times 10^9/L$, and if neutrophils $<1.0 \times 10^9/L$ were used, the best performing granulocyte count would be $<1.13 \times 10^9/L$. Both of these scenarios had a NPV of 99.8%, which translates clinically into 1 in 500 results would be misclassified as above the threshold, when they were truly below it.

Source	Adverse Event	Grade				
		0	1	2	3	4
CTCAE 4.03 (17)	Neutrophil count decreased	Within normal limits	<LLN to 1.5 $\times 10^9/L$	<1.5 to 1.0 $\times 10^9/L$	<1.0 to 0.5 $\times 10^9/L$	<0.5 $\times 10^9/L$
		Definition: A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen				
Pether et al. (191)	Granulocyte count ranges equivalent to CTCAE neutropenia grades	<7.73 to 2.12 $\times 10^9/L$	<2.12 to 1.60 $\times 10^9/L$	<1.60 to 1.08 $\times 10^9/L$	<1.08 to 0.56 $\times 10^9/L$	<0.56 $\times 10^9/L$

Table 24: Common Terminology Criteria for Adverse Events (CTCAE) neutropenia grades and equivalent granulocyte counts.

LLN – lower limit of normal and is $2.0 \times 10^9/L$ at LTHT. Upper limit of normal at LTHT is $7.5 \times 10^9/L$.

4.5.1.2 Neutrophil count thresholds predicting clinically significant thrombocytopenia

As expected, the frequency of clinically significant thrombocytopenia reduced as the neutrophil threshold used as the surrogate marker increased. However, there were incidences of isolated thrombocytopenia even when there was neutrophilia. This means it is not possible to identify a neutrophil threshold in the neutropenic range, as a surrogate for clinically significant thrombocytopenia, which would not produce any false negative results. That said, using all 4 of the neutrophil thresholds investigated (<0.5, <1.0, <1.5, < $2.0 \times 10^9/L$), the negative predictive value was 99.9. This translates clinically into 1 in 1000 patients whose neutrophil result indicated they do not have a platelet count less than $10 \times 10^9/L$, and truly do have a platelet count less than $10 \times 10^9/L$. However, this is an analysis of blood count results only, with no consideration of symptoms. The odds may reduce further in symptom-led clinical practice, thus enhancing the performance of the neutrophil thresholds in identifying clinically significant thrombocytopenia.

Given that all thresholds analysed have the same NPV, if the sole purpose of the neutrophil test was to identify patients with a platelet count of less than $10 \times 10^9/L$, then the correct neutrophil threshold to use would be identified by maximising the product of sensitivity and specificity of a continuum of thresholds. Albeit with an interval of $0.5 \times 10^9/L$ neutrophils between thresholds in this analysis, the best performing threshold was $<1.5 \times 10^9/L$, closely followed by $<1.0 \times 10^9/L$. This is conveniently the range of thresholds which are in consideration for use in point of care testing to identify patients during chemotherapy who need urgent assessment to exclude febrile neutropenia. As there is discrepancy even between laboratory reference analysers for haematological values (192), error always has to be considered in clinical practice, and 1 in 1000 being incorrectly identified as having platelets greater than $10 \times 10^9/L$ is debatably acceptable.

4.5.2 Strengths and weaknesses

An important strength was that this work was conducted on a very large dataset, using an unselected population of patients with solid tumours. This was reflected in the range of neutrophil counts represented, including 44,764 counts of grade 4 neutropenia in the granulocyte versus neutrophil analysis. Both analyses were conducted either in full or on a subset of results from patients who had received chemotherapy within forty-two days of the blood result, enabling the results to be applicable to patients receiving chemotherapy, which is highly relevant to the ongoing work and future applications of point of care devices measuring three-part differential counts. In addition, there were clear national or international guidelines for the neutrophil and platelet counts which advocated a threshold beyond which there should be clinical intervention. These provided benchmarks against which performance of the surrogate counts could be measured.

It should be noted that these analyses are based solely on full blood count results and did not take symptoms into account. Therefore many of the patients who have been identified as having clinically significant neutropenia or thrombocytopenia, but who had a surrogate blood result above the specified threshold, may have been identified in clinical practice as being “at risk” through clinical assessment. Exclusion of these patients would likely further enhance the performance of the neutrophil thresholds. In addition, the analysis was done by blood results and not by patient. So, for example, if a patient was admitted and had thrombocytopenia, they would usually have had blood tests done on

consecutive days and all of these tests have been included in this analysis. As a consequence, there would have been intra-patient variability in the dataset, but as this is true of routine practice, it was considered of greater value to include the data from patients with multiple samples than to exclude it.

The granulocyte counts were derived from the sum of measured differential counts. Therefore there may be an underestimation of error between readings (pre-analytical variation) and of the variation between different ADVIA 2120 analysers in the laboratory (analytical variation)(86). However, in current clinical practice at Leeds Cancer Centre, it is the results from the laboratory ADVIA 2120 analysers that are used to make clinical management decisions. Therefore it remained appropriate that we compared performance to this, accepting there would have been variation around the reliability of what was considered the “true” neutrophil or granulocyte counts. Moreover, in the context of considering the feasibility of point of care blood count monitoring, it should be highlighted that these analyses were performed on venous blood counts only, meaning future work will need to address how this applies to comparison of capillary versus venous counts.

After anonymisation of the data, it was not possible to retrospectively select subsets of patients by characteristics not included in the original extract. For example, by chemotherapy regimen; it would have been preferable to analyse the performance of neutrophils in identifying clinically significant thrombocytopenia in those patients who received carboplatin chemotherapy, as this is a group of patients most likely to have a disconnect between neutrophil and platelet counts. In addition, it was not possible to retrospectively analyse individual patient characteristics. For example, it would have been preferable to explore individual patient characteristics such as regimen, age and cancer diagnosis for those patients whose blood counts gave false negative results. Although it would be possible to extract the necessary data and perform analyses to achieve the two examples discussed, this was considered not a priority at this time, and will be considered in the future in the ongoing work.

4.5.3 Implications

The intention is not to use measurement of neutrophils in place of measurement of platelets in practice, but to ensure using home blood count monitoring during

chemotherapy would not put patients at undue risk of undiagnosed clinically significant thrombocytopenia. These analyses show this can be done safely for the vast majority of patients. The same is true for granulocytes as a surrogate for neutrophils, but in defining situations where point of care testing is to be used, there should always be a risk assessment that would include a baseline laboratory full blood count to exclude patients at high risk of misclassification using the surrogate markers. High risk patients would include those prone to or with a history of thrombocytopenia, those with eosinophilia or basophilia, and those with allergic conditions such as Churg-Strauss syndrome or who experience an allergic reaction during monitoring.

It is imperative that concern over any one of blood results, clinical symptoms or clinical signs, should prompt more comprehensive clinical assessment. This is true of both current clinical practice using laboratory reference analyser blood results and any future practice that may involve home blood count monitoring. There is an element of variability in all reference laboratory blood count measurements as a result of pre-analytic, analytic and post analytic variability (193). This is often poorly understood by clinicians. When comparing reference automated analysers, a correlation co-efficient of greater than 0.9 is generally considered acceptable (86), making the correlation of granulocyte counts versus neutrophils at the upper end of what is technically acceptable.

However, clinical and technical acceptability are different, with what is acceptable clinically being dependent upon the consequences of misclassifying a blood result. The important clinical question is: "If using the surrogate blood count parameter, how sure can we be that it correctly classifies either the platelet or neutrophil count?" Using granulocytes to indicate a neutrophil result is less than $1.0 \times 10^9/L$ as an example, the best performing granulocyte count in terms of balancing false negatives with false positives would be $<1.13 \times 10^9/L$, but in order to obtain no false negative results, a significantly higher threshold needs to be used. This would be offset by increasing the false positives, and possibly negating the benefits of using home blood count monitoring in the scenario where febrile neutropenia is to be excluded. Using the threshold of <1.13 granulocytes, 1 in 500 results would be misclassified as above the threshold. This may be clinically unacceptable to some clinicians, and may be further justification of the approach to using the trend of granulocyte counts, which addresses the issue of variation around single measurements and would reduce the chances of misclassification.

4.5.4 Conclusions

Granulocyte and neutrophil counts perform well as surrogate indicators of neutrophil and platelet counts respectively in this population. The definition of equivalent granulocyte counts to CTCAE v4.03 neutropenia grades also performs well and is widely applicable for three-part differential analysers, both within oncological care and other specialties. This work shows how sure we can be that neutrophil and granulocyte counts correctly classify the platelet or neutrophil counts respectively above or below a threshold, thus indicating there is potential to use these surrogate parameters in point of care testing in oncological practice. It also justifies the use of using granulocyte counts to rapidly detect neutropenia when a five-part differential analyser is not available in the same time-frame. However, surrogate parameters are not a substitute for direct laboratory reference analyser results, which should always be used to confirm the diagnosis.

Chapter 5 Performance of the Hemocue WBC DIFF in oncological practice.

5.1 Introduction

Neutropenia occurs after chemotherapy administration due to the cytotoxic insult to the committed myeloid progenitor cells, which would otherwise differentiate into neutrophils. Neutrophils are the body's primary haematological defence mechanism against bacterial pathogens. Thus, the grade and duration of neutropenia is directly proportional to the risk of infective complications. Neutropenia complicated by infection remains a life-threatening toxicity of chemotherapy. Therefore, the safe delivery of chemotherapy is partly dependent upon neutrophil count recovery. It is mandatory to have the facility to accurately determine neutrophil counts on patients receiving chemotherapy.

In current oncological practice, there tend to be two key decision points where neutrophil count is important. One is around the safe delivery of a cycle of chemotherapy, which is dependent upon, amongst other factors, recovery of neutrophils usually to greater than $1.5 \times 10^9/L$ in a 3-weekly chemotherapy regimen, or greater than $1.0 \times 10^9/L$ in a weekly chemotherapy regimen. The second key decision point is around the management of toxicity, specifically patients with suspected febrile neutropenia, where management is changed when a neutrophil count is less than $0.5 \times 10^9/L$ or expected to fall to less than $0.5 \times 10^9/L$ within 48 hours. Therefore, the performance of any point of care device capable of measuring neutrophil counts which is being considered for use in oncological practice, needs to be verified in the neutropenic range.

The original plan with this project was to proceed with the Philips XBC finger-prick blood count monitor. There are published results of the performance of this device, but only across the normal granulocyte range, with no analyses specifically reporting the performance in neutropenic ranges (184, 194, 195). An unpublished performance analysis of this device compared to the Siemens ADVIA 2120 was carried out at Leeds Cancer Centre, and the results were analysed as part of this project, and shown in Appendix 4.

With progression of the plans to exchange use of the XBC analyser for the Hemocue WBC DIFF analyser, it was necessary to assess the performance of the Hemocue WBC DIFF on capillary samples. This gave the opportunity to address the shortcomings of the XBC

performance analysis, such as lack of data to enable precision analysis and recording patients who declined to participate. Evaluation of the performance of devices measuring a biological parameter in comparison to the gold standard test or true value should be expressed in terms of accuracy and precision, which are described in the introduction, section 1.3.1.1.1 (187, 196). This is demonstrated succinctly by Haneder et al. describing the performance of a handheld creatinine measurement device, where they used the gold standard Jaffe method of creatinine determination as the comparator, and evaluated both accuracy and precision (197).

Many of these methods of assessing accuracy and precision have been used by the manufacturer of the Hemocue WBC DIFF device to assess its performance. They report accuracy of the analyser in measuring neutrophil counts in both venous and capillary samples, as shown in Table 25, but neither the mean or range of the neutrophil counts were reported. They report precision by low, medium or high white cell counts, as shown in Table 26. The neutrophil range is not reported, but can be inferred from the mean and SD. Performance analyses independent from the manufacturer, have most commonly been evaluated in venous samples due to ease of access to samples. Table 27 displays the accuracy of the Hemocue WBC DIFF reported in articles published independently from the manufacturers. There are no published reports of accuracy of the Hemocue WBC DIFF specifically in the neutropenic range. One of the advantages of the Hemocue WBC DIFF performance analyses is that, in contrast to the XBC analyses, neutrophils are directly measured and therefore there is less risk of error which is introduced by inferring neutrophil counts from granulocyte counts. However, none of the existing Hemocue WBC DIFF performance analyses target oncology populations, neutropenic populations or explore the ability of patients to self-test.

Much of the data available on the performance of the Hemocue WBC DIFF refers to venous samples. To realise the potential advantages of using such a point of care device, capillary samples need to be used. It is, therefore, important to understand the comparability of neutrophil counts in venous and capillary samples, and to consider whether the application of venous reference decision points to capillary measurements are accurate and lead to correct clinical management. It has been recognised for decades, that there are discrepancies in haematological blood count parameters between venous and capillary blood samples (198, 199). The focus of this earlier work has been on platelets,

Sample	Reference analyser	Number of samples (n)	Correlation co-efficient (r)	Regression line of best fit ($y = mx + c$)
Capillary	Sysmex XS-1000i	96	0.931	$0.88x + 0.33$
Venous	Beckman Coulter LH750	596	0.984	$0.96x + 0.16$

Table 25: Table displaying the accuracy of the Hemocue WBC DIFF analyser as reported by the manufacturer in the Operating Manual (200).

Number of samples (n)	Neutrophil count		
	Mean ($\times 10^9/L$)	SD ($\times 10^9/L$)	CV (%)
31	1.5	0.11	7.3
31	3.4	0.13	3.7
31	14.4	0.61	4.3

Table 26: Table displaying the precision of the Hemocue WBC DIFF analyser as reported by the manufacturer in the Operating Manual.

These data were calculated using results from venous blood samples where one sample was measured many times on a single analyser.

Report	Sample	Reference analyser	Number of samples (n)	Correlation co-efficient (r)	Regression line of best fit ($y = mx + c$)
Russcher et al. (201)	Capillary (children <12 years only)	Sysmex XE-5000	133	0.98	$0.95x + 0.2$
Lindberg et al. (202)	Venous	Sysmex XE-2100	101	0.994	$0.87x + 0.02$
Reed et al. (203)	Venous	Beckman Coulter LH750	343	0.984	$0.98x + 0.17$

Table 27: Table summarising accuracy of the Hemocue WBC DIFF as available in published articles.

The mean and range of neutrophil counts were not reported in any of the 3 articles. Russcher et al. reported the total white cell count range to be $2.6 - 26.9 \times 10^9/L$, and Reed et al. reported the total white cell count sample distribution in bands, indicating $n=2$ in the range $0.3 - 2.0 \times 10^9/L$.

haematocrit and red cells, with some neglect of the effect of sample site on white cell counts. Finger-prick blood sampling provides a leukocyte-rich sample as it accesses arteriolar blood (204), in which there is a central rapid stream of the large leukocytes and erythrocytes, while the smaller platelets move more slowly adjacent to the vessel wall (205). However, for the purposes of this thesis, capillary blood refers to finger-prick samples.

Finger or heel-prick samples are commonly obtained from neonates and some older children, so there are studies comparing these and venous sample white cell counts (206-208). However, the neutrophil system in neonates is underdeveloped, has different neutrophil kinetics and is in a state of maturation (1). Table 28 summarises the findings of the limited published work on the comparison of white cell counts in venous and capillary blood in older children and adults (205, 209-212). All five studies reported the total white cell count to be greater in finger-prick capillary blood than venous samples. The range of mean percentage difference in adults was 3.3-9.3%, but this was either not tested statistically or not statistically significant in two of the studies (209, 210). Only Schalk et al. did a separate analysis of leukopenic samples and found the difference not to be statistically significant ($p=0.06$). The main limitation of this literature search is that none of the publications reported paired measurements, so comparison of individual results and the impact on clinical management decisions could not be performed. Much of this work was also quite dated; importantly, as a result there is little specifically on neutrophil counts and the AVIA2120 was not one of the four reference automated analysers used (Ortho ELT 800 WS, Coulter S Plus, Sysmex F-820, ADVIA 120).

However, there is much to be gained from scrutinising the methods in these studies. In particular, the attention paid to reporting sources of pre-analytic variability, which can be greater than analytic variations (213). For example, all studies discarded the first blood droplet. This is because (i) the first drop is rich in interstitial fluid, and (ii) tissue damage caused by the puncture initiates thromboplastin release, which initiates platelet aggregation, changing the platelet concentration in the first drops. Aggregated platelets can be mistaken for large white cells when measured by the Coulter counter technique. Two studies stated the patients had been resting before the samples were obtained, significant as body posture and exercise can effect leukocyte concentration (214, 215). Of

Study	Blood counts (patients)	Age (years)	White cell parameter	Venous range (x10 ⁹ /L)	Venous mean (x10 ⁹ /L)	Mean percentage difference (capillary - venous)	P value
Daae et al., 1988 (205)	40 (40)	22-62	total white cell count	4.0 - 15.1	7.13	+8.17	<0.005
			granulocytes	2.4 - 13.2	4.51	+8.19	<0.005
Daae et al., 1991 (209)	16 (16)	<1 - 14	total white cell count	3.2-35.3	9.60	+19.2	not reported
			granulocytes	1.1 - 9.9	5.00	+17.2	not reported
Leppanen et al. (210)	13 (13)	not reported	total white cell count	not reported	6.88	+3.3*	≥0.05
	25 (25)	22 - 58	immature neutrophils	not reported	not reported	negative**	≥0.05
			mature neutrophils	not reported	not reported	negative**	<0.05
			eosinophils	not reported	not reported	no difference**	≥0.05
			basophils	not reported	not reported	negative**	≥0.05
Schalk et al. (211)	463 (428)	18 - 82	total white cell count	0.1 - 299.5	8.90	+3.5	0.002
	18 (18)	not reported	total white cell count	≤1.00	not reported	not reported***	0.06
Yang et al. (212)	24 (24)	20 - 22	total white cell count	not reported	6.89	+9.2	≤0.05
			granulocytes	not reported	4.65	+12.6	≤0.05

Table 28: Summary of published comparisons of capillary and venous sample white cells counts.

“Mean percentage difference” refers to the mean difference of all the data, not mean difference of paired samples. Not reported = not written in paper and cannot be derived. *Derived from mean values in paper, not reported. **Paper reports mean concentration, description refers to capillary minus venous mean concentrations. ***Absolute difference is +0.1 x10⁹/L.

the four studies in adults, two described promoting formation of the finger-prick blood droplet by pre-heating the site or gentle massage, whereas the other two described allowing the blood droplet to form freely. This may be important as finger massage may cause demargination of neutrophils, potentially falsely elevating the capillary count. There are lessons to be learned here regarding the importance of standardising the technique used for performance analysis, and choosing one which can be easily replicated on a larger clinically relevant scale.

In this chapter, the performance of the Hemocue WBC DIFF analyser is evaluated when measuring capillary sample neutrophil counts in comparison to the current standard of care, which is venous sample neutrophil counts. This work addresses the shortfalls described in published literature by using populations of oncology patients, specifically in the neutropenic range, and using Leeds Teaching Hospitals NHS Trust standard of care analyser as reference (Siemens ADVIA 2120). It includes an analysis of paired capillary versus venous neutrophil results, and provided the first opportunity to assess patients doing the self-test procedure.

5.2 Objectives

5.2.1 Primary objectives

1. Evaluate capillary neutrophil counts measured by the Hemocue WBC DIFF in comparison to venous neutrophil counts measured by the Siemens ADVIA 2120, where venous neutrophil counts are $<2.0 \times 10^9/L$.
2. Identify the minimum capillary Hemocue WBC DIFF neutrophil count which indicates with 95% confidence that the venous ADVIA 2120 neutrophil count is $\geq 1.0 \times 10^9/L$.
3. Identify the maximum capillary Hemocue WBC DIFF neutrophil count which indicates with 95% confidence that the venous ADVIA 2120 neutrophil count is $<1.5 \times 10^9/L$.

5.2.2 Secondary objectives

1. Assess the ability of trained patients to collect the self-test capillary sample for measurement on the Hemocue WBC DIFF.

2. Evaluate capillary neutrophil counts measured by the Hemocue WBC DIFF from patient self-test samples.
3. Evaluate capillary neutrophil counts measured by the Hemocue WBC DIFF in comparison to venous neutrophil counts measured by the Hemocue WBC DIFF, where venous neutrophil counts are $<2.0 \times 10^9/L$.
4. Obtain feedback to define training needs for future patients.

5.3 Materials and Methods

Approval was obtained from the Leeds Teaching Hospitals NHS Trust Research and Development department and clinical director of non-surgical oncology to carry out this study of device performance. Samples and data were collected at two locations within Leeds Teaching Hospitals NHS Trust, each with different selection criteria and methods. These are described for each under Section 5.3.2 (“Neutropenic range evaluation”) and Section 5.3.3 (“Patient self-test evaluation”). Methods of neutrophil count measurement and statistical analysis were common to both evaluations. This evaluation was reported according to the principles of the Standards for Reporting Diagnostic Accuracy (STARD) Statement (180).

5.3.1 Methods of neutrophil count measurement

At Leeds Teaching Hospitals NHS Trust, the Siemens ADVIA 2120 automated blood count analyser is used to measure neutrophil counts from venous samples in ethylenediaminetetraacetic acid (EDTA) tubes. This was used as the reference neutrophil count in evaluating the performance of the Hemocue WBC DIFF neutrophil counts.

EDTA is used as it inhibits clotting by chelating calcium, removing it from the blood. The ADVIA 2120 measures six white cell differentials through cytochemical staining and forward focused laser light scatter and gives the result to two decimal places. The manufacturer only publishes accuracy and precision figures for the differential white cell counts within normal ranges; independently published validation of the ADVIA 2120 also does not analyse performance specifically in neutropenic ranges (86). However, the Leeds Teaching Hospitals ADVIA 2120 analysers are subject to standard internal and external quality control procedures at defined intervals throughout the day, including testing and reporting of measurements on UK National External Quality Assessment Service (NEQAS)

reference samples, which include neutropenic specimens. The analysers are used in routine clinical practice to make clinical management decisions on neutropenic patients.

The Haemocue WBC DIFF uses imaging analysis techniques referring to a validated photographic library to count and differentiate white cells, primarily in capillary blood; the result is given to one decimal place. The Hemocue WBC DIFF is intended for use on capillary blood samples. Performance data is already described in Table 25, and Table 26. The Hemocue WBC DIFF was used in accordance with the Leeds Teaching Hospitals NHS Trust point of care testing policy. A daily internal Quality Control test was performed and it was cleaned in accordance with the Leeds Teaching Hospitals NHS Trust decontamination of medical devices policy. All members of the research team using the device were trained and deemed competent to carry out the procedure.

5.3.2 Neutropenic range evaluation

5.3.2.1 Study population

Patients were approached in the oncology in-patient wards of Leeds Cancer Centre between November 2016 and April 2017. The inclusion criteria were; (i) diagnosis of a solid tumour, (ii) at least 18 years old, (iii) required a full blood count test for routine care purposes, (iv) anticipated to have a neutrophil count of $<2.0 \times 10^9/L$, and (v) present when the trial nurse was available to perform the finger-prick test. Exclusion criteria were; (i) history of haematological malignancy, (ii) on warfarin and the most recent INR >3 , (iii) known inherited or acquired bleeding disorder, (iv) known red blood cell abnormality e.g. sickle cell disease, (v) considered by the clinical ward team that inclusion is inappropriate given their acute clinical state. Informed written consent was obtained. The target recruitment of 100 sets of neutrophil results was pragmatically chosen based on expected prevalence of patients with neutrophil count $<2.0 \times 10^9/L$, and availability of the research nurse; recruitment ended after 85 sets of results had been collected due to limited nurse availability.

5.3.2.2 Blood sampling

All patients had a routine full blood count obtained by venepuncture, which was processed and analysed by a Siemens ADVIA 2120 in the standard way. All patients also had a capillary finger-prick sample attempted and measured on the Hemocue WBC DIFF, as soon

as possible after the venepuncture, for comparison with the venous ADVIA 2120. Blood droplet formation was promoted by warming the hand under warm water, and gentle finger massage. The first two droplets were discarded, and the third used for measurement. A blood droplet was also taken from the standard full blood count vial using a Diff-safe dispenser and analysed on the Hemocue WBC DIFF device for comparison of venous neutrophil counts measured by both analysers, but also to compare capillary versus venous neutrophil counts both measured by the Hemocue WBC DIFF. In addition, patients had a second EDTA tube of blood collected to measure precision of the Hemocue WBC DIFF in venous blood samples. Three microcuvettes were filled from one blood droplet, so one droplet was used to measure neutrophil counts in 3 different devices to enable calculation of between-device variation. Three different blood droplets from the same EDTA blood tube were also used to measure neutrophil counts by the same Hemocue WBC DIFF device to enable calculation of within-device variation.

Blood samples were obtained from the same patients on consecutive days using the methods detailed above, if they were expected to continue to have a neutrophil count $<2.0 \times 10^9/L$. Nurses were blind to the standard of care venous ADVIA 2120 neutrophil measurements at the time of performing the finger-prick test and measurement on the Hemocue WBC DIFF.

5.3.3 Patient self-test evaluation

5.3.3.1 Study population

Patients were approached in the oncology outpatient departments of Leeds Cancer Centre between November 2016 until April 2017. The inclusion criteria were; (i) diagnosis of a solid tumour diagnosis, (ii) were at least 18 years old, (iii) required a full blood count test on the same visit, and (iv) were present in the outpatient departments at the times the trial nurses were available. Exclusion criteria were; (i) unable to give informed consent, (ii) concurrent haematological malignancy, (iii) on warfarin and the most recent INR >3 , (iv) known inherited or acquired bleeding disorder, (v) known red blood cell abnormality e.g. sickle cell disease or β -thalassaemia major. Informed written consent was obtained. A target recruitment of 100 sets of neutrophil results was pragmatically chosen based on expected research nurse availability, but recruitment ended after 50 sets of neutrophil results had been collected due to limited availability of research nurses.

5.3.3.2 Blood sampling

All patients had a routine venous full blood count and trial finger-prick sample obtained and measured as described in 5.3.2.2., excluding the second EDTA tube of blood. In addition, following training and observation of the finger-prick done by the nurse, patients attempted to obtain their own finger-prick sample using the blood-letting lancet and microcuvette to collect the blood droplet as described. The nurse used this microcuvette to obtain the neutrophil count from the Hemocue WBC DIFF device.

No patient in this part of the performance evaluation provided more than 1 set of neutrophil count results. The venous ADVIA 2120 analyser neutrophil count result was obtained from the trust results server.

5.3.4 Statistical analysis

Descriptive analyses were performed using Microsoft Excel 2010 and statistical analyses using StataSE 13 (64-bit) (188, 189). Statistical significance was assumed at $p < 0.05$. The accuracy of using the Hemocue WBC DIFF on both capillary and venous blood samples in predicting the venous ADVIA 2120 neutrophil count was determined using Pearson's correlation co-efficient (r), the co-efficient of determination (r^2), linear regression and agreement analysis as described by Bland and Altman (187). Scatter plots were used to represent the correlation graphically. Bland-Altman plots were performed to visualise the agreement between the two methods.

To test the accuracy of the Hemocue WBC DIFF in identifying patients with ADVIA 2120 neutrophil counts of either $<1.0 \times 10^9/L$ (those at risk of febrile neutropenia) or $>1.5 \times 10^9/L$ (those in whom there is sufficient neutrophil recovery to safely deliver further chemotherapy), ROC curves were generated. A cut-off of $<1.0 \times 10^9/L$ was chosen to identify those at risk of febrile neutropenia as international guidelines for management of complicated neutropenia suggest neutrophils of $\leq 0.5 \times 10^9/L$ or in those patients where it is expected to fall to $\leq 0.5 \times 10^9/L$ within 24 hours should invoke a change of management. A cut-off of $>1.5 \times 10^9/L$ was chosen to identify those with sufficient neutrophil recovery to safely deliver chemotherapy as this is considered the safe threshold for most chemotherapy regimens given on a 3-weekly schedule. Sensitivity, specificity, negative predictive value (NPV), positive predictive value, false negative rate (FNR) and false

positive rate (FPR) were calculated to answer the following two questions (Introduction section 1.3.1.1.1 describes these statistical terms);

1. What is the minimum capillary Hemocue WBC DIFF neutrophil count we can be 95% confident the venous ADVIA 2120 neutrophil count is $\geq 1.0 \times 10^9/L$?
2. What is the maximum capillary Hemocue WBC DIFF neutrophil count we can be 95% confident the venous ADVIA 2120 neutrophil count is $< 1.5 \times 10^9/L$?

Precision was determined using the second venous EDTA blood sample collected immediately after the EDTA sample for routine care purposes. The co-efficient of variation was calculated using the SD and mean of a set of 3 neutrophil measurements ($CV = \frac{\text{standard deviation}}{\text{mean}}$). Then the mean of the squared CVs for each set of 3 measurements was square rooted to give the mean CV for all the sets of 3 results.

5.4 Results

5.4.1 Neutropenic range evaluation

5.4.1.1 Descriptive data

One hundred and thirteen patients were screened for this study, of whom 52 signed the consent form and gave at least one blood sample over and above that required for routine care. Table 29 shows the reasons why the remaining 61 patients were not entered into the study. In total, 86 sets of samples were collected from the 52 patients; 29 patients participated once only, 16 patients participated twice, 4 patients participated 3 times, 2 patients participated 4 times and 1 patient participated 5 times. Of the 86 sets of samples;

- 85 had a routine venous laboratory reference neutrophil count available.
- 69 have both the routine venous neutrophil count and the **capillary** Hemocue WBC DIFF measured neutrophil count available.
- 54 have both the routine venous neutrophil count and the **venous** Hemocue WBC DIFF measured neutrophil count available (both from the same EDTA tube).
- 53 have both the **venous** and **capillary** Hemocue WBC DIFF measured neutrophil count available.

These numbers are explained in the Consort diagram in Figure 19.

Reason patient was not enrolled	Number of patients
Declined as needle phobic	1
Declined as feels unwell	2
Declined as not interested in research	1
Considered not appropriate by staff	4
Language was a barrier to consent	2
INR raised	1
Routine blood sample already collected the same day	16
Routine blood test not planned for the same day	31
Patient discharged	3
Total	61

Table 29: Frequency table of reason patients who were screened did then not participate in the study.

INR, international normalise ratio, which was one of the exclusion criteria.

Room temperature was recorded when 67 of the 69 capillary samples were measured by the Hemocue WBC DIFF; it ranged from 21.9 to 23.7 °Celsius. Only time of collection and not time of measurement was recorded for the routine venous laboratory sample. The time difference between collection of the venous sample for laboratory measurement and collection of the capillary sample for Hemocue WBC DIFF measurement ranged from 1 to 59 minutes (mean 8 minutes). The time difference between collection and measurement by the Hemocue WBC DIFF of the capillary sample ranged from 0 to 48 minutes (mean 4.6 minutes).

Table 30 describes the neutrophil measurements according to whether it was a venous or capillary sample and according to the device used to measure the neutrophil count. There were 15 Hemocue WBC DIFF measured capillary samples where the device indicated the total white cell count was $<1.0 \times 10^9/L$ and therefore did not display the differential counts.

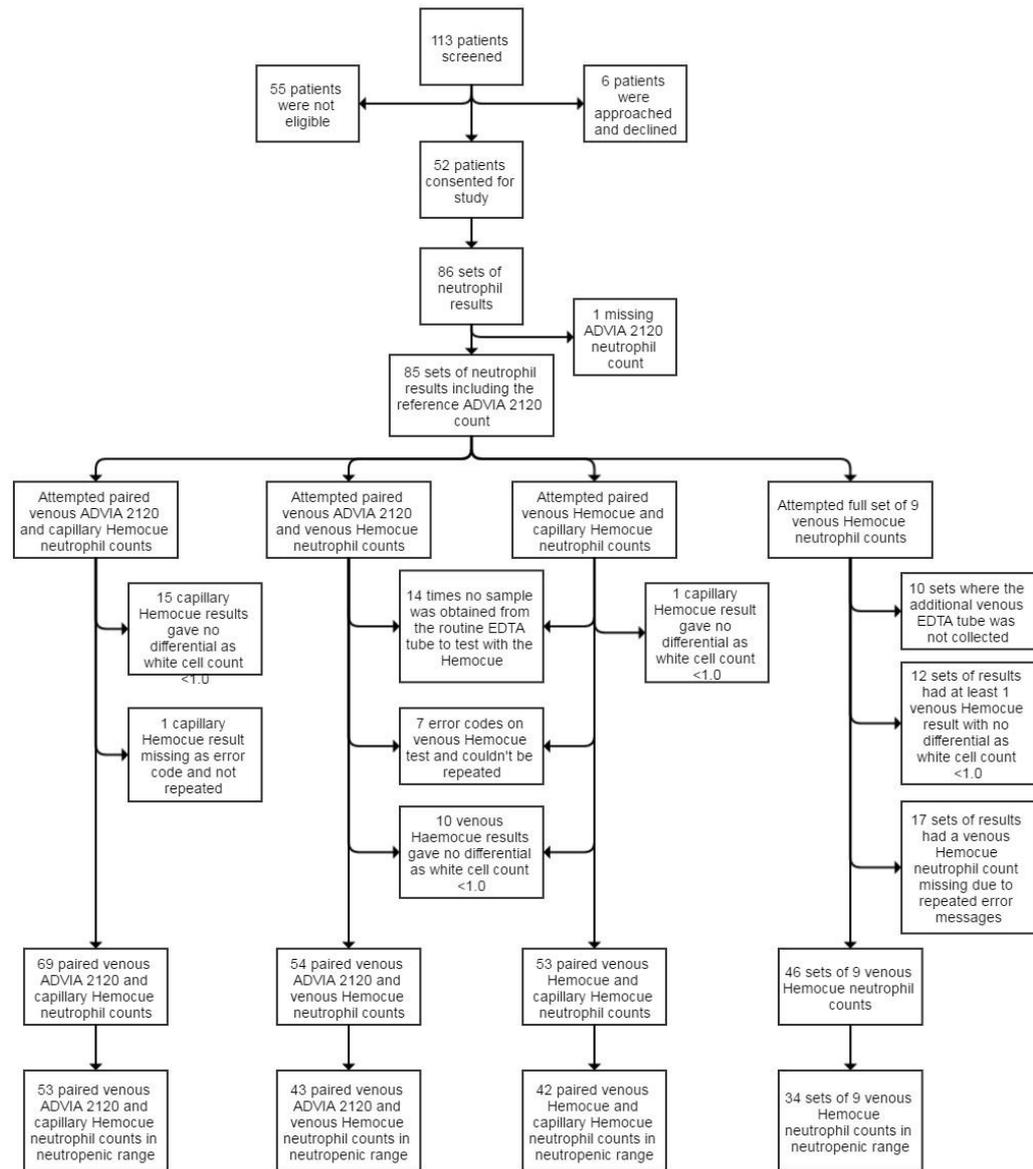


Figure 19: Consort diagram of study participants and sets of blood samples with paired neutrophil counts available for analysis.

Neutropenic range refers to venous ADVIA 2120 neutrophil count $<2.0 \times 10^9/L$. EDTA stands for ethylenediaminetetraacetic acid.

This concurs with the laboratory measured venous neutrophil counts in 10 corresponding samples that were also reported to have a total white cell count $<1.0 \times 10^9/L$. Five of the corresponding laboratory total white cell counts were $>1.0 \times 10^9/L$. They were 1.38, 1.20, 1.16, 1.10, $1.55 \times 10^9/L$, with differential neutrophil counts of 0.40, 0.27, 0.26, 0.23 and 0.06. Only one capillary Hemocue sample was indicated to be outside of the stated lower limit of detection of total white cell count ($0.3 \times 10^9/L$).

Device & sample used to measure neutrophils	Venous ADVIA 2120	Capillary Hemocue WBC DIFF	Venous Hemocue WBC
Neutrophil count ($\times 10^9/L$)			
Range	0.06 - 10.70	0.2 - 5.8	0.1 - 4.1
Mean	1.26	1.3	1.2
Sample frequency			
Neutrophils <2.0 ($\times 10^9/L$)	69	54	48
Neutrophils <1.5 ($\times 10^9/L$)	63	44	37
Neutrophils <1.0 ($\times 10^9/L$)	41	28	24
Neutrophils <0.5 ($\times 10^9/L$)	23	9	8
Total number of neutrophil results	85	69	54

Table 30: Characteristics of venous and capillary sample neutrophil measurements from the Siemens ADVIA 2120, and the Hemocue WBC DIFF.

The neutrophil counts are reported to the number of decimal places reported by the measuring device; ADVIA 2120 to 2 decimal places and Hemocue WBC DIFF to 1 decimal place.

There were 85 attempted capillary sample measurements on the Hemocue WBC DIFF. Of these, there were 6 error messages (2 error code 02, 1 error code 05, 3 error code 60; Table 31 explains the error codes and recommended actions). Error code 60 always appeared before insertion of the microcuvette and was resolved by cleaning the optical parts, resulting in delay of sample measurement only. Where error code 02 was shown, the finger-prick was repeated and the second samples gave valid results. In the one case where error code 05 was shown, it was not possible to repeat the finger-prick sample collection due to time constraints complicated by the fact the device also needed cleaning

Error code	Explanation	Action
01	Part of the image area cannot be analysed. Potential causes may be: <ul style="list-style-type: none"> • Air bubbles in the sample • Incorrect handling of the sample • Abnormalities in sample 	1) Take a new microcuvette, repeat the measurement 2) If the problem persists, the sample should be verified with a suitable laboratory method
02	Uneven spatial distribution of detected cells	Take a new microcuvette, repeat the measurement.
04	Acceptable light level cannot be achieved	Take a new microcuvette, repeat the measurement. If the problem persists, the analyser needs service.
05	Cuvette holder was not inserted in correct menu mode	Remove the microcuvette. Take a new microcuvette, repeat the measurement. NOTE: Make sure the “insert cuvette” symbol is displayed before inserting a new microcuvette
60	General hardware error	Try one or more of the following: <ol style="list-style-type: none"> 1a) clean the optical parts 1b) If an error code appears when connecting a USB device, remove the device and re-start the analyser 1c) wait 30 seconds and re-start the analyser 2) If the problem persists, the analyser needs service.

Table 31: Table explaining the Hemocue WBC DIFF error codes which occurred during the analysis, and suggested actions to resolve them.

Reproduced from the Hemocue WBC DIFF operating manual.

prior to the second sample measurement. There were 71 attempted venous Haemocue WBC DIFF measurements of the sample obtained from the same EDTA tube as sent to the laboratory. Of these, 7 gave an error code 01 and could not be repeated as the EDTA tube had been sent to the laboratory.

For the precision analysis, the full set of 9 neutrophil results were obtained 46 times out of 75 attempts. Within this, 152 sets of valid neutrophil results were obtained where a single blood droplet was measured successfully in 3 different devices. There were also 148 sets of valid neutrophil results where 3 droplets of blood from the same EDTA tube were measured on the same device. There was a high frequency of error messages when collecting these data for the precision analysis. There were 158 code 01 and 4 code 02, meaning many measurements had to be repeated to obtain valid results.

No adverse effects of obtaining the capillary sample were reported, but 2 different patients commented; “it didn’t hurt” and “I would prefer to have a finger-prick rather than blood taken out of my arm”.

5.4.1.2 Venous ADVIA 2120 reference analyser versus venous Hemocue WBC DIFF neutrophil counts

Accuracy of the Hemocue WBC DIFF measured venous samples was analysed in comparison to the ADVIA 2120 measured venous sample from the same EDTA tube. There were 54 paired neutrophil counts in total, of which, 43 were in the neutropenic range (i.e. neutrophils <2.0 on the ADVIA 2120). The scatter plot and correlation of these is shown in Figure 20. The agreement analysis is shown as a Bland-Altman plot in Figure 21.

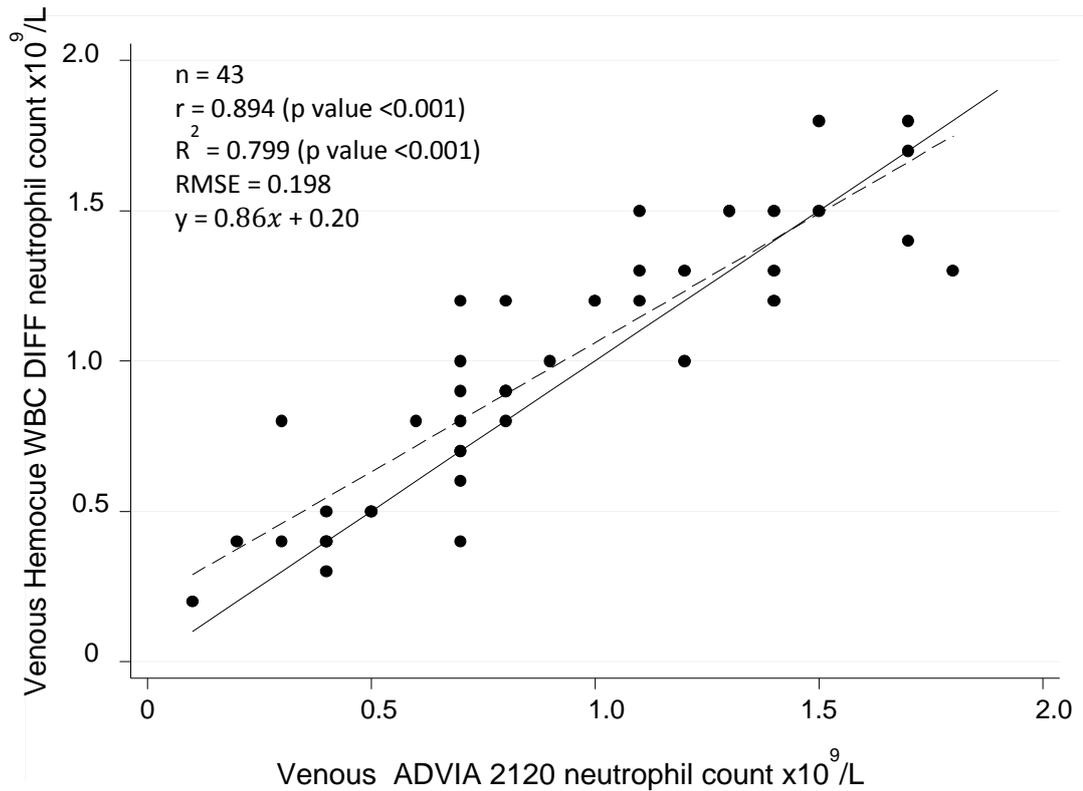


Figure 20: Scatter plot showing the relationship of venous ADVIA 2120 and venous Hemocue WBC DIFF neutrophil counts in the neutropenic range.

Solid black line is $x=y$, dashed black line is line of best fit. RMSE, root mean square error. Seven of the dots represent more than one pair of results.

5.4.1.3 Venous Hemocue WBC DIFF versus capillary Hemocue WBC DIFF neutrophil counts

Accuracy of the Hemocue WBC DIFF measured capillary samples was analysed in comparison to the Hemocue WBC DIFF measured venous samples. There were 53 paired neutrophil counts in total. The correlation of these results gave an r value of 0.847 (p value <0.001), R^2 was 0.717 (p value <0.001), the root mean squared error (RMSE) was 0.390, and the line of best fit was $y = 0.85x + 0.15$. This full range data is not represented on a scatter graph.

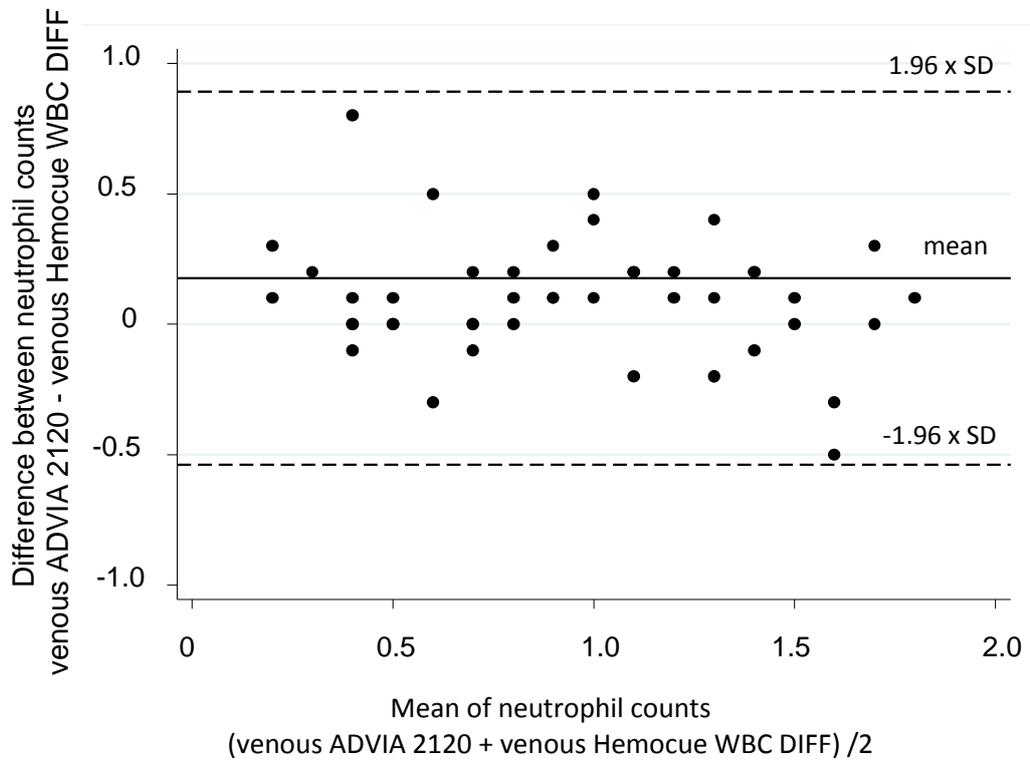


Figure 21: Agreement analysis between venous ADVIA 2120 and venous Hemocue WBC DIFF neutrophil counts in the neutropenic range.

This is a Bland-Altman plot of the mean neutrophil count against the difference between the counts from the two analysers. SD, standard deviation and is 0.37. The solid black line represents the mean difference and is 0.178. The black dashed lines labelled “1.96 x SD” represent the upper and lower limits of agreement which are the 95% CIs. The upper dashed line is 0.89 and the lower dashed line is -0.54.

There were 42 paired neutrophil counts in the neutropenic range (neutrophils <2.0 on the ADVIA 2120) from venous Hemocue WBC DIFF and capillary Hemocue WBC DIFF samples. The scatter plot and correlation of these is shown in Figure 22. The agreement analysis is shown as a Bland-Altman plot in Figure 23.

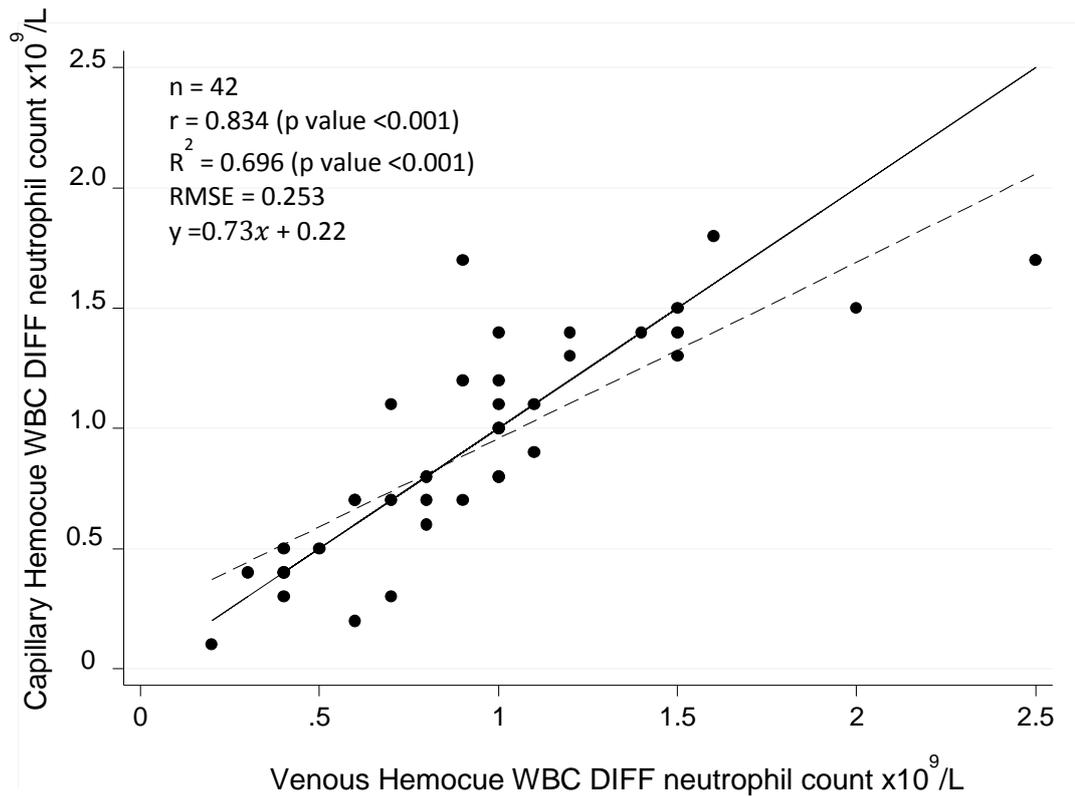


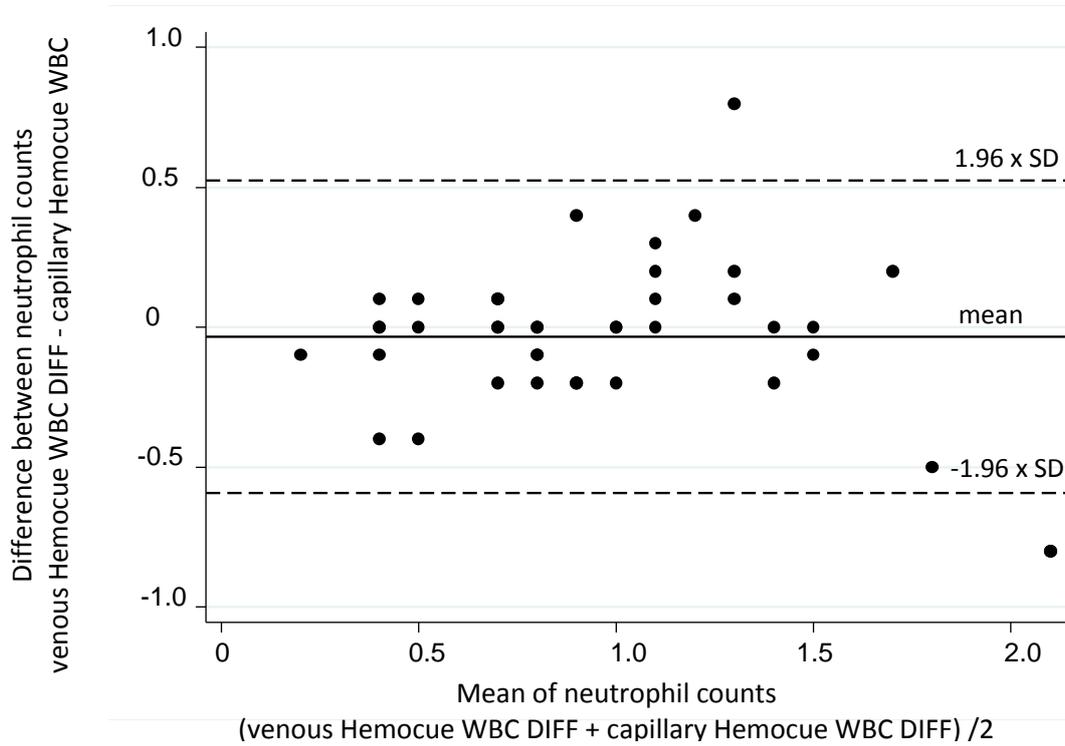
Figure 22: Scatter plot showing the relationship of venous Hemocue WBC DIFF and capillary Hemocue WBC DIFF neutrophil counts in the neutropenic range. Solid black line is $x=y$, dashed black line is line of best fit. RMSE, root mean square error. There are 33 observations as 9 observations represent more than one pair of results.

5.4.1.4 Venous ADVIA 2120 reference analyser versus capillary Hemocue WBC DIFF neutrophil counts

5.4.1.4.1 Accuracy

There were 69 paired neutrophil counts in total from venous ADVIA 2120 and capillary Hemocue WBC DIFF samples. Of these, 53 paired neutrophil counts were in the neutropenic range (neutrophils <2.0 on the ADVIA 2120) from venous ADVIA 2120 and capillary Hemocue WBC DIFF samples. The scatter plot and correlation of the neutropenic paired samples are shown in Figure 24. The agreement analysis is shown as a Bland-Altman plot in Figure 25.

a)



b)

Neutrophil counts $\times 10^9/L$	
Venous Hemocue WBC DIFF	Capillary Hemocue WBC DIFF
1.7	2.5
1.7	0.9

Figure 23: Agreement analysis between venous Hemocue and capillary Hemocue WBC DIFF neutrophil counts in the neutropenic range.

a) Bland-Altman plot of the mean neutrophil count against the difference between the counts from the two analysers. SD, standard deviation and is 0.29. The solid black line represents the mean difference and is -0.03. The black dashed lines labelled "1.96 x SD" represent the upper and lower limits of agreement which are the 95% CIs. The upper dashed line is 0.53 and the lower dashed line is -0.59. b) Table displaying the neutrophil counts of the two results lying out with the limits of agreement.

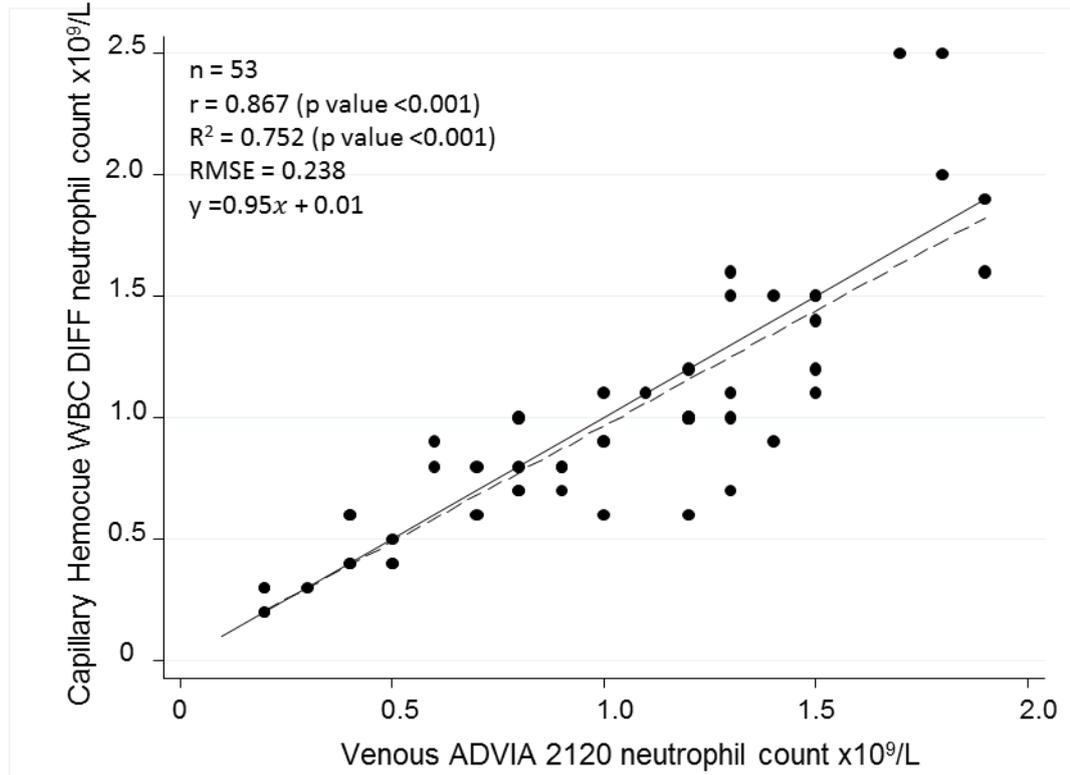
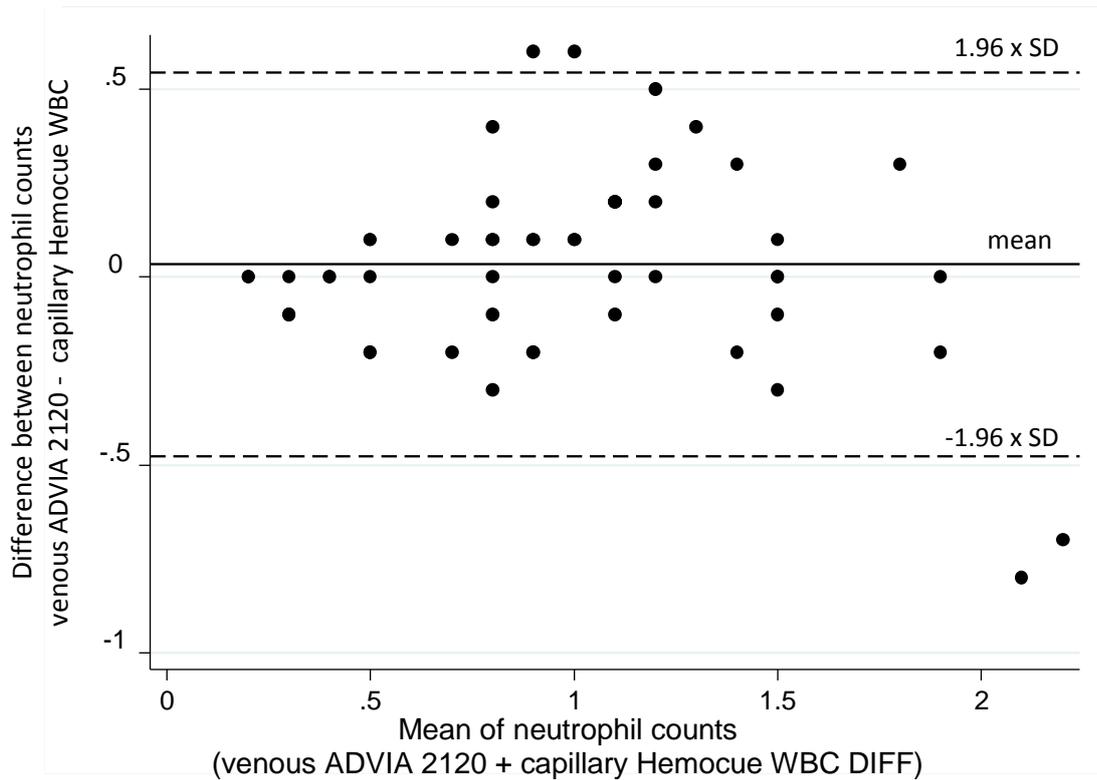


Figure 24: Scatter plot showing the relationship of venous ADVIA 2120 and capillary Hemocue WBC DIFF neutrophil counts in the neutropenic range.

Solid black line is $x=y$, dashed black line is line of best fit. RMSE, root mean square error. Fourteen dots represent more than one pair of results.

a)



b)

Neutrophil counts $\times 10^9/L$	
Venous ADVIA 2120	Capillary Hemocue WBC DIFF
1.2	0.6
1.3	0.7
1.7	2.5
1.8	2.5

Figure 25: Agreement analysis between venous ADVIA and capillary Hemocue WBC DIFF neutrophil counts in the neutropenic range.

a) Bland-Altman plot of the mean neutrophil count against the difference between the counts from the two analysers. SD, standard deviation and is 0.26. The solid black line represents the mean difference and is 0.03. The black dashed lines labelled “1.96 x SD” represent the upper and lower limits of agreement which are the 95% CIs. The upper dashed line is 0.54 and the lower dashed line is -0.48. b) Table displaying the neutrophil counts of the four results lying out with the limits of agreement.

5.4.1.4.2 Performance around thresholds in oncological practice

What is the minimum capillary Hemocue WBC DIFF neutrophil count we can be 95% confident the venous ADVIA 2120 neutrophil count is $\geq 1.0 \times 10^9/L$?

The AUC of the ROC analysis for the capillary Hemocue WBC DIFF neutrophil count indicating a venous ADVIA 2120 neutrophil count of $< 1.0 \times 10^9/L$ demonstrated a high accuracy (AUC 0.956). This is shown in Figure 26. The capillary Hemocue WBC DIFF neutrophil count of $< 1.1 \times 10^9/L$ is the lowest threshold with no false negatives, and the sensitivity is 100% and specificity is 73.3%. Table 32 displays the performance analysis of Hemocue WBC DIFF neutrophil count thresholds as surrogates for a venous ADVIA 2120 neutrophil threshold of $< 1.0 \times 10^9/L$. Using the capillary Hemocue WBC DIFF neutrophil threshold of $< 1.0 \times 10^9/L$ as an example, 22 patients were correctly categorised as neutropenic (true positive), 6 were incorrectly categorised as neutropenic (false positive), 2 were incorrectly categorised as not neutropenic (false negative), and 39 were correctly categorised as not neutropenic (true negative). The statistical terms were calculated as described in Table 4, section 1.3.1.1.1.

Maximising the product of sensitivity and specificity indicated that the WBC DIFF neutrophil threshold of $< 1.0 \times 10^9/L$ performed the best. However, this did not take into consideration clinical acceptability, or otherwise, of the false negative rate using this threshold. Using the threshold of $< 1.1 \times 10^9/L$, there were no false negatives, which is reflected in the false negative rate of 0%, and sensitivity and negative predictive values of 100%. Using this same threshold, only 33.3% of those asked to come to hospital for an acute assessment would have been found to have a neutrophil count $\geq 1.0 \times 10^9/L$ on the ADVIA 2120 ($\frac{\text{false positive}}{\text{true positive} + \text{false positive}} \times 100$). These patients would have been inconvenienced by a trip to hospital that would not have altered management. This is 17.4% of all the patient samples analysed who would have been incorrectly advised to come to hospital ($\frac{\text{false positive}}{n} \times 100$).

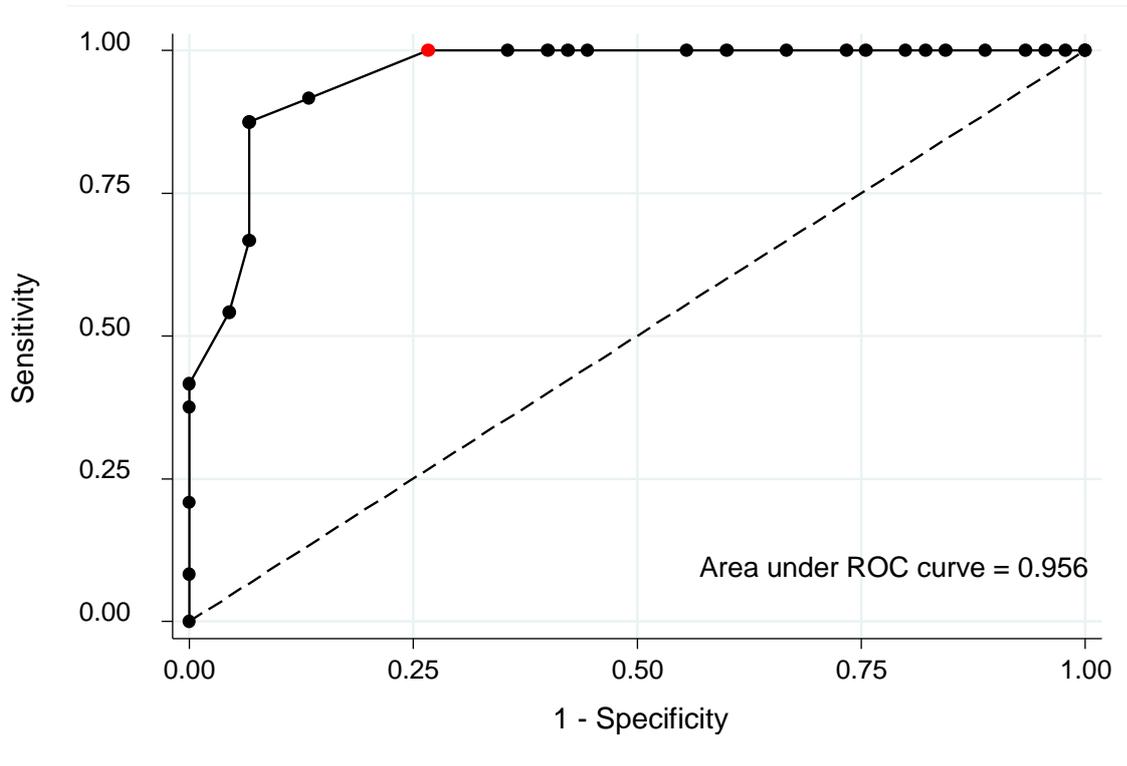


Figure 26: Receiver operator characteristic (ROC) curve evaluating the performance of capillary Hemocue WBC DIFF neutrophil count as a surrogate of venous ADVIA 2120 neutrophil count threshold of $<1.0 \times 10^9/L$.

The red observation represents the plot for capillary Hemocue WBC DIFF neutrophil count of $<1.1 \times 10^9/L$. This is the lowest threshold with no false negatives, the sensitivity is 100% and specificity is 73.3%.

What is the maximum capillary Hemocue WBC DIFF neutrophil count we can be 95% confident the venous ADVIA 2120 neutrophil count is $<1.5 \times 10^9/L$?

The AUC of the ROC analysis for the capillary Hemocue WBC DIFF neutrophil count indicating a venous ADVIA 2120 neutrophil count of $<1.5 \times 10^9/L$ also demonstrated a high accuracy (AUC 0.981). This is shown in Figure 27. Table 33 displays the performance analysis of Hemocue WBC DIFF neutrophil count thresholds as surrogates for a venous ADVIA 2120 neutrophil threshold of $<1.5 \times 10^9/L$. Using the capillary Hemocue WBC DIFF neutrophil threshold of $<1.0 \times 10^9/L$ as an example, 28 patients were correctly categorised as neutropenic (true positive), 0 were incorrectly categorised as neutropenic (false positive), 15 were incorrectly categorised as not neutropenic (false negative), and 26 were

Capillary Hemocue WBC DIFF threshold ($\times 10^9/L$)	Raw Data				Performance Analysis						
	True Positive	False Positive	False Negative	True Negative	Sensitivity % (95% CI)	Specificity % (95% CI)	NPV % (95% CI)	PPV % (95% CI)	FNR %	FPR %	Correctly classified %
<1.0	22	6	2	39	91.7 (73.0-99.0)	86.7 (73.2-95.0)	95.1 (83.5-99.4)	78.6 (59.1-91.7)	8.3	13.3	88.4
<1.1	24	12	0	33	100.0 (85.8-100.0)	73.3 (58.1-85.4)	100.0 (89.4-100.0)	66.7 (49.0-81.4)	0	26.7	82.6
<1.2	24	16	0	29	100.0 (85.8-100.0)	64.4 (48.8-78.1)	100.0 (88.1-100.0)	60.0 (43.3-75.1)	0	35.6	76.8
<1.3	24	19	0	26	100.0 (85.8-100.0)	57.8 (42.2-72.3)	100.0 (86.8-100.0)	55.8 (39.9-70.9)	0	42.2	72.5
<1.4	24	20	0	25	100.0 (85.8-100.0)	55.6 (40.0-70.4)	100.0 (86.3-100.0)	54.6 (38.9-69.6)	0	44.4	71.0
<1.5	24	20	0	25	100.0 (85.8-100.0)	55.6 (40.0-70.4)	100.0 (86.3-100.0)	54.6 (38.9-69.6)	0	44.4	71.0

Table 32: Performance analysis of capillary Hemocue WBC DIFF neutrophil count thresholds as surrogate indicators of the venous ADVIA 2120 neutrophil count threshold of $1.0 \times 10^9/L$.

CI, confidence interval. NPV, negative predictive value. PPV, positive predictive value. FNR, false negative rate. FPR, false positive rate. Prevalence of neutropenia ($<1.0 \times 10^9/L$) measured on the venous sample by the ADVIA 2120 was 34.8%.

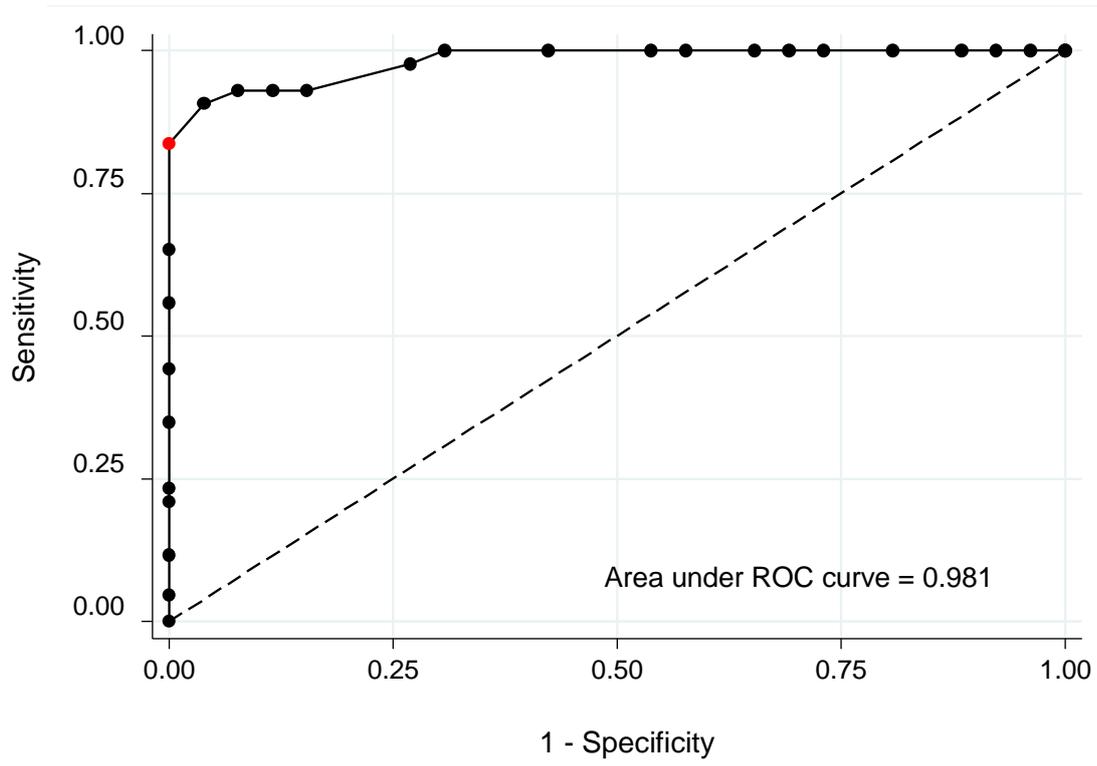


Figure 27: Receiver operator characteristic (ROC) curve evaluating the performance of capillary Hemocue WBC DIFF neutrophil count as a surrogate of venous ADVIA 2120 neutrophil count threshold of $<1.5 \times 10^9/L$.

The red observation represents the plot for capillary Hemocue WBC DIFF neutrophil count of $<1.1 \times 10^9/L$. This is the highest threshold with no false positives, the specificity is 100% and sensitivity 83.7%.

correctly categorised as not neutropenic (true negative). The statistical terms were calculated as described in Table 4, section 1.3.1.1.1.

Maximising the product of sensitivity and specificity indicated that the WBC DIFF neutrophil thresholds of <1.3 and $<1.4 \times 10^9/L$ performed the best. However, taking into consideration clinical acceptability of the threshold, $<1.1 \times 10^9/L$ was the safest performing Hemocue WBC DIFF neutrophil count threshold indicating the venous ADVIA 2120 neutrophil count is $<1.5 \times 10^9/L$. Using the Hemocue WBC DIFF neutrophil threshold of $<1.1 \times 10^9/L$, there were no false positives, which was reflected in both the positive predictive value and specificity of 100%. Sensitivity was 83.7%, indicating the proportion of those who were neutropenic and were correctly identified by the test. However, 21.2% of patients who would have been advised their neutrophil count had recovered sufficiently to

Capillary Hemocue WBC DIFF threshold ($\times 10^9/L$)	Raw Data				Performance Analysis						
	True Positive	False Positive	False Negative	True Negative	Sensitivity % (95% CI)	Specificity % (95% CI)	NPV % (95% CI)	PPV % (95% CI)	FNR %	FPR %	Correctly classified %
<1.0	28	0	15	26	65.1 (49.1-79.0)	100.0 (86.8-100.0)	63.4 (46.9-77.9)	100.0 (87.7-100.0)	34.9	0	78.3
<1.1	36	0	7	26	83.7 (69.3-93.2)	100.0 (86.8-100.0)	78.8 (61.1-91.0)	100.0 (90.3-100.0)	16.3	0	89.9
<1.2	39	1	4	25	90.7 (77.9-97.4)	90.7 (77.9-97.4)	86.2 (68.3-96.1)	97.5 (86.8-99.9)	9.3	3.8	92.8
<1.3	40	3	3	23	93.0 (80.9-98.5)	93.0 (80.9-98.5)	88.5 (69.9-97.6)	93.0 (80.9-98.5)	7.0	11.5	91.3
<1.4	40	4	3	22	93.0 (80.9-98.5)	93.0 (80.9-98.5)	88.0 (68.8-97.5)	90.9 (78.3-97.5)	7.0	15.4	89.9
<1.5	40	4	3	22	93.0 (80.9-98.5)	84.6 (65.1-95.6)	88.0 (68.8-97.5)	90.9 (78.3-97.5)	7.0	15.4	89.9
<1.6	42	7	1	19	97.7 (87.7-99.9)	73.1 (52.2-88.4)	95.0 (75.1-99.9)	85.7 (72.8-94.1)	2.3	26.9	88.4

Table 33: Performance analysis of capillary Hemocue WBC DIFF neutrophil count thresholds as surrogate indicators of the venous ADVIA 2120 neutrophil count threshold of $1.5 \times 10^9/L$.

CI, confidence interval. Prevalence of neutropenia ($<1.5 \times 10^9/L$) measured on the venous sample by the ADVIA 2120 was 62.3%.

deliver chemotherapy safely using the capillary Hemocue WBC DIFF sample, would have been found to be neutropenic on the ADVIA 2120 blood count, as reflected by 1-negative predictive value. This was 10.1% of all the patient samples analysed where the patient would have been incorrectly advised to come to hospital for chemotherapy delivery

$$\left(\frac{\text{false negative}}{n}\right).$$

5.4.1.5 Precision

Both within-device and between-device variation was calculated using neutrophil results measured by the Hemocue WBC DIFF from the second EDTA tube sample collected immediately after that used for routine care purposes. Table 34 displays the calculated within-device and between-device co-efficient of variations. The mean within-device co-efficient of variation was 13.1%, and the mean between-device co-efficient of variation was 13.0%.

Within-device variation		
Device	Number with all 3 sample neutrophil measurements available (n)	Co-efficient of variation (%)
1	52	12.4
2	47	14.7
3	49	21.1
Between-device variation		
Sample	Number with all 3 device neutrophil measurements available (n)	Co-efficient of variation (%)
1	48	13.1
2	52	16.2
3	52	9.6

Table 34: Table showing within and between Hemocue WBC DIFF device co-efficient of variations (CV).

All samples within one set of results were obtained from the same venous EDTA tube and measured on the Hemocue WBC DIFF device. The results were limited to sets of data where all 3 neutrophil results were available; either 3 blood droplets from the same EDTA tube each measured on the same device (within-device variation), or 1 blood droplet measured on each of 3 devices (between-device variation).

5.4.2 Patient self-test evaluation

5.4.2.1 Descriptive data

Sixty-seven patients were approached to enter this study; of these, 51 patients consented to participate. Of the 16 who declined, only 1 gave the reason that they did not want to finger-prick themselves. In total, 50 patients provided at least one capillary blood sample for analysis on the Hemocue WBC DIFF; the remaining patient left the clinic before providing a sample. Each patient participated once only. Thirty-seven of these patients were receiving chemotherapy. Of the 50 sets of samples available;

- 45 had a venous ADVIA 2120 neutrophil count available.
- 50 had a capillary nurse-obtained Hemocue WBC DIFF neutrophil count available.
- 41 had a capillary patient-obtained Hemocue WBC DIFF neutrophil count available.
- 38 had neutrophil counts available for all 3 samples; the venous ADVIA 2120 sample, the capillary nurse and the capillary patient-obtained samples.

The Consort diagram in Figure 28 explains the number of paired neutrophil count results available for the analysis.

Nine patients did not have a self-obtained capillary sample neutrophil count available. Of these, 3 declined, each with a different one of the following explanations;

- Patient not confident enough to do the finger-prick.
- Happy for the professional test, but not the self-test.
- The nurse test hurt more than expected and therefore declined self-test.

One of the 9 patients was unable to fill the microcuvette due to a tremor, despite 3 attempts. The error codes displayed on the Hemocue WBC DIFF for 5 of the 9 patients without a self-obtained capillary sample neutrophil count were;

- Error 1(n=1): The sample was noted to be a small blood droplet and there was a visible air bubble in the microcuvette.
- Error 4(n=2): One of these had a visible air bubble in the microcuvette and the sample was not repeated. The other had a repeat sample and the same error code was displayed for a second time.
- Error 60 (n=2): Neither sample was repeated.

No error codes occurred when the nurse obtained and measured the capillary sample.

Room temperature was recorded when 48 of the 50 nurse-obtained capillary samples were measured by the Hemocue WBC DIFF; it ranged from 21.1 to 23.4 °Celsius. Only time of collection and not time of measurement was recorded for the routine venous laboratory sample. The time differences between collection and measurement of all the samples is summarised in Table 35.

Table 36 summarises the neutrophil results according to the sample and device used to measure the neutrophil count. There were no Hemocue WBC DIFF measured capillary samples where the device did not display the differential counts due to the total white cell count being $<1.0 \times 10^9/L$. This agrees with the venous ADVIA 2120 measured neutrophil counts where there were also no total white cell counts less than $1.0 \times 10^9/L$.

5.4.2.2 Accuracy

Accuracy of both the nurse and patient-obtained capillary Hemocue WBC DIFF measured neutrophil counts were analysed in comparison to the paired venous ADVIA 2120 measured neutrophil counts and to each other. The correlations were all comparable (Table 37). The scatter plot and correlation of capillary nurse versus patient-obtained Hemocue WBC DIFF neutrophil counts is shown in Figure 29. The agreement analysis of the same is shown as a Bland-Altman plot in Figure 30.

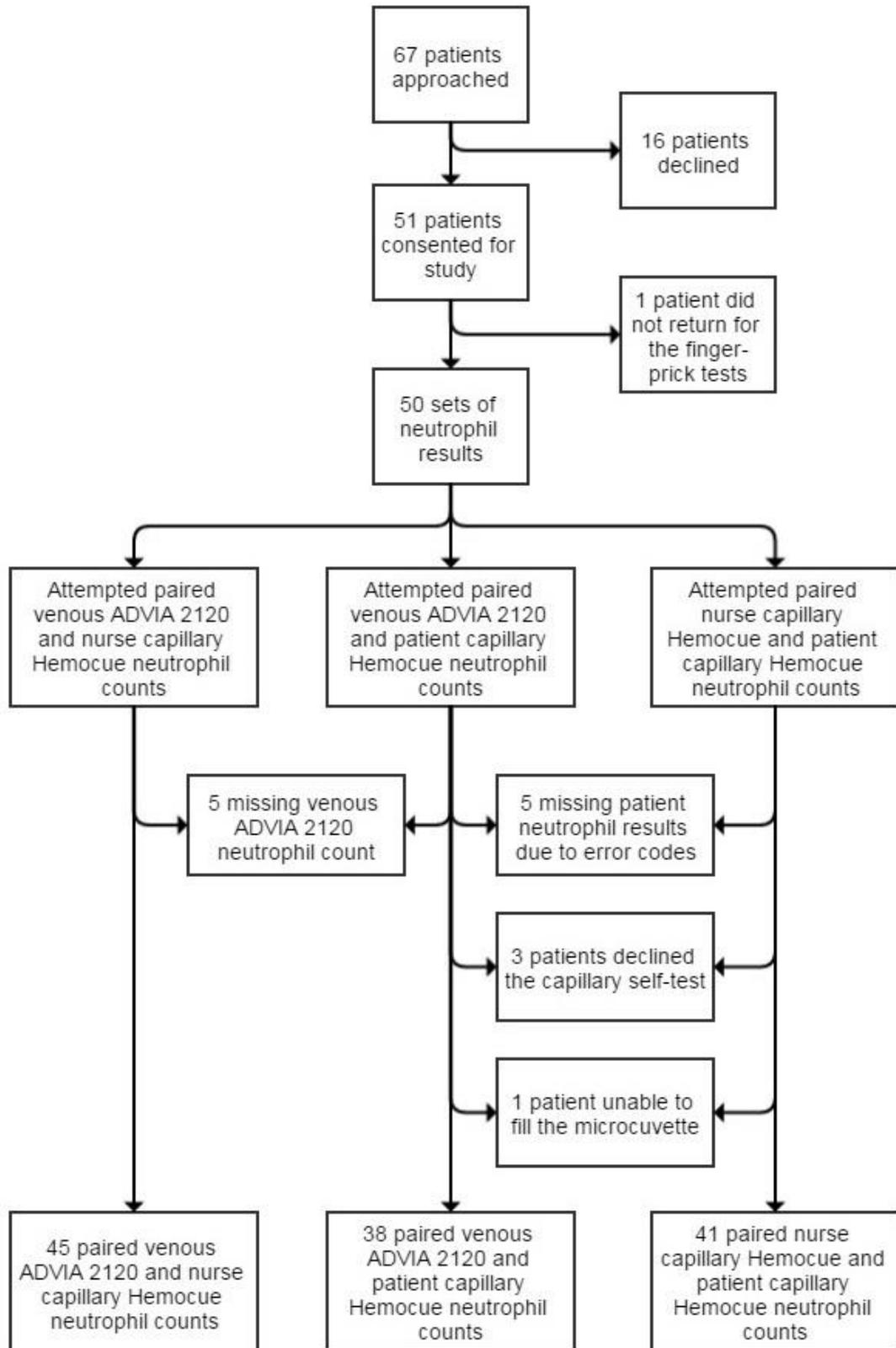


Figure 28: Consort diagram of study participants and sets of blood samples with paired neutrophil counts available for analysis.

Parameters	Mean time difference in minutes (range)
Venous ADVIA 2120 sample collection & capillary nurse Hemocue WBC DIFF sample collection	25 (2-78)
Venous ADVIA 2120 sample collection & capillary patient- obtained Hemocue WBC DIFF sample collection	29 (2-78)
Capillary nurse Hemocue WBC DIFF sample collection & capillary patient-obtained Hemocue WBC DIFF sample collection	8 (0-36)
Capillary nurse Hemocue WBC DIFF sample collection and measurement	3 (0-11)
Capillary patient-obtained Hemocue WBC DIFF sample collection & measurement	4 (0-14)

Table 35: Table summarising the time differences between collection and measurements of the 3 different samples.

Device & sample used to measure neutrophils	Venous ADVIA 2120 (n=45)	Capillary nurse obtained Hemocue WBC DIFF (n=50)	Capillary patient obtained Hemocue WBC (n=41)
Neutrophil count (x10⁹/L)			
Range	0.40 - 11.86	0.6 - 15.4	0.4 - 13.1
Mean	3.79	3.68	3.59
SD	2.25	2.46	2.37

Table 36: Table summarising the neutrophil results according to the sample and device used to measure the neutrophil count.

The neutrophil counts are reported to the number of decimal places reported by the measuring device; ADVIA 2120 to 2 decimal places and Hemocue WBC DIFF to 1 decimal place.

Samples compared	R	R ²	Root mean square error	Line of best fit
Capillary patient Hemocue WBC DIFF vs venous ADVIA 2120 (n=38)	0.953	0.908	0.756	$Y=0.99x - 0.15$
Capillary nurse Hemocue WBC DIFF vs venous ADVIA 2120 (n=45)	0.961	0.924	0.718	$Y=1.10x - 0.43$
Capillary patient vs nurse Hemocue WBC DIFF (n=41)	0.960	0.921	0.747	$Y=1.06x - 0.12$

Table 37: Table showing correlation between the 3 blood sample neutrophil counts (nurse and patient finger-prick Hemocue samples and venous ADVIA 2120 samples).

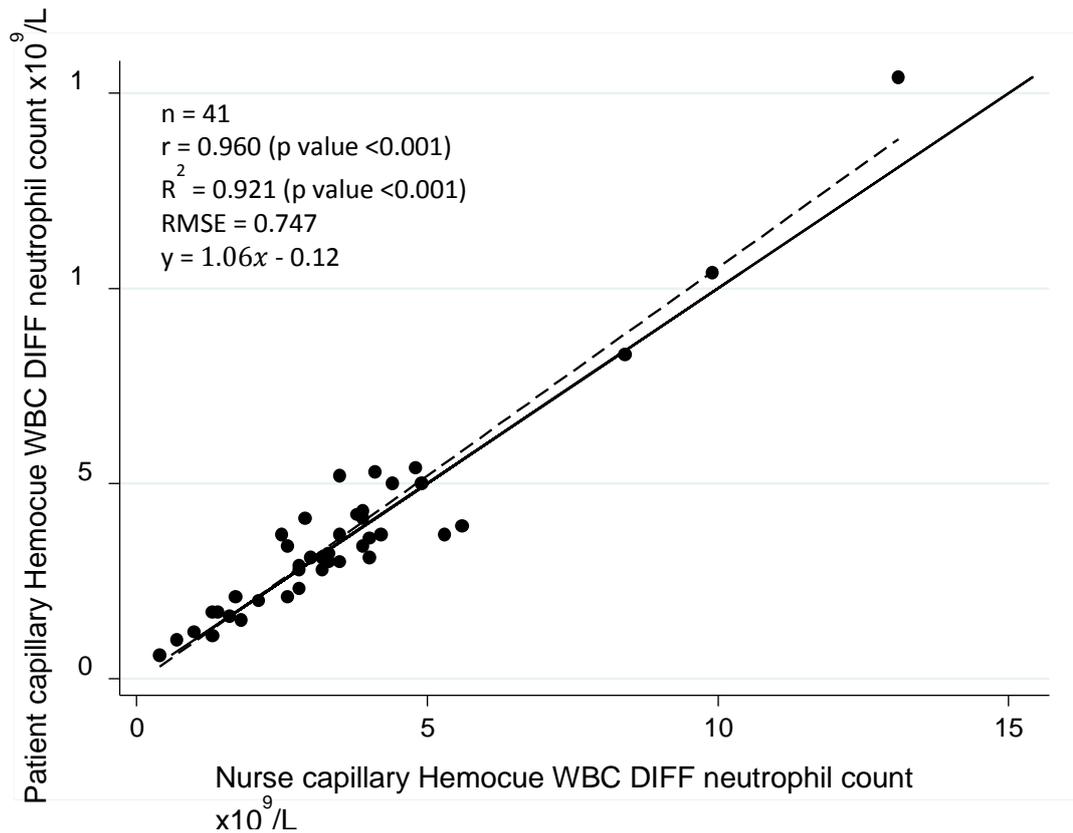
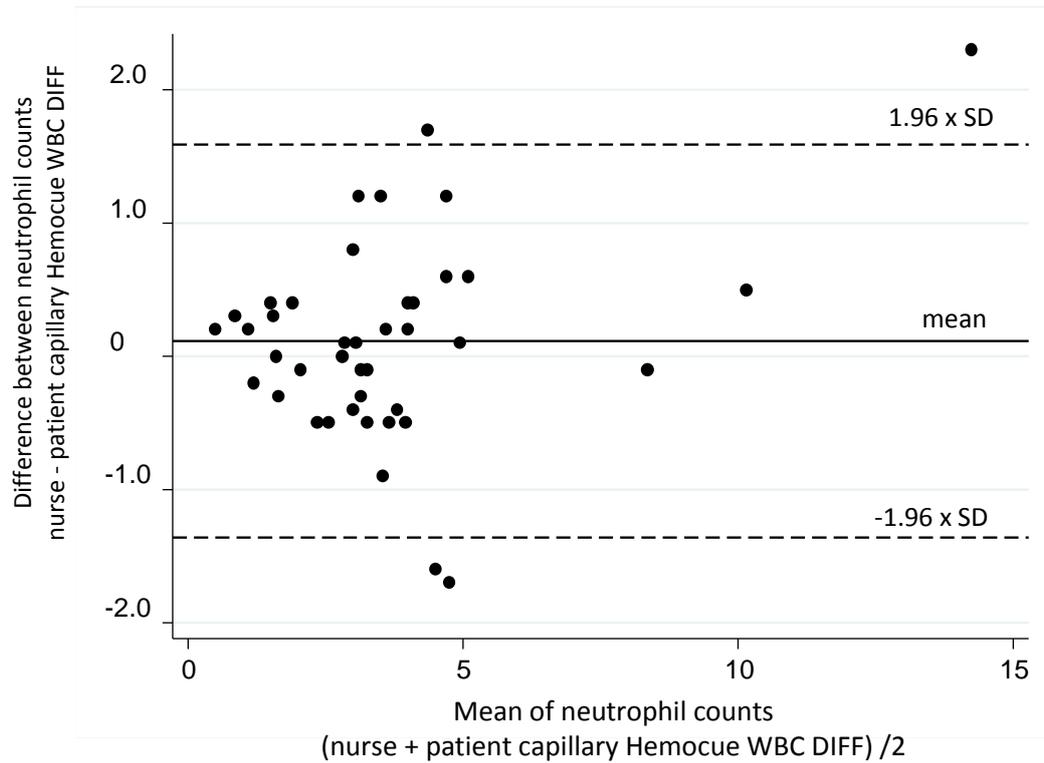


Figure 29: Scatter plot showing the relationship of capillary nurse-obtained Hemocue WBC DIFF and capillary patient-obtained Hemocue WBC DIFF neutrophil counts. Solid black line is $x=y$, dashed black line is line of best fit. RMSE, root mean square error.

a)



b)

Neutrophil counts $\times 10^9/L$		
Capillary nurse Hemocue WBC DIFF	Capillary patient Hemocue WBC DIFF	Venous ADVIA 2120
3.7	5.3	3.62
5.2	3.5	4.39
3.9	5.6	4.51
15.4	13.1	11.86

Figure 30: Agreement analysis between capillary nurse-obtained and capillary patient-obtained Hemocue WBC DIFF neutrophil counts.

a) Bland-Altman plot of the mean neutrophil count against the difference between the counts from the two samples. SD, standard deviation and is 0.75. The solid black line represents the mean difference and is 0.11. The black dashed lines labelled "1.96 x SD" represent the upper and lower limits of agreement which are the 95% CIs. The upper dashed line is 1.59 and the lower dashed line is -1.36. b) Table displaying the neutrophil counts of the four results lying out with the limits of agreement.

5.5 Discussion

5.5.1 Main findings

Capillary Hemocue WBC DIFF neutrophil counts perform to a clinically acceptable standard in the neutropenic range, which is essential if these are to be used as intended in oncological practice. The device performs well when measuring capillary neutrophil counts in comparison to venous ADVIA 2120 neutrophil counts. The linear regression in the neutropenic range is remarkably close to the line of equality, with the data fitting this line well for counts outside of the normal range. The capillary Hemocue WBC DIFF neutrophil count performs satisfactorily to identify patients at risk of febrile neutropenia, with a count of $<1.1 \times 10^9/L$ being the lowest threshold that indicates the venous ADVIA 2120 neutrophil count is $<1.0 \times 10^9/L$ with no false negatives. Similarly, capillary Hemocue WBC DIFF neutrophil counts perform sufficiently well to be used to identify patients whose count has not recovered adequately for subsequent chemotherapy delivery. A neutrophil count $<1.1 \times 10^9/L$ is the highest threshold which indicates the venous ADVIA 2120 neutrophil count is $<1.5 \times 10^9/L$ with no false positives.

In the scenario where the device is to be used to exclude patients from being treated on the febrile neutropenia pathway, the clinical priority should be patient safety, i.e. ensuring the capillary Hemocue WBC DIFF does not identify patients as not neutropenic, when the paired venous ADVIA 2120 neutrophil count is $<1.0 \times 10^9/L$. The most desirable statistical characteristics are maximal sensitivity and negative predictive value. When these parameters are satisfied, it is preferable to maximise the positive predictive value to reduce wasted patient journeys to hospital, and to gain from use of point of care testing compared to current practice. Taking all of the above into consideration, $\geq 1.1 \times 10^9/L$ is the best performing Hemocue WBC DIFF neutrophil count threshold indicating the venous ADVIA 2120 neutrophil count is $\geq 1.0 \times 10^9/L$. However, using the 95% confidence intervals, the sensitivity is 100% with a minimum of 85.8% certainty, and the negative predictive value is 100% with a minimum of 89.4% certainty. More data are required to reduce the confidence intervals. When such a method of neutrophil determination is introduced into clinical practice, it may be necessary to use a higher threshold, until the confidence intervals can be narrowed. This would be at the expense of positive predictive value, initially increasing the number of patients who are advised they need to be on the febrile neutropenic pathway, who are subsequently taken off

this when the venous ADVIA 2120 neutrophil count indicates otherwise after attendance at hospital.

The potential gain in using the device before subsequent chemotherapy delivery is to identify patients whose neutrophil count has not recovered sufficiently, to prevent a wasted journey to hospital. In patients deemed by the device to have sufficient neutrophil recovery, a repeat venous ADVIA 2120 neutrophil measurement will still be done on attendance to confirm platelet recovery. This should prevent the scenario where the device incorrectly identifies sufficient neutrophil recovery leading to inappropriately delivered chemotherapy. This means the worst case scenario when using home blood count monitoring prior to attendance at hospital for delivery of chemotherapy would be that the patient is incorrectly identified as having insufficient neutrophil recovery, and so does not attend, leading to them potentially receiving suboptimal dose density of chemotherapy. This could adversely affect survival in the neo/adjuvant setting, but is unlikely to be relevant in patients in the palliative setting (59, 216-218). Any such “risk” could be mitigated by repeating home testing on subsequent days.

The most desirable statistical characteristic in the scenario of use of home blood counts before subsequent chemotherapy is, therefore, maximal positive predictive value. Once this is satisfied, the next most desirable statistical characteristic is maximal sensitivity, which corresponds to correctly identifying which patients have not sufficiently recovered their neutrophil counts. Once this is satisfied, the next most desirable statistical characteristic is maximal negative predictive value, which corresponds to minimising the number of patients who are incorrectly identified as being safe to chemotherapy delivered by the Hemocue WBC DIFF who are subsequently proven otherwise by the ADVIA 2120 count. Taking all of the above into consideration, $<1.1 \times 10^9/L$ is the highest neutrophil count threshold which is clinically acceptable to indicate the venous ADVIA 2120 neutrophil count is $<1.5 \times 10^9/L$. Again, more data would reduce the confidence intervals around this threshold.

As expected, when measuring a parameter below the reference range, the correlation of the neutropenic data appears to be less good than the reported performance of capillary samples in the normal range ($r=0.867$ compared to 0.98 and 0.931 in published data (200, 201)). This is a measure of how well the data points fit the regression line, but the regression line is surprisingly comparable to the published full range data ($y= 0.95x + 0.01$ compared to $y= 0.88x + 0.33$ and $y= 0.95x + 0.2$). None of the four data points that fall outside of the limits of agreement in the Bland-Altman plot comparing capillary Hemocue WBC DIFF to

venous ADVIA 2120 neutrophil counts in Figure 25 would have resulted in inappropriate management of the patient. In comparison to the XBC analyser performance, the Hemocue WBC DIFF performed better in the neutropenic range. As there is more data the performance around the thresholds can be stated with more certainty and the error margins can be tighter, thus maximising the benefit of such a point of care device. Moreover, the precision analysis of intra- and inter-device variability produced co-efficients of variation of 13.1% and 13.0% respectively. Again, this is higher than the co-efficient of variation quoted by the manufacturer, but it is clinically acceptable and is considered reasonable for neutropenic results by local pathology experts.

The Hemocue WBC DIFF is capable of measuring venous neutrophil counts, as evidenced by the fact much of the published work predating this study has been done on venous samples. However, despite using a droplet of blood from the same EDTA tube as was sent to the laboratory for measurement by the ADVIA 2120, the slightly improved r value (0.894) compared to the r value for capillary samples (0.867) was offset by the less good linear regression of $y = 0.86x + 0.2$. In addition, the error code incidence was far greater using the venous samples than the capillary, making measurement on the capillary samples a more attractive proposition. The comparison of venous to capillary blood in the chapter appeared to show no consistent bias, and all but 2 of the agreement analysis data points fell within the 95% limits of agreement. One of these was outside the upper limit of agreement and the other was outside the lower limit of agreement (Figure 23). Use of capillary samples, therefore, appears to be a feasible option within oncology practice.

This work provided the first opportunity to explore the feasibility of patients performing the self-test finger-prick procedure and filling the Microcuvette correctly. There is no published data on patient self-test use of the Hemocue WBC DIFF. Only one out of the 16 who declined to participate did so as they did not want to self-test. Nine out of the 50 (18%) who did consent to self-test did not produce a result. Only one of these 9 was unable to fill the Microcuvette. The training of patients in this study was limited to observation of a nurse-obtained finger-prick sample, and verbal teaching. This could be improved by, for example, video training. With enhanced training and careful patient selection, there is potential for the Hemocue WBC DIFF to be converted to a patient self-test device.

5.5.2 Strengths and weaknesses

The major strength of this work is that the main analysis has been carried out on neutropenic blood samples from the patient population in whom it is intended to be used. This has not been done before with the Hemocue WBC DIFF on such a large number of samples to such level of detail, and informs the feasibility of using it in oncological practice. It has enabled scrutiny of the performance of the device in both direct comparison of neutrophil counts, but also performance around thresholds used in oncological practice to change patient management. Involvement of laboratory haematology experts early in the methods planning maximised the opportunity to gather detailed performance data such as intra- and inter-device precision. Although in haematological practice, the gold standard method of white cell count differential measurement is manual counting, it is common practice to use automated analysers in laboratories with high demand. The ADVIA 2120 used in this analysis is an internationally recognised laboratory analyser, making the results applicable to both clinical practice in Leeds Teaching Hospitals NHS Trust, but also further afield.

It should be remembered, however, that this analysis was not carried out under laboratory conditions as samples were collected from patients who were navigating the health-care system as part of their routine cancer care. As a consequence, aspects of pre-analytic variability were different between measurements by each device, and there was more potential for variability with the venous ADVIA 2120 measurements; for example, the venous samples were transported to the laboratory for measurement via either the internal pod system or manual porter transfer, and the time of venous sample collection was recorded, but not sample measurement.

Neither this study nor standard practice as part of routine clinical care take into consideration biological variability of neutrophil counts. Biological variability is described as “fluctuation of the concentration of constituents around their homeostatic set-point” (219). Neutrophil count within-subject variation and between-subject variation is reported to be 17.1% and 32.8% respectively by a database of biological variability data, which is updated every two years using literature searches of newly published articles (220-222). For example, a study of 7685 men showed a steady increase in mean value of white cell count up to around 4-5pm, followed by a reduction in late afternoon (223). Some white cell count diurnal variation can be attributed to neutrophils moving from the margined to circulating pool of neutrophils,

which they do in minutes in scenarios such as sepsis, high dose steroid use and immediately after vigorous exercise (9, 223).

The potential benefits of using a point of care device in oncological practice would be harnessed by using a device suitable for patient self-test use with capability to transfer the results electronically to the hospital. This performance analysis incorporated an aspect of patient self-testing, but used samples which involved a professional in at least one aspect of the measurement. As such, it demonstrated the ability to use a professionally operated Hemocue WBC DIFF in the pathway of patients on chemotherapy, but leaves further work required in the field of patient self-testing.

5.5.3 Implications

The primary objectives of this chapter were to obtain data on the performance of capillary Hemocue WBC DIFF neutrophil counts in comparison to venous ADVIA 2120 neutrophil counts in the neutropenic range, including performance around thresholds important in suspected febrile neutropenia and that indicate safe delivery of subsequent chemotherapy. This data could not be obtained through published trials, but was achieved in this study. The Hemocue WBC DIFF performed sufficiently well in the hands of professionals when neutrophil counts were less than $2.0 \times 10^9/L$, to justify use of the device and further work investigating the potential role of point of care blood count monitoring in oncological practice. The inability to measure platelets on the Hemocue WBC DIFF necessitated consideration of the risk of isolated thrombocytopenia in solid tumour patients in whom such a device is intended to be used; this was addressed in Chapter 4.

Further work needs to address how and where in the pathway of patients on chemotherapy the benefits of both a professionally-operated and a patient self-test device can be maximised. The limited analysis of patient self-testing to obtain the capillary sample in this work suggests there is potential for conversion of the existing device to a patient self-use device. The Philips Minicare H-2000 device was “Conformité Européene” (CE) marked for patient self-test use and had connectivity such that the blood count measurements could be transferred via the 3G, 4G or GPRS network. The pieces around patient self-test use and connectivity of the Hemocue WBC DIFF need to be solved in order to gain the benefits of preventing unnecessary patient journeys to hospital.

Regarding how it can be used, there is merit in a stepwise introduction into clinical practice, both for clinicians to gain confidence and to collect further performance data in order to narrow the confidence intervals around the thresholds, and hence be able to minimise the false positives in the case of suspected febrile neutropenia. Based on this performance analysis, there are plans in motion to use capillary Hemocue WBC DIFF neutrophil counts on Leeds Teaching Hospitals NHS Trust acute oncology decision unit, as part of a febrile neutropenia risk stratification process. The patient pathway will be changed depending on whether the patients are deemed low, medium or high risk of febrile neutropenia according to the device neutrophil count. The intention to start with is to use this device to save the time, financial and opportunity cost burden, such as antibiotic resistance, brought about by unnecessary insertion of intravenous cannulas and administration of single doses of broad spectrum antibiotics in low and medium risk patients, whilst waiting for the venous ADVIA 2120 neutrophil count, which commonly takes over two hours to obtain the result.

In order to understand where in the patient pathway such a device could be used, the baseline patient pathways were mapped and quantified to define the starting point of the burden of neutropenic complications. The process of doing this was described in Chapter 2, and provided the baseline model which can be used for health economic analysis of potential gains and true gains after introduction into clinical practice. Moreover, the data in this chapter confirm the adequate performance of capillary Hemocue WBC DIFF samples, indicating suitability to be used to determine neutrophil profiles during chemotherapy. Chapter 6 describes the trial of this, using the Hemocue WBC DIFF to profile neutrophil counts during chemotherapy in order to explore the potential to build a predictive model for neutropenic complications based on neutrophil count changes early in a cycle of chemotherapy, and to determine the incidence of suboptimal chemotherapy dosing (through inadequate grade and duration of bone marrow suppression).

5.5.4 Conclusion

This analysis provides data on the performance of the Hemocue WBC DIFF when measuring neutrophil counts that are specifically relevant to oncological practice and are not available through published trials. It indicates that the device performs adequately to be of use in oncology when assessing patients for suspected febrile neutropenia and for sufficient neutrophil recovery to safely deliver subsequent chemotherapy. It justifies the continued use of the Hemocue WBC DIFF as the point of care device used to profile neutrophil counts during

chemotherapy, as described in chapter six. It remains to be seen if subsequent iterations of the Hemocue WBC DIFF have at least equivalent performance in the hands of patients and can address the connectivity aspect sufficiently.

Chapter 6 Profiling neutrophil counts during chemotherapy.

6.1 Introduction

The first uses of combination chemotherapy to achieve disease remission through administering maximal tolerable therapy started in the 1960s with vincristine, methotrexate, 6-mercaptopurine and prednisolone (VAMP) in childhood leukaemias (224). Chemotherapy then was all given as in-patient regimens, with dosage and intervals changing on a weekly basis, depending on the outcome of regular meetings of clinicians, biostatisticians and pharmacologists based on disease response and tolerance, particularly bone marrow toxicity monitored by daily early morning venous blood samples(225). As the number of patients being treated with cytotoxic chemotherapy increased, there was a need to standardise best practice, which is usually now based largely on phase III clinical trials.

There is a paucity of data on the white blood count profiles during chemotherapy regimens commonly given today to patients with solid tumours. This is in part due to the inconvenience of obtaining blood samples when the majority of chemotherapy regimens are now outpatient-based; also daily blood counts are not clinically indicated, with counts at or around day one of each cycle being sufficient. More detailed knowledge on the profile of blood counts during chemotherapy regimens comes from early phase clinical trials in which counts are obtained at least weekly, but also pharmacological and clinical studies of GCSF (62, 68, 226). These show that patients receiving GCSF preparations have an earlier and lower grade neutrophil nadir, of shorter duration with more rapid recovery. In a placebo-controlled trial of 211 patients receiving cyclophosphamide, doxorubicin and etoposide for small cell lung cancer, the incidence of grade 4 neutropenia was 98% in the placebo group and 84% in the GCSF group ($p < 0.001$), with the mean duration of grade 4 neutropenia being 6 and 3 days respectively ($p < 0.001$) (62).

There are also published physiological, mechanistic and pharmacodynamics model studies describing the time-course of neutropenia over several drugs, indicating that the profile of neutrophils during chemotherapy can be fitted to mathematical models (227-232). Only one study produced a predictive model of neutrophil counts that incorporated variation due to individual patient characteristics, such as gender, previous anti-cancer therapy, performance status, and as such provided a potential basis for the rationale for chemotherapy dosing to be tailored to individual patients (227). Friberg et al. described a model of chemotherapy-

induced neutropenia that performed with individual drugs; but much chemotherapy is given in combination in clinical practice, and the time course of neutropenia for combinations of drugs have not been reported. The data informing the Friberg et al. model was low volume for some drugs; for example, that for irinotecan used neutrophil counts from only 20 patients. Moreover, all this and other models were formulated for a specific dose of drug, and are unlikely to accurately reflect myelosuppression for variable drug doses. In addition, the neutrophil counts informing the models were usually sparse in days 1 to 5 compared to days 7 to 20, and as such will not have incorporated signals in changes in neutrophil counts in these days.

In clinical practice dosing of chemotherapy is most often adjusted for body surface area, notwithstanding the paucity of data to support this practice (233). Therapeutic drug monitoring has been advocated to achieve a “target” therapeutic drug exposure, but is only widely used in high dose drug regimens administered with stem cell transplantation, and to identify those at increased risk of toxicity due to slow elimination of high dose methotrexate.

Toxicity is usually identified through symptom reporting, but potential under-dosing measured, for example by the lack of myelotoxicity, usually does not lead to dose increments, especially in patients with metastatic disease where treatment is almost always “palliative”. There are some exceptions, such as vinorelbine, but the recommended dose escalation in later cycles in the absence of toxicity has not been shown to improve outcome. In the adjuvant setting, under-dosing of chemotherapy based on an inadequate neutrophil nadir may lead to as high as a 20% relative reduction in survival in node positive breast cancer patients receiving cyclophosphamide, doxorubicin and 5-fluorouracil, and an estimated reduced cure rate of greater than 10% in intermediate prognosis testicular cancer (59, 216-218, 234). For example, in the testicular cancer trial, patients who did not reach a nadir white cell count of $<2.0 \times 10^9/L$ or platelet count $<90 \times 10^9/L$ had a higher relapse rate (28% versus 14% $p=0.04$).

There is further evidence in the adjuvant breast cancer and palliative non-small cell lung cancer setting, indicating prognostic value in attaining a degree of neutropenia during chemotherapy (89-93). This supports the rationale behind a randomised controlled trial in high risk breast cancer patients, where the dose of adjuvant fluorouracil, epirubicin and cyclophosphamide was tailored according to the haematological toxicity, and improved

relapse-free survival (32.3% breast cancer relapse in tailored chemotherapy group versus 41.2% relapse in standard chemotherapy plus high dose chemotherapy group, $p=0.04$) (94).

Tailoring of chemotherapy as discussed so far, refers largely to adjusting the dose based on neutrophil nadir to adjust the dose intensity, which is expressed as $\frac{\text{total dose}}{\text{time}}$. Dose intensity can, therefore, be increased by either decreasing the dose interval or increasing the dose. There is convincing evidence in the adjuvant breast cancer setting that increasing optimal dose intensity by escalating the dose is associated with better disease-free and overall survival, as described above. Achieving an increase dose intensity by reducing the dose interval, often referred to as “dose dense” chemotherapy, can also improve outcomes. Citron et al. reported that dose dense combinations of doxorubicin, paclitaxel and cyclophosphamide administered with GCSF support (2-weekly compared to 3-weekly) improved disease-free survival with a hazard ratio of 0.74, $p = 0.01$ and overall survival hazard ratio of 0.69, $p=0.013$ (120). It has subsequently been hypothesized that increased frequency of administration of cytotoxic chemotherapy may be a more effective way of minimising residual tumour burden than dose escalation (235). There is, therefore, scope in regimens used in routine practice to optimise the dose density on an individual basis, based on the neutrophil profile incorporating both depth and duration of nadir and timing of recovery to a suitable threshold for further chemotherapy.

As discussed in Chapter 1, there is evidence to support the prophylactic use of either antibiotics or granulocyte colony stimulating factor in patients at high risk of neutropenic complications. “High risk” is defined by population-based trial data, but with the caveat that international guidelines advocate taking into account known risk factors on an individual patient basis. Studies could not be identified that aimed to define changes in white cell counts early during a chemotherapy cycle, which could be used to instigate a prophylactic intervention and abrogate neutropenic complications. In addition, trials assessing efficacy of cytotoxic chemotherapy do not usually report patients assessed for suspected febrile neutropenia who were subsequently proven not to be neutropenic. In an unpublished audit of all cases of suspected febrile neutropenia in adult patients with solid tumours at Leeds Cancer Centre, over a 3 month period from September to November 2017, the mean number of patients assessed acutely with suspected febrile neutropenia was 28 per month; the mean number of patients with neutrophil count $<1.0 \times 10^9/L$ was 9, and the mean number of patients with neutrophil count $<0.5 \times 10^9/L$ was 5. Thus on average 19 patients per month

suspected of having febrile neutropenia were proven to have a neutrophil count $> 1.0 \times 10^9/L$ (Young & Turner, 2017). These data demonstrate the burden of febrile neutropenia for both patients and service providers.

It is hypothesized that there are four time points during a cycle of chemotherapy where there is scope to explore the potential role of home neutrophil count monitoring in individualising patient care;

1. After chemotherapy delivery to identify early changes in neutrophil counts that may be predictive of neutropenic complications.
2. Any time during the cycle to exclude neutropenia in patients with suspected febrile neutropenia.
3. At intervals of up to daily during the cycle to quantify neutrophil nadir.
4. Prior to delivery of the subsequent chemotherapy cycle to identify patients with sufficient neutrophil recovery for continuation of chemotherapy.

These scenarios are illustrated in Figure 31, which is a line graph demonstrating potential neutrophil profiles during chemotherapy, and illustrates where testing of home blood counts may be useful.

The aim of the work described in this chapter was to perform an exploratory analysis of neutrophil profiles of patients receiving chemotherapy as part of routine clinical practice, to determine if there is scope to develop the role of home neutrophil count monitoring during chemotherapy. A trial used daily home blood count monitoring to profile neutrophil counts during chemotherapy in adult patients with solid tumours with the intention of enrolling approximately 200 patients. Recruitment was underway, with some patients having finished participation, when the partners providing the device (Hemocue) and the funding through the Small Business Research Initiative grant (Philips Home Clinical Monitoring) discontinued their commercial relationship, so the trial halted recruitment. This chapter describes and discusses the neutrophil profiles obtained up until that point, which coincided with a planned early cohort analysis.

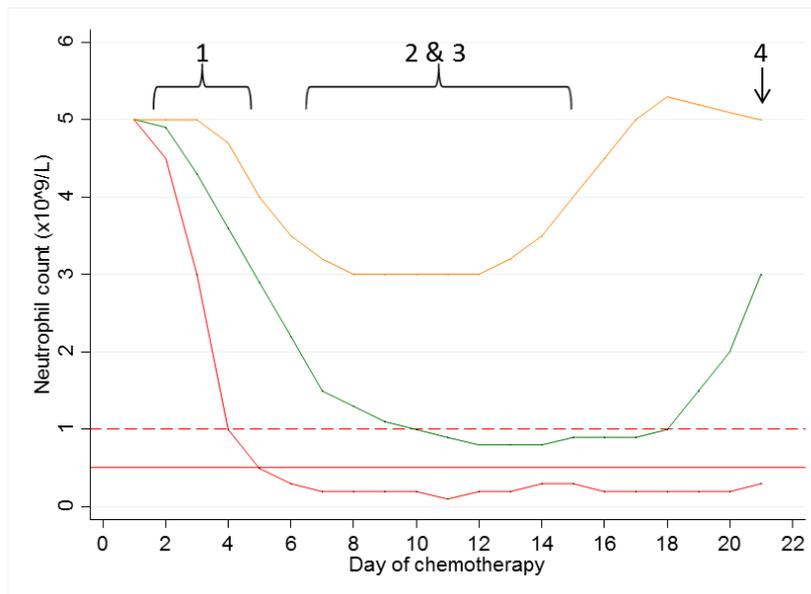


Figure 31: Line graph showing potential neutrophil count profiles during chemotherapy.

This graph was drawn to demonstrate possible scenarios during chemotherapy, but was not informed by true neutrophil profiles. The orange profile represents “under-dosing” with the nadir being insufficiently low and recovery in advance of the scheduled subsequent cycle on day 22. The green profile represents “optimal” dosing with the nadir being less than $1.0 \times 10^9/L$, but not less than $0.5 \times 10^9/L$ and rapid recovery in-time for the subsequent cycle on day 21 (and potentially the opportunity to treat early on day ≥ 19). The red profile represents that of a patient who has been “overdosed” putting them at high risk of neutropenic complications, with a rapid descent to neutropenia less than $0.5 \times 10^9/L$ with no signs of recovery prior to subsequent cycle on day 22. The numbers 1-4 refer to points in the cycle where it is hypothesized there may be a role for home neutrophil count monitoring.

6.2 Objectives

6.2.1 Primary

1. Profile neutrophil counts for the duration of first cycles of chemotherapy.
2. Determine the potential of home neutrophil count monitoring during chemotherapy.

6.2.2 Secondary

1. Confirm acceptability to patients of daily finger-prick capillary blood tests.
2. Record the prevalence of grade ≥ 3 neutropenia and its complications for first cycles of different classes of chemotherapy regimen.
3. Determine whether early changes in the neutrophil count soon after chemotherapy administration have the potential to predict severe neutropenia and its complications.

4. Explore the potential to optimise the dose of chemotherapy based on;
 - a. the neutrophil nadir.
 - b. the timing of neutrophil recovery above the threshold for retreatment.
5. Explore the potential for re-scheduling the subsequent chemotherapy cycle prior to patient attendance at the hospital, based on insufficient neutrophil recovery.

6.3 Methods

This was a single-centre, single-arm trial using a professionally operated finger-prick blood count device, the Hemocue WBC DIFF, to obtain daily neutrophil counts for the duration of the first cycle of chemotherapy in adult patients with solid tumours. Profiles from the first cohort of patients enrolled in this study are reported and discussed in this chapter. This was to be an interim analysis of the larger trial, which aimed to recruit up to 250 patients.

6.3.1 Patient population

Patients were eligible if they had a confirmed diagnosis of a solid tumour, were ≥ 18 years old, and were commencing the first cycle within the first or subsequent course of single agent or combination cytotoxic chemotherapy. Patients were enrolled between 1st April 2017 and 16th October 2017. Patients receiving primary prophylactic antibiotics or GCSF were eligible. Exclusion criteria were; living outside the service provision boundaries of Local Care Direct, who provided nurses to perform the finger-prick measurements in patients' homes, inability to give informed consent, concurrent haematological malignancy, known bleeding disorder, known sickle cell disease, known β -thalassaemia major, known poorly controlled anti-coagulation (INR >3.5 within 6 months for those on warfarin). The pathway modelling described in chapter 2, provided real-life prevalence of neutropenic complications at Leeds Cancer Centre. This was used to identify chemotherapy regimens with differing incidences and prevalence of neutropenic fever, including those in which it might be possible to explore whether early changes in the neutrophil count following administration of chemotherapy have the potential to predict severe neutropenia and its complications.

6.3.2 Approvals and Funding

This trial was approved by the Yorkshire & the Humber Leeds West Research Ethics Committee (reference 16/YH/0457), by the Health Research Authority, by the University of

Leeds, by the NHS Research and Innovation department of Leeds Teaching Hospitals NHS Trust and Leeds Cancer Centre Clinical Trials Research Approvals Board (CTRAB). It was registered on the public database clinicaltrials.gov and assigned the National Clinical Trial number NCT02806557. The trial was funded through the Small Business Research Initiative grant awarded to Philips Healthcare who supported it through an unrestricted educational grant to the University of Leeds, provision of the devices and consumables, and supported the services of Local Care Direct.

6.3.3 Procedures followed

6.3.3.1 Clinical procedures

All trial procedures were carried out in addition to standard care. Data generated as part of the trial were not made available to the treating clinical team. Trial activity directly involving patients at the hospital was performed during attendances for standard care.

Eligible patients signed written, informed consent to participate, including for a nurse to visit their house daily to perform finger-prick blood tests. The trial team notified the patient's general practitioner and Local Care Direct (LCD) of the patient's consent. A LCD nurse attended the participant's home, with the Hemocue WBC DIFF system device that was left in a secure locked bag at their house for the duration of participation.

On each visit, the LCD nurse obtained and recorded continuing verbal consent, collected the sample and measured the count, performed a visual check of the finger-tips, recorded any feedback they received regarding the procedure and enquired about acute illness indicators. If the participant had any questions regarding symptoms or their treatment, the LCD nurse directed them to the routine advice sheets provided by their treating team and the chemotherapy alert card they were given as part of standard care. Where these did not answer the concern, the participant was advised to ring the acute oncology advice number provided in the chemotherapy folder.

With their consent, participants continued to have their blood count measured daily up to and including the day of delivery of the 2nd cycle of chemotherapy where possible. This final measurement was performed using the Hemocue WBC DIFF either at the participant's home or at the hospital, whichever was most convenient for the participant. At one week and on completion of the test schedule, the trials team contacted the participant to record

acceptability of regular finger-prick tests, complications and to identify any unplanned participant contact with health-care professionals, and particularly initiation of any treatments which may have affected neutropenia or its complications such as granulocyte colony stimulating factor or antibiotics.

If a participant was admitted to Leeds Teaching Hospitals, they had capillary finger-prick samples performed daily where possible by the trial nurse and measured on the Hemocue WBC DIFF. On days where it was not possible to do a capillary finger-prick test, if venous blood was taken and analysed by the laboratory as part of routine care, this neutrophil count was recorded for trial purposes.

If the device failed to measure a neutrophil count, due to procedural problems, insufficient filling of the microcuvette or technical failure, the participant was asked if they were willing to repeat the test once more. Participants were not asked to repeat the test if it failed on the 2nd attempt.

6.3.3.2 Blinding to neutrophil count results

The LCD nurse and participant did not have access to the neutrophil result at the time of the test as the device stored it internally and on a USB stick, but it was not displayed. If there was a problem measuring the blood count, the device displayed only an error message, indicating a repeat test was necessary.

6.3.3.3 Quality assurance

Every Hemocue WBC DIFF device was quality assurance checked by laboratory technicians in Leeds Teaching Hospitals NHS Trust Point of Care team, within 2 weeks prior to release for use on trial participants and within 2 weeks of return after completion of use during one cycle of chemotherapy. All devices used in this trial performed at both quality assurance checks within 10% of the laboratory ADVIA 2120 neutrophil counts when this reference neutrophil count was $\geq 1.0 \times 10^9/L$ and within $0.1 \times 10^9/L$ neutrophils when the reference neutrophil count was $< 1.0 \times 10^9/L$.

In addition, the method of obtaining the finger-prick was standardised as per recommendations by the manufacturer and as defined in the performance analysis (chapter

4); wash participant hands with soap under warm running water, dry hands, clean finger-tip with an alcohol wipe and allow to dry freely, finger-prick side of chosen finger, minimise milking finger as allowed by blood flow, discard first blood droplet, collect second droplet in microcuvette for measurement.

6.3.3.4 Definitions of neutropenic complications

Common toxicities of chemotherapy include asymptomatic neutropenia, febrile neutropenia and neutropenic sepsis. For the purposes of this trial, the “complications” of severe neutropenia referred to febrile neutropenia and neutropenic sepsis.

6.3.3.4.1 Neutropenia

Neutropenia was defined into grades 0 to 4 as per the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) in Table 24 (17). For the purposes of this trial, severe neutropenia was considered to be grades 3 and 4.

6.3.3.4.2 Febrile neutropenia

Febrile neutropenia was defined as a venous laboratory neutrophil count $<0.5 \times 10^9/L$ or expected by the senior clinician to fall to $<0.5 \times 10^9/L$ within 48 hours AND one documented fever of $>38.0^\circ C$ (in-keeping with Leeds Teaching Hospitals NHS Trust and National Institute for Health and Care Excellence (NICE) guidelines (19)).

6.3.3.4.3 Neutropenic sepsis

Neutropenic sepsis was defined as a venous laboratory neutrophil count $<0.5 \times 10^9/L$ AND documented or suspected infection in the presence of systemic manifestations of infection.

Table 3 lists the parameters present in systemic infection-related clinical states, as endorsed by the International “Surviving Sepsis Campaign” (20, 21). Some of the parameters listed would be present in patients with cancer on chemotherapy in the absence of sepsis, therefore this was interpreted with caution and each parameter considered in relation to an individual’s baseline. The diagnosis of sepsis had to be confirmed by the trial physician.

6.3.4 Data analyses

The neutrophil profiles obtained were from the first cohort of patients of the larger trial. It was intended to enrol between 20 – 30 patients for this interim analysis, which was chosen pragmatically, as the prevalence of neutropenic complications was expected to be too small to apply statistical tests at this stage. Moreover, the primary objectives were exploratory and, therefore, did not lend themselves to statistical tests. Descriptive analyses were performed using Microsoft Excel 2010 and the neutrophil profiles were generated using StataSE 13 (64-bit) (188, 189).

6.4 Results

6.4.1 Descriptive

Forty-four patients were approached for this trial, of whom 22 entered and 21 completed participation. Of the 22 who were not entered, 21 declined and 1 was ineligible. The 1 patient who entered but did not complete, left the trial on day 2 due to non-compliance with the daily visits for finger-prick testing, without specifically indicating the reason.

Of the 21 patients for whom neutrophil profiles were generated, twelve were female and 9 were male. The mean age of participants was 48 years, with a range of 20 to 82 years, and a median age of 50 years. Ten patients had a Eastern Co-operative Oncology Group performance status of 0, 9 patients had a performance status of 1 and 2 patients had a performance status of 2 (236). Eleven patients had co-morbidities, noted as present if recorded in medical records from patient consultations with the oncologist; 6 had just 1 co-morbidity, 2 patients had 2 co-morbidities, 2 patients had 3 co-morbidities and 1 patient had 4 co-morbidities. Only 1 patient had received chemotherapy prior to the first cycle of this regimen and that patient had received 2 different regimens on separate occasions, one 35 years previously and the other 24 years previously.

Table 38 shows the chemotherapy regimens received by patients in whom neutrophil profiles were obtained. Bleomycin / etoposide / cisplatin regimen (BEP) was the most commonly included regimen (n=7).

Chemotherapy regimen	Doses (cycle length in days)	Frequency	Neutrophil threshold for delivery cycle 2 ($\times 10^9/L$)
Bleomycin / etoposide / cisplatin (BEP)	30,000 units D1, D8, D15 / 165mg/m ² D1-D3 / 50mg/m ² D1-D3 (21)	3	>1.0
	30,000 units D1, D8, D15 / 100mg/m ² D1-D5 / 20mg/m ² D1-D5 (21)	4	>1.0
Carboplatin	AUC 7 D1 (21)	1	>1.5
Carboplatin / etoposide	AUC 5 D1 / 120mg/m ² D1, 100mg/m ² D2 & D3 (21)	2	>1.5
Paclitaxel / carboplatin	AUC 5 D1 / 175mg/m ² D1 (21)	1	>1.2
	AUC 2 D1, D8, D15 / 70mg/m ² D1, D8, D15 (28)	1	>1.0
Carboplatin / pemetrexed	AUC 5 D1 / 500mg/m ² D1 (21)	2	>1.5
Doxorubicin	75mg/m ² D1 (21)	1	>1.5
Epirubicin / cyclophosphamide (EC)	90 mg/m ² D1 / 600 mg/m ² D1 (21)	3	>1.5
Gemcitabine / carboplatin	1000mg/m ² D1 & D8/ AUC 4.2 D1	3	>1.5
Total		21	

Table 38: Table of chemotherapy parameters and frequency of regimens for which the neutrophil profiles were obtained.

AUC, area under the curve. D, day.

Of the 21 neutrophil profiles obtained;

- 13 patients completed daily neutrophil counts on the Hemocue WBC DIFF for the duration of participation
- 5 patients missed one day of the profile only
- 1 patient missed one day of the profile and had 3 days where there was the laboratory ADVIA 2120 neutrophil count only due to an inpatient stay
- 2 patients had 3 or more days where there was the laboratory ADVIA 2120 neutrophil counts only due to inpatient stays

None of the patients enrolled in this trial received prophylactic or therapeutic granulocyte colony stimulating factor during the cycle of chemotherapy. Those who received intravenous antibiotics did so as part of admissions for febrile neutropenia and are described in section 6.4.2.1 on febrile neutropenia. One patient received oral co-amoxiclav antibiotics for a wound infection that did not require admission to hospital; their neutrophil profile never fell below $0.5 \times 10^9/L$. The profile is shown later in Figure 36b. None of the participants experienced prolonged bleeding or infections at the site of the finger pricks.

6.4.2 The profiles

Across the 21 profiles obtained, the mean neutrophil count nadir was $0.8 \times 10^9/L$ (range $0.0 - 3.0 \times 10^9/L$) and mean day of the nadir was day 15 (range 8 - 26). Ten profiles had a nadir $<0.5 \times 10^9/L$, with a mean duration of neutropenia $<0.5 \times 10^9/L$ of 6.8 days. The profiles are displayed across Figure 32 to Figure 38. The categories are explained by phenotype in sections 6.4.2.1 to 6.4.2.3.

6.4.2.1 Febrile neutropenia

Four of the 10 patients with a neutrophil nadir of $<0.5 \times 10^9/L$ were admitted with febrile neutropenia; their profiles are shown in Figure 32. The profiles of the other 6 patients are shown in Figure 33. All 4 profiles were from males who received BEP chemotherapy; 2 received the 3-day regimen, 2 the 5-day regimen. Only 1 of these patients had a significant co-morbidity, asthma.

The duration of neutrophils $<0.5 \times 10^9/L$ was 4, 9, 7 and 7 days respectively in patients with febrile neutropenia, compared to 5, 5, 5, 7, 10 and 10 days in the 6 patients with a nadir <0.5

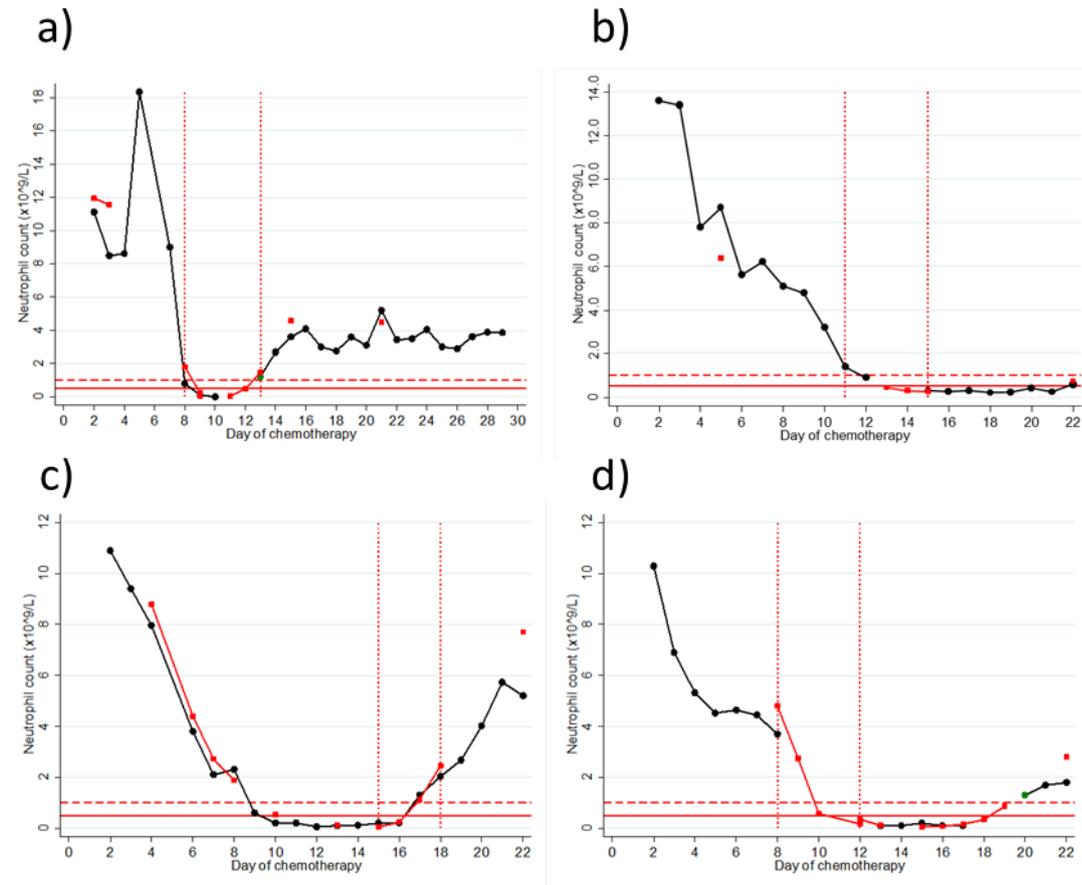


Figure 32: Neutrophil profiles of the patients who were admitted and treated for febrile neutropenia.

These are the 4 profiles where the patient was treated for febrile neutropenia, out of the 10 profiles where the neutrophil nadir was $<0.5 \times 10^9/\text{L}$. All 4 of these profiles belonged to males who received BEP chemotherapy regimen. Profile a) and d) received 3-day BEP regimen, profiles b) and c) received 5-day BEP regimen. Black observations represent capillary samples measured by the Hemocue WBC DIFF. Red observations represent venous samples measured by the laboratory ADVIA 2120. Observations are linked if they were measured by the same device and occurred on consecutive days. The solid horizontal red line represents absolute neutrophil count of $0.5 \times 10^9/\text{L}$. The dashed horizontal red line represents absolute neutrophil count of $1.0 \times 10^9/\text{L}$. The days between the vertical short dashed red lines represent the admission to hospital during which the patient was treated for febrile neutropenia.

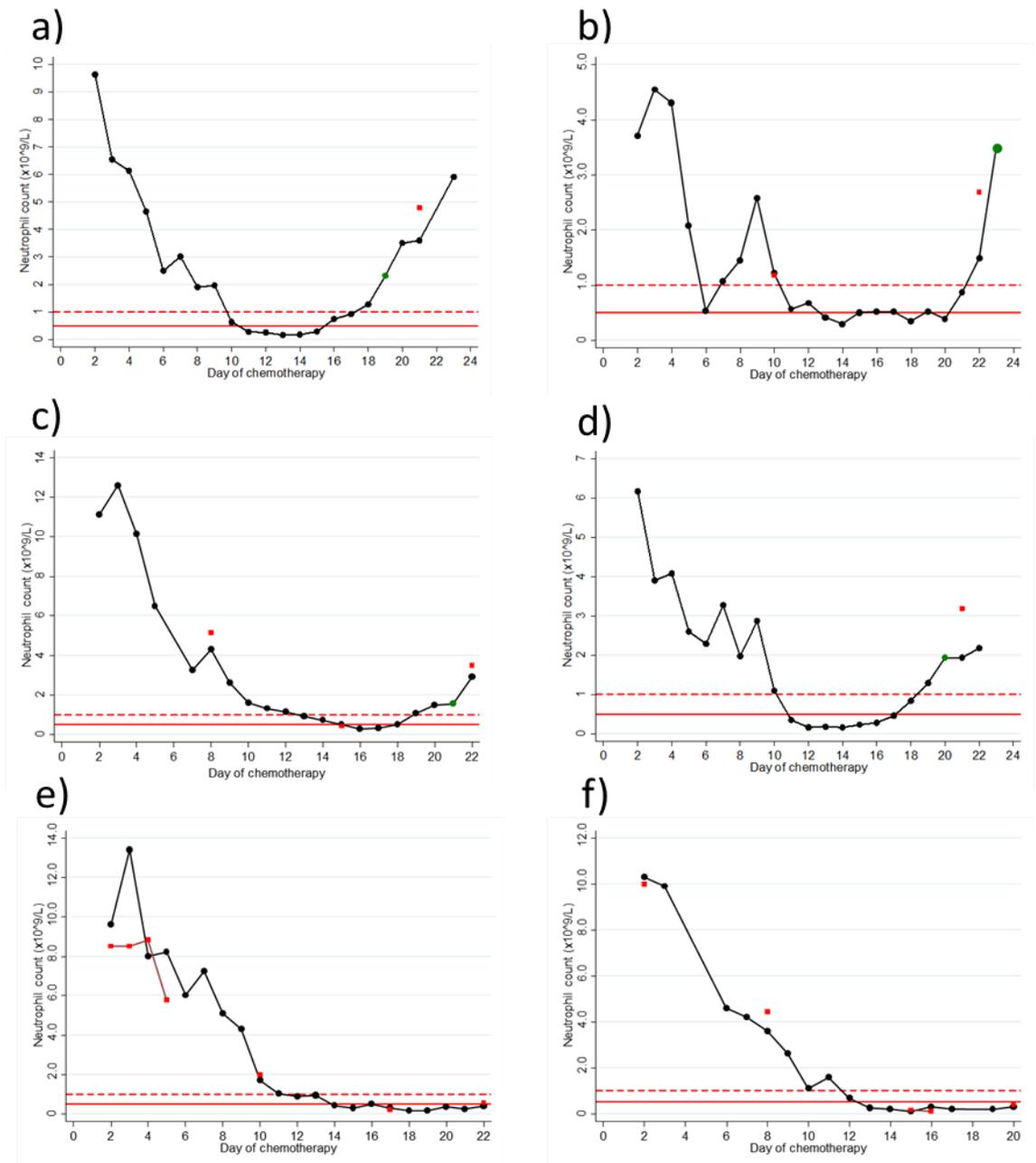


Figure 33: Neutrophil profiles of the patients with a neutrophil nadir $< 0.5 \times 10^9/L$ who were not admitted to hospital for febrile neutropenia.

These are the 6 profiles where the patient was not treated for febrile neutropenia, out of the 10 profiles where the neutrophil nadir was $< 0.5 \times 10^9/L$. The chemotherapy regimen delivered for each profile were; a) & b) epirubicin and cyclophosphamide, c) BEP 3-day, d) doxorubicin, e) and f) BEP 5-day. Black observations represent capillary samples measured by the Hemocue WBC DIFF. Red observations represent venous samples measured by the laboratory ADVIA 2120. Observations are linked if they were measured by the same device and occurred on consecutive days. The solid horizontal red line represents absolute neutrophil count of $0.5 \times 10^9/L$. The dashed horizontal red line represents absolute neutrophil count of $1.0 \times 10^9/L$.

$\times 10^9/L$ who did not experience febrile neutropenia (mean 6.8 versus 7.0 days). The proportion of days during a cycle of chemotherapy spent with the neutrophil count $<0.5 \times 10^9/L$ was higher in those who experienced febrile neutropenia than those who did not (29.6% versus 11.2%). Table 39 shows the proportions and number of days spent neutropenic according to regimen received.

Febrile neutropenia was identified on day 1, 2, 6 and 1 after the first occurrence of neutrophil count $<0.5 \times 10^9/L$. Three of the 4 patients were admitted from a scheduled clinic attendance; 2 were admitted on day 8, 1 on day 11 and 1 on day 15. All 4 patients had peripheral and PICC line blood cultures sent which were negative for growth of organisms. Two had urine cultures sent which were also negative for growth of any organisms. One patient experienced rigors indicating a bacteraemia, but this was not confirmed on blood cultures. None of the patients met the criteria for neutropenic sepsis, but 4 had documented fever $>38.0^\circ C$ and were treated for febrile neutropenia.

6.4.2.2 Neutrophil recovery

Four of the 21 neutrophil counts had not recovered above the threshold for safe delivery of cycle 2 by day 21 (thresholds in Table 38). The regimens delivered to these 4 patients were EC, BEP 5-day (n=2) and gemcitabine/carboplatin. In addition, the neutrophil count for the patient treated with single agent carboplatin subsequently fell below the threshold beyond day 21, albeit for a single day. The neutrophil count continued to be tested beyond day 21 as there was only 1 cycle of chemotherapy planned. One of the BEP 5-day profiles was collected until day 20 only and the count had not reached the safe threshold for delivery of cycle 2 by that day. These 6 profiles are shown in Figure 34.

Of the 15 profiles where the neutrophil count threshold for safe delivery of cycle 2 was met by day 21, 6 did not fall below this threshold at any point during cycle 1; profiles shown in Figure 35. The profiles of the remaining 9 patients had recovered in advance of day 21 with a range of 0 to 8 days, mean of 2.1 days and median of 1 day.

Regimen	Admitted with FN	Total days ANC recorded during cycle	Proportion of cycle days	
			ANC <0.5 x10 ⁹ /L in % (days)	ANC <1.0 x10 ⁹ /L in % (days)
Bleomycin / etoposide / cisplatin (BEP)	No	22	13.6 (3)	27.3 (6)
	Yes	29	13.8 (4)	17.2 (5)
	Yes	22	31.8 (7)	36.4 (8)
	Yes	22	40.9 (9)	45.5 (10)
	Yes	22	40.9 (9)	50.0 (11)
	No	22	31.8 (7)	40.9 (9)
	No	20	35.0 (7)	40.0 (8)
Carboplatin	No	29	0 (0)	20.1 (6)
Carboplatin / etoposide	No	23	0 (0)	0 (0)
	No	23	0 (0)	13.0 (3)
Carboplatin / paclitaxel	No	22	0 (0)	0 (0)
	No	22	0 (0)	0 (0)
Carboplatin / pemetrexed	No	21	0 (0)	0 (0)
	No	22	0 (0)	0 (0)
Doxorubicin	No	23	30.4 (7)	34.8 (8)
Epirubicin / cyclophosphamide (EC)	No	23	21.7 (5)	34.8 (8)
	No	23	17.4 (4)	52.2 (12)
	No	22	0 (0)	31.8 (7)
Gemcitabine / carboplatin	No	23	0 (0)	0 (0)
	No	22	0 (0)	0 (0)
	No	24	0 (0)	33.3 (8)

Table 39: Table showing the proportion of each cycle the neutrophil count is <0.5 x10⁹/L and <1.0 x10⁹/L by chemotherapy regimen.

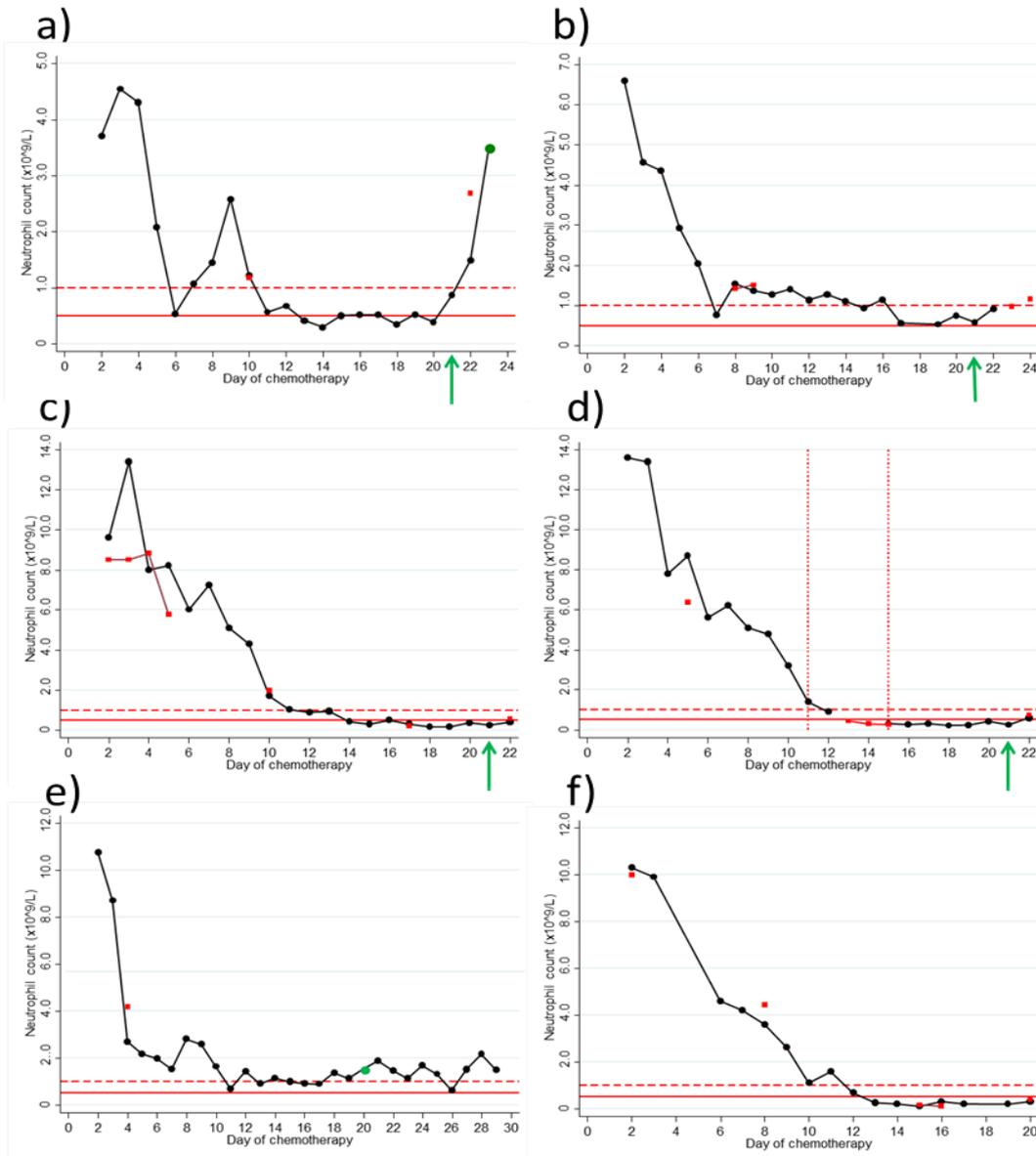


Figure 34: Profiles of the neutrophil counts where the neutrophils had not recovered sufficiently for delivery of the subsequent cycle of chemotherapy.

The chemotherapy regimens delivered with neutrophil threshold for safe delivery of the subsequent cycle at day 21 were; a) epirubicin and cyclophosphamide, $>1.5 \times 10^9/L$, b) carboplatin and gemcitabine, $>1.5 \times 10^9/L$, c) BEP 5-day, $>1.0 \times 10^9/L$, d) BEP 3-day, $>1.0 \times 10^9/L$, e) carboplatin AUC 7, f) BEP 3-day, $>1.0 \times 10^9/L$, but the profiles stops at day 20. Black observations represent capillary samples measured by the Hemocue WBC DIFF. Red observations represent venous samples measured by the laboratory ADVIA 2120. Green observations represent the first measurement after the nadir when the count recovered above the threshold for safe delivery of the subsequent chemotherapy cycle. Observations are linked if they were measured by the same device and occurred on consecutive days. The solid horizontal red line represents absolute neutrophil count of $0.5 \times 10^9/L$. The dashed horizontal red line represents absolute neutrophil count of $1.0 \times 10^9/L$. The days between the vertical short dashed red lines represent the admission to hospital during which the patient was treated for febrile neutropenia. The green arrow indicates the day the subsequent chemotherapy was due.

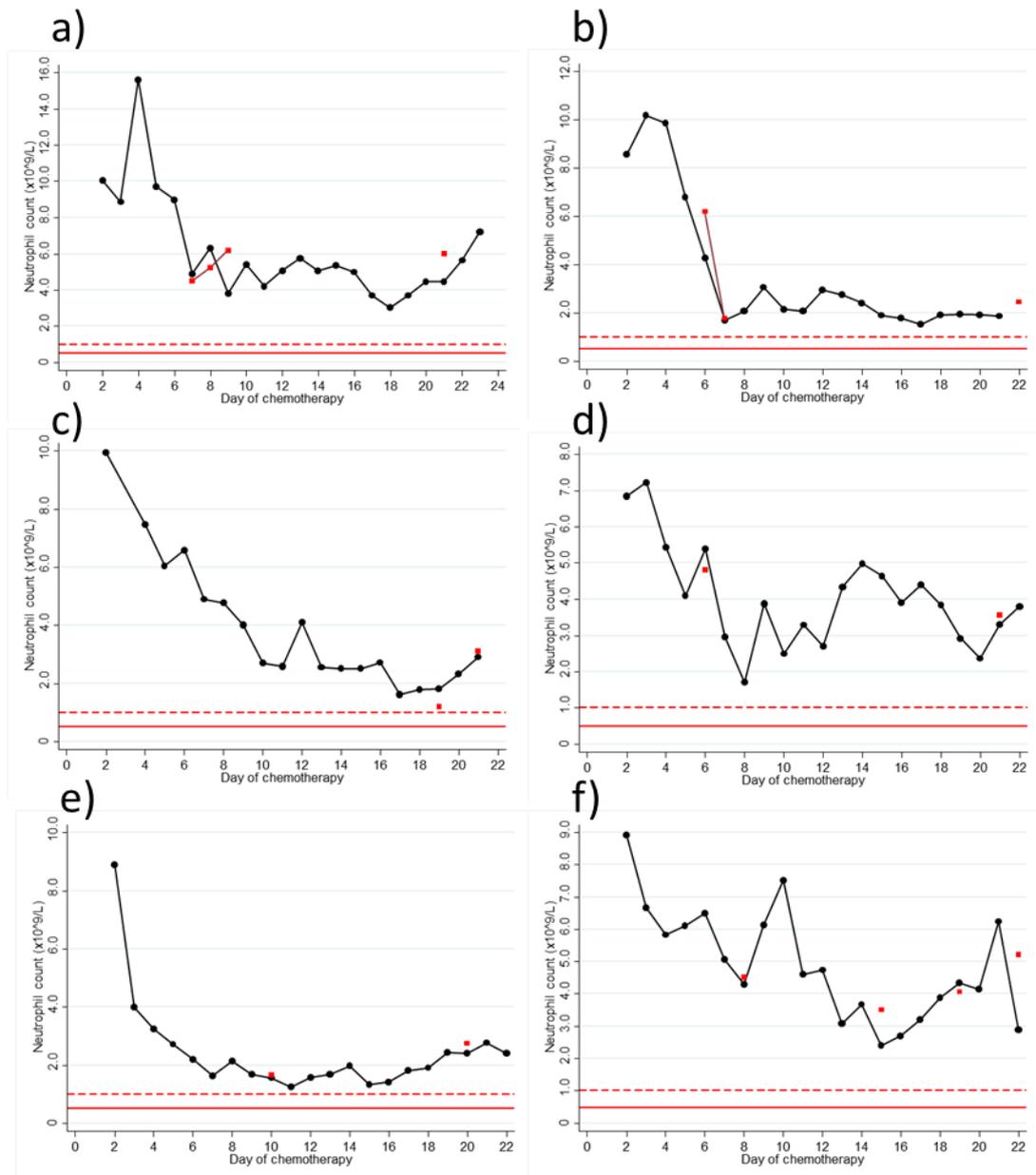


Figure 35: The six neutrophil profiles where the neutrophil count never fell below the threshold for delivery of the subsequent cycle of chemotherapy.

The chemotherapy regimens delivered for each profile were; a) & b) gemcitabine and carboplatin, c) & d) carboplatin and pemetrexed, e) paclitaxel and carboplatin 3-weekly, f) paclitaxel and carboplatin weekly. Black observations represent capillary samples measured by the Hemocue WBC DIFF. Red observations represent venous samples measured by the laboratory ADVIA 2120. Observations are linked if they were measured by the same device and occurred on consecutive days. The solid horizontal red line represents absolute neutrophil count of $0.5 \times 10^9/\text{L}$. The dashed horizontal red line represents absolute neutrophil count of $1.0 \times 10^9/\text{L}$.

6.4.2.3 By chemotherapy regimen

In all 3 profiles from patients receiving epirubicin and cyclophosphamide, there appeared to be a “falter” in the descent of the neutrophil count to the nadir, with a rise in neutrophil count at days 7, 7, and 6. In the second of these patients, the rise continued for 3 consecutive days. Then again all 3 appeared to have a second rise at day 8, 11 and 10, but for one day only. The duration of neutropenia at $<1.0 \times 10^9/L$ during epirubicin and cyclophosphamide was relatively long (8, 12 and 7 days). The recovery from the nadir was late but rapid; 2 of the 3 recovered the neutrophil count sufficiently in time for safe delivery of cycle 2 on day 21. These 3 profiles are shown in Figure 36.

All 7 of the profiles from patients treated with bleomycin, etoposide and cisplatin (BEP), descended to a nadir of $<0.5 \times 10^9/L$, with the mean nadir being $0.12 \times 10^9/L$ (range 0.00 to 0.28) and mean duration of neutrophil count $<0.5 \times 10^9/L$ being 6.6 days (range 3 to 9). Three of the 7 profiles did not recover sufficiently for delivery of cycle 2 on time. The gradient of the neutrophil recovery appeared less steep and less profound than that of other regimens such as epirubicin and cyclophosphamide. These 7 profiles are shown in

Figure 37.

None of the 7 profiles for chemotherapy regimens used to treat patients with lung cancer (gemcitabine and carboplatin, carboplatin and pemetrexed, and carboplatin and etoposide) had a neutrophil nadir $<0.5 \times 10^9/L$. All 3 of the gemcitabine / carboplatin patients' neutrophil profiles were similar with a rapid descent of neutrophil count over 3-6 days and then a flat profile with 2 out of the 3 showing little sign of neutrophil recovery from the nadir by day 21.

None of the carboplatin / pemetrexed (n=2), doxorubicin (n=1) or weekly carboplatin / paclitaxel (n=1) neutrophil profiles were smooth curves and they had a jagged appearance to the neutrophil descent. All the profiles of patients not included in either Figure 36 or

Figure 37 are shown in Figure 38.

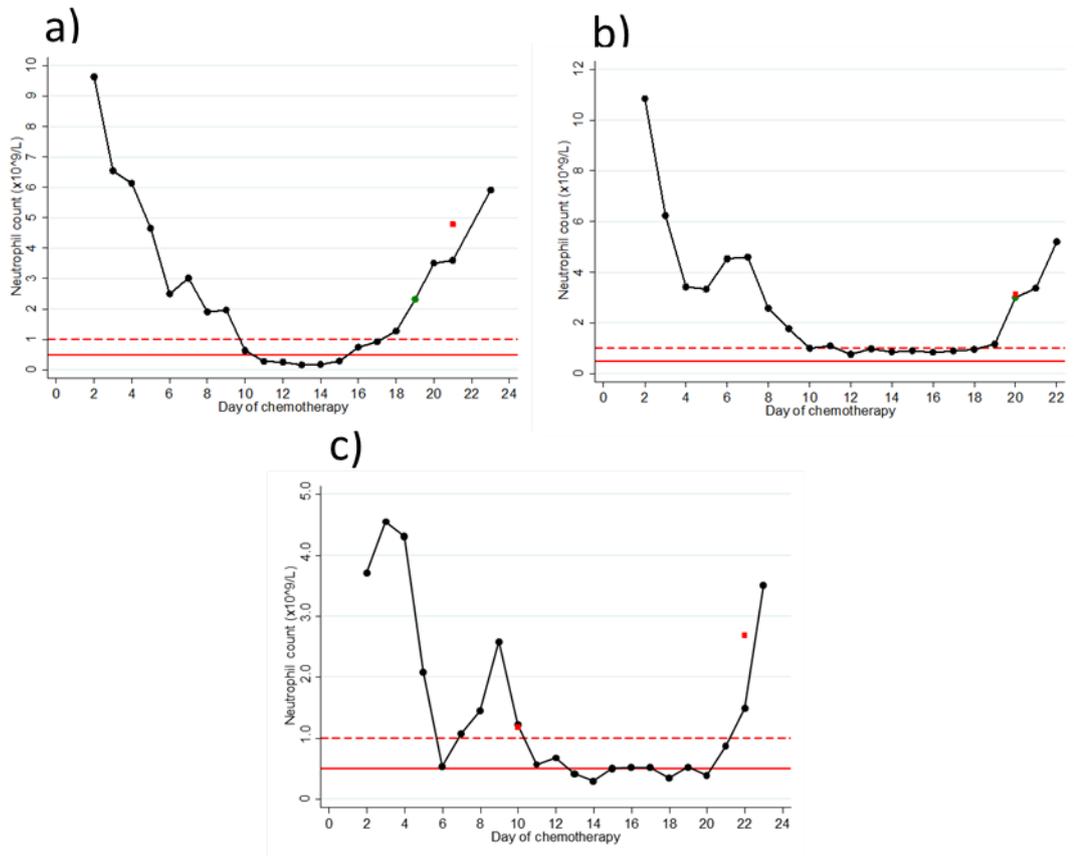


Figure 36: The neutrophil profiles for epirubicin and cyclophosphamide chemotherapy regimen.

In profile b) the patient received oral antibiotics from day 4 to day 11 for a wound infection. Black observations represent capillary samples measured by the Hemocue WBC DIFF. Red observations represent venous samples measured by the laboratory ADVIA 2120. Observations are linked if they were measured by the same device and occurred on consecutive days. The solid horizontal red line represents absolute neutrophil count of $0.5 \times 10^9/\text{L}$. The dashed horizontal red line represents absolute neutrophil count of $1.0 \times 10^9/\text{L}$.

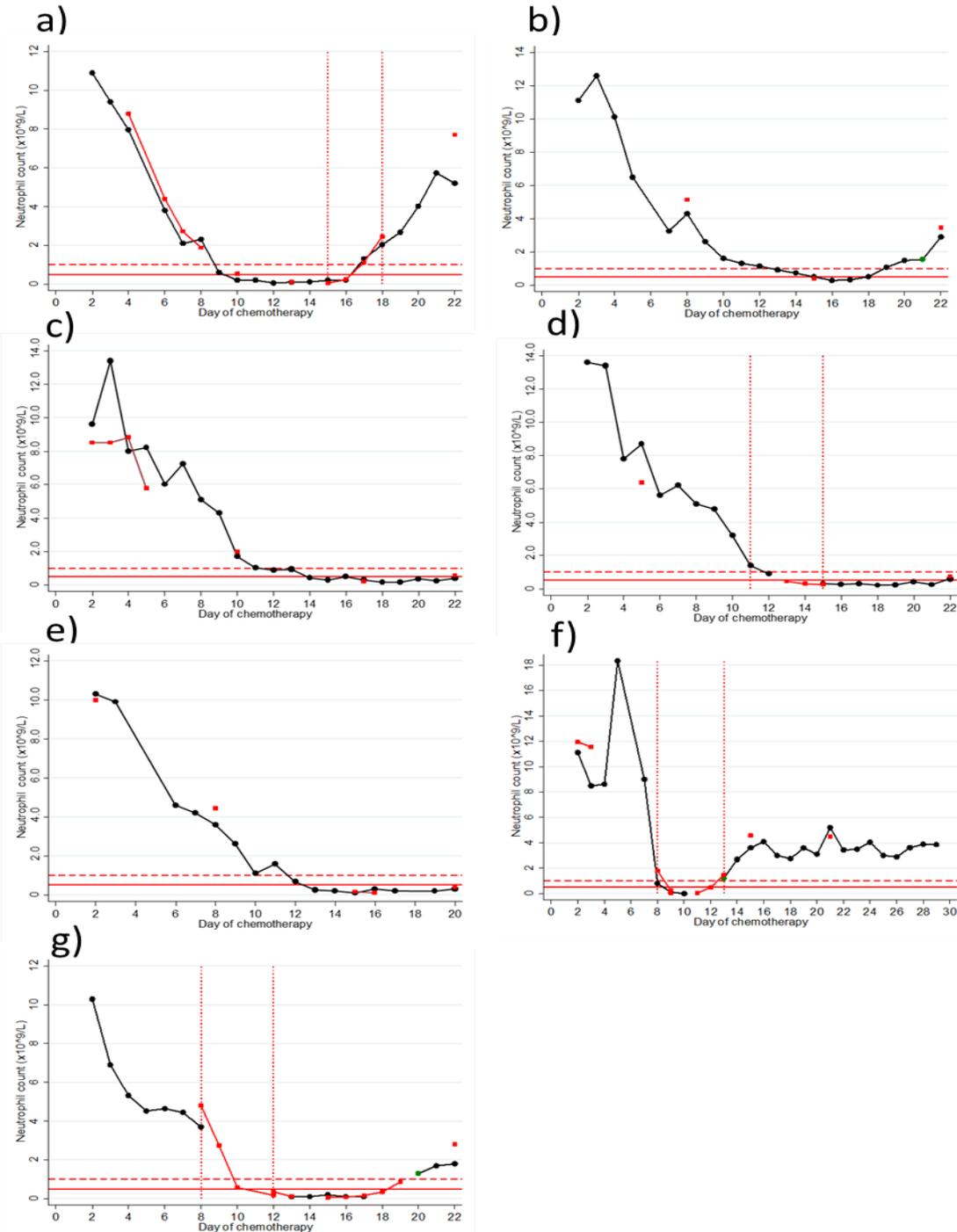
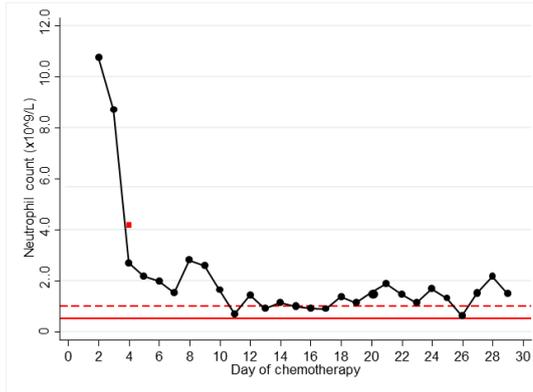


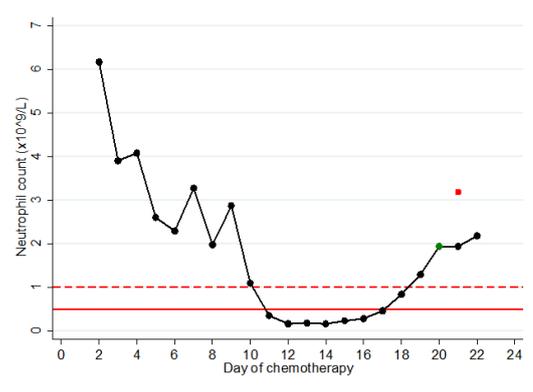
Figure 37: The neutrophil profiles for bleomycin, etoposide and cisplatin (BEP) chemotherapy regimens.

Profiles a), b), c) and d) were during BEP 5-day regimen. Profiles e), f) and g) were during BEP 3-day regimen. Black observations represent capillary samples measured by the Hemocue WBC DIFF. Red observations represent venous samples measured by the laboratory ADVIA 2120. Observations are linked if they were measured by the same device and occurred on consecutive days. The solid horizontal red line represents absolute neutrophil count of $0.5 \times 10^9/L$. The dashed horizontal red line represents absolute neutrophil count of $1.0 \times 10^9/L$. The days between the vertical short dashed red lines represent the admission to hospital during which the patient was treated for febrile neutropenia.

Single agent carboplatin



Single agent doxorubicin



Gemcitabine and carboplatin

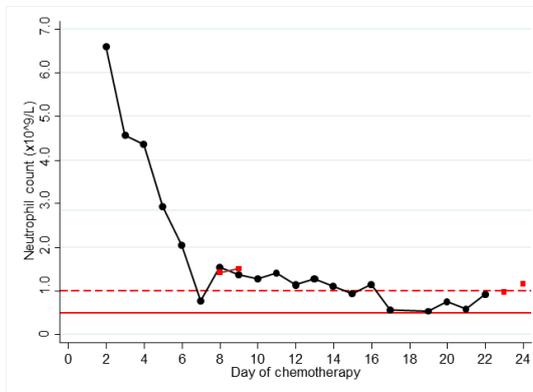
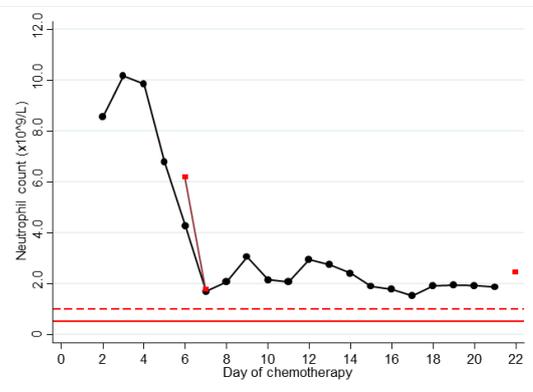
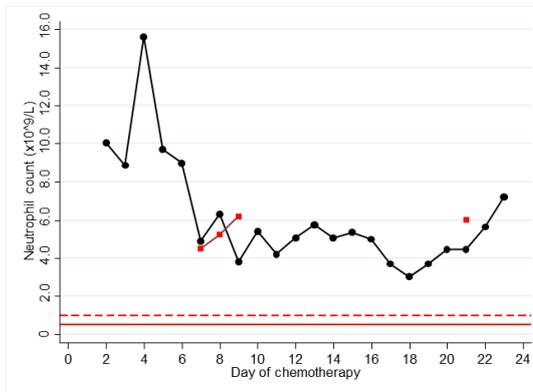
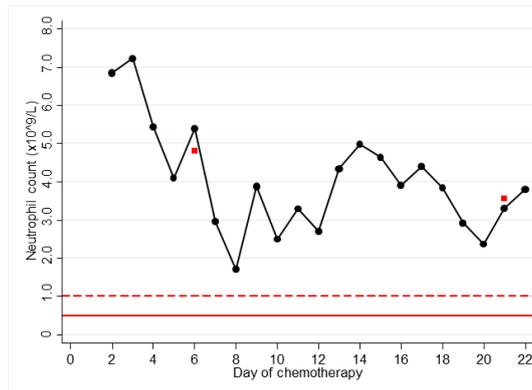
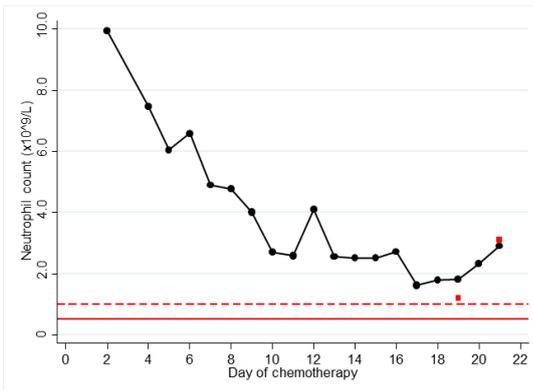
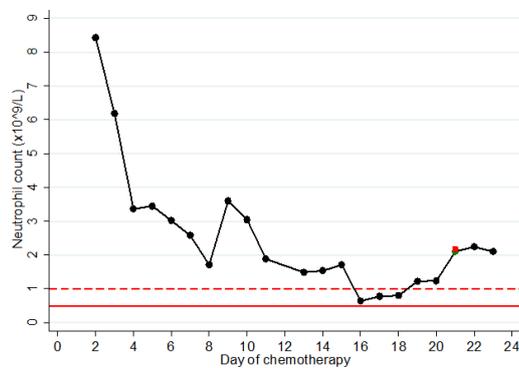
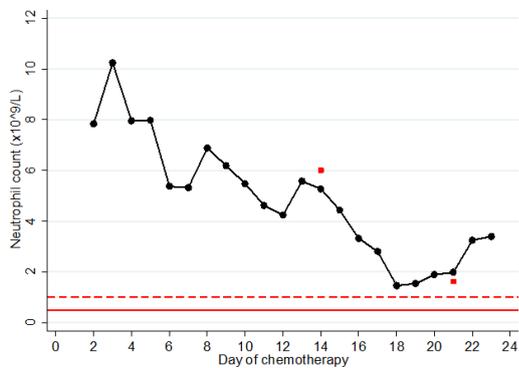


Figure 38: Continued on following page.

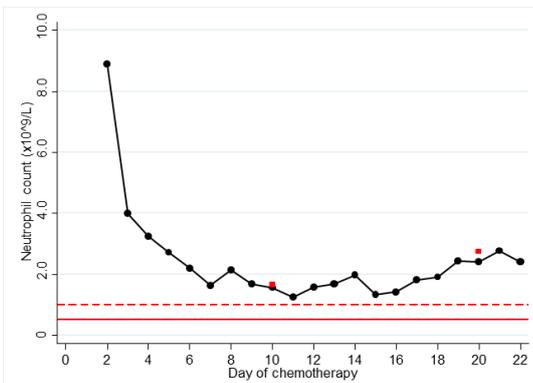
Carboplatin and pemetrexed



Carboplatin and etoposide



Paclitaxel and carboplatin 3-weekly



Paclitaxel and carboplatin weekly

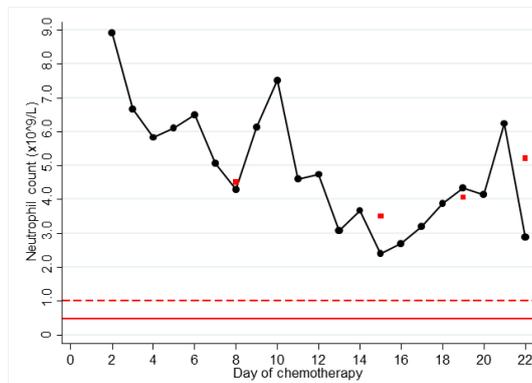


Figure 38: The neutrophil profiles from patients by chemotherapy regimen received, excluding epirubicin and cyclophosphamide (EC) and bleomycin, etoposide and cisplatin (BEP).

Black observations represent capillary samples measured by the Hemocue WBC DIFF. Red observations represent venous samples measured by the laboratory ADVIA 2120. Observations are linked if they were measured by the same device and occurred on consecutive days. The solid horizontal red line represents absolute neutrophil count of $0.5 \times 10^9/L$. The dashed horizontal red line represents absolute neutrophil count of $1.0 \times 10^9/L$.

6.4.2.4 Telephone consultations

Ten of the 21 patients telephoned the acute assessment unit on a total of 17 separate occasions for advice regarding symptoms during their chemotherapy. From these 17 phone-calls, 6 patients attended the acute assessment unit once each for review. Of these 6 patients, 3 had suspected febrile neutropenia, 1 of which was proven and admitted, the other 2 were disproven because they were not febrile or neutropenic, but 1 was still admitted for nausea and vomiting. This is shown in a flow diagram in Figure 39.

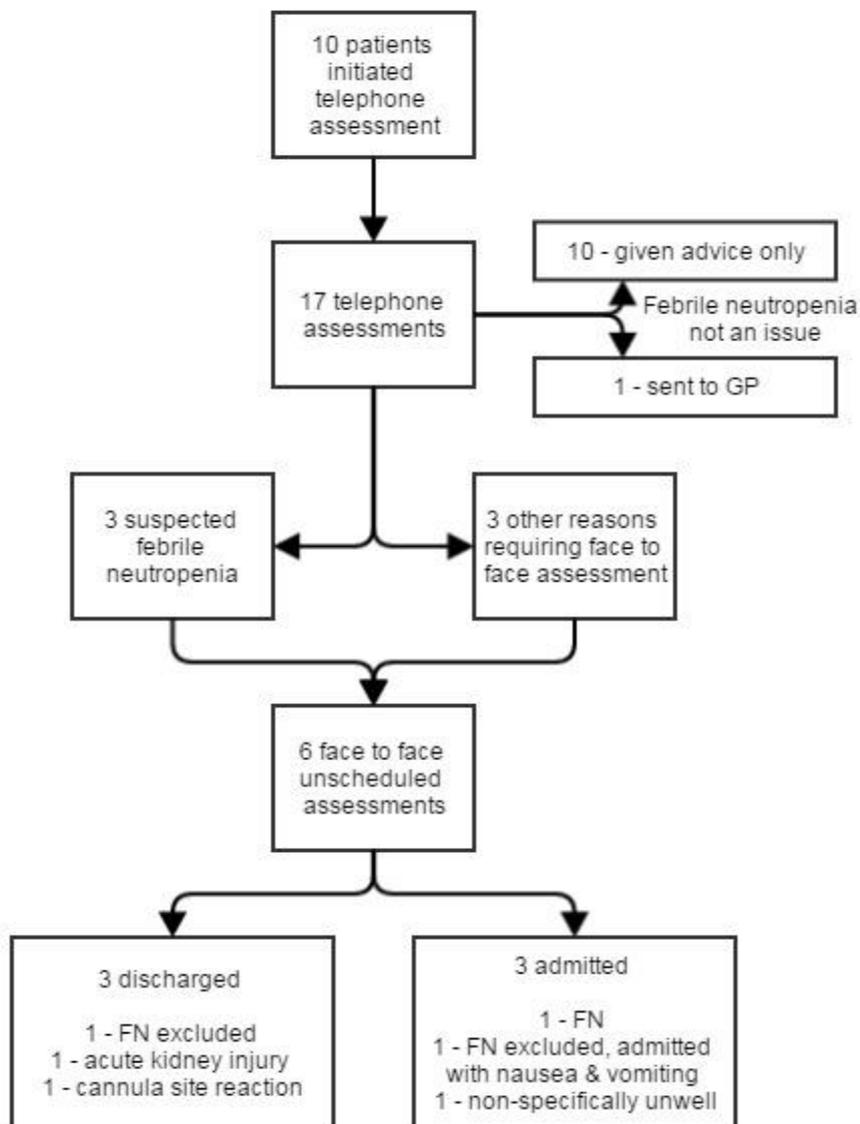


Figure 39: Flow diagram of the unplanned patient-initiated telephone consultations during chemotherapy with the nurse practitioner manning the acute assessment line.

6.5 Discussion

6.5.1 Main findings

Comprehensive neutrophil profiles were generated for 21 out of 22 patients on chemotherapy. The main findings from these profiles were;

- (i) They demonstrated it is feasible to measure home neutrophil counts regularly on patients during chemotherapy, albeit that the measurements in this trial were carried out by health-care professionals.
- (ii) They showed heterogeneity of neutrophil profiles from patients in routine practice.
- (iii) They challenged some preconceptions around neutrophil counts and toxicity during chemotherapy, for example, that the risk of febrile neutropenia is proportional to the extent and duration of neutropenia.
- (iv) They highlighted the potential of using neutrophil counts during a cycle to personalise chemotherapy treatment.

In some instances, the patients' neutrophil profiles showed insufficient neutrophil recovery prior to the subsequent planned chemotherapy cycle, they identified sub-optimal dosing indicated by an inadequate neutrophil nadir, and they demonstrated that some patients were neutropenic prior to non-elective symptom-led assessment at hospital. There were not sufficient patients with neutropenic complications in this cohort to analyse patterns in early changes in neutrophil counts that may be indicative of neutropenic complications.

Grade 4 neutropenia occurred in ten out of the 21 profiles, with a mean duration of 6.8 days. As expected and in keeping with the pathway modelling described in chapter 2, bleomycin / etoposide / cisplatin (BEP) and single agent doxorubicin chemotherapy regimens were associated with the highest proportion of days spent with grade 4 neutropenia. The BEP chemotherapy regimen was associated with the highest prevalence of febrile neutropenia, with no obvious difference in rate between 3- and 5-day regimens, which concurs with previous studies (237). However, in contrast to the literature, the proportion of days during the chemotherapy cycle spent neutropenic, were not directly related to the risk of febrile neutropenia. Moreover, the day of onset of febrile neutropenia was not consistently related to the day of onset of uncomplicated neutropenia. The profiles of those patients who were treated for febrile neutropenia show a very rapid descent to neutropenia in 1 out of the 4,

compared to a more steady descent in the other 3. There were not enough profiles with the outcome of neutropenic complications to identify recurring patterns. For example, in Figure 32 the rapid descent to neutropenia associated with a fever was preceded by a spike in neutrophil count; further similar profiles are needed to see if this was by chance or in fact repeats due to an underlying physiological process which is indicative of neutropenic complications.

Interestingly, many of the profiles display a step-wise and in some cases changing orientation of the profile whilst ultimately descending to the neutrophil nadir. This is best demonstrated in Figure 32b, Figure 33a, b, d, Figure 34a, c, d, Figure 35a, d and f. Endogenous granulocyte colony stimulating factor and other cytokines, such as interleukin 1, 5, 6 and 11 are produced by multiple cell types including fibroblasts, endothelial cells and macrophages that promote the proliferation of bone marrow neutrophil precursors and accelerate release of mature neutrophils into the circulating blood (1). Granulocyte colony stimulating factor is elevated in patients during chemotherapy (238), but despite the extensive work on colony stimulating factors the feedback mechanism and driver for effect is not understood. Perhaps the changing orientation of the profiles in descent to the neutrophil nadir is an effect of endogenous granulocyte colony stimulating factor, which is limited by the effect of the chemotherapy insult on the committed multipotent haematopoietic stem cells in the bone marrow, but driven either by the change in neutrophil count or by another mechanism of insult caused by the chemotherapy.

There is potential to optimise the delivery of chemotherapy by personalising it according to recovery of a patient's neutrophil counts and the neutrophil nadir obtained. Recovery of the neutrophil count was later than expected, with the median number of days that the count recovered in advance of delivery of cycle 2 being 1 day. In addition, in 4 out of the 21 profiles, the neutrophil count did not recover sufficiently in time for cycle 2, and hence use of home blood count monitoring could have prevented a wasted trip to hospital for these patients. In contrast, 6 out of the 21 profiles showed that the neutrophil nadir failed to even fall to the threshold for safe delivery of cycle 2. Four of the chemotherapy regimens in this group were delivered for non-small cell lung cancer, and none of the 7 regimens given for lung cancer achieved a neutrophil nadir $<0.5 \times 10^9/L$. There is strong evidence in the advanced non-small cell lung cancer setting that the higher the grade of neutropenia achieved during chemotherapy, the better the survival (hazard ratio death 0.65 with grade 3-4 neutropenia, 0.74 with grade 1-2 neutropenia compared to no neutropenia, and an absolute survival

benefit of 12.3 weeks, $p=0.0118$ of grade 1 or 2 neutropenia compared to no neutropenia) (93). Often patients with lung cancer have underlying chronic lung disease and as such have anatomical abnormalities which predispose them to deep-seated infection, hence the caution in real-life practice dosing, but all the more important to be able to individually dose patients based on their toxicity profile.

The proportion of patients who telephoned the acute assessment unit for advice was unexpectedly high, albeit that this trial was during first cycles of chemotherapy, which may be associated with uncertainty of the unknown. Only one out of the 17 phone-calls resulted in admission to hospital for treatment of febrile neutropenia, as the other three patients with febrile neutropenia were admitted from clinic, which may have been due to coincidence, but also possibly reflects delay in symptom reporting due to scheduled appointments, or lack of recognition by patients of concerning symptoms. The phone-calls made to the hospital by the patients on chemotherapy represented a significant volume of work for staff, as well as inconvenience for the patients, and should be considered an integral part of assessing the role of home blood count monitoring.

6.5.2 Strengths and weaknesses

This trial had significant strengths. We generated comprehensive finger-prick neutrophil measurements for the duration of the first cycle of chemotherapy from patients who were being treated within routine clinical care protocols. As all trial activity was carried out in addition to standard care, and the patients and professionals measuring the neutrophil counts were blinded to the Hemocue WBC DIFF results, the intervention should not have influenced the prevalence of febrile neutropenia. As there were both venous laboratory neutrophil counts and capillary Hemocue WBC DIFF neutrophil counts measured on occasions on the same day, the results corroborated the performance analysis of the Hemocue WBC DIFF in the neutropenic range, where the two results were largely comparable. In fact, in some of the profiles the laboratory venous curves were almost continuous with those of the capillary Hemocue WBC DIFF results. On the occasions where there was discrepancy between the venous laboratory neutrophil count and capillary Hemocue WBC DIFF result, the mean neutrophil count tended to be well above the grade 3 neutropenia threshold.

The major limitation of this trial was that recruitment was limited to 22 patients, and that 50% of patients declined participation. This would limit, but not preclude, home blood count

monitoring in this format in clinical practice. Perhaps patients were put off by the “intrusion” of a home visit, or the need to arrange their diaries around the visit. If so, self-test devices may prove more attractive. It would probably be “best” to give patients the choice of self- or nurse-delivered testing. The small numbers enrolled rendered statistical analyses inconsequential, as results could not be described without very large CIs. Moreover, although the proportion of those who experienced febrile neutropenia was actually quite high, the absolute number was not enough to identify patterns in neutrophil counts related to this. The broader picture limitation was that this data were collected using a professional to operate the blood count measuring device. Although effective to meet the aims of this trial, many of the potential gains of using a point of care finger-prick blood count monitor in oncological clinical practice are dependent upon a patient self-test device. This trial cannot prove proof of principle of patient self-test home blood count monitoring, but justifies the continued collection of neutrophil profiles to identify with more confidence where in the pathway of patients on chemotherapy there is potential for use of home blood count monitoring.

6.5.3 Implications

Even with the small number of patients in this trial, the ability to collect patient profiles and the profiles themselves demonstrated that there is value in pursuing development of home blood count monitoring in patients on chemotherapy. For example, the one patient with proven febrile neutropenia, of the three suspected patients, could have been identified prior to attendance at hospital, and could have been directed straight to the ward for admission, thus empowering the patient to improve their own experience of healthcare by receiving prompt, high quality care, without the interim often long wait on an acute assessment unit. The other two patients with suspected febrile neutropenia in whom this was not confirmed, could have been spared an unnecessary visit to hospital (although in one case there was a secondary cause for admission). This would meet very much the aims of local practice strategies, but also of the Five Year Forward View, which recommends changes for delivery of healthcare in the NHS on a National level, published in 2014 (239). One proposed direction of change described in this, is for a more patient-centred and involved healthcare service, with more confluent movement of patients between primary and secondary care.

Most notably, there were a number of patients in this trial where there was evidence of “under-dosing” of chemotherapy, whether that be due to an inadequate neutrophil nadir, or early recovery of neutrophils prior to the subsequent cycle of chemotherapy. Given that

published data demonstrates improved relapse-free survival from high-risk breast cancer using the neutrophil nadir to dose chemotherapy (94), it is warranted to investigate the true extent of this under-dosing further by collecting more data, which may support analysis of improved dosing of standard chemotherapy. This may be of particular interest in cancer types where the newer biological therapies have yet to have a significant impact on the current standard cytotoxic chemotherapies, or where the dosing is crucial to maintaining good outcomes, such as in germ cell tumour practice. This “personalised” increase in dose intensity is most obviously applicable in the curative setting (adjuvant breast, colorectal, osteosarcoma cancers), but potentially relevant in the metastatic setting where benefits in overall survival have been shown (non-small cell lung cancer) (93).

Neutropenic sepsis remains a life-threatening toxicity of cytotoxic chemotherapy (47, 49, 95), and there is support in some circumstances for the use of prophylactic measures (65-67, 72, 75). This, and the ability to successfully profile neutrophil counts, provides the rationale in part to continue to collect more neutrophil profiles during chemotherapy in an attempt to define a biomarker in the form of early changes in the neutrophil count that is predictive of neutropenic complications. The small number of patients with neutropenic complications in this study precluded identification or disproof of such indicative changes. Collection of a larger number of profiles may facilitate pattern recognition and enable segregation of early changes into groups according to risk of neutropenic complications. If such changes exist, the intention is to quantify how closely data fits the recognised patterns and thus define the limits of low, medium and high risk groups with CIs. This would complement the existing modelling work on neutrophil time-course during chemotherapy, as the data from early days following chemotherapy used to inform these were sparse, so may have missed key signals, and the models were mostly developed for single-agent drugs, not the regimen combinations commonly used in practice.

Projecting beyond collection of more profiles to identify potential uses for home blood count monitoring during chemotherapy, evidence needs to be generated to support the principles identified. As discussed, home blood count monitoring could be used in at least four different time points during chemotherapy (early on in predictive capacity, mid-cycle identifying neutropenia, mid-cycle defining the neutrophil nadir, and end-of-cycle identifying sufficient neutrophil recovery), and as such is a complex intervention (170). Generation of evidence to support change of routine clinical practice to incorporate home blood count monitoring will

involve careful selection of patients for a “test and treat” trial, possibly using home blood count monitoring at more than one time-point during chemotherapy.

6.5.4 Conclusion

The work in this chapter serves to demonstrate proof of principle, first and foremost, that home blood count monitoring is possible. Even within the confines of small numbers of profiles, it demonstrates that home neutrophil count monitoring provides information on the neutrophil count that is otherwise unknown. Collection of further profiles will demonstrate the true extent of this across chemotherapy regimens in routine practice and enable the application of statistical tests to define CIs. This will provide baseline information, much like the previous chapter on defining clinical pathways, so that the gains of changing future clinical practice can be quantified. Profiling neutrophil counts has the potential to feed into the evidence base for the national agenda of personalising medicine, which in this case, is delivery of chemotherapy. The data in this chapter supports on-going development of the technology to facilitate patient self-test home blood count monitoring.

Chapter 7 Overall discussion

Chemotherapy delivery continues to play an important role as part of often multi-modality treatment for patients with malignant tumours. Current chemotherapy dosing schedules and supportive therapies are usually based on evidence from clinical trials, which report the clinical effectiveness as well as toxicities at a trial population level. Both complicated and uncomplicated neutropenia are well recognised toxicities of cytotoxic chemotherapy, with prevalence varying depending on the source and methods of evidence. As the absolute number of patients receiving chemotherapy is projected to increase year on year over the coming decades, the burden of neutropenia associated with cytotoxic chemotherapy is also expected to increase. The vast majority of cancer care within the United Kingdom is carried out within the National Health Service, which is under ever increasing financial constraints, with targets to improve outcomes of cancer care, which include clinical outcomes such as survival rates, but also social outcomes such as patient satisfaction.

The work described in this thesis aimed to explore the feasibility and potential role of home blood count monitoring in patients during chemotherapy. It started the journey towards investigating whether home blood count monitoring could be used to personalise chemotherapy delivery with the ultimate goal of improving outcomes for patients with cancer. In current standard clinical practice, blood counts are measured through venous blood samples, obtained by a health-care professional and measured in a haematology laboratory. Using finger-prick blood samples has the advantage that it may be possible for patients to self-test and therefore obtain results remote from the health-care provider, negating the requirement for venepuncture and for the patient to travel for the procedure. This provides the possibility of more frequent blood tests, thus diversifying the potential role of home blood count monitoring.

This thesis is formulated of discrete chapters where different aspects of home blood count monitoring were addressed within each and include;

1. pathway modelling to define and quantify baseline patient pathways.
2. patient and professional attitudes towards home blood count monitoring.
3. use of parameters available on finger-prick devices as surrogate markers of the venous blood count.

4. performance of the finger-prick device in the neutrophil range relevant to oncological practice.
5. collecting neutrophil profiles of patients on chemotherapy.

Overall, this work showed that amongst patients and professionals there is an enthusiasm for and a willingness to embrace home blood count monitoring, and to engage in clinical research. It demonstrated that existing data collected as part of routine clinical care are detailed and robust enough to be transformed into quantifiable patient pathways of clinical relevance. It showed that the finger-prick blood count measuring technology is appropriately advanced to facilitate finger-prick blood count measurements that perform sufficiently in the extreme neutropenic range, which is necessary for use in oncological clinical practice. All this built towards using home blood count monitoring to profile the neutrophil counts of patients on chemotherapy. Certainly the profiles obtained confirm the feasibility to use home blood count monitoring, with the caveat that these results were obtained by professional tests and with manual electronic transfer of the results. The heterogeneity of the neutrophil profiles challenged preconceptions such as, for example, that the risk of febrile neutropenia is proportional to the extent and duration of neutropenia. As such, the neutrophil profiles of patients on chemotherapy confirmed there is a potential role for home blood count monitoring to be used to personalise chemotherapy delivery. Further neutrophil profiles are needed to define and quantify the patients in whom it is considered that home blood count monitoring has the potential to improve care.

When assessing the performance of a test, it is important to consider the intended clinical use, hence the requirement to assess performance specifically in neutropenic ranges relevant to oncological practice. In the scenario of using home blood count monitoring to exclude neutropenia in a patient at home with suspected febrile neutropenia, the benefit of avoiding hospital attendance has to be off-set against the risk of mis-management. If the threshold indicating neutropenia is set too high, the benefit of using the test will not be realised. If the threshold is set too low, the risk of using the test may be unacceptable. Moreover, there will always be a range of uncertainty around thresholds, where a small error in the result could classify the patient on a different side of the threshold than the comparator laboratory result. This is where use of the trend of results may be of benefit, and action such as test repetition for results that fall within predefined limits of the threshold can be included in treatment algorithms. An alternative approach is to build error margins into clinical algorithms. For example, national guidelines for initiating intravenous antibiotic therapy for febrile

neutropenia use neutrophil counts of $<0.5 \times 10^9/L$ as the cut-off. Using a neutrophil threshold of $<1.0 \times 10^9/L$ incorporates an error margin which is 100% of the true value, and allows for the area of uncertainty around the threshold.

The pathway modelling described in chapter five was performed to inform patient selection for the home blood count monitoring in chapter six, but also to provide a mechanism by which any future changes to patient care as a result of introducing home blood count monitoring can be measured. In addition, it stands alone as an exemplar of how data collected for routine clinical care can be transformed into a format that can be meaningfully shared with stakeholders involved in service improvement. This approach was acknowledged as being a vanguard in this field when it was presented at the 4th UK Diagnostics Forum in Oxford in 2015 (155), and has since initiated interest from the Medicines and Healthcare products Regulatory Agency (MHRA) as a method of identifying and confirming signals held within data across diagnostic, device and medicines boundaries.

It is disappointing that during the time-frame of this research, that there was not a device available for patient self-test use with remote connectivity capability. The soft- and hardware exist to enable automated electronic transfer of the blood results, but there is work to be done to make this compatible with the Hemocue WBC DIFF device. The self-test data in chapter four is the first available on patients using the Hemocue WBC DIFF device, but the absence of more robust data on both self-test and the automated transfer of results is the most significant limitation of this work. Progression of this is a key part of realising the benefits of home blood count monitoring. In addition, greater numbers of patients with comprehensive neutrophil profiles are needed to inform a “test and treat” trial protocol, hence only limited conclusions could be drawn about the potential uses and predicted impact of home blood count monitoring. There were multiple potential uses within a cycle of chemotherapy proposed. If further patients’ neutrophil profiles support the continuation to a test and treat trial, this will necessarily be a complex intervention, which will require careful multi-disciplinary planning in order to collect appropriate data on all the potential outcomes.

In contrast to the limitations, the work described in this thesis has significant strengths. It was conducted in collaboration with the National Health Service, academia and industry, drawing on the expertise of specialists in all fields, such as patients, data analysts and laboratory professionals, to name a few. Some of the collaborative work was beyond the scope of this thesis, but was informed by work within it, such as health economic analysis which is on-going

and is dependent upon the Markov model built during the patient pathway modelling described in chapter five. Robust methods were used throughout this research as demonstrated by the publication of work from two of the chapters to date (115, 191), with plans to submit the content completed later in time (chapters three and six). The neutrophil profiles obtained were comprehensive, with few missing results from daily schedules, indicating patient acceptance of the procedure. In addition, the findings are widely applicable to oncology practice as a whole, for example, the performance analysis in the neutropenic range may open up the opportunity for use of finger-prick blood count monitoring for accurate drug dose escalation in early-phase clinical trials. The patient pathway mapping described reproducible methods which can be applied to many clinical scenarios, providing a mechanism of quantifying current service provision that can be applied to identify problems in service delivery, inform health economic analysis, and measure the effect of intervention on the real-life patient pathway. Moreover, the principles of this project (which are aiming to reduce the frequency and severity of neutropenic complications of chemotherapy, reduce patient attendance at and admissions to hospital, improve patient experience and make financial savings) are very much in keeping with both local and national health-care agendas.

In October 2014, NHS England published the “Five Year Forward View” that set out approaches for sustaining and improving the NHS, to make it fit for the purpose of serving the healthcare needs of the nation with a high quality service (239). It focused on key areas such as ;

- giving patients more control of their care.
- new models of care.
- exploiting the information revolution.
- accelerating useful health innovation.

The vision for giving patients greater control of their care involved recognising patients can be “experts by experience”, and acknowledged merit in allowing patients to manage conditions and thus avoid complications. This approach was also considered to facilitate suggested new models of care that break down the boundaries between secondary and primary care, allowing more health-care delivery in the community. It recognised that evaluation of new models of care should address healthcare outcomes, of which patient experience and value for money are of paramount importance. It looked to providers of “specialised care”, necessary where the relationship between number of patients and quality of care is strong, to

develop services deliverable over large geographical areas. It uses cancer care as an example, where service re-design could enable making “supporting care available much closer to people’s homes” and can “allow more chemotherapy to be provided in the community”.

Oncological practice is an ideal specialty to use as an exemplar of service development in line with the principles of the Five Year Forward View. The National Confidential Enquiry into Patient Outcomes and Death (NCEPOD) and the subsequent National Chemotherapy Advisory Group recommendations outlined the need for certain “specialised services” (95, 96). The presence of national audit data, as collected in the National Cancer Waiting Times Monitoring Dataset, Cancer Outcomes and Services Dataset, Systemic Anticancer Therapy Dataset and cancer registries, serve as a baseline of large scale information collection against which subsequent service improvement project outcomes can be measured. At a more local level, Leeds Teaching Hospitals NHS Trust uses an advanced integrated electronic health record (PPM) that provides a single interface to access healthcare records from secondary/tertiary care, general practice and health and social care, and thus can facilitate collection of integrated data. In addition, the National Institute for Health Research (NIHR) selected Leeds (partnership between University of Leeds and Leeds Teaching Hospitals NHS Trust) as one of four Diagnostic Evaluation Co-operatives (DECs), which recently evolved into a Medtech and In Vitro Diagnostics Co-operative (MIC), with the aim of working collaboratively with the NHS and industry to generate evidence to support diagnostics adoption. Home blood count monitoring in patients on chemotherapy is a project with principles that complement the aims of national and local NHS-wide and cancer-specific agendas.

The use of home blood count monitoring in patients on chemotherapy may have the potential to (i) improve cancer survival through personalising chemotherapy delivery according to neutrophil nadir and recovery, (ii) predict neutropenic complications through identifying critical early changes in neutrophils, and (iii) improve the patient pathway and experience through triaging those with suspected febrile neutropenia on remote contact with the hospital, before unplanned assessment. Home blood count monitoring in patients on chemotherapy would complement the aims of both the 5-Year Forward View, and the latest cancer strategy published in 2015, “Achieving World-Class Cancer Outcomes; a strategy for England 2015-2020” (240). The latter aligns with the former with respect to supporting patient empowerment, self-management, and better integration of patient care between primary and secondary/tertiary care environments. The strategy also emphasizes delivery of outcomes that matter to patients, including patient experience, high quality modern services

and financial savings. In parallel with these strategies, the National Cancer Patient Survey has been carried out annually since 2010. The field-work for the 2016 survey was carried out between October 2016 and March 2017 and had a 66.4% response rate (n=72,788 respondents) (241). It reported 87% of patients to score $\geq 8/10$ for overall satisfaction with their care. However, the questionnaire described in chapter 2 of this thesis demonstrated a willingness amongst patients to use home blood count monitoring during chemotherapy on the basis that it would save time, a luxury often not afforded by people with a terminal illness, and thus indicating that the use of home blood count monitoring may provide a mechanism to further improve patient experience.

At local levels, non-surgical oncology Clinical Service Units are looking to implement the National Cancer Strategy through tangible, step-wise targets to provide high quality patient experience. An example of this is through waste reduction programmes aiming to reduce length of in-patient stays, reduction in drug costs and admission avoidance. There is potential for home blood count monitoring to impact all three of the latter targets through earlier diagnosis of febrile neutropenia thus reducing complications and length of intravenous antibiotics and in-patient stays, through reduction in wasted chemotherapy by identifying those patients with insufficient neutrophil recovery before subsequent chemotherapy is made up, and through reducing attendance at acute assessment units by excluding neutropenia remotely.

Both the 5-Year Forward View and “Achieving World-Class Cancer Outcomes; a strategy for England 2015-2020” acknowledge and plan for increasing demand on services over the coming decades. There has been a 10% increase in patients being managed by oncology services each year between 2000-2015 (approximately 25,000 additional patients per year) (242), which is expected to continue to rise primarily due to an aging population and better survival outcomes. There has been no increase in the proportion of NHS budget that is allocated to cancer services in the same time period (approximately 6.7%), thus delivery of a high quality, efficient, safe and cost-effective clinical service to increasing numbers of patients remains challenging. Moreover, perhaps the greatest challenge in a modern NHS is bringing about change in an organisation of such scale. There is a requirement for a culture shift of those working within it to embrace working with patients, making joint decisions, rather than the old-fashioned approach of “doctor knows best” (243). The phrase “no decision about me, without me” was coined by the government in 2012 in a paper addressing this (244). Use of home blood count monitoring would be a step in the right direction towards joint decision

making and patient empowerment. However, it is well known that despite the NHS being heavily involved in the research and development of innovations, it is notoriously slow to adopt them (245).

The Accelerated Access Review was published in October 2016, providing a Department of Health vision for faster adoption of innovation into the NHS, by describing an approach to selecting, accessing, funding and adopting the best innovations (246). It states that there should be “a single set of clear national and local routes to get medical technologies, diagnostics, pharmaceutical and digital products to patients”, and that “digital infrastructure should enable the system to capture information on the use of innovations and associated outcomes”. The patient pathway mapping described in chapter five serves as an example of how electronic patient records can be used to capture health service delivery. It is proposed that re-running of the scripts generated to produce these pathways after introduction of home blood count monitoring would enable re-quantification of the pathways, and thus be used to quantify how the innovation has changed patient pathways. This pathway modelling also informed preliminary health economic modelling of home blood count monitoring in patients during epirubicin and cyclophosphamide chemotherapy, where it was estimated that early detection of febrile neutropenia using home blood count monitoring would lead to cost savings where the cost of home blood count monitoring was <£45 per patient per cycle (247). This health economic modelling was, however, based on clinical assumptions of effectiveness and used the estimated costs of the original “Minicare H-2000” device for patient self-test use.

There remains work to be done to define the national and local routes to be followed to get innovations into the NHS efficiently. The work described in this thesis is preparatory work which is contributing to the generation of sufficient evidence to support introduction of home blood count monitoring in patients on chemotherapy. This work, in conjunction with that of the larger working party funded by the same Small Business Research Initiative grant, went some way towards mapping out a potential pathway to innovation introduction by using methods including lean patient pathway mapping (identify the problem), large scale pathway mapping (quantify the problem), health economic modelling (cost modelling of proposed solution). Future work will involve bringing together the whole project as an exemplar of generating sufficient evidence to support innovation adoption, aligning with the principles of the Accelerated Access Review and going part-way towards addressing the following six key questions within it;

1. *How will this innovation change clinical pathways and establish a new standard of care?*
2. *What will be the clinical, social and economic impacts from this new standard of care?*
3. *How will we measure the impacts with sufficient precision to provide evidence for adoption?*
4. *What changes in workflow will be required?*
5. *How will the re-engineering of this workflow be resourced?*
6. *How can the benefits be spread across and between healthcare delivery systems?*

With respect to the future of home blood count monitoring, the profiling trial described in chapter six is proof of principle that home blood count monitoring via finger-prick is feasible, but it lacks the patient self-test element to the testing, which is crucial to the concept moving forwards. The Minicare H-2000 device had remote connectivity capability and was "Conformité Européenne" (CE) marked for patient self-test use. The next steps involve enabling connectivity and self-test use of the Hemocue WBC DIFF, testing proof of principle of the self-test process and connectivity. Meanwhile, there are plans to continue collecting neutrophil profiles from patients on chemotherapy as per the trial protocol to more accurately define and quantify projections of potential uses of home blood count monitoring. The Hemocue WBC DIFF is being introduced as a professionally-operated device on an acute oncology assessment unit to serve as a triage tool to stratify patients according to their risk of febrile neutropenia, with the aim of minimising both the time spent at hospital and wasted resource use for those deemed at low or intermediate risk. This is enabling collection of further performance data in order to narrow the CIs around clinically significant thresholds, and is building clinician confidence in using results from the device. It is planned for continuation of the wider project in collaboration with the National Institute for Health Research (NIHR) Leeds Medtech and In Vitro Diagnostic Co-operative (MIC), working towards a "test and treat" trial to measure the complex clinical outcomes and pathways of using home blood count monitoring.

Further work is needed to develop the package of care and idealised patient pathways that will ultimately be needed to realise the potential benefits of home blood count monitoring. This should include novel pathways such as diverting patients at low risk of febrile neutropenia from acute assessment units to alternative health-care provision possibly including urgent outpatient appointments, telephone consultations, general practice. It may

require creation of new roles or evolution of current roles to manage the service and data, including addressing the challenges associated with twenty-four hours a day, seven days a week patient real-time measuring and/or reporting results that could indicate life-threatening chemotherapy toxicity. A patient education and support package would need to be developed, and how home blood count monitoring can complement the trend towards using patient-reported outcome measures should be considered.

In conclusion, home blood count monitoring is acceptable and in fact desirable to some patients during chemotherapy. The technology exists to measure finger-prick blood counts with sufficient performance for use within oncological clinical practice, and to facilitate patient self-test use and remote data connection. The real-life impact of innovations, such as home blood count monitoring, can be recorded using electronic health records to quantify patient pathways. This project is working towards goals that complement national health-care agendas in so many ways. The research to date goes part-way towards generating the necessary evidence to support adoption of home blood count monitoring into routine clinical practice. Hopefully the planned future work in this field will define the true potential.



In a situation where you had chemotherapy seven days ago, you feel tired, otherwise OK, but you have a high temperature.

2. Please indicate which scenario you would prefer to happen (either A or B).

Scenario A:

- You telephone the oncology patient enquiries number you have been given.
- You are required to travel to the hospital for assessment.
- You have a blood test taken in the usual manner by a healthcare professional.
- You wait one to three hours for the blood test result.
- You are re-assured face-to-face by a health-care professional.
- You are advised you do not need any treatment and can go home, but to telephone again if you become more unwell.

Scenario B:

- You do not ring the oncology patient enquiries number.
- You test your own blood via a finger-prick blood sample which you obtain and put into the new device at home (like a diabetic finger-prick test).
- You wait 2 minutes for the blood test result.
- You are re-assured by the blood result delivered on the device screen.
- You are advised by the device you do not need any treatment and can stay at home, but to telephone the hospital if you become more unwell.

Which scenario would you prefer?

Prefer scenario A

Prefer scenario B

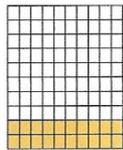
If you feel strongly, please write what influences your decision towards the chosen scenario in this box.

Please answer question 3 on the next page whichever scenario you chose.

3. There may be a chance in scenario B, that you later become unwell, possibly with a dangerous infection and your management is delayed.

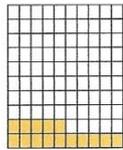
Please indicate what risk of becoming dangerously unwell you would be prepared to take, in order to get the benefits of preventing unnecessary trips to hospital.

If you cannot decide you can choose more than one answer.



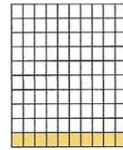
20 out of 100 (20%)

Tick if acceptable



15 out of 100 (15%)

Tick if acceptable



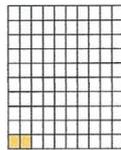
10 out of 100 (10%)

Tick if acceptable



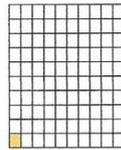
5 out of 100 (5%)

Tick if acceptable



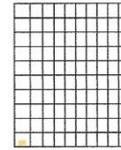
2 out of 100 (2%)

Tick if acceptable



1 out of 100 (1%)

Tick if acceptable



Less than 1 out of 1000 (0.1%)

Tick if acceptable

Please write any comments in this box

Thank you.
The Research team, Room 26, Level 6, Bexley Wing, Leeds Cancer Centre, Leeds, LS9 7TF

Appendix 2 – Consultant questionnaire



Home Blood Count Monitoring Questionnaire

1. The device is undergoing assessment of feasibility and accuracy comparable to laboratory methods, in patients with cancer on chemotherapy. Once the device has been tested and validated in patients on chemotherapy;

Would you be willing for your patients on chemotherapy, who are deemed competent, to use the Minicare H-2000 at home in the following scenarios?
Please circle your answers.

- a. In patients who feel unwell at home and require neutropenia to be excluded.

Yes No Not sure

- b. Prior to delivery of subsequent chemotherapy cycles to avoid hospital attendance in patients whose neutrophil count has not recovered sufficiently.

Yes No Not sure

- c. In the days following chemotherapy delivery to identify those patients at high risk of neutropenic complications, based on changes in the neutrophil count (once this method has been tested and validated).

Yes No Not sure



2. The LTHT guidelines recommend intravenous antibiotics for patients with a fever and neutrophil count $<0.5 \times 10^9/L$. The majority of international guidelines use the same definition or a neutrophil count expected to fall to $<0.5 \times 10^9/L$ within 48 hours.

We have to define the threshold neutrophil count below which we recommend urgent assessment on ward 95 for suspected febrile neutropenia. Given that no method of measuring the neutrophil count, home or laboratory, is perfect, a minority of patients, who are deemed to have a neutrophil count above the threshold by the home device, will in reality have a neutrophil count lower than this threshold when measured in the laboratory.

In the scenario where a patient on chemotherapy has a fever and is otherwise well, those with a neutrophil count measured at home that is above the threshold, will be advised to stay at home, unless they become more unwell.

- a) Please tick the neutrophil threshold you suggest we use in this scenario to recommend urgent clinical assessment? (units are $\times 10^9/L$)

<0.5	<input type="checkbox"/>	<1.5	<input type="checkbox"/>
<0.75	<input type="checkbox"/>	<2.0	<input type="checkbox"/>
<1.0	<input type="checkbox"/>	<3.0	<input type="checkbox"/>
<1.25	<input type="checkbox"/>	>3.0	<input type="checkbox"/>

- b) Using the threshold you've selected, please tick the maximum risk of incorrectly advising a patient to stay at home, which you consider to be acceptable.

$<0.1\%$	<input type="checkbox"/>	5%	<input type="checkbox"/>
0.1%	<input type="checkbox"/>	10%	<input type="checkbox"/>
1%	<input type="checkbox"/>	15%	<input type="checkbox"/>
2%	<input type="checkbox"/>	20%	<input type="checkbox"/>



Please write any comments in this box.

Thank you for your time.

Please return to Yvonne Robson, outside Chris Twelves' office, level 4, Bexley Wing.

Appendix 3 – Tables of free-text comments from questionnaire respondents

Free-text comments
I wouldn't feel confident carrying out a self-blood test.
I would need face to face reassurance. I would not trust my own findings and I would feel anxious and worried.
When you are feeling unwell or old and on your own it's nice to talk to a person to be reassured.
Speaking to someone would make me feel more comfortable.
I think scenario B is more useful for the patient but given the situation I think it is worth seeing a doctor face to face.
My wife worries a lot about me - she would feel stressed about this responsibility.
I personally prefer to be reassured by a professional. As an improvement on scenario B, I would like to phone a professional as well as having the blood sample
Reassurance

Appendix 3, Table 1: Free-text comments from respondents who indicated they would prefer scenario A in question 2, which is the current practice of attending hospital for a blood test and face-to-face consultation with a health-care professional.

Free-text comments
Staying at home is a safer option especially if your immune system is compromised, if it is only a matter of a couple of hours for your temperature to normalise.
It is very convenient, saves time and advantageous both to patient and medical staff. Get easily result and the information give the patient assurance of the situation. One thing I'm afraid of finger pricking, it's a bit painful compare to venepuncture.
I wouldn't want to travel to hospital and hang around for 3 hours if only my temperature was of concern.
My only concern is if you fall through the net and the computer is not given the right info by us or just not picked up through the net.
Such a long way to come - prefer to stay at home.
Saves me time.
As long as I know how to use it.
The waiting time for a blood test though being by nature a panicker I would like the reassurance of a health care professional.
I rely on family to get me to/from hospital so this scenario would put less pressure on them and less travelling for me.
Drive - not able to drive during chemo as felt so weak and partner at work -hard to get to hospital. Tired - on chemo felt too fatigued to come to hospital. 1 hour away - too tired to drive an hour. No strength to drive.
I spent a month in hospital anyway - I'd be happy to use the device rather than come here and sit for hours. I would still ring if I felt unwell.
Would rather stay at home unless it's needed to come into hospital.
Having to rely on my daughter to bring me to hospital, for something that would only take a few minutes at home.
Travelling over 1 hour to get to hospital when feeling unwell every time (sometimes when it could be avoided). Would be so helpful and aid recovery so much better.
No need to travel as it takes a lot of time and inconvenience. You are not going to be worried whether you have infection if the result is ok and it takes a few minutes.
If I feel as ok as I usually would but just a temperature I don't see the need to instantly rush off to be checked over. I would rather wait and see if I got any worse before going to be checked.
What is needed most in the situation is reassurance, which I think I would trust the device to give - saving time, energy, travel etc. The important factor is the further option of telephoning the hospital if I became more unwell.
I would be happy to trial scenario "B" but with the assurance if I am worried I could still follow scenario "A".
Being at home is less stressful than waiting for results in the hospital (3-4 hrs). There is still the availability to call the hospital if you worsen.
No travelling and results are quick.
Would rather be at home and not have to visit hospital. I know I can always call if I want to.
Lives hour away.
Felt unwell recently. Could not get through on bleep number.
Don't like coming to hospital. Never been ill until now.
Keeps me in a bit more control. Just so much more user friendly, although I can see why some patients may not feel confident enough.

Appendix 3, Table 2: Continued on next page

Previously had to wait 5/6 hours for blood result at the hospital only to be sent home but needed admission later in the same week. Less invasive of time and comfort when feeling unwell.
In the night this would be good - would save a trip in the ambulance.
"B" would be ideal as its 3hr or more in traveling and appointment time.
I was in and out like a yoyo when I was on chemo with a high temp. Once I was in A&E for 6 hours waiting for a bed when I was on chemo.
More simple. On transport.
Travel time when you feel ill better off staying home. To have the reassurance of your blood results there and then.
Travelling to and from hospital, waiting, parking. All time consuming and worrying. Plus convenience!
It's progress is that.
Better conveniency. Less time off work.
During my chemotherapy I have had a low white count and having a device at home to test quickly would have been reassuring and time saving.
Seems easier and probably cost effective. I can see that some people would prefer to be reassured face to face however.
Had to come in one Sunday during chemo for suspected infection. Understandably the dept. was lightly staffed but it was still frustrating to have to wait 7 hours. Glad I came in the end, but a test at home would have eased my mind considerably.
As well as there is the opportunity to phone the hospital. This is essential.
Hospital is a very busy place and if you can prevent patients from waiting about for hours they can be at home in the comfort of their own surroundings when not feeling very well.
If it's easy to use, it's no problem.

Appendix 3, Table 2: Free-text comments from respondents who indicate they would prefer scenario B in question 2, which is using the home blood count monitoring device.

Free-text comments
This is a hard question to answer as no one wants to be dangerously unwell but would you not be considered to be managed by the machine from the beginning. If your condition worsened you can contact or come to the hospital at any time. It could just save the trip for the people who came just because they are unsure. The machine would help you to be better informed.
Proper procedure of finger pricking by the patient minimizes the infection. Overall this new method is very advantageous to all.
It's difficult to understand how to fill in this question! It's very hypothetical; if I felt unwell I'd do the test again or ring the hospital.
I know what to do - I have had so many chemo treatments
I would not take the risk of becoming unwell due to the seriousness of the possible outcome.
I would not take any risks. I would not like to reproach myself for not acting upon me feeling unwell and the thought that I might have made my illness worse by not contacting the hospital when I was at the start of feeling unwell.
I wouldn't want to take a higher risk with regard to having a dangerous infection because once the infection has spread you might not recover. The other argument is if the reading of the machine is accurate it would mean that if one attended hosp. would the result also have shown no infection and you will be sent home and then later become unwell and have a serious infection.
For my own well-being, I wouldn't mind taking an unnecessary trip to the hospital. This may be the fact that I only live 10 mins for Leeds Hospital.
If the blood test at home said I was ok then I would be willing to take the 20% risk to see how I went on until the next day. If I had other symptoms then maybe I wouldn't take such a risk.
I'm not sure that is a good question. What does 5% risk actually mean? Might be better as a worded question. Would want device to alert at a level set by hospital not lower/not higher
If I was feeling very ill I would have no reluctance in ringing hospital no matter what the test "B" had resulted in. Just know your own body really. I think common sense is the rule. Thanks!
I was admitted into hospital twice while having chemo with an infection. In my experience your situation changes very fast and I think in these situations you need to get to hospital ASAP. This process may slow down your decision.
Given the risks outlined to me regarding feeling unwell/temperature fluctuations, I would wish to have all but certain assurance that my symptoms did not require a visit to the hospital.
If I was dangerously unwell I would be on my way to hospital straight away.
My husband is a natterer and will not sleep with anxiety if I am unwell. I would not take any extra risk as he would be too anxious.
Should I ever need more chemo, I hope this system is in place!
On the one hand saving trips to the hospital is attractive. On the other if the risk of infection is higher than I would opt for inconvenience rather than take any risks. It is not difficult to decide.
So many things have gone wrong - once I nearly "missed the window" and was so unwell I nearly could not have chemo. My time is limited - I am running out of options - I do not want to take any risk.
I think this is a good idea as the slightest thing makes you worry which can cause back up in hospital and there is always reassurance at the end of the phone.
I have peculiar blood - antibodies. I would like to be safe.

Appendix 3, Table 3: Continued on next page

The risks involved of treatment by chemo are acceptable on any level. The treating of cancer is the priority, everything else is secondary.
There's a risk in anything.
During my treatment, I was more willing to take the risk to enable me to stay at home for as long as possible. However, this was sometimes an unwise decision. Therefore, this should not always be indicative of whether a person actually needs to be seen. How will the patient know if they are just slightly unwell due to chemo or home with a serious infection that requires treatment?
I think the new way of monitoring your bloods is good as long as full training is given
Very difficult choice to make.

Appendix 3, Table 3: Free-text comments from respondents in question 3 regarding risk they are willing to take in order to gain the benefit of avoiding unnecessary trips to hospital.

Comments
<ul style="list-style-type: none"> I don't give much chemo these days.
<ul style="list-style-type: none"> The whole idea is to accept a "zero tolerance" for misdiagnosis and management of sepsis (neutropenia/otherwise) during chemotherapy. Therefore not sure if 2b is relevant.
<ul style="list-style-type: none"> Would need a lot more info about error and validation of device.
<ul style="list-style-type: none"> Use of machines would be encouraged by availability of data on its successful use. Risk question is arbitrary - patient dying due to incorrect information/interpretation might be more useful (i.e. Is question specific enough?). FBC in concert with some clinical information e.g. EWS might be more useful? Good/interesting idea though.
<ul style="list-style-type: none"> I worry about the sort of black and white questioning. Q2a answer dependent upon what chemo they have received, where they are in the cycle and what other supportive meds (?GCSF) they have received. Q1a Yes but only as part of the assessment.
<ul style="list-style-type: none"> Q2a. I assumed the WBC will be checked again next day to ensure it is not low. Do we know how frequently is worth checking WBC - we do daily in hospital. Any data on 6 hourly? 8 hourly?
<ul style="list-style-type: none"> I'd need to know that the test was validated in prospective cohort and reliable and consistent.
<ul style="list-style-type: none"> Death as a complication of management of suspected febrile neutropenia should be a never event in terms of failure to establish the correct diagnosis. The test does not replace clinical assessment in this context. I am more comfortable with scenarios 2 & 3 as the patients are well not potentially ill (less consequences) but may have an improved experience. We need to assess feasibility/usability of device first. Do not get me wrong, I am on-side with this technology. Step-by-step, walk before running etc. etc.
<ul style="list-style-type: none"> Only need "clinical assessment" if high risk and low risk only need clinical assessment if become "unwell"; however one defines this. There is lots of evidence to prove that low risk patients with neutropenia can be managed at home. I would say 20% would be ok for "incorrect advise to stay at home" as they would have a repeat blood count next day, they would be advised to have a clinical assessment if unwell.

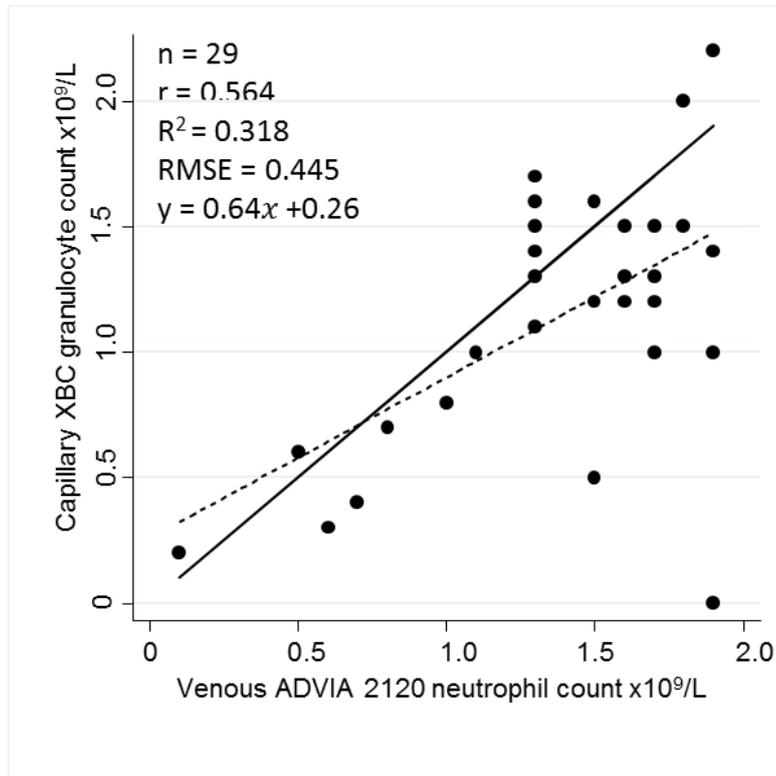
Appendix 3, Table 4: General comments volunteered at the end of the consultant questionnaire. FBC, full blood count. EWS, early warning score. GCSF, granulocyte colony stimulating factor. WBC, white blood cell count.

Appendix 4 - Summary of the performance analysis of the Philips XBC blood count analyser

Paired Philips XBC capillary granulocyte counts and standard of care Siemens ADVIA 2120 venous neutrophil counts were measured in patients attending the oncology outpatient department from November 2012 to July 2013.

There were 115 sets of blood samples collected where there was both a finger-prick granulocyte count measured on the XBC and a venous ADVIA 2120 neutrophil result. Of these, 29 sets had a standard of care Siemens ADVIA 2120 venous granulocyte count $<2.0 \times 10^9/L$. This range was used to encompass neutrophil counts around the threshold of $1.5 \times 10^9/L$, which is often used to denote safe delivery of chemotherapy, and also around the threshold of $1.0 \times 10^9/L$, which is used to change management in suspected febrile neutropenia.

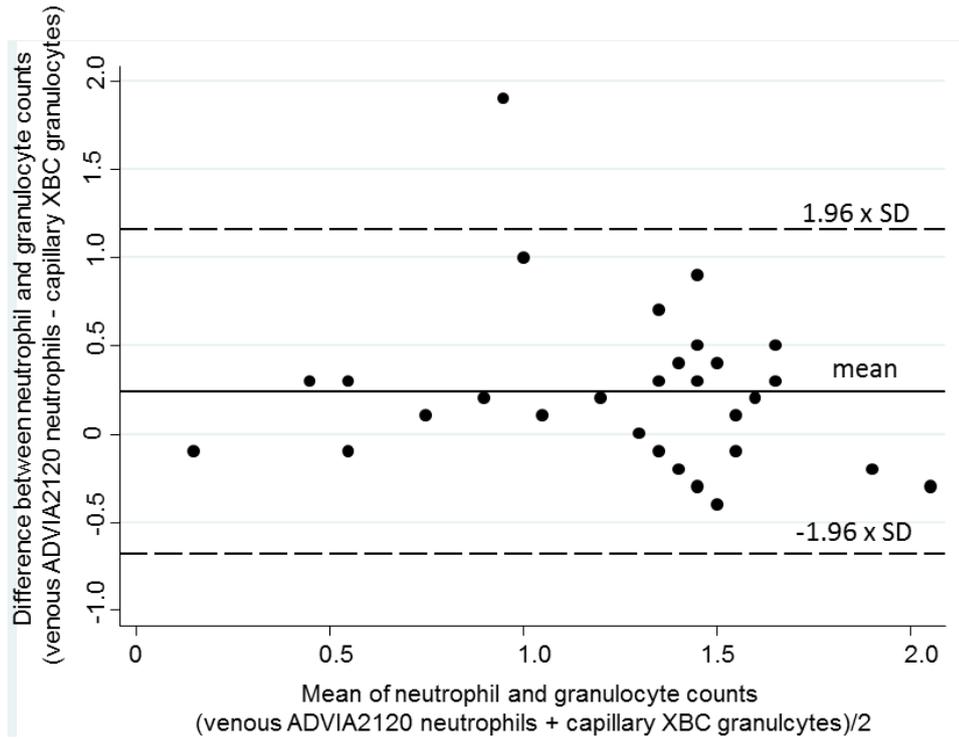
Correlation in the neutropenic range was, as expected, lower than across the full range of counts (neutrophils 0.1 to $2.0 \times 10^9/L$; $r = 0.564$, $p < 0.001$, neutrophils 0.1 to $19.6 \times 10^9/L$; $r = 0.975$, $p < 0.001$). The scatter plot of the neutropenic data is shown in Appendix 4, Figure 1 and the Bland-Altman plot is shown in Appendix 4, Figure 2. However, the performance of the device in identifying granulocyte counts either side of a neutrophil threshold of $1.5 \times 10^9/L$, was clinically acceptable using an XBC granulocyte count of $1.8 \times 10^9/L$. The statistical analysis of accuracy of incremental capillary granulocyte thresholds, measured using the XBC, at identifying venous ADVIA neutrophil counts $<1.5 \times 10^9/L$ is shown in Appendix 4, Table 1. This showed that a capillary XBC granulocyte count of $\geq 1.8 \times 10^9/L$, was the minimum granulocyte count with a clinically acceptable performance. Using this threshold, there were no false negatives, sensitivity was 100% (95% CI 75.3-100.0%) and negative predictive value was 100% (95% CI 95.6-100.0%). Appendix 4, Figure 3 shows the receiver operator characteristic curve of accuracy of the capillary XBC granulocyte count at identifying venous neutrophil counts.



Appendix 4, Figure 1: Scatter plot showing the relationship of venous ADVIA 2120 neutrophil counts and capillary XBC granulocyte counts in the extreme neutropenia range. Solid black line is $x = y$, dashed black line is line of best fit. RMSE, root mean square error.

Part of this unpublished analysis involved comparison of patient self-tested capillary granulocyte counts with nurse-obtained capillary granulocyte counts, both using the XBC device. There were 24 paired results across a reference venous ADVIA 2120 neutrophil count of 1.07 to 7.84 $\times 10^9/L$. Patient and nurse granulocyte results were more similar to each other than either were to the venous ADVIA 2120 neutrophil counts, but correlation was still poorer than expected, with nurse versus patient capillary XBC granulocyte counts giving an r value of 0.848, $p < 0.001$. The bias was not unidirectional, meaning neither nurse nor patient-generated granulocyte counts were consistently above or below the standard of care venous ADVIA 2120 measurements.

The main limitations of this work were that precision could not be analysed as there were no repeat tests on either the same patient or device, and the number of patients approached who declined the self-test was not recorded.



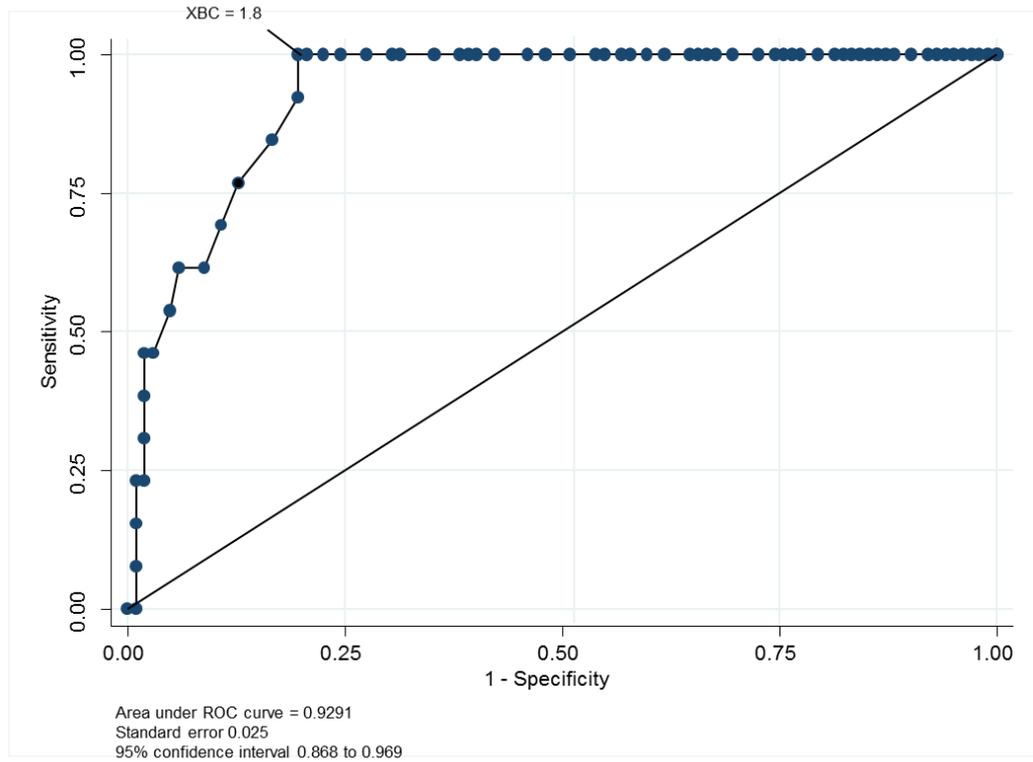
Appendix 4, Figure 2: Bland-Altman plot of venous ADVIA 2120 neutrophil counts and capillary XBC granulocyte counts in the extreme neutropenic range.

SD, standard deviation and is 0.47. The solid black line represents the mean difference and is 0.24. The black dashed lines labelled “1.96 SD” represent the upper and lower limits of agreement, which are the 95% CIs. The upper dashed line is 1.16 and the lower dashed line is -0.68. The single data point outside of the 95% CIs represented a venous ADVIA 2120 neutrophil count of $1.9 \times 10^9/L$ and a capillary XBC granulocyte count of $0.0 \times 10^9/L$.

XBC GRN cut-off (prevalence %)	Raw Data				Accuracy Analysis										
	A	B	C	D	Sensitivity (%)	95% CI		NPV (%)	95% CI		PPV (%)	95% CI		FNR	FPR
<2.0 (11.0)	1	2	7		100.00	75.3	100.0	100.0	95.4	100.0	36.1	20.8	53.8	0.00	22.5
	3	3	0	9		0	0	0	0	0	0	0	0		0
<1.9 (11.0)	1	2	8		100.00	75.3	100.0	100.0	95.5	100.0	38.2	22.2	56.4	0.00	20.5
	3	1	0	1		0	0	0	0	0	0	0	0		0
<1.8 (11.0)	1	2	8		100.00	75.3	100.0	100.0	95.6	100.0	39.4	22.9	57.9	0.00	19.6
	3	0	0	2		0	0	0	0	0	0	0	0		0
<1.7 (11.0)	1	2	8		92.30	64.0	99.80	98.80	93.5	100.0	37.5	21.1	56.3	7.69	19.6
	2	0	1	2		0	0	0	0	0	0	0	0		0
<1.6 (11.0)	1	1	8		84.60	54.6	98.10	97.70	91.9	99.70	39.3	21.5	59.4	15.3	16.6
	1	7	2	5		0	0	0	0	0	0	0	0		8
<1.5 (11.0)	1	1	8		76.90	46.2	95.00	96.70	90.8	99.30	43.5	23.2	65.5	23.0	12.7
	0	3	3	9		0	0	0	0	0	0	0	0		8

Appendix 4, Table 1: Statistical analysis of accuracy of using capillary XBC granulocyte thresholds to indicate venous ADVIA 2120 neutrophil count of $<1.5 \times 10^9/L$.

CI, confidence interval. NPV, negative predictive value. FNR, false negative rate. FPR, false positive rate. Please refer to the introduction for description of NPV, FNR, and FPR.



Appendix 4, Figure 3: Receiver operator characteristic (ROC) curve evaluating performance of the capillary XBC granulocyte count as a surrogate of venous ADVIA 2120 neutrophil count threshold of $<1.5 \times 10^9/L$.

The data point indicated to represent capillary XBC granulocyte count of $1.8 \times 10^9/L$ is the lowest threshold with no false negatives, with sensitivity of 100.0% and specificity is 80.0%.

References

1. Greer, J., Foerster, J., Rodgers, G., Paraskevas, F., Glader, B., Arber, D. and Means, R. *Wintrobe's Clinical Hematology*. Twelfth ed. Philadelphia: Lippincott Williams & Wilkins, 2009, p183-194.
2. Diamond, M.S. and Springer, T.A. A subpopulation of Mac-1 (CD11b/CD18) molecules mediates neutrophil adhesion to ICAM-1 and fibrinogen. *J Cell Biol.* 1993, **120**(2), pp.545-556.
3. Genco, R.J., Van Dyke, T.E., Levine, M.J., Nelson, R.D. and Wilson, M.E. 1985 Kreshover lecture. Molecular factors influencing neutrophil defects in periodontal disease. *J Dent Res.* 1986, **65**(12), pp.1379-1391.
4. Goldschmeding, R., van Dalen, C.M., Faber, N., Calafat, J., Huizinga, T.W., van der Schoot, C.E., Clement, L.T. and von dem Borne, A.E. Further characterization of the NB 1 antigen as a variably expressed 56-62 kD GPI-linked glycoprotein of plasma membranes and specific granules of neutrophils. *Br J Haematol.* 1992, **81**(3), pp.336-345.
5. Perry, S., Craddock, C.G., Jr. and Lawrence, J.S. Rates of appearance and disappearance of white blood cells in normal and in various disease states. *J Lab Clin Med.* 1958, **51**(4), pp.501-515.
6. Marsh, J.C., Boggs, D.R., Cartwright, G.E. and Wintrobe, M.M. Neutrophil kinetics in acute infection. *J Clin Invest.* 1967, **46**(12), pp.1943-1953.
7. Herbert, V. *Megaloblastic anemias: mechanisms and management*. Chicago: Year Book Medical Publishers, 1965.
8. Papayannopoulou, T. and Finch, C.A. On the in vivo action of erythropoietin: a quantitative analysis. *J Clin Invest.* 1972, **51**(5), pp.1179-1185.
9. Athens, J.W., Raab, S.O., Haab, O.P., Mauer, A.M., Ashenbrucker, H., Cartwright, G.E. and Wintrobe, M.M. Leukokinetic studies. III. The distribution of granulocytes in the blood of normal subjects. *J Clin Invest.* 1961, **40**, pp.159-164.
10. Price, T.H., Chatta, G.S. and Dale, D.C. Effect of recombinant granulocyte colony-stimulating factor on neutrophil kinetics in normal young and elderly humans. *Blood.* 1996, **88**(1), pp.335-340.
11. Boggs, D.R., Athens, J.W., Haab, O.P., Raab, S.O., Cartwright, G.E. and Wintrobe, M.M. Leukokinetic studies. VIII. A search for an extramedullary tissue pool of neutrophilic granulocytes. *Proc Soc Exp Biol Med.* 1964, **115**, pp.792-796.
12. Craddock, C.G., Jr., Perry, S., Venzke, L.E. and Lawrence, J.S. Evaluation of marrow granulocytic reserves in normal and disease states. *Blood.* 1960, **15**, pp.840-855.
13. Sompayrac, L. *How the immune system works*. 3rd ed. Blackwell Publishing, 2008, p17-24.
14. Wickremasinghe, R. and Hoffbrand, A. Biochemical and genetic control of apoptosis: relevance to normal hematopoiesis and hematological malignancies. *Blood.* 1999, **93**(11), pp.3587-3600.
15. Domen, J. The role of apoptosis in regulating hematopoiesis and hematopoietic stem cells. *Immunological Research.* 2000, **22**, pp.88-94.
16. Bodey, G.P., Buckley, M., Sathe, Y.S. and Freireich, E.J. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med.* 1966, **64**(2), pp.328-340.
17. National Cancer Institute (NCI). *Common Terminology criteria for Adverse Events (CTCAE) version 4.03*. NCI, 2010.

18. American Society of Clinical Oncology. Recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. *J Clin Oncol.* 1994, **12**(11), pp.2471-2508.
19. National Collaborating Centre for Cancer. Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients. Evidence review, search strategies, health economics, evidence review & health economics plan. [Online], National Institute for Health and Care Excellence, 2012. [Accessed 12th february 2015]. Available from: <https://www.nice.org.uk/guidance/cg151/documents/cg151-neutropenic-sepsis-evidence-review2>
20. Levy, M.M., Fink, M.P., Marshall, J.C., Abraham, E., Angus, D., Cook, D., Cohen, J., Opal, S.M., Vincent, J.L. and Ramsay, G. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med.* 2003, **31**(4), pp.1250-1256.
21. Dellinger, R.P., Levy, M.M., Rhodes, A., Annane, D., Gerlach, H., Opal, S.M., Sevransky, J.E., Sprung, C.L., Douglas, I.S., Jaeschke, R., Osborn, T.M., Nunnally, M.E., Townsend, S.R., Reinhart, K., Kleinpell, R.M., Angus, D.C., Deutschman, C.S., Machado, F.R., Rubenfeld, G.D., Webb, S.A., Beale, R.J., Vincent, J.L. and Moreno, R. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med.* 2013, **41**(2), pp.580-637.
22. Klastersky, J., Paesmans, M., Rubenstein, E.B., Boyer, M., Elting, L., Feld, R., Gallagher, J., Herrstedt, J., Rapoport, B., Rolston, K. and Talcott, J. The Multinational Association for Supportive Care in Cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol.* 2000, **18**(16), pp.3038-3051.
23. de Naurois, J., Novitzky-Basso, I., Gill, M.J., Marti, F.M., Cullen, M.H. and Roila, F. Management of febrile neutropenia: ESMO Clinical Practice Guidelines. *Ann Oncol.* 2010, **21 Suppl 5**, pp.v252-256.
24. Aapro, M.S., Bohlius, J., Cameron, D.A., Dal Lago, L., Donnelly, J.P., Kearney, N., Lyman, G.H., Pettengell, R., Tjan-Heijnen, V.C., Walewski, J., Weber, D.C. and Zielinski, C. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. *Eur J Cancer.* 2011, **47**(1), pp.8-32.
25. Crawford, J., Caserta, C. and Roila, F. Hematopoietic growth factors: ESMO Clinical Practice Guidelines for the applications. *Ann Oncol.* 2010, **21 Suppl 5**, pp.v248-251.
26. Freifeld, A.G., Bow, E.J., Sepkowitz, K.A., Boeckh, M.J., Ito, J.I., Mullen, C.A., Raad, II, Rolston, K.V., Young, J.A., Wingard, J.R. and Infectious Diseases Society of, A. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clin Infect Dis.* 2011, **52**(4), pp.e56-93.
27. Rosenberg, P.S., Alter, B.P., Bolyard, A.A., Bonilla, M.A., Boxer, L.A., Cham, B., Fier, C., Freedman, M., Kannourakis, G., Kinsey, S., Schwinzer, B., Zeidler, C., Welte, K. and Dale, D.C. The incidence of leukemia and mortality from sepsis in patients with severe congenital neutropenia receiving long-term G-CSF therapy. *Blood.* 2006, **107**(12), pp.4628-4635.
28. Baden, L.R., Bensinger, W., Angarone, M., Casper, C., Dubberke, E.R., Freifeld, A.G., Garzon, R., Greene, J.N., Greer, J.P., Ito, J.I., Karp, J.E., Kaul, D.R., King, E., Mackler, E., Marr, K.A., Montoya, J.G., Morris-Engemann, A., Pappas, P.G., Rolston, K., Segal, B., Seo, S.K., Swaminathan, S., Naganuma, M. and Shead, D.A. Prevention and treatment of cancer-related infections. *J Natl Compr Canc Netw.* 2012, **10**(11), pp.1412-1445.
29. Schimpff, S.C. Empiric antibiotic therapy for granulocytopenic cancer patients. *Am J Med.* 1986, **80**(5C), pp.13-20.

30. Flowers, C.R., Seidenfeld, J., Bow, E.J., Karten, C., Gleason, C., Hawley, D.K., Kuderer, N.M., Langston, A.A., Marr, K.A., Rolston, K.V. and Ramsey, S.D. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2013, **31**(6), pp.794-810.
31. Bodey, G.P., Rodriguez, V., Chang, H.Y. and Narboni. Fever and infection in leukemic patients: a study of 494 consecutive patients. *Cancer*. 1978, **41**(4), pp.1610-1622.
32. Cancer Incidence Statistics. London: Cancer Research UK, 2017. [Accessed 26th September 2017]. Available from: <http://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence#heading-Zero>
33. Menzies, A.M., Haydu, L.E., Visintin, L., Carlino, M.S., Howle, J.R., Thompson, J.F., Kefford, R.F., Scolyer, R.A. and Long, G.V. Distinguishing clinicopathologic features of patients with V600E and V600K BRAF-mutant metastatic melanoma. *Clin Cancer Res*. 2012, **18**(12), pp.3242-3249.
34. Fong, P.C., Boss, D.S., Yap, T.A., Tutt, A., Wu, P., Mergui-Roelvink, M., Mortimer, P., Swaisland, H., Lau, A., O'Connor, M.J., Ashworth, A., Carmichael, J., Kaye, S.B., Schellens, J.H.M. and de Bono, J.S. Inhibition of Poly(ADP-Ribose) Polymerase in Tumors from BRCA Mutation Carriers. *New England Journal of Medicine*. 2009, **361**(2), pp.123-134.
35. Pfizer Limited. Sutent Summary of Product Characteristics. [Online]. 2017. [Accessed 26th September 2017]. Available from: <https://www.medicines.org.uk/emc/medicine/18531>
36. Dale, D.C., McCarter, G.C., Crawford, J. and Lyman, G.H. Myelotoxicity and dose intensity of chemotherapy: reporting practices from randomized clinical trials. *J Natl Compr Canc Netw*. 2003, **1**(3), pp.440-454.
37. Lyman, G.H., Kuderer, N.M., Crawford, J., Wolff, D.A., Culakova, E., Poniewierski, M.S. and Dale, D.C. Predicting individual risk of neutropenic complications in patients receiving cancer chemotherapy. *Cancer*. 2011, **117**(9), pp.1917-1927.
38. Shayne, M., Culakova, E., Poniewierski, M.S., Wolff, D., Dale, D.C., Crawford, J. and Lyman, G.H. Dose intensity and hematologic toxicity in older cancer patients receiving systemic chemotherapy. *Cancer*. 2007, **110**(7), pp.1611-1620.
39. Balducci, L., Hardy, C.L. and Lyman, G.H. Hematopoietic growth factors in the older cancer patient. *Curr Opin Hematol*. 2001, **8**(3), pp.170-187.
40. Lyman, G.H., Dale, D.C. and Crawford, J. Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: a nationwide study of community practices. *J Clin Oncol*. 2003, **21**(24), pp.4524-4531.
41. Lyman, G.H., Dale, D.C., Friedberg, J., Crawford, J. and Fisher, R.I. Incidence and predictors of low chemotherapy dose-intensity in aggressive non-Hodgkin's lymphoma: a nationwide study. *J Clin Oncol*. 2004, **22**(21), pp.4302-4311.
42. Shayne, M., Crawford, J., Dale, D.C., Culakova, E. and Lyman, G.H. Predictors of reduced dose intensity in patients with early-stage breast cancer receiving adjuvant chemotherapy. *Breast Cancer Res Treat*. 2006, **100**(3), pp.255-262.
43. Lyman, G.H., Morrison, V.A., Dale, D.C., Crawford, J., Delgado, D.J. and Fridman, M. Risk of febrile neutropenia among patients with intermediate-grade non-Hodgkin's lymphoma receiving CHOP chemotherapy. *Leuk Lymphoma*. 2003, **44**(12), pp.2069-2076.
44. Lyman, G.H. Impact of chemotherapy dose intensity on cancer patient outcomes. *J Natl Compr Canc Netw*. 2009, **7**(1), pp.99-108.
45. Crawford, J., Dale, D.C., Kuderer, N.M., Culakova, E., Poniewierski, M.S., Wolff, D. and Lyman, G.H. Risk and timing of neutropenic events in adult cancer patients receiving

- chemotherapy: the results of a prospective nationwide study of oncology practice. *J Natl Compr Canc Netw*. 2008, **6**(2), pp.109-118.
46. Lyman, G., Lyman, C. and Agboola, O. Risk models for predicting chemotherapy-induced neutropenia. *Oncologist*. 2005, **10**(6), pp.427-437.
 47. Kuderer, N.M., Dale, D.C., Crawford, J., Cosler, L.E. and Lyman, G.H. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. *Cancer*. 2006, **106**(10), pp.2258-2266.
 48. Qureshi, A., Adil, M., Zacharatos, H. and Suri, F. Factors associated with length of hospitalization in patients admitted with transient ischemic attack in United States. *Stroke*. 2013, **44**, pp.1601-1605.
 49. Oakley, C., Hill, A. and Chowdhury, S. Benefits of a network approach to managing neutropenic sepsis. *Cancer Nursing Practice*. 2010, **9**(5), pp.17-21.
 50. Lucas, K.G., Brown, A.E., Armstrong, D., Chapman, D. and Heller, G. The identification of febrile, neutropenic children with neoplastic disease at low risk for bacteremia and complications of sepsis. *Cancer*. 1996, **77**(4), pp.791-798.
 51. Kuderer, N.M., Dale, D.C., Crawford, J., Cosler, L.E. and Lyman, G.H. Mortality, morbidity and cost associated with febrile neutropaenia in adult cancer patients. *Cancer*. 2006, **106**, pp.2258-2266.
 52. Courtney, D.M., Aldeen, A.Z., Gorman, S.M. and al, e. Cancer-associated neutropaenic fever: clinical outcome and economic costs of emergency department care. *Oncologist*. 2007, **12**, pp.1019-1026.
 53. Hughes, W., Armstrong, D., Bodey, G., Bow, E., Brown, A., Calandra, T., Feld, R., Pizzo, P., Rolston, K., Shenep, J. and Young, L. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis*. 2002, **34**(6), pp.730-751.
 54. Cameron, D. Management of chemotherapy-associated febrile neutropaenia. *British Journal of Cancer*. 2009, **101**(Suppl 1), pp.S18-22.
 55. Padilla, G. and Ropka, M. Quality of life and chemotherapy-induced neutropaenia. *Canc Nurs*. 2005, **28**, pp.167-171.
 56. Wagner, L.I., Beaumont, J.L., Ding, B., Malin, J., Peterman, A., Calhoun, E. and Cella, D. Measuring health-related quality of life and neutropenia-specific concerns among older adults undergoing chemotherapy: validation of the Functional Assessment of Cancer Therapy-Neutropenia (FACT-N). *Support Care Cancer*. 2008, **16**(1), pp.47-56.
 57. Krell, D. and Jones, A. Impact of effective prevention and management of febrile neutropenia. *British Journal of Cancer*. 2009, **101**((Suppl 1)), pp.S23-26.
 58. Hirsch, B.R. and Lyman, G.H. Pharmacoeconomics of the myeloid growth factors: a critical and systematic review. *Pharmacoeconomics*. 2012, **30**(6), pp.497-511.
 59. Budman, D.R., Berry, D.A., Cirincione, C.T., Henderson, I.C., Wood, W.C., Weiss, R.B., Ferree, C.R., Muss, H.B., Green, M.R., Norton, L. and Frei, E., 3rd. Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. The Cancer and Leukemia Group B. *J Natl Cancer Inst*. 1998, **90**(16), pp.1205-1211.
 60. Gabilove, J.L., Jakubowski, A., Scher, H., Sternberg, C., Wong, G., Grous, J., Yagoda, A., Fain, K., Moore, M.A., Clarkson, B. and et al. Effect of granulocyte colony-stimulating factor on neutropenia and associated morbidity due to chemotherapy for transitional-cell carcinoma of the urothelium. *N Engl J Med*. 1988, **318**(22), pp.1414-1422.
 61. Morstyn, G., Campbell, L., Lieschke, G., Layton, J.E., Maher, D., O'Connor, M., Green, M., Sheridan, W., Vincent, M., Alton, K. and et al. Treatment of chemotherapy-induced neutropenia by subcutaneously administered granulocyte colony-stimulating factor with optimization of dose and duration of therapy. *J Clin Oncol*. 1989, **7**(10), pp.1554-1562.
 62. Crawford, J., Ozer, H., Stoller, R., Johnson, D., Lyman, G., Tabbara, I., Kris, M., Grous, J., Picozzi, V., Rausch, G. and et al. Reduction by granulocyte colony-stimulating factor

- of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. *N Engl J Med.* 1991, **325**(3), pp.164-170.
63. Trillet-Lenoir, V., Green, J., Manegold, C., Von Pawel, J., Gatzemeier, U., Lebeau, B., Depierre, A., Johnson, P., Decoster, G., Tomita, D. and et al. Recombinant granulocyte colony stimulating factor reduces the infectious complications of cytotoxic chemotherapy. *Eur J Cancer.* 1993, **29A**(3), pp.319-324.
 64. Welte, K., Gabrilove, J., Bronchud, M.H., Platzter, E. and Morstyn, G. Filgrastim (r-metHuG-CSF): the first 10 years. *Blood.* 1996, **88**(6), pp.1907-1929.
 65. Vogel, C.L., Wojtukiewicz, M.Z., Carroll, R.R., Tjulandin, S.A., Barajas-Figueroa, L.J., Wiens, B.L., Neumann, T.A. and Schwartzberg, L.S. First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: a multicenter, double-blind, placebo-controlled phase III study. *J Clin Oncol.* 2005, **23**(6), pp.1178-1184.
 66. Timmer-Bonte, J.N., de Boo, T.M., Smit, H.J., Biesma, B., Wilschut, F.A., Cheragwandi, S.A., Termeer, A., Hensing, C.A., Akkermans, J., Adang, E.M., Bootsma, G.P. and Tjan-Heijnen, V.C. Prevention of chemotherapy-induced febrile neutropenia by prophylactic antibiotics plus or minus granulocyte colony-stimulating factor in small-cell lung cancer: a Dutch Randomized Phase III Study. *J Clin Oncol.* 2005, **23**(31), pp.7974-7984.
 67. Kuderer, N.M., Dale, D.C., Crawford, J. and Lyman, G.H. Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. *J Clin Oncol.* 2007, **25**(21), pp.3158-3167.
 68. Holmes, F., Jones, S., O'Shaughnessy, J., Vukelja, S., George, T., Savin M, Richards, D., Glaspy, J., Meza, L., Cohen, G., Dhami, M., Budman, D., Hackett, J., Brassard, M., Yang, B. and Liang, B. Comparable efficacy and safety profiles of once-per-cycle pegfilgrastim and daily injection filgrastim in chemotherapy-induced neutropenia: a multicenter dose-finding study in women with breast cancer. *Annals of Oncology.* 2002, **13**(6), pp.903-909.
 69. Lyman, G.H., Kuderer, N.M., Greene, J.N. and Balducci, L. The economics of febrile neutropenia: implications for the use of colony-stimulating factors. *European Journal of Cancer.* 1998, **34**(12), pp.1857-1864.
 70. Timmer-Bonte, J.N., Adang, E.M., Smit, H.J., Biesma, B., Wilschut, F.A., Bootsma, G.P., de Boo, T.M. and Tjan-Heijnen, V.C. Cost-effectiveness of adding granulocyte colony-stimulating factor to primary prophylaxis with antibiotics in small-cell lung cancer. *J Clin Oncol.* 2006, **24**(19), pp.2991-2997.
 71. Lyman, G. and Kuderer, N. The economics of the colony-stimulating factors in the prevention and treatment of febrile neutropenia. *Critical Reviews in Oncology/Haematology.* 2004, **50**, pp.129-146.
 72. Leibovici, L., Paul, M., Cullen, M., Bucaneve, G., Gafter-Gvili, A., Fraser, A. and Kern, W.V. Antibiotic prophylaxis in neutropenic patients: new evidence, practical decisions. *Cancer.* 2006, **107**(8), pp.1743-1751.
 73. Cullen, M., Steven, N., Billingham, L., Gaunt, C., Hastings, M., Simmonds, P., Stuart, N., Rea, D., Bower, M., Fernando, I., Huddart, R., Gollins, S. and Stanley, A. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. *N Engl J Med.* 2005, **353**(10), pp.988-998.
 74. Cullen, M.H., Billingham, L.J., Gaunt, C.H. and Steven, N.M. Rational selection of patients for antibacterial prophylaxis after chemotherapy. *J Clin Oncol.* 2007, **25**(30), pp.4821-4828.
 75. Gafter-Gvili, A., Fraser, A., Paul, M., Vidal, L., Lawrie, T.A., van de Wetering, M.D., Kremer, L.C. and Leibovici, L. Antibiotic prophylaxis for bacterial infections in afebrile

- neutropenic patients following chemotherapy. *Cochrane Database Syst Rev.* 2012, **1**, p.CD004386.
76. Heneghan, C., Ward, A., Perera, R., Bankhead, C., Fuller, A., Stevens, R., Bradford, K., Tyndel, S., Alonso-Coello, P., Ansell, J., Beyth, R., Bernardo, A., Christensen, T.D., Cromheecke, M.E., Edson, R.G., Fitzmaurice, D., Gadisseur, A.P., Garcia-Alamino, J.M., Gardiner, C., Hasenkam, J.M., Jacobson, A., Kaatz, S., Kamali, F., Khan, T.I., Knight, E., Kortke, H., Levi, M., Matchar, D., Menendez-Jandula, B., Rakovac, I., Schaefer, C., Siebenhofer, A., Souto, J.C., Sunderji, R., Gin, K., Shalansky, K., Voller, H., Wagner, O. and Zittermann, A. Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data. *Lancet.* 2012, **379**(9813), pp.322-334.
 77. Bossuyt, P. Quis Custodiet? Evaluating the evaluations of medical tests. *The Pathologist.* 2016, (#0816). Available at: <https://thepathologist.com/outside-the-lab/quis-custodiet>
 78. ISO POCT Standard: Point of Care Testing (POCT) – Requirements for quality and competence Geneva: International Standards Organisation (ISO), 2006.
 79. Management and use of IVD point of care devices. London, Medicines and Healthcare products Regulatory Agency (MHRA), 2010.
 80. England, J., Hyde, K., Lewis, S., Mackie, I., Rowan, R., Bain, B., Matutes, E., Murphy, M., Reilly, J., Shinton, K., Stephens, A., Wood, J., Colvin, B., Machin, S., Baglin, T., Barrowcliffe, T., Greaves, M., Ludlam, C., Preston, F., Rose, P., Walker, I. and Wood, J. Guide-lines for near patient testing: haematology. Near Patient Testing Working Party. General Haematology Task Force of BCSH. Thrombosis and Haemostasis Task Force of BCSH. *Int J Lab Hematol.* 1995, **17**(4), pp.301-310.
 81. Briggs, C., Carter, J., Lee, S., Sandhaus, L., Simon-Lopez, R. and Vives-Corrans, J. ICSH Guideline for worldwide point-of-care testing in haematology with special reference to the complete blood count *Int J Lab Hematol.* 2008, **30**(2), pp.105-116.
 82. Reference leukocyte (WBC) differential count (proportional) and evaluation of instrumental methods; Approved standard. Wayne: Clinical and Laboratory Standards Institute, 2007.
 83. Ross, D. and McMaster, K. Neutropenia: the accuracy and precision of the neutrophil count in leukopenic patients. *Cytometry.* 1983, **3**, pp.287-291.
 84. Hubl, W., Wolfbauer, G., Andert, S., Thum, G., Streicher, J., Hubner, C., Lapin, A. and Bayer, P. Toward a new reference method for the leukocyte five-part differential. *Cytometry.* 1997, **30**, pp.72-84.
 85. Amundsen, E.K., Urdal, P., Hagve, T.A., Holthe, M.R. and Henriksson, C.E. Absolute neutrophil counts from automated hematology instruments are accurate and precise even at very low levels. *Am J Clin Pathol.* 2012, **137**(6), pp.862-869.
 86. Harris, N., Jou, J.M., Devoto, G., Lotz, J., Pappas, J., Wranovics, D., Wilkinson, M., Fletcher, S.R. and Kratz, A. Performance evaluation of the ADVIA 2120 hematology analyzer: an international multicenter clinical trial. *Laboratory hematology : official publication of the International Society for Laboratory Hematology.* 2005, **11**(1), p.62.
 87. Horizon Scan report 0011, Diagnostic technology: Point-of-care test for total white blood cell count. Oxford: Primary Care Diagnostic Horizon Scanning Centre, 2010. Available from <https://www.oxford.dec.nihr.ac.uk/reports-and-resources/horizon-scanning-reports/horizon-scan-reports-non-dec-funded>
 88. Oakley C, Chambers P, Board R, Gallagher C, Young E, Purcell S, Mansi J. Good Practice Guideline: Promoting Early Identification of Systemic Anti-Cancer Therapies Side Effects:- Two approaches. London: National Chemotherapy Board, 2016.
 89. Cameron, D.A., Massie, C., Kerr, G. and Leonard, R.C. Moderate neutropenia with adjuvant CMF confers improved survival in early breast cancer. *Br J Cancer.* 2003, **89**(10), pp.1837-1842.

90. Mayers, C., Panzarella, T. and Tannock, I.F. Analysis of the prognostic effects of inclusion in a clinical trial and of myelosuppression on survival after adjuvant chemotherapy for breast carcinoma. *Cancer*. 2001, **91**(12), pp.2246-2257.
91. Poikonen, P., Saarto, T., Lundin, J., Joensuu, H. and Blomqvist, C. Leucocyte nadir as a marker for chemotherapy efficacy in node-positive breast cancer treated with adjuvant CMF. *Br J Cancer*. 1999, **80**(11), pp.1763-1766.
92. Saarto, T., Blomqvist, C., Rissanen, P., Auvinen, A. and Elomaa, I. Haematological toxicity: a marker of adjuvant chemotherapy efficacy in stage II and III breast cancer. *Br J Cancer*. 1997, **75**(2), pp.301-305.
93. Di Maio, M., Gridelli, C., Gallo, C., Shepherd, F., Piantedosi, F.V., Cigolari, S., Manzione, L., Illiano, A., Barbera, S., Robbiati, S.F., Frontini, L., Piazza, E., Ianniello, G.P., Veltri, E., Castiglione, F., Rosetti, F., Gebbia, V., Seymour, L., Chiodini, P. and Perrone, F. Chemotherapy-induced neutropenia and treatment efficacy in advanced non-small-cell lung cancer: a pooled analysis of three randomised trials. *Lancet Oncol*. 2005, **6**(9), pp.669-677.
94. Bergh, J., Wiklund, T., Erikstein, B., Lidbrink, E., Lindman, H., Malmström, P., Kellokumpu-Lehtinen, P., Bengtsson, N.-O., Söderlund, G., Anker, G., Wist, E., Ottosson, S., Salminen, E., Ljungman, P., Holte, H., Nilsson, J., Blomqvist, C. and Wilking, N. Tailored fluorouracil, epirubicin, and cyclophosphamide compared with marrow-supported high-dose chemotherapy as adjuvant treatment for high-risk breast cancer: a randomised trial. *The Lancet*. 2000, **356**, pp.1384-1391.
95. National Confidential Enquiry into Patient Outcome & Death (NCEPOD). For better, for worse? A review of the care of patients who died within 30 days of receiving systemic anti-cancer therapy. NCEPOD: London, 2008.
96. National Chemotherapy Advisory Group (NCAG). Chemotherapy Services in England: Ensuring quality and safety. NCAG: London, 2009.
97. Kinsman, L., Rotter, T., James, E., Snow, P. and Willis, J. What is a clinical pathway? Development of a definition to inform the debate. *BMC medicine*. 2010, **8**(1), p.1.
98. Rotter, T., Kinsman, L., James, E., Machotta, A., Willis, J., Snow, P. and Kugler, J. The effects of clinical pathways on professional practice, patient outcomes, length of stay, and hospital costs: Cochrane systematic review and meta-analysis. *Evaluation & the health professions*. 2011, p.0163278711407313.
99. Rotter, T., Kinsman, L., James, E., Machotta, A. and Steyerberg, E.W. The quality of the evidence base for clinical pathway effectiveness: Room for improvement in the design of evaluation trials. *BMC medical research methodology*. 2012, **12**(1), p.1.
100. Yu, P., Artz, D. and Warner, J. Electronic health records (EHRs): supporting ASCO's vision of cancer care. *Am Soc Clin Oncol Educ Book*. 2014, pp.225-231.
101. Agarwal, P. and Owzar, K. Next generation distributed computing for cancer research. *Cancer Inform*. 2014, **13**(Suppl 7), pp.97-109.
102. Van Der Aalst, W. Process mining: discovery, conformance and enhancement of business processes. 1st ed. Berlin: Springer-Verlag, 2011, p7-11.
103. Rojas, A. and Munoz-Gama, J. Process mining in healthcare: A literature review *Journal of Biomedical Informatics*. 2016, **61**, pp.224-236.
104. Kurniati, A., Johnson, O., Hogg, D. and Hall, G. Process mining in oncology: A literature review In: 6th International conference on information communication and management (ICICM), 2016, pp.291-297.
105. Bettencourt-Silva, J.H., Clark, J., Cooper, C.S., Mills, R., Rayward-Smith, V.J. and de la Iglesia, B. Building Data-Driven Pathways From Routinely Collected Hospital Data: A Case Study on Prostate Cancer. *JMIR Med Inform*. 2015, **3**(3), p.e26.

106. Caron, F., Vanthienen, J., Vanhaecht, K., Van Limbergen, E., De Weerd, J. and Baesens, B. Monitoring care processes in the gynecologic oncology department. *Comput Biol Med.* 2014, **44**, pp.88-96.
107. Bowman, S. Impact of electronic health record systems on information integrity: quality and safety implications. *Perspect Health Inf Manag.* 2013, **10**(1c).
108. Weiskopf, N. and Weng, C. Methods and dimensions of electronic health record data quality assessment: enabling reuse for clinical research. *J Am Med Inform Assoc.* 2013, **20**, pp.144-151.
109. National Cancer Intelligence Network. Cancer Outcomes and Services dataset (COSD). London: Public Health England, 2015. [Accessed 14th July 2016]. Available from: http://www.ncin.org.uk/collecting_and_using_data/data_collection/cosd
110. Sonnenberg, F.A. and Beck, J.R. Markov models in medical decision making: a practical guide. *Med Decis Making.* 1993, **13**(4), pp.322-338.
111. Briggs, A. and Sculpher, M. An introduction to Markov modelling for economic evaluation. *Pharmacoeconomics.* 1998, **13**(4), pp.397-409.
112. Bourne, M. and P, B. Successful change management in a week. London: Hodder & Stoughton, 2002, p29.
113. Chemocare software. Belfast: Clinisys, 2013.
114. MOSAIQ Radiation Oncology software. Stockholm, 2016.
115. Baker, K., Dunwoodie, E., Jones, R.G., Newsham, A., Johnson, O., Price, C.P., Wolstenholme, J., Leal, J., McGinley, P., Twelves, C. and Hall, G. Process mining routinely collected electronic health records to define real-life clinical pathways during chemotherapy. *International Journal of Medical Informatics.* 2017, **103**, pp.32-41.
116. Dingsøyr, T., Nerur, S., Balijepally, V. and Moe, N.B. A decade of agile methodologies: Towards explaining agile software development. *Journal of Systems and Software.* 2012, **85**(6), pp.1213-1221.
117. DeVita Junior, V., Lawrence, T. and Rosenberg, S. DeVita, Hellman, and Rosenberg's Cancer. 10th ed. Wolters Kluwer Health, 2015.
118. Caldicott, F. Review of data security, consent and opt-outs. London: National Data Guardian, 2016.
119. Shulman, L.N., Cirrincione, C.T., Berry, D.A., Becker, H.P., Perez, E.A., O'Regan, R., Martino, S., Atkins, J.N., Mayer, E., Schneider, C.J., Kimmick, G., Norton, L., Muss, H., Winer, E.P. and Hudis, C. Six cycles of doxorubicin and cyclophosphamide or Paclitaxel are not superior to four cycles as adjuvant chemotherapy for breast cancer in women with zero to three positive axillary nodes: Cancer and Leukemia Group B 40101. *J Clin Oncol.* 2012, **30**(33), pp.4071-4076.
120. Citron, M.L., Berry, D.A., Cirrincione, C., Hudis, C., Winer, E.P., Gradishar, W.J., Davidson, N.E., Martino, S., Livingston, R., Ingle, J.N., Perez, E.A., Carpenter, J., Hurd, D., Holland, J.F., Smith, B.L., Sartor, C.I., Leung, E.H., Abrams, J., Schilsky, R.L., Muss, H.B. and Norton, L. 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. *J Clin Oncol.* 2003, **21**(8), pp.1431-1439.
121. Burtneß, B., Goldwasser, M.A., Flood, W., Mattar, B., Forastiere, A.A. and Eastern Cooperative Oncology, G. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. *J Clin Oncol.* 2005, **23**(34), pp.8646-8654.

122. Jacobs, C., Lyman, G., Velez-Garcia, E., Sridhar, K., Knight, W., Hochster, H., Goodnough, L., Mortimer, J., Einhorn, L., Schacter, L., Cherng, N., Dalton, T., Burroughs, J. and Rozenzweig, M. A Phase III Randomized Study Comparing Cisplatin and Fluorouracil as Single Agents and in Combination for Advanced Squamous Cell Carcinoma of the Head and Neck. *Journal of Clinical Oncology*. 1992, **10**, pp.257-263.
123. de Wit, R., Skoneczna, I., Daugaard, G., De Santis, M., Garin, A., Aass, N., Witjes, A.J., Albers, P., White, J.D., Germa-Lluch, J.R., Marreaud, S. and Collette, L. Randomized phase III study comparing paclitaxel-bleomycin, etoposide, and cisplatin (BEP) to standard BEP in intermediate-prognosis germ-cell cancer: intergroup study EORTC 30983. *J Clin Oncol*. 2012, **30**(8), pp.792-799.
124. Culine, S., Kerbrat, P., Kramar, A., Theodore, C., Chevreau, C., Geoffrois, L., Bui, N., Peny, J., Caty, A., Delva, R., Biron, P., Fizazi, K., Bouzy, J. and Droz, J. Refining the optimal chemotherapy regimen for good-risk metastatic nonseminomatous germ-cell tumors: a randomized trial of the Genito-Urinary Group of the French Federation of Cancer Centers (GETUG T93BP). *Annals of Oncology*. 2007, **18**, pp.917-924.
125. Schmittel, A., Sebastian, M., Fischer von Weikersthal, L., Martus, P., Gauler, T.C., Kaufmann, C., Hortig, P., Fischer, J.R., Link, H., Binder, D., Fischer, B., Caca, K., Eberhardt, W.E., Keilholz, U. and Arbeitsgemeinschaft Internistische Onkologie Thoracic Oncology Study, G. A German multicenter, randomized phase III trial comparing irinotecan-carboplatin with etoposide-carboplatin as first-line therapy for extensive-disease small-cell lung cancer. *Ann Oncol*. 2011, **22**(8), pp.1798-1804.
126. Socinski, M.A., Smit, E.F., Lorigan, P., Konduri, K., Reck, M., Szczesna, A., Blakely, J., Serwatowski, P., Karaseva, N.A., Ciuleanu, T., Jassem, J., Dediu, M., Hong, S., Visseren-Grul, C., Hanauske, A.R., Obasaju, C.K., Guba, S.C. and Thatcher, N. Phase III study of pemetrexed plus carboplatin compared with etoposide plus carboplatin in chemotherapy-naïve patients with extensive-stage small-cell lung cancer. *J Clin Oncol*. 2009, **27**(28), pp.4787-4792.
127. Allegra, C.J., Yothers, G., O'Connell, M.J., Sharif, S., Colangelo, L.H., Lopa, S.H., Petrelli, N.J., Goldberg, R.M., Atkins, J.N., Seay, T.E., Fehrenbacher, L., O'Reilly, S., Chu, L., Azar, C.A. and Wolmark, N. Initial safety report of NSABP C-08: A randomized phase III study of modified FOLFOX6 with or without bevacizumab for the adjuvant treatment of patients with stage II or III colon cancer. *J Clin Oncol*. 2009, **27**(20), pp.3385-3390.
128. de Gramont, A., Figuer, A., Seymour, M., Homerin, M., Hmissi, A., Cassidy, J., Boni, C., Cortes-Funes, H., Cervantes, A., Freyer, G., Papamichael, D., Le Bail, N., Louvet, C., Hendlér, D., de Braud, F., Wilson, C., Morvan, F. and Bonetti, A. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol*. 2000, **18**(16), pp.2938-2947.
129. du Bois, A. A Randomized Clinical Trial of Cisplatin/Paclitaxel Versus Carboplatin/Paclitaxel as First-Line Treatment of Ovarian Cancer. *CancerSpectrum Knowledge Environment*. 2003, **95**(17), pp.1320-1329.
130. Pujade-Lauraine, E., Wagner, U., Aavall-Lundqvist, E., GebSKI, V., Heywood, M., Vasey, P.A., Volgger, B., Vergote, I., Pignata, S., Ferrero, A., Sehouli, J., Lortholary, A., Kristensen, G., Jackisch, C., Joly, F., Brown, C., Le Fur, N. and du Bois, A. Pegylated liposomal Doxorubicin and Carboplatin compared with Paclitaxel and Carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. *J Clin Oncol*. 2010, **28**(20), pp.3323-3329.
131. O'Shaughnessy, J., Miles, D., Vukelja, S., Moiseyenko, V., Ayoub, J.P., Cervantes, G., Fumoleau, P., Jones, S., Lui, W.Y., Mauriac, L., Twelves, C., Van Hazel, G., Verma, S. and Leonard, R. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol*. 2002, **20**(12), pp.2812-2823.

132. Harvey, V., Mouridsen, H., Semiglazov, V., Jakobsen, E., Voznyi, E., Robinson, B.A., Groult, V., Murawsky, M. and Cold, S. Phase III trial comparing three doses of docetaxel for second-line treatment of advanced breast cancer. *J Clin Oncol.* 2006, **24**(31), pp.4963-4970.
133. Cunningham, D., Starling, N., Rao, S., Iveson, T., Nicolson, M., Coxon, F., Middleton, G., Daniel, F., Oates, J. and Norman, A. Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer. *N Engl J Med.* 2008, **358**, pp.36-46.
134. Wang, Y., Zhuang, R., Yu, Y., Yu, S., Hou, J., Ji, Y., Sun, Y., Shen, K., Shen, Z., Liu, F., Zhao, N. and Liu, T. Efficacy of preoperative chemotherapy regimens in patients with initially unresectable locally advanced gastric adenocarcinoma: capecitabine and oxaliplatin (XELOX) or with epirubicin (EOX). *Oncotarget.* 2016, **7**(46).
135. Gronberg, B.H., Bremnes, R.M., Flotten, O., Amundsen, T., Brunsvig, P.F., Hjelde, H.H., Kaasa, S., von Plessen, C., Stornes, F., Tollali, T., Wammer, F., Aasebo, U. and Sundstrom, S. Phase III study by the Norwegian lung cancer study group: pemetrexed plus carboplatin compared with gemcitabine plus carboplatin as first-line chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol.* 2009, **27**(19), pp.3217-3224.
136. Kosmidis, P.A., Kalofonos, H.P., Christodoulou, C., Syrigos, K., Makatsoris, T., Skarlos, D., Bakogiannis, C., Nicolaidis, C., Bafaloukos, D., Bamias, A., Samantas, E., Xiros, N., Boukovinas, I., Fountzilas, G. and Dimopoulos, M.A. Paclitaxel and gemcitabine versus carboplatin and gemcitabine in patients with advanced non-small-cell lung cancer. A phase III study of the Hellenic Cooperative Oncology Group. *Ann Oncol.* 2008, **19**(1), pp.115-122.
137. Lara, P.N., Jr., Natale, R., Crowley, J., Lenz, H.J., Redman, M.W., Carleton, J.E., Jett, J., Langer, C.J., Kuebler, J.P., Dakhil, S.R., Chansky, K. and Gandara, D.R. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. *J Clin Oncol.* 2009, **27**(15), pp.2530-2535.
138. Eckardt, J.R., von Pawel, J., Papai, Z., Tomova, A., Tzekova, V., Crofts, T.E., Brannon, S., Wissel, P. and Ross, G. Open-label, multicenter, randomized, phase III study comparing oral topotecan/cisplatin versus etoposide/cisplatin as treatment for chemotherapy-naive patients with extensive-disease small-cell lung cancer. *J Clin Oncol.* 2006, **24**(13), pp.2044-2051.
139. Cesne, A., Judson, I., Crowther, D., Rodenhuis, S., Keizer, H., Van Hoesel, Q., Blay, J., Frisch, J., Van Glabbeke, M.M., Hermans, C., Van Oosterom, A., Tursz, T. and Verweij, J. Randomized Phase III Study Comparing Conventional-Dose Doxorubicin Plus Ifosfamide Versus High-Dose Doxorubicin Plus Ifosfamide Plus Recombinant Human Granulocyte-Macrophage Colony-Stimulating Factor in Advanced Soft Tissue Sarcomas: Trial of the European Organization for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group. *Journal of Clinical Oncology.* 2000, **18**(14), pp.2676-2684.
140. Judson, I., Verweij, J., Gelderblom, H., Hartmann, J.T., Schöffski, P., Blay, J.-Y., Kerst, J.M., Sufliarsky, J., Whelan, J., Hohenberger, P., Krarup-Hansen, A., Alcindor, T., Marreaud, S., Litière, S., Hermans, C., Fisher, C., Hogendoorn, P.C.W., dei Tos, A.P. and van der Graaf, W.T.A. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. *The lancet oncology.* 2014, **15**(4), pp.415-423.
141. Lorigan, P., Verweij, J., Papai, Z., Rodenhuis, S., Le Cesne, A., Leahy, M.G., Radford, J.A., Van Glabbeke, M.M., Kirkpatrick, A., Hogendoorn, P.C., Blay, J.Y., European Organisation for, R., Treatment of Cancer Soft, T. and Bone Sarcoma Group, S. Phase III trial of two investigational schedules of ifosfamide compared with standard-dose

- doxorubicin in advanced or metastatic soft tissue sarcoma: a European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. *J Clin Oncol.* 2007, **25**(21), pp.3144-3150.
142. McMeekin, S., Dizon, D., Barter, J., Scambia, G., Manzyuk, L., Lisyanskaya, A., Oaknin, A., Ringuette, S., Mukhopadhyay, P., Rosenberg, J. and Vergote, I. Phase III randomized trial of second-line ixabepilone versus paclitaxel or doxorubicin in women with advanced endometrial cancer. *Gynecol Oncol.* 2015, **138**(1), pp.18-23.
 143. Aapro, M.S. Doxorubicin versus doxorubicin and cisplatin in endometrial carcinoma: definitive results of a randomised study (55872) by the EORTC Gynaecological Cancer Group. *Annals of Oncology.* 2003, **14**(3), pp.441-448.
 144. Pfisterer, J., Plante, M., Vergote, I., du Bois, A., Hirte, H., Lacave, A.J., Wagner, U., Stahle, A., Stuart, G., Kimmig, R., Olbricht, S., Le, T., Emerich, J., Kuhn, W., Bentley, J., Jackisch, C., Luck, H.J., Rochon, J., Zimmermann, A.H. and Eisenhauer, E. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. *J Clin Oncol.* 2006, **24**(29), pp.4699-4707.
 145. ICON2: randomised trial of single-agent carboplatin against three-drug combination of CAP (cyclophosphamide, doxorubicin, and cisplatin) in women with ovarian cancer. *The Lancet.* 1998, **352**(9140), pp.1571-1576.
 146. Motzer, R., Hutson, T., Tomczak, P., Michaelson, M., Bukowski, R., Rixe, O., Oudard, S., Negrier, S., Szczylik, C., Kim, S., Chen, I., Bycott, P., Baum, C. and Figlin, R. Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma. *N Engl J Med.* 2007, **356**(2), pp.115-124.
 147. Motzer, R.J., Hutson, T.E., Cella, D., Reeves, J., Hawkins, R., Guo, J., Nathan, P., Staehler, M., de Souza, P., Merchan, J.R., Boleti, E., Fife, K., Jin, J., Jones, R., Uemura, H., De Giorgi, U., Harmenberg, U., Wang, J., Sternberg, C.N., Deen, K., McCann, L., Hackshaw, M.D., Crescenzo, R., Pandite, L.N. and Choueiri, T.K. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med.* 2013, **369**(8), pp.722-731.
 148. Joensuu, H., Kellokumpu-Lehtinen, P.-L., Bono, P., Alanko, T., Kataja, V., Asola, R., Utriainen, T., Kokko, R., Hemminki, A., Tarkkanen, M., Turpeenniemi-Hujanen, T., Jyrkkiö, S., Flander, M., Helle, L., Ingalsuo, S., Johansson, K., Jääskeläinen, A.-S., Pajunen, M., Rauhala, M., Kaleva-Kerola, J., Salminen, T., Leinonen, M., Elomaa, I. and Isola, J. Adjuvant Docetaxel or Vinorelbine with or without Trastuzumab for Breast Cancer. *New England Journal of Medicine.* 2006, **354**, pp.809-820.
 149. Roche Products Limited. Herceptin summary of product characteristics. [Online], 2010. [Accessed 12th April 2017]. Available from: <https://www.medicines.org.uk/emc/medicine/28179>
 150. Marty, M., Cognetti, F., Maraninchi, D., Snyder, R., Mauriac, L., Tubiana-Hulin, M., Chan, S., Grimes, D., Anton, A., Lluch, A., Kennedy, J., O'Byrne, K., Conte, P., Green, M., Ward, C., Mayne, K. and Extra, J.M. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol.* 2005, **23**(19), pp.4265-4274.
 151. Taylor, H. Accelerated access review: final report. London: Department of Health, 2016.
 152. Wright, L. Lean mapping patient flow in an oncology outpatient department. *Journal of Improvement Science.* 2016, **37**, pp.1-18.
 153. Dinan, M.A., Hirsch, B.R. and Lyman, G.H. Management of chemotherapy-induced neutropenia: measuring quality, cost, and value. *Journal of the National Comprehensive Cancer Network.* 2015, **13**(1), pp.e1-e7.

154. Johnson, O., Hall, P. and Hulme, C. NETIMIS: Dynamic simulation of health economics outcomes using big data. *Pharmacoeconomics*. 2016, **34**(2), pp.107-114.
155. Dunwoodie, E. Defining unmet needs of clinical practice. 4th UK Diagnostics Forum, Oxford, 19th May 2015.
156. Dunwoodie, E. Home clinical monitoring of patients receiving chemotherapy. 1st Leeds Precision Oncology Symposium, Leeds, 19th October 2016.
157. Dunwoodie, E. Quantifying innovation impact. Health and Care conference, London, 24th June 2015.
158. Price, C.P. Point-of-care testing in diabetes mellitus. *Clin Chem Lab Med*. 2003, **41**(9), pp.1213-1219.
159. Berlin, I., Bisserbe, J.C., Eiber, R., Balssa, N., Sachon, C., Bosquet, F. and Grimaldi, A. Phobic symptoms, particularly the fear of blood and injury, are associated with poor glycemic control in type I diabetic adults. *Diabetes Care*. 1997, **20**(2), pp.176-178.
160. Grieve, R., Beech, R., Vincent, J. and Mazurkiewicz, J. Near patient testing in diabetes clinics: appraising the costs and outcomes. *Health Technol Assess*. 1999, **3**(15), pp.1-74.
161. Edelman, S.V., Callahan, P. and Deeb, L.C. Multisite evaluation of a new diabetes self-test for glucose and glycated protein (fructosamine). *Diabetes Technol Ther*. 2000, **2**(2), pp.233-238.
162. So, C.F., Choi, K.S., Wong, T.K. and Chung, J.W. Recent advances in noninvasive glucose monitoring. *Med Devices (Auckl)*. 2012, **5**, pp.45-52.
163. Thomas, A., Heinemann, L., Ramirez, A. and Zehe, A. Options for the Development of Noninvasive Glucose Monitoring: Is Nanotechnology an Option to Break the Boundaries? *J Diabetes Sci Technol*. 2016, **10**(3), pp.782-789.
164. Natrass, M. Improving results from home blood-glucose monitoring: accuracy and reliability require greater patient education as well as improved technology. *Clin Chem*. 2002, **48**(7), pp.979-980.
165. Heinemann, L., Overmann, H. and Muhlhauser, I. How well do patients with type 1 diabetes measure their blood glucose in daily life. *Diabetes Care*. 1998, **21**(3), pp.461-462.
166. Kabadi, U.M., O'Connell, K.M., Johnson, J. and Kabadi, M. The effect of recurrent practice at home on the acceptability of capillary blood glucose readings. Accuracy of self blood glucose testing. *Diabetes Care*. 1994, **17**(10), pp.1110-1123.
167. Dunson, W., Mooney, K., Beck, S., Wong, B. and Wujcik, D. NCCN symptom guidelines coupled with nurse practitioner follow-up reduced moderate to severe symptom days by half or greater in cancer patients receiving chemotherapy. National Comprehensive Cancer Network Annual Conference, Florida, 15th March 2013.
168. McCann, L., Maguire, R., Miller, M. and Kearney, N. Patients' perceptions and experiences of using a mobile phone-based advanced symptom management system (ASyMS) to monitor and manage chemotherapy related toxicity. *Eur J Cancer Care (Engl)*. 2009, **18**(2), pp.156-164.
169. Kennedy, F., Clayton, B. and Absolom, K. REPORT-UK (Real-time electronic patient outcome reporting of adverse events in UK cancer trials - preliminary findings of the feasibility pilot study. National Cancer Research Institute Conference, London, 2015.
170. P, C., Dieppe, P., Macintyre, S., Mitchie, S., Nazareth, I. and Petticrew, M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *British Medical Journal*. 2008, **337**, pp.979-983.
171. Campbell, M., Fitzpatrick, R., Haines, A., Kinmonth, A.L., Sandercock, P., Spiegelhalter, D. and Tyrer, P. Framework for design and evaluation of complex interventions to improve health. *BMJ*. 2000, **321**(7262), pp.694-696.

172. Baruch, Y. and Holtom, B.C. Survey response rate levels and trends in organizational research. *Human Relations*. 2008, **61**(8), pp.1139-1160.
173. Asch, D.A., Jedrzejewski, M.K. and Christakis, N.A. Response rates to mail surveys published in medical journals. *J Clin Epidemiol*. 1997, **50**(10), pp.1129-1136.
174. Ryan, M. and Farrar, S. Using conjoint analysis to elicit preferences for health care. *BMJ : British Medical Journal*. 2000, **320**(7248), pp.1530-1533.
175. Sculpher, M., Bryan, S., Fry, P., de Winter, P., Payne, H. and Emberton, M. Patients' preferences for the management of non-metastatic prostate cancer: discrete choice experiment. *BMJ*. 2004, **328**(7436), p.382.
176. van der Pol, M. and Cairns, J. Establishing patient preferences for blood transfusion support: an application of conjoint analysis. *J Health Serv Res Policy*. 1998, **3**(2), pp.70-76.
177. Ratcliffe, J. and Buxton, M. Patients' preferences regarding the process and outcomes of life-saving technology. An application of conjoint analysis to liver transplantation. *Int J Technol Assess Health Care*. 1999, **15**(2), pp.340-351.
178. Weber, E.U., Blais, A.R. and Betz, N.E. A domain-specific risk-attitude scale: Measuring risk perceptions and risk behaviors. *Journal of behavioral decision making*. 2002, **15**(4), pp.263-290.
179. Briggs, C., Kimber, S. and Green, L. Where are we at with point-of-care testing in haematology? *Br J Haematol*. 2012, **158**(6), pp.679-690.
180. Bossuyt, P.M., Reitsma, J.B., Bruns, D.E., Gatsonis, C.A., Glasziou, P.P., Irwig, L.M., Moher, D., Rennie, D., de Vet, H.C. and Lijmer, J.G. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Ann Intern Med*. 2003, **138**(1), pp.W1-12.
181. Jaeschke, R., Guyatt, G. and Sackett, D. Users' Guides to the Medical Literature III. How to Use an Article About a Diagnostic Test A. Are the Results of the Study Valid? *JAMA*. 1994, **271**(5), pp.389-391.
182. Jaeschke, R., Guyatt, G. and Sackett, D. Users' Guides to the Medical Literature III. How to Use an Article About a Diagnostic Test B. What Are the Results and Will They Help Me in Caring for My Patients? *JAMA*. 1994, **271**(9), pp.703-707.
183. British Society for Haematology. Guidelines for the use of platelet transfusions. London: British Society Haematology, 2016. Available from: <https://b-s-h.org.uk/guidelines>
184. Rao, L.V., Ekberg, B.A., Connor, D., Jakubiak, F., Vallaro, G.M. and Snyder, M. Evaluation of a new point of care automated complete blood count (CBC) analyzer in various clinical settings. *Clin Chim Acta*. 2008, **389**(1-2), pp.120-125.
185. Green, S., Woolley, T., Aylan, S. and Campbell, M. Comparing granulocyte / neutrophil counts using four methodologies. [Online]. 2011. [Accessed]. Available from: http://www.horiba.com/fileadmin/uploads/Medical-Diagnostics/Documents/News_Images/UK/Spire_comparison_poster_FINAL.pdf
186. International classification of diseases for mortality and morbidity statistics (ICD-10). Online: World Health Organisation, 1990. [Accessed 7th December 2016]. Available from: <http://www.who.int/classifications/icd/en/>
187. Bland, J.M. and Altman, D.G. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986, **1**(8476), pp.307-310.
188. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP, 2013.
189. Microsoft Excel. Redmond, Washington: Microsoft, 2010. Computer Software.
190. R Core Team. R: A language and environment for statistical computing. R foundation for statistical computing, Vienna, 2015.

191. Pether, N.S., Brothwood, J.L., van Berkel, C., Dunwoodie, E., Blake, R., Price, C.P., Jones, R.G., Baker, K. and Hall, G. Comparative diagnostic performance of the granulocyte and neutrophil counts. *Practical Laboratory Medicine*. 2017, **9**, pp.45-52.
192. Ike, S.O., Nubila, T., Ukaejiofo, E.O., Nubila, I.N., Shu, E.N. and Ezema, I. Comparison of haematological parameters determined by the Sysmex KX - 2IN automated haematology analyzer and the manual counts. *BMC Clin Pathol*. 2010, **10**, p.3.
193. Buttarello, M. Quality specification in haematology: the automated blood cell count. *Clin Chim Acta*. 2004, **346**(1), pp.45-54.
194. Rao, L.V., Moiles, D., Vallero, G.M. and Snyder, M. Finger-Stick Complete Blood Counts: comparison between venous and capillary blood. *Point of Care The Journal of Near-Patient Testing & Technology*. 2011, **10**(3), pp.120-122.
195. Chempaq XBC eXpress blood counter manufactured by Chempaq A/S. Online: SKUP Scandinavian Evaluation of Laboratory Equipment for Primary Healthcare, 2006. [Accessed 22/07/2015]. Available from: www.skup.nu/getFile.ashx?fileid=312
196. Bland, J.M. and Altman, D.G. Statistics Notes: Correlation, regression, and repeated data. *BMJ : British Medical Journal*. 1994, **308**, p.896.
197. Haneder, S., Gutfleisch, A., Meier, C., Brade, J., Hannak, D., O'Schoenberg, S., Becker, C. and Michaely, H. Evaluation of a handheld creatinine measurement device for real-time determination of serum creatinine in radiology departments. *World Journal of Radiology*. 2012, **28**(4(7)), pp.328-334.
198. Seigneurin, D. and Girardini, M. Comparative study for blood counts using capillary and venous blood. *Am J Clin Pathol*. 1980, **74**(3), pp.362-364.
199. Feusner, J.H., Behrens, J.A., Detter, J.C. and Cullen, T.C. Platelet counts in capillary blood. *Am J Clin Pathol*. 1979, **72**(3), pp.410-414.
200. Hemocue. Hemocue WBC DIFF: Operating Manual. Angelholm: Hemocue AB. (Year not specified)
201. Russcher, H., Van Deursen, N. and de Jonge, R. Evaluation of the HemoCue WBC DIFF system for point-of-care counting of total and differential white cells in pediatric samples. *Ned Tijdschr Klin Chem Labgeneesk*. 2013, **38**(3), pp.140-141.
202. Lindberg, S., Jönsson, I., Nilsson, M., Johnsson, E. and Jonasson-Bjäräng, T. A Novel Technology for 5-Part Differentiation of Leukocytes Point-of-Care. *Point of Care*. 2014, **13**(2), pp.27-30.
203. Hockum, S., Johnsson, E. and Reed, J. Novel POC Analysis for Determination of Total and 5-Part Differential WBC Counts Among a US Population, in Comparison to Beckman Coulter LH750. *Point of Care*. 2014, **13**(1), pp.12-14.
204. Dacie, J. and Lewis, S. *Practical Haematology*. 6th ed. London: Churchill Livingstone, 1984, p1-6.
205. Daae, L.N., Halvorsen, S., Mathisen, P.M. and Mironska, K. A comparison between haematological parameters in 'capillary' and venous blood from healthy adults. *Scand J Clin Lab Invest*. 1988, **48**(7), pp.723-726.
206. Ozbek, N., Gurakan, B. and Kayiran, S.M. Complete blood cell counts in capillary and venous blood of healthy term newborns. *Acta Haematol*. 2000, **103**(4), pp.226-228.
207. Kayiran, S.M., Ozbek, N., Turan, M. and Gurakan, B. Significant differences between capillary and venous complete blood counts in the neonatal period. *Clin Lab Haematol*. 2003, **25**(1), pp.9-16.
208. Peevy, K.J., Grant, P.H. and Hoff, C.J. Capillary venous differences in neonatal neutrophil values. *Am J Dis Child*. 1982, **136**(4), pp.357-358.
209. Daae, L.N., Hallerud, M. and Halvorsen, S. A comparison between haematological parameters in 'capillary' and venous blood samples from hospitalized children aged 3 months to 14 years. *Scand J Clin Lab Invest*. 1991, **51**(7), pp.651-654.

210. Leppanen, E.A. Experimental basis of standardized specimen collection: the effect of the site of venipuncture on the blood picture, the white blood cell differential count, and the serum albumin concentration. *Eur J Haematol.* 1988, **41**(5), pp.445-448.
211. Schalk, E., Heim, M.U., Koenigsmann, M. and Jentsch-Ullrich, K. Use of capillary blood count parameters in adults. *Vox Sang.* 2007, **93**(4), pp.348-353.
212. Yang, Z.W., Yang, S.H., Chen, L., Qu, J., Zhu, J. and Tang, Z. Comparison of blood counts in venous, fingertip and arterial blood and their measurement variation. *Clin Lab Haematol.* 2001, **23**(3), pp.155-159.
213. Grasbeck, R. Reference values: relevant controls for clinical decision-making. *Eur J Haematol.* 1988, **40**(1), pp.1-6.
214. Leppanen, E.A. and Grasbeck, R. Experimental basis of standardized specimen collection: effect of posture on blood picture. *Eur J Haematol.* 1988, **40**(3), pp.222-226.
215. McCarthy, D.A., Perry, J.D., Melsom, R.D. and Dale, M.M. Leucocytosis induced by exercise. *Br Med J (Clin Res Ed).* 1987, **295**(6599), p.636.
216. Polychemotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet.* 1998, **352**(9132), pp.930-942.
217. Silber, J.H., Fridman, M., DiPaola, R.S., Erder, M.H., Pauly, M.V. and Fox, K.R. First-cycle blood counts and subsequent neutropenia, dose reduction, or delay in early-stage breast cancer therapy. *J Clin Oncol.* 1998, **16**(7), pp.2392-2400.
218. Samson, M.K., Rivkin, S.E., Jones, S.E., Costanzi, J.J., LoBuglio, A.F., Stephens, R.L., Gehan, E.A. and Cummings, G.D. Dose-response and dose-survival advantage for high versus low-dose cisplatin combined with vinblastine and bleomycin in disseminated testicular cancer. A Southwest Oncology Group study. *Cancer.* 1984, **53**(5), pp.1029-1035.
219. Ricos, C., Alvarez, V., Perich, C., Fernandez-Calle, P., Minchinela, J., Cava, F., Biosca, C., Boned, B., Domenech, M., Garcia-Lario, J.V., Simon, M., Fernandez, P.F., Diaz-Garzon, J. and Gonzalez-Lao, E. Rationale for using data on biological variation. *Clin Chem Lab Med.* 2015, **53**(6), pp.863-870.
220. Ricos, C., Alvarez, V., Cava, F., Garcia-Lario, J.V., Hernandez, A., Jimenez, C.V., Minchinela, J., Perich, C. and Simon, M. Current databases on biological variation: pros, cons and progress. *Scand J Clin Lab Invest.* 1999, **59**(7), pp.491-500.
221. Desirable biological variation database specification. Online: Westgard QC, 2014. [Accessed January 2016]. Available from: www.westgard.com/biodatabase1.htm
222. Perich, C., Minchinela, J., Ricos, C., Fernandez-Calle, P., Alvarez, V., Domenech, M.V., Simon, M., Biosca, C., Boned, B., Garcia-Lario, J.V., Cava, F., Fernandez-Fernandez, P. and Fraser, C.G. Biological variation database: structure and criteria used for generation and update. *Clin Chem Lab Med.* 2015, **53**(2), pp.299-305.
223. Pocock, S.J., Ashby, D., Shaper, A.G., Walker, M. and Broughton, P.M. Diurnal variations in serum biochemical and haematological measurements. *J Clin Pathol.* 1989, **42**(2), pp.172-179.
224. Freireich, E.J., Karon, M. and Frei, E. Quadruple combination therapy (VAMP) for acute lymphoblastic leukaemia of childhood. In: *Proceedings of the American Association for Cancer Research* 5, 1964, p.20.
225. DeVita Junior, V. and DeVita-Raeburn, E. *The death of cancer.* 1st ed. New York: Farrar, Straus and Giroux, 2015.
226. Rossi, L., Tomao, F., Lo Russo, G., Papa, A., Zoratto, F., Marzano, R., Basso, E., Giordani, E., Verrico, M., Ricci, F., Pasciuti, G., Francini, E. and Tomao, S. Efficacy and safety analysis of once per cycle pegfilgrastim and daily lenograstim in patients with breast cancer receiving adjuvant myelosuppressive chemotherapy FEC 100: a pilot study. *Ther Clin Risk Manag.* 2013, **9**, pp.457-462.

227. Kloft, C., Wallin, J., Henningsson, A., Chatelut, E. and Karlsson, M.O. Population pharmacokinetic-pharmacodynamic model for neutropenia with patient subgroup identification: comparison across anticancer drugs. *Clin Cancer Res.* 2006, **12**(18), pp.5481-5490.
228. Friberg, L.E., Henningsson, A., Maas, H., Nguyen, L. and Karlsson, M.O. Model of chemotherapy-induced myelosuppression with parameter consistency across drugs. *J Clin Oncol.* 2002, **20**(24), pp.4713-4721.
229. Hansson, E.K., Wallin, J.E., Lindman, H., Sandstrom, M., Karlsson, M.O. and Friberg, L.E. Limited inter-occasion variability in relation to inter-individual variability in chemotherapy-induced myelosuppression. *Cancer Chemother Pharmacol.* 2010, **65**(5), pp.839-848.
230. Soto, E., Staab, A., Tillmann, C., Trommeshauser, D., Fritsch, H., Munzert, G. and Troconiz, I.F. Semi-mechanistic population pharmacokinetic/pharmacodynamic model for neutropenia following therapy with the Plk-1 inhibitor BI 2536 and its application in clinical development. *Cancer Chemother Pharmacol.* 2010, **66**(4), pp.785-795.
231. Quartino, A.L., Friberg, L.E. and Karlsson, M.O. A simultaneous analysis of the time-course of leukocytes and neutrophils following docetaxel administration using a semi-mechanistic myelosuppression model. *Invest New Drugs.* 2012, **30**(2), pp.833-845.
232. Sandstrom, M., Lindman, H., Nygren, P., Johansson, M., Bergh, J. and Karlsson, M.O. Population analysis of the pharmacokinetics and the haematological toxicity of the fluorouracil-epirubicin-cyclophosphamide regimen in breast cancer patients. *Cancer Chemother Pharmacol.* 2006, **58**(2), pp.143-156.
233. Gurney, H. How to calculate the dose of chemotherapy. *Br J Cancer.* 2002, **86**(8), pp.1297-1302.
234. Horwich, A., Sleijfer, D.T., Fossa, S.D., Kaye, S.B., Oliver, R.T., Cullen, M.H., Mead, G.M., de Wit, R., de Mulder, P.H., Dearnaley, D.P., Cook, P.A., Sylvester, R.J. and Stenning, S.P. Randomized trial of bleomycin, etoposide, and cisplatin compared with bleomycin, etoposide, and carboplatin in good-prognosis metastatic nonseminomatous germ cell cancer: a Multiinstitutional Medical Research Council/European Organization for Research and Treatment of Cancer Trial. *J Clin Oncol.* 1997, **15**(5), pp.1844-1852.
235. Comen, E., Morris, P. and Norton, L. Translating Mathematical Modeling of Tumor Growth Patterns into Novel Therapeutic Approaches for Breast Cancer. *Journal of mammary gland biology and neoplasia.* 2012, **17**(3), pp.241-249.
236. Oken, M., Creech, R., Tormey, D., Horton, J., Davis, T., McFadden, E. and Carbone, P. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology.* 1982, **5**(6), pp.649-655.
237. de Wit, R., Roberts, T., Wilkinson, P., de Mulder, P., Mead, G., Fosså, S., Cook, P., de Prijck, L., Stenning, S. and Collette, L. Equivalence of three or four cycles of bleomycin, etoposide, and cisplatin chemotherapy and of a 3- or 5- day schedule in good-prognosis germ cell cancer: a randomized study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group and the Medical Research Council. *Journal Clinical Oncology.* 2001, **16**(6), pp.1629-1640.
238. Kavgaci, H., Ozdemir, F., Aydin, F., Yavuz, A. and Yavuz, M. Endogenous granulocyte colony-stimulating factor (G-CSF) levels in chemotherapy-induced neutropenia and in neutropenia related with primary diseases. *Journal Experimental Clinical Cancer Research.* 2002, **21**(4), pp.475-479.
239. Stevens, S. *Five Year Forward View.* London: NHS England, 2014.
240. *Achieving world-class cancer outcomes; a strategy for England 2015-2020.* London: NHS England, 2015.

241. National cancer patient experience survey 2016. Online: Quality Health, 2017. Available at: <https://www.quality-health.co.uk/surveys/national-cancer-patient-experience-survey>
242. Progress in improving cancer services and outcomes in England. London: Department of Health, NHS England and Public Health England, 2015.
243. Tomlinson, J. Cultural barriers to shared decision making. *British Medical Journal*. 2018, **360**, p.69.
244. Liberating the NHS; no decision about me, without me. London: Department of Health, 2012.
245. Life science competitiveness indicators report. London: Department of Health, 2016.
246. Taylor, H. Accelerated access review: final report. London: Department of Health, 2016.
247. Wolstenholme, J. Economic modelling of diagnostic innovations: early detection/prevention of neutropenic sepsis in cancer patients: a cost utility evaluation. 4th UK Diagnostics Forum, Oxford, 19th May 2015. [Accessed 15th January 2018]. Available from: <https://www.community.healthcare.mic.nihr.ac.uk/reports-and-resources/120-delegates-and-speakers-from-industry-academia-and-healthcare-organisations-coming-together-to-share-ideas-to-facilitate-the-utilisation-and-adoption-of-innovative-tests-through-good-quality-evidence>