An investigation of the treatment journey of paediatric patients with Acute Lymphoblastic Leukaemia in hospital

Dudzayi Caxton Nhiwatiwa

Australian Institute of Health Innovation,

Macquarie University

A thesis in partial fulfilment of the Master of Research degree

Principal supervisor: Professor Johanna Westbrook

Associate supervisor: Dr Melissa Baysari

Clinical supervisor: Dr Luciano Dalla-Pozza

10th October 2016

Table of contents

List of Tables……5

List of Figures……6

List of Appendices……7

Abbreviations……8

Statement of Originality and Ethics Approval……9

Acknowledgements……10

Abstract……11

Chapter One: Introduction

1.1 Overview of Acute Lymphoblastic Leukaemia……12

1.1.1 Classification of ALL……12

1.1.2 Diagnosis of ALL……13

1.1.3 Treatment of ALL……13

1.1.4 Supportive care in childhood ALL……15

1.1.5 Survival and relapse from ALL……18

1.2 Patient journeys……19

1.2.1 What are patient journeys?……19

1.2.2 Why is mapping a patient journey important?……19

1.2.3 Methods used to map patient journeys……20

1.3 Patient journeys in cancer……24

1.4 Aims and significance……28

Chapter Two: Methods

2.1 Study site……29

2.2 Study sample……29

2.3 ALL treatment protocols……29

2.3.1 Study 9 Protocol for treatment of ALL: AIEOP-BFM ALL 2009……30

SR/MR treatment phases……32

HR treatment phases……34

2.4 Procedures……36

2.5 Ethics……39

Chapter Three: Results

3.1 Patient characteristics……40

3.2 Time from presentation to diagnosis and start of treatment……41

3.3 Completion of key treatment milestones……41

3.4 Total hospital admissions and oncology clinic visits……42

3.5 Treatment delays……44

3.5.1 SR/MR treatment delays……44

Reasons for treatment delays in SR/MR patients……47

3.5.2 HR treatment delays……49

Reasons for treatment delays in HR patients……51

3.5.3 SR/MR versus HR patients……52

3.6 Map of the ALL journey……53

Chapter Four: Discussion

4.1 Treatment delays……55

4.2 Reasons for treatment delays……57

4.3 The ALL journey……60

4.4 Delays in diagnosis and commencement of treatment……61

4.5 Effects of patient characteristics on treatment delays……62

4.6 Strengths and limitations of the study……64

4.7 Conclusions……64

References……66

Appendices……74

List of Tables

Chapter 1: Introduction

Table 1 Summary of studies that have mapped patient journeys in cancer……25

Chapter 2: Methods

Table 2 Phases of Study 9 ALL Protocol for HR and SR/MR patients, including duration of each Phase……30

Table 3 Sources of data and data elements extracted……37

Table 4 Delay classification codes, definitions and examples……39

Chapter 3: Results

Table 5 Patient characteristics and risk classification……40

Table 6 The number and percentage of treatment visits which were delayed in the SR/MR patient group……46

Table 7 Number of SR/MR patients experiencing delays in treatment visits by reason for delay……47

Table 8 Distribution of treatment delays by reasons and average length of each delay experienced by SR/MR patients (n=24)……48

Table 9 Number and percentage of treatment visits which were delayed in the HR patient group……50

Table 10 No. of HR patients experiencing delays in treatment visits by reason for delay……51

Table 11 Distribution of treatment delays by reasons and average length of each delay experienced by HR patients (n=6)……52

Table 12a SR/MR milestones, including expected number of days to reach each milestone and the average number of days taken to reach each milestone by patients in the study……54

Table 12b HR milestones, including expected number of days to reach each milestone and the average number of days taken to reach each milestone by patients in the study……54

List of Figures

Chapter 2: Methods

Figure 1 Study 9 – AIEOP-BFM ALL Protocol Flow Diagram……31

Chapter 3: Results

Figure 2 Average number of hospital admissions and oncology clinic visits for SR/MR (n=24) and HR (n=6) patients……42

Figure 3 Some of the supportive care provided to SR/MR (n=24) and HR (n=6) patients during their treatment journey……43

Figure 4a Average length of delays (raw and cumulative) experienced by SR/MR patients across their treatment journey……44

Figure 4b The treatment journey of a single patient who experienced the longest cumulative delays the SR/MR treatment group (Patient no. 14)……45

Figure 5a The average length of treatment delays (raw and cumulative) experienced by HR patients across their treatment journey (n=5)……49

Figure 5b The treatment journey of a single patient who experienced the longest delays in the HR treatment group (Patient no. 21)…….....50

Figure 6 Proportion of treatment delays by reason for SR/MR (n=24) and HR (n=6) patients across the treatment journey……..53

List of Appendices

Appendix A Phases of Study 9 - AIEOP-BFM ALL 2009 Including drugs, doses, routes and days given……74

Appendix B ALL Patient Journey including expected no. of days to reach milestones (& average no. of days taken to reach milestones)……..76

Appendix C Ethics approval letter……77

Abbreviations

ALL – acute lymphoblastic leukaemia

AML – acute myeloid leukaemia

BMA – bone marrow aspirate

BSA – body surface area

CNS – central nervous system

CRT – cranial radiotherapy

ED – emergency department

FBC – full blood count

HD Ara-C – high dose cytarabine

HD MTX – high dose methotrexate

HR – high risk

MR – medium risk

MRD – minimal residual disease

MTX - methotrexate

OTC – oncology treatment centre

PICU – paediatric intensive care unit

6-MP – 6-mercaptopurine (mercaptopurine)

SR – standard risk

WCC – white cell count

Statement of Originality and Ethical Approval

I, Dudzayi Caxton Nhiwatiwa declare that this submission is my own work and does not represent the work or view of others, except where acknowledged in the text. No part of this thesis has been submitted for a higher degree to any other university or institution.

Ethics approval was obtained from the Sydney Children's Hospitals Network Human Research Ethics Committee:

HREC Reference number: LNR/16/SCHN/101.

And ratified by Macquarie University Human Ethics Committee:

MQ Ethics Reference number: 5201600326

Dudzayi Nhiwatiwa was supported by the Research Training Pathway Scholarship Scheme for the duration of the project. Research studies were funded by internal funding from Macquarie University and NHMRC grants awarded to the Australian Institute of Health Innovation.

_____

Dudzayi Caxton Nhiwatiwa

Date 10/10/2016

Acknowledgements

Firstly, I would like to express my sincere gratitude to my supervisors, Principal supervisor Professor Johanna Westbrook; Associate supervisor Dr Melissa Baysari and Clinical supervisor Dr Luciano Dalla-Pozza, for patiently and tirelessly guiding me throughout this project, providing me with confidence for research. I am thankful for the weekly assistance and all the feedback provided during the project.

I would also like to thank Dr Bhavna Padhye and your team at the study hospital's Oncology Department for all your assistance in data extraction and answering my clinical questions. I feel incredibly lucky to have had your support and friendship over the past year. I am also grateful to staff at the hospital's Medical Records Department (particularly Ms Lenise Barakat) and Blood Bank (particularly Ms Marguerite Ogg) for their special assistance and support in data extraction.

I am also thankful to everyone in the Australian Institute of Health Innovation, particularly the Centre for Health Systems and Safety Research (CHSSR) team for their ongoing support and help in many areas of the project. A am very grateful to Dr Wu Yi Zheng for assisting with statistical analysis. A special thank you goes to Ms Denise Pottumati and Ms Rebecca Lake for assistance with formatting this thesis.

Finally, a special thank you to my wife, Sekai and our children, Samson (Jnr) and Linda; my family and friends for all your support and encouragement throughout this year. I am especially grateful to my late father, Mr Samson Musapokane Nhiwatiwa for always being my pillar of strength, unfortunately you passed away this year before seeing this project come to completion.

Thank you all.

Abstract

Background and aims: Leukaemia is the most prevalent childhood cancer, with acute lymphoblastic leukaemia (ALL) the most common sub-type. ALL cure rate is high, however, the treatment journey is long and complex. There has been limited research quantifying or describing the types and causes of delays experienced by ALL patients. This study aimed to summarise the characteristics of ALL patients; identify key milestones of the ALL treatment journey; and identify when and why delays occurred.

Methods: *Site:* The Oncology Department of a paediatric tertiary hospital in Sydney.

Sample: All patients diagnosed with ALL during a one-year period (January 10th 2013 to January 10th 2014) and treated using the Study 9 Protocol.

Procedure: Data on: demographics; treatment delays and causes; and supportive care for patients were extracted via an in-depth retrospective audit of clinical information systems as well as review of the treatment protocol and discussions with key oncology clinicians at the hospital.

Results: The average delays experienced during the two-year treatment journey were 33 days and 94 days for standard risk/medium risk and high risk patients respectively. Nearly 90% of treatment delays were due to low counts, other toxicities or a combination of these factors. Nine percent and 1% of the delays were attributed to organisational factors and patient factors respectively. Despite these delays, most patients completed all milestones of ALL treatment.

Conclusions: The ALL patient journey is often interrupted by treatment delays, mostly due to treatment-related toxicity, but also due to patient factors and organisational issues. The use of electronic health records systems may potentially reduce delays due to organisational issues by improving care coordination.

Chapter One: Introduction

Acute lymphoblastic leukaemia or acute lymphocytic leukaemia (ALL) is the most common childhood cancer, accounting for about 25% of all childhood cancers.[1, 2] and approximately 80% of childhood leukaemias.[2, 3] The annual incidence rate for childhood ALL varies across the world, and ranges from between one to four new cases per 100,000 children under 15 years with incidence peaking between two to five years of age.[2, 4] ALL can be defined as a lymphocyte (white blood cell) malignancy in which there is extensive proliferation of immature forms of lymphocytes ("blasts") in the bone marrow and their subsequent release into blood circulation.[2]

1.1 OVERVIEW OF ACUTE LYMPHOBLASTIC LEUKAEMIA

It is now widely accepted that ALL is a heterogeneous disease, comprising of several molecularly and cytogenetically distinct group of diseases with different underlying pathobiology. [5, 6, 7]

1.1.1 Classification of ALL

ALL can be broadly classified according to the lymphocyte lineage involved, that is, B-cell ALL and T-cell ALL.[1, 5, 8] B-cell ALL accounts for approximately 85% of childhood ALL while about 10-15% of cases are of T-cell lineage.[1, 5] Through high resolution genome-wide profiling of genetic alterations/mutations, it is now clear that there are many additional subtypes of the disease.[4, 9] Further refinement of the classification of ALL continues and is making it possible to identify treatment resistant sub-types, hence enabling further research for better targeted therapy for such sub-types.[6]

There are some specific high-risk sub-groups of ALL which require special attention. These include: Philadelphia (Ph) chromosome positive ALL; Philadelphia-like ALL; early T-cell precursor ALL; ALL with intra-chromosomal amplification of chromosome 21; mixed lineage leukaemia(MLL); and infant ALL.[1, 10, 11, 12] All these sub-groups are associated with poorer outcomes.

1.1.2 Diagnosis of ALL

ALL typical clinical signs include: fever; pallor; fatigue; bruises; bone pain; petechial (non-raised, flat to touch) skin rash and enlarged liver, spleen and lymph nodes.[2] A full blood count (FBC) in most patients shows anaemia, thrombocytopenia and granulocytopenia without leucocytosis. As these signs are not necessarily specific to ALL, diagnosis is confirmed through cytomorphological and cytochemical examination of bone marrow aspirate (BMA).[2, 4] The presence of 25% or more lymphoblasts confirms a positive diagnosis of ALL and central nervous system (CNS) involvement is also diagnosed if there are blasts in the cerebrospinal fluid (CSF) or if intracerebral infiltrates are detected.[2] For male patients, testes are also a sanctuary site for leukaemia cells. Flow cytometric immunophenotyping is used to determine B-cell or T-cell lineage and sub-types while cytogenetic and molecular genetic or genome-wide analysis (if available) are used to detect leukemic specific translocations, chromosomal abnormalities and cellular DNA content.[2, 4, 13] Molecular genetics and flow cytometry are used during treatment to monitor response to treatment and residual burden of disease through measurement of minimal residual disease (MRD).[2]

1.1.3 Treatment of ALL

The total duration of treatment for childhood ALL is two to two and a half years (24-30 months), but can be longer depending on the treatment protocol used and individual patient factors.[4, 5] There is risk stratification of ALL patients into low (standard), intermediate (medium), high and very high risk groups.[2, 8] It is important to tailor the treatment according to the risk.[2, 8] Over-treating low risk patients may result in unnecessary toxicity and under-treating high or very high risk patients is associated with increased risk of treatment failure or relapse.[2, 8] Patients classified as high risk therefore receive more intense treatment to increase chance of cure whilst low risk patients receive less, thus sparing them of unnecessary treatment related toxicity.[2, 8]

Regardless of the risk stratification, the protocol driven ALL treatment essentially consists of four main elements: induction; CNS-directed treatment and consolidation; re-induction; and maintenance.[5, 9] The aim of treatment is to achieve “complete remission” without “relapse” over time.[2] Complete remission is “the absence of leukaemia blasts in the blood and cerebrospinal fluid, fewer than 5% lymphoblasts in bone marrow aspirate smears and no

evidence of localised disease".[2] Relapse is "the recurrence of lymphoblasts or localised leukemic infiltrates at any site".[2]

Induction (remission-induction)

The aim of induction therapy is to produce remission and restore normal haematopoiesis within four to six weeks.[2, 5] Three systemic drugs are used in induction. These are: a glucocorticoid (usually oral prednisolone or dexamethasone); vincristine; and L-asparaginase.[2, 5] A fourth drug, an anthracycline (e.g. daunorubicin) is added in certain protocols used and/or based on risk stratification.[2, 5] This three to four drug regimen is usually sufficient for low risk patients, however, high risk patients require four or more drugs.[4] The intensity of the induction therapy as well as the choice of drugs have a significant impact on the overall outcome.[2] For example, using dexamethasone instead of prednisolone is associated with better outcomes, in certain groups of patients although there are more toxic effects, such as increased severe infections and osteonecrosis.[2, 9]

CNS-directed therapy and consolidation

CNS-directed therapy and consolidation is aimed at preventing central nervous system relapses and reducing minimal residual disease burden.[2, 5] CNS-directed therapy includes weekly or fortnightly administration of intrathecal methotrexate and 24-hour continuous intravenous administration of high dose methotrexate (MTX) and oral 6-mercaptourine (6-MP).[5, 13] Some treatment protocols also use cyclophosphamide and cytarabine to further reduce systemic tumour burden.[5] Cranial radiation has also been successfully used to reduce CNS relapses but drugs with sufficient CNS penetration (e.g. high dose methotrexate, high dose cytarabine) are now preferable[2, 9] because radiation exposure is associated with late occurring effects (e.g. secondary cancers, infertility, growth retardation and other neuro-endocrine and neurocognitive effects).[9] The intensity of CNS-directed therapy is adjusted according to the disease status, leukaemia subtype and perceived relapse risk originating from the CNS, particularly CNS involvement at diagnosis.[2]

Re-induction (delayed intensification)

Delayed intensification or re-induction uses similar drugs used during remission induction and consolidation (e.g. L-asparaginase, vincristine, dexamethasone with/without an

anthracycline like doxorubicin)[2, 5, 9] The aim of this phase of treatment is to further improve outcomes by decreasing the risk of relapse.[2, 5]

Maintenance (continuation)

This phase aims at further stabilising remission and consists of oral daily 6-mercaptopurine and weekly methotrexate with/without pulses of dexamethasone, vincristine and intrathecal therapy.[2, 5, 9] The 6-mercaptopurine and methotrexate doses are regularly adjusted according to absolute leucocyte, neutrophil and platelet counts so as to maintain disease control without causing excessive toxicities e.g. bone marrow suppression.[2, 9] The total duration of the maintenance phase alone is 18-24 months or longer depending on the protocol.[5]

Allogenic stem cell transplantation (SCT)

This is the fifth element of ALL treatment reserved for a small number of patients in first remission with poor prognostic factors at diagnosis and poor response to treatment.[2, 5]

1.1.4 Supportive care in childhood ALL

Almost all chemotherapy side effects experienced by children treated for ALL are reversible upon completion of treatment or cessation of the drugs.[5] However, the timely and effective management of these side effects is crucial for the successful treatment of ALL.[13] Infections (due to immunosuppression) and bleeding are the most common side effects and often result in many deaths.[5, 13] Other treatment related side effects include anaemia/thrombocytopenia/neutropenia; malnutrition; nausea and vomiting; thrombosis and pain.[5, 13] The intensity of ALL treatment that can be given at any institution or hospital should be matched with the corresponding level of supportive care available at that institution in order to prevent or minimise treatment related morbidity and mortality.[13, 15] Developed nations, such as, Australia have sufficient resources to provide maximum supportive care, hence can also maximise treatment intensity as necessary.

Infection control

Simple infection control measures (e.g. hand hygiene, admitting oncology patients in separate wards, isolating infectious patients etc.) go a long way in preventing or reducing infections to cancer patients.[13, 15] Low dose cotrimoxazole (trimethoprim and

sulfamethoxazole combination) is commonly used for Pneumocystis jiroveci pneumonia (PCP) prophylaxis.[13, 15] Antifungal and antiviral prophylaxis may also be appropriate for some patients, particularly high risk, relapsed and allogenic SCT patients.[16] Hospitals need clear febrile neutropenia protocols/guidelines so that effective intravenous antibiotic treatment can be initiated in a timely manner when required and bacterial culture and sensitivity testing carried out to identify causative organisms and then rationalise antibiotic use.[13, 15] Fever in an immunosuppressed cancer patient is a medical emergency and should always be assumed to be due to bacterial infection until proven otherwise.[15] Antifungal and then antiviral treatment can also be added as necessary if indicated.[15]

Nutrition support

Malnutrition can develop quickly in paediatric cancer patients soon after start of chemotherapy treatment and may be associated with reduced immunity; decreased tolerance to chemotherapy; increased risk of infection; increased intestinal parasite infestation; and hence an increase in overall morbidity and mortality.[13, 15] Nutritional support is therefore necessary and may include providing total parenteral nutrition (TPN) and enteral (nasogastric tube) feeding; involving hospital dieticians; and having definite nutritional plans for vulnerable patients.[15]

Blood products infusions

Safe blood products (platelets, red or packed cells etc.) need to be readily available for transfusion to patients who experience thrombocytopenia (hence increased risk of bleeding) and anaemia due to their disease or chemotherapy treatment.[13, 15]

Antiemetics

Chemotherapy drugs for ALL treatment cause considerable nausea and vomiting in paediatric patients.[13] As such, treatment of nausea and vomiting is an important part of ALL patient care. Setrons (5-hydroxytryptamine [5-HT] antagonists) are very effective antiemetics and they are well tolerated so are often used as first line.[13, 15] However, they are expensive.[13] Metoclopramide and diphenhydramine are alternatives or can be used in combination with setrons.[13, 15] Extrapyramidal side effects can be an issue with

metoclopramide, particularly in paediatric patients.[15] Other adjunctive antiemetic drugs that can be used include lorazepam, dexamethasone and chlorpromazine.[13, 15]

Pain management

ALL patients require pain control for procedures (e.g. lumbar punctures), mucositis, infections, blood taking, other rare complications (e.g. haemorrhagic cystitis), etc. The World Health Organisation (WHO) guideline on pain control can be followed for the management of paediatric ALL patients.[17] Paracetamol is sufficient for mild pain, escalating to opioids as clinically necessary for moderate and severe pain.[13] Morphine, in oral and intravenous dosage forms, is the most preferable opioid because it is very effective and affordable.[13, 15] Unfortunately, misconceptions about addiction, and actual or possible narcotic drug abuse can be barriers to accessibility.[13, 15] Aspirin and non-steroidal anti-inflammatory drugs (NSAID's) e.g. Ibuprofen, should be avoided because of their antiplatelet effect.[13]

Psychosocial support

Like all other cancers, ALL treatment cost is high.[13, 15] However, in Australia, most of the cost is covered by national and health insurance but there is a cost involved to parents to cover travelling to and from the hospital and staying away from home. Other additional costs to parents may include: financial costs (e.g. cost of additional childcare or additional support at home, cost of food); educational; emotional; the effects on siblings and family members; and the change in relationship between child (patient), parents and siblings. Some parents may have to stop working or reduce their working hours to care for children as they undergo treatment. Social support is made available to parents to enable access and completion of treatment.[13, 15] And parents are assisted to access all the available social and financial support.[15] Emotional support for some patients, parents and families may also be required.[18] Play and learning (for older children) should be provided during hospital in-patient stays.[13]

Palliative care

Palliative care is part of the ALL treatment journey for those patients whose disease cannot be cured.[13, 15] Working in collaboration with hospital-wide specialist palliative care teams is

necessary as it reduces suffering for patients and parents, particularly if it emphasises comfort and quality of life.[13]

1.1.5 Survival and relapse from ALL

Survival

Successful treatment of childhood ALL is one of the most significant medical achievements of the modern era with many high income countries now approaching or even exceeding 90% five-year survival.[8, 10, 13] In Australia during the period 1997-2006, five-year relative survival for childhood ALL was approximately 85%.[19] This is in contrast to the 1960's when five-year relative survival was less than 10% worldwide.[20] This remarkable transformation of childhood ALL from being fatal to curable can be attributed to a better understanding of the disease pathobiology; improved risk stratification of patients and better risk directed therapy; improved supportive care; centralisation of care; toxicity assessment; and following protocols during and after treatment.[8, 10, 13] This in turn has come about as a result of the collaboration of specialist oncologists in very large international clinical trials.[10 22] However, in high income countries, e.g. Australia, non-compliance with treatment protocols by both patients and clinicians is regarded as one of the major reasons for treatment failure. [21, 22]

Improvement in long term survival of childhood ALL patients has exposed the long-term morbidity from late effects which need to be managed accordingly.[2] These late effects include: anthracycline therapy-related cardiomyopathy; neuropsychological effects (methotrexate-related); secondary cancers (e.g. acute myeloid leukaemia or AML); osteonecrosis and radiotherapy-related brain tumours and infertility.[2]

Relapse

While there has been remarkable success in childhood ALL treatment, the challenge is that risk prediction is not accurate, some children who are initially predicted as low risk or standard risk do relapse.[10] Presence of minimal residual disease (leukaemia disease burden still remaining) at the end of remission induction is an important predictor of poor prognosis and relapse ≥3years post diagnosis.[23] Late relapse has also been attributed to outgrowth of minor drug resistant sub-clones, acquisition of additional genetic abnormalities by pre-leukemic clones or development of secondary ALL.[23] Next generation genome sequencing

and profiling are successfully being utilised to provide a better understanding of these sub-types,[1, 10, 11] hence enabling research efforts to find more specific therapies for these chemotherapy resistant sub-types.[10, 23]

Initial childhood ALL treatment duration can be up to two and a half years and if the patient is unfortunate to relapse, they will require a similar length of time of relapsed treatment.[4, 5] The treatment journey is long and complex.[2] After completion of treatment patients are also followed up for many years to monitor and manage late effects of ALL treatment.[2] Overall, these children are in contact with the health system for a very long time. Improving their treatment journeys or experiences during all those years of contact with the health system is very important.

1.2 PATIENT JOURNEYS

1.2.1 What are patient journeys?

A patient journey can be defined as the steps taken by a patient as he/she progresses through different stages of the disease from diagnosis to management.[24] Alternatively, it refers to the experiences and processes a patient undergoes during the course of their disease and its treatment.[25] A map of a patient's journey is a picture or model of the procedures and administrative processes that a patient experiences (not what a patient should experience) as they transverse through the health system during the treatment of their disease.[26]

1.2.2 Why is mapping a patient journey important?

Mapping a patient journey helps to highlight the roles and views of all the people or teams that are involved in patient care.[26] Patient journey mapping also identifies areas for improvement and diagnoses problems along the patient steps, and suggests ways of solving the problems.[26] Mapping a patient journey can therefore be an important strategy for improving patient journeys e.g. addressing safety concerns, identifying delays and identifying additional needs of patients.

1.2.3 Methods used to map patient journeys

Some of the methods used to map a patient journey include: conventional models of process mapping; alternative conventional (non-conventional) process mapping; patient perspectives; reviewing patient pathways - mapping your last ten patients; value adding steps (value stream mapping); patient journey templates (process templates); and spaghetti diagrams.[26]

Conventional process mapping

Conventional process mapping (CPM) is a detailed form of clinical audit used across different teams and organisations. It involves convening a large meeting of all the different teams/organisations caring for patients.[26, 27] This includes administrative staff and porters, whose perspectives about patients may be quite different to that of clinicians. The meeting is facilitated by an external, skilled facilitator and requires many other resources e.g. good venue (large room); time for people to attend; etc.[26] The main output of the meeting is an accurate picture of the entire patient journey as it stands. This picture will help reveal any apparent delays (bottlenecks), duplications, unnecessary steps and also highlight any efficient steps in the patient's journey.[26]

A key strength of the conventional process mapping method is that it brings together all stakeholders which makes it easier to implement any subsequent improvements to the patient journey.[28, 29] The coming together of the stakeholders is likely to make them 'process literate', they begin to appreciate the different roles played by the different teams/groups and how complex the patient journey can be.[29] However, conventional process mapping is very resource intensive and is logistically difficult to organise.[26-28] For this reason its use is limited.[26]

Non-conventional process mapping

To overcome some of the challenges associated with mapping the whole patient journey, non-conventional process mapping is sometimes used as an alternative to conventional process mapping. It involves mapping only part of the patient journey, or undertaking a small stream-lined mapping session.[26] This is a quicker approach and is suitable when there is insufficient time and resources to perform a full patient journey mapping. It can also be a useful starting point with plans to eventually progress to a full conventional process

mapping.[26] Non-conventional process mapping focuses on particular steps or teams deemed to have more problems or likely to have the biggest impact on patients.[26] Unfortunately redesigning only some steps or teams may result in additional problems being created elsewhere along the patient journey.[26, 30] For example reducing waiting times for patients in emergency departments (ED) without simultaneously enhancing in-patient discharge processes would still result in a 'bottleneck' as emergency department patients ready for admission would still have to wait for hospital beds to become available.[30]

Patient (patient/parent/carer) perspectives

Obtaining patient perspectives is another approach used for mapping or redesigning a patient journey. There are several ways of obtaining the perspectives of patients, including patient questionnaires, interviews, focus groups and patient shadowing.[26]

A questionnaire is a simple way of getting patient perspectives about their experiences/treatment journeys from a large number of people.[26, 31] However, a good balance of questions is necessary, bearing in mind that free text questions, while often providing much richer information tend to take much longer to analyse compared to multiple choice and Likert scale type questions.[26, 31] Deciding how to reach the target group is very important. For example, postal questionnaires can sometimes have very low response rates.[32] To increase response rates, questionnaires can be given to patients when they attend appointments and filled in while they wait to be seen then collected on the same day.[32]

Focus groups can also be used to collect data on patient perspectives. These provide more in-depth information on patient experiences than questionnaires, however, they can be quite difficult to set up. They require a good, accessible venue (with parking), a good facilitator and it may be a good idea to also provide refreshments for participants.[26, 33] Careful selection of participants is important as well as how to invite them to participate.[33]

Like focus groups, interviews tend to yield more information from participants than questionnaires. However, they require a trained interviewer (preferably external), suitable venue, audio recording and tend to take a much longer time to analyse than quantitative responses.[26, 33, 34] Questionnaires, focus groups and interviews all require informed consent from the participants.[26, 31, 33, 34] Ethics approval may also be required.

Shadowing a patient requires finding an external person to walk through the patient journey as a patient or with a patient, informally interviewing staff and patients and directly observing and experiencing the patient journey.[26, 27] Observation is a powerful approach as it can identify issues that staff are not willing to reveal in a formal interview or group setting, such as a conventional process mapping meeting.[26] The challenge is to find an external shadower who is unfamiliar with the processes but can confidently ask relevant questions.[26] Junior doctors/nurses or interns/students have been suggested as suitable for shadowing patients,[27] particularly at the start of their secondments before they become too familiar with the organisational processes.

When research involves children, ethics committees may stipulate additional requirements, such as working-with-children clearance and obtaining consents from older children that have reached the age of consent (in addition to parents' consents). This adds to the challenges of doing research in children.

Reviewing patient pathways

Patient journeys can also be mapped by reviewing patient pathways: mapping your last ten patients. In this method a sample of at least ten patients is selected and their medical information is retrieved to determine what they have experienced along their treatment journey over a period of time.[26, 35, 36] This technique focuses on major clinical milestones. It is relatively quick and easy to use but may not provide details on why particular things happen. A sample size of ten may also be too small to identify meaningful patterns or differences.[26] Accessing hospital medical information is not easy, particularly for external investigators.[35] Special permission from hospital clinical governance units is required and the information may be in different sources/formats including paper. Data extraction can be time consuming and requires the assistance of relevant staff from medical record departments.[35, 36] Assistance from relevant clinicians may also be needed. The use of a larger sample size (if possible) can improve the quality of the results and ensure results are more representative.[37]

Value stream mapping

Value stream mapping (VSM) or value adding steps is another technique for mapping a patient journey. Value stream mapping starts by examining the "current state" of the

patient pathway/journey and identifying all the key steps.[26, 27] Then, using 'lean thinking', all steps that "add value" (that is enhance patient experiences) are enhanced and "non-value" steps ("wastes") are eliminated or minimised.[27, 38] This will essentially result in the redesign of a "future state" which is more streamlined, efficient and of a higher quality than the current state.[26, 38] Some health care systems, (e.g. Flinders Medical Centre in Adelaide, South Australia) have successfully adopted and applied this approach in redesigning clinical processes.[39] Non-value steps tend to overlap with bottlenecks in the patient journey (e.g. waiting for lab results/waiting for a bed to be admitted from emergency department) thus removing these steps may result in improved flow.[38, 40] While it can be relatively easy to identify a bottleneck (non-value step) e.g. waiting for radiology tests, it may not always be possible to completely eliminate the bottleneck.[40] Similarly, removal of one bottleneck may create another one along the patient pathway,[38, 40] thus some bottlenecks can never be completely removed but can only be eased or minimised.

Patient journey templates

A patient journey template (process template) refers to a picture or a 'template' of what patients experience as they transverse through a process, measured in real time and developed based on professionals' and patients' perspectives.[25, 26] Key activities (milestones) from start to finish are identified and the time taken for each activity recorded for each patient in a small sample of patients.[26] The detailed unique experiences of each individual patient may not be revealed in the produced template – only the overall outline of the patient journey is revealed.[25] There can also be differences in the phases (milestones) of patient journeys identified by patients compared to those identified by professionals.[41]

Spaghetti diagrams

The spaghetti diagram is a simple technique used to establish the optimum layout for a department or ward based on the distances travelled by patients.[26] Initially, a floor plan of the department/ward is obtained. Lines are then drawn on the floor plan to map the movement or flow of patients as they navigate through different steps, processes or procedures.[26] Once drawn, the spaghetti diagram is a visual representation of patient processes and so helps to identify unnecessary patient movements (movement wastes) and where time can be saved.[26] For example, on days and times when there is increased number

of patients and space is limited in a department such as emergency or oncology clinic, there can be decreased flow of movement of patients due to overcrowding. Redesigning the patient movements thus may reduce delays and improve patient care.

1.3 PATIENT JOURNEYS IN CANCER

A number of studies have mapped the patient journeys of individuals with cancer. These are summarised in Table 1. Only one study[42] used conventional process mapping, the ideal methodology for whole patient journey mapping.[26] Four studies[36, 37, 44, 45] 'reviewed patient pathways' and five studies[31, 47, 48, 49, 50] obtained 'patient perspectives' as a means of mapping the patient journey.

Table 1.

Summary of studies that have mapped patient journeys in cancer

Author and year (Cancer type) **[ref. list no.]**	**Main country studied**	**Sample size**	**Methodology/ Methods**	**Key findings**	**Recommendations**
Paul et al. 2012 **(All types)** **[31]**	Australia (NSW)	146	Patient perspectives	52% of patients reported experiencing concern during at least one treatment phase	More research required into the factors which underlie these concerns in order to intervene and reduce distress to cancer patients
Murray et al. 2011 **(Colorectal)** **[36]**	New Zealand	1128	Reviewing patient pathways	Days from referral to treatment were longer for indigenous Maori people	Strategies are needed to increase the number of patients passing through each part of their cancer journey in a timely manner
Sloans et al. 2004 + Scott-Findlay et al. 2005 **(Various types**) **[37; 43]**	Canada	1979	Reviewing patient pathways	The initial staging of various cancers was revised and standardised	Accurate cancer staging is essential as survival estimates depend on this
Evans et al. 2013 **(Lung cancer)** **[42]**	Canada	None (N/A)	Conventional process mapping	Lung cancer disease pathways were refined through multi-disciplinary meetings	New lung cancer disease pathways for diagnosis and treatment became the standard of care for whole region of Ontario
Elliss-Brookes et al. 2012 **(Various types)** **[44]**	England, UK	739,667	Reviewing patient pathways	Patients presenting via the emergency route to diagnosis had substantially lower one-year relative survival	No recommendations made
Gerrand et al. 2015 **(Sarcoma)** **[45]**	England, UK	8,956	Reviewing patient pathways	GP referral/ED presentation were common diagnostic routes for sarcoma. ED presentation was common for the elderly/ paediatrics	Interventions to improve sarcoma diagnostic experience should target the very young, elderly and reduce emergency presentations
Crepaz & Curry 2013 **(Lymphoma)** **[46]**	Australia (NSW)	No sample size given	Multiple methods	Identification of areas where constraints/ delays for patients existed	A new 'future' more efficient patient journey with fewer steps (31 instead of 49 in the original journey)

Table 1 cont.

Author and year (Cancer type) [ref. list no.]	**Main country studied**	**Sample size**	**Methodology/ Methods**	**Key findings**	**Recommendations**
Guilhot et al. 2013 **(CML)** **[47]**	Brazil, France, Germany, Russia, Spain	50	Patient perspectives	Five stages of CML journey identified – crisis, hope, adaptation, new normal & uncertainty	CML patients require different kinds of information and support during different stages of their disease
Bhatnagar et al. 2014 **(Various types)** **[48]**	India	101	Patient perspectives	Cancer diagnosis delays were associated with poorer outcomes, but the delays can be prevented or reduced	Cancer patients' journey time can be improved by increasing awareness in the general population and educating primary care clinicians and getting the NGOs and governments on board
Molassiotis et al. 2010 **(Various types)** **[49]**	UK	74	Patient perspectives	Patient-related and PCP factors (e.g. initial misdiagnosis) were mainly responsible for delays in diagnosis of cancer	There is urgent need to raise public awareness of cancer and also improve cancer detection rates of primary care practitioners
Lowe et al. 2008 **(ALL)** **[50]**	England, UK	16 (4 focus groups)	Patient Perspectives (Focus groups)	The majority of families were satisfied with the care that they received	Paediatric Oncology Day Care Units should design, coordinate and deliver patient care around the needs of families – this is achieved only through listening to the families/patients themselves who are users of the services

Abbreviations:
ALL = acute lymphoblastic leukaemia
CML = chronic myeloid leukaemia
GP = general practitioner
ED = emergency department
NGO = non-governmental organisation
PCP = primary care practitioner

One study[46] used multiple methods (reviewing patient pathways, non-conventional process mapping, clinician/staff interviews and Essomenic technique). This study recommended a reduction in the processes a patient must experience from 49 to 31,[46] however, it did not mention the sample size used in the study. Using a combination of methods (e.g. patient perspectives and reviewing patient pathways) has been associated with improved quality of results.[26] Other mapping techniques, e.g. value stream mapping, patient templates and spaghetti diagrams[26] appear not to be commonly used for cancer patient journeys.

One of the studies that obtained patients' perspectives through focus groups,[51] investigated the experiences of parents of ALL patients with out-patient oncology care and found that families were generally satisfied with the care they received.

For the studies that used the patient pathways methodology,[36, 37, 44, 45] the sample sizes (1,128-729,667) were considerably larger than the minimum recommended for this technique (i.e. ten).[26]

Obtaining patient perspectives is an effective way of assessing quality of care from the patient's point of view. [26, 28] The patient is the only person who sees the whole journey as they move from one department (or unit) to another,[28] thus can be considered the best judge of their care. However, when mapping paediatric patient journeys, the patients may be too young to judge their experiences or give their perspectives. As such, parents are involved as representatives for the patients. When older children are involved, additional consent of the children (that have reached age of consent) should be sought so that their views are considered in addition to their parents' views. Unfortunately, patient perspectives about quality of care received are often obtained retrospectively (as was the case with the cancer journey studies reviewed) using questionnaires, interviews and focus groups, which depend on the patients recalling past care experiences.[31] Results may therefore be affected by recall bias.[31]

The eleven studies in Table 1 made general recommendations on how the cancer patient journey could be improved, however, they did not provide any concrete examples of practical strategies that could be implemented, e.g. potential use of electronic medical record (EMR) systems. EMRs are increasingly being adopted as a means of achieving total management of oncology patients.[51] However, limited work has investigated how the

introduction of an EMR could impact on the patient journey, in particular, the possibility of positively impacting on treatment delays.

1.4 AIMS AND SIGNIFICANCE

To date, acute lymphoblastic leukaemia (ALL) efforts have focused on the clinical management of this disease and on finding a cure through well-organised international efforts and clinical trials. Although previous research has mapped the patient journeys for other cancers in an attempt to improve the patient experience, there are a few studies that have sought to investigate the patient journeys of children with ALL.

ALL treatment has evolved significantly over the last few decades and the cure rate is now high. However, the treatment journey is long and complex, with patients on active treatment for 24 months or longer. Delays in treatment may occur in response to patients' individual reactions to treatments, which are difficult to predict, but also due to organisational issues, for example tests not being ordered or results unavailable to inform specific decision-making processes. Limited research has been conducted to identify the number, types and reasons for disruptions that occur during the journeys of patients with ALL. This study sought to explore in-depth, the current journey of ALL patients using a comprehensive review of patient medical record information. Specifically, the aims of the study were to:

1. Summarise the characteristics of acute lymphoblastic leukaemia (ALL) patients.

2. Identify key milestones of the ALL treatment journey.

3. Identify points in the treatment journey where a delay occurred, determine whether the delay could have been avoided and identify areas where efficiency of care delivery processes could potentially be improved.

Chapter Two: Methods

2.1 Study Site

The study was undertaken in the Oncology Department of a paediatric tertiary hospital in Sydney, New South Wales (NSW), Australia. This Oncology Department is the largest children's cancer unit in NSW. The Department comprises the main oncology ward (20 bed unit) and an isolation ward (17 bed unit, shared with non-oncology patients) for inpatient care, the Oncology Clinic or Oncology Treatment Centre (OTC) for outpatient care and rural/metropolitan outreach services. An estimated 120-150 new children with suspected cancer are referred to the department every year, 20-40 of whom are diagnosed with ALL. Patients are referred to the department after preliminary investigations at a primary health centre (general practitioner or small hospital).

2.2 Study Sample

Every patient aged 1-18 years who was newly diagnosed with ALL (ICD-10 classification of C91.0) during a one-year period (January 10th 2013 to January 10th 2014) was eligible for inclusion in the study. Patients who were not treated using the current registered international ALL clinical trial (Protocol AIEOP-BFM ALL 2009; clinical trial registry identifier: NCT01117441)[51] were excluded. Infants less than one-year-old and patients with relapsed ALL were also excluded as they are eligible for different protocols. Thus 30 consecutive patients (female, n=11; male, n=19) who were newly diagnosed with ALL at the hospital during the period were included in this study. Patients were grouped into two treatment groups according to their risk classification, namely, standard risk/medium risk (SR/MR; n=24) and high risk (HR; n=6).

2.3 ALL treatment protocols

"A protocol is a detailed plan of a scientific or medical experiment, treatment or procedure."[53] An ALL treatment protocol is a detailed plan for treatment of ALL. It contains information on what processes and procedures will be done, how and why; what drugs/treatments to be given; when they are to be given; what tests are done and when;

what to do when expected and unexpected adverse drug events happen etc.[53] ALL protocols, like other cancer treatment protocols are formulated by leading experts under the auspices of international leading children cancer research organisations, such as, BFM (Berlin-Frankfurt-Munster) study group, AIEOP (Associazione Italiana di Ematologia ed Oncologia Pediatrica) study group, Children's Oncology Group (COG) and St Judes Children's Research Hospital. They can be open (running) or closed international clinical trials where a number of developed countries collaborate in cancer treatment and research. AIEOP-BFM ALL 2009 (Study 9), the protocol in use at the study hospital is currently open and was still recruiting participants at the time of this study.

2.3.1 The Study 9 Protocol for treatment of ALL: AIEOP-BFM ALL 2009[52,54]

The Study 9 protocol comprises 24 months or 104 weeks of active treatment. The protocol is divided into a number of phases which are summarised in Figure 1 and Table 2.

Table 2.

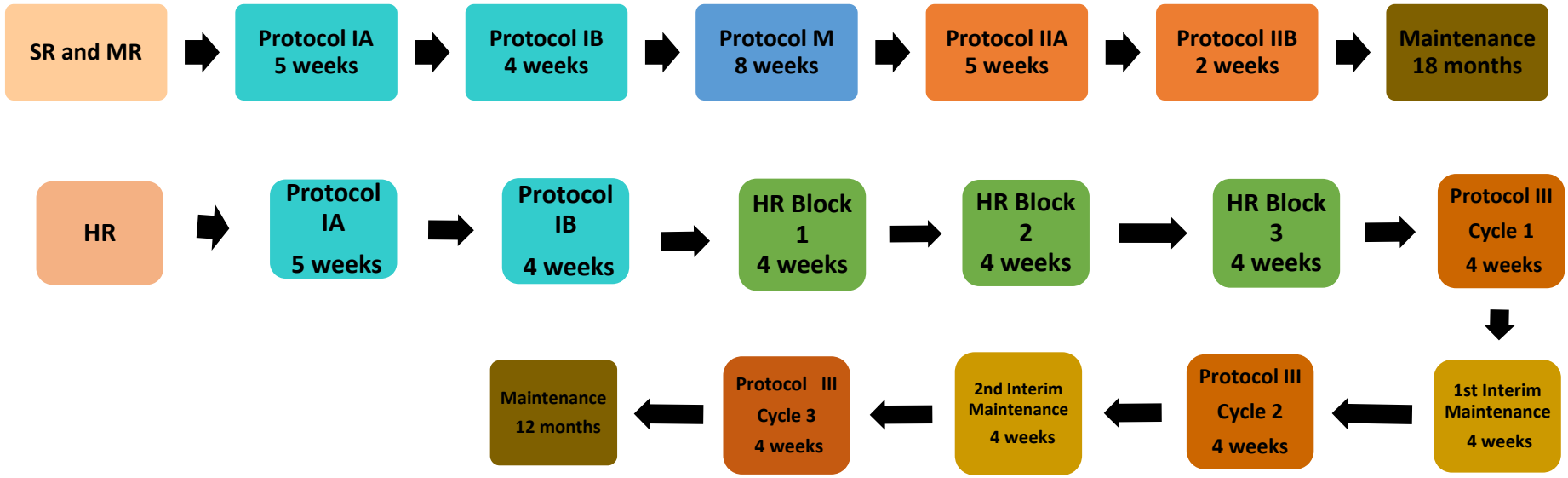
Phases of Study 9 ALL Protocol for HR and SR/MR patients, including duration of each phase

HR patients			**SR/MR patients**		
PROTOCOL I	A B	Days 1-29 Days 36-64	PROTOCOL I	A B	Days 1-29 Days 36-64
HR Block 1		Days 1-11	PROTOCOL	M	Days 1-56
HR Block 2		Days 1-11			
HR Block 3		Days 1-11			
PROTOCOL III Cycle 1 of 3	A&B	Days 1-28			
			PROTOCOL II	A B	Days 1-35 Days 36-49
1st INTERIM MAINTENANCE		Days 1-28			
PROTOCOL III Cycle 2 of 3	A&B	Days 1-28			
2nd INTERIM MAINTENANCE		Days 1-28			
PROTOCOL III Cycle 3 of 3	A&B	Days 1-28			
MAINTENANCE		12 Months	MAINTENANCE		18 Months

The first phase of treatment (Protocol IA and IB [induction consolidation] – Days 1-64) is the same for all patients. Thereafter the phases are different for SR/MR and HR patients. Patient risk classification is based on the results of a bone marrow test performed on Day 33 of treatment to assess burden of disease (or minimal residual disease or MRD) after response to initial treatment. Patients classified as HR receive more intensive treatment compared to SR/MR patients, as described below. Please also see Appendix A for further details on the drugs, doses, days given and routes of administration.

Figure 1.

Study 9 ALL Treatment Protocol: AIEOP-BFM ALL 2009 Flow Diagram



Adapted from Conter et al. 2010 and Clinical Trials Registry NCT01117441
SR = standard risk
MR = medium risk
HR = high risk

SR/MR Treatment Phases

A total of 12-18 hospital admissions and 64-85 out-patient visits were expected of each SR/MR patient in order to complete all treatments and procedures.

Protocol IA (Induction) is the first component of the initial phase of treatment. It starts as soon as possible following confirmation of a diagnosis. Five drugs are given:

- Prednisolone /or dexamethasone orally on Days 1-28 then tapered over 9 days
- Intrathecal Methotrexate on Day 1 and 15 (additional dose on Day 19 for CNS positive patients)
- Vincristine and Daunorubicin, four doses each on Days 8, 16, 22 and 29 (some patients maybe randomised to receive only two Daunorubicin doses on Day 8 and 16)
- Peg-Asparaginase, two doses on Day 12 and 26 (14 days apart)

The first eight days of treatment are given to patients during their initial admission as an in-patient. Patients are usually discharged on Day 8 and further treatments in this component are given to patients as an out-patient in the hospital's oncology out-patient clinic on Days 12, 15, 16, 22 and 29. Unlike in other phases, treatments in this Induction phase are usually given irrespective of blood counts, unless the patient is very unwell. This is because the leukaemia disease process itself can lower blood cell counts and chemotherapy is necessary to keep the disease under control.

Protocol IB (Consolidation), the second component of Protocol I is 28 days in duration from Day 36-64. Patients are still tapering prednisolone/or dexamethasone from IA when they start IB. They are also required to have satisfactory blood counts and a general good clinical condition before commencing Protocol IB. Four drugs are given in this component:

- Cyclophosphamide, two doses on Days 36 and 64
- Cytarabine, four consecutive doses on each of the four weeks (total of 16 doses)
- Mercaptopurine orally Days 36-63
- Intrathecal Methotrexate on Day 45 and 59

Patients attend oncology clinic on Days 36, 43, 45, 50, 57, 59 and 64. For each of the four Cytarabine blocks, patients only attend the clinic to be commenced treatment, the other three days of treatment are given at home by an oncology nurse.

Protocol M (CNS prophylaxis) phase begins two weeks after completion of IB. Four drugs are given:

- Oral Mercaptopurine daily on Days 1-56.
- High dose Methotrexate (HD MTX) and intrathecal Methotrexate every two weeks on Days 8, 22, 36 and 50. Patients need to be admitted into hospital for these four treatments as they require monitoring and clinical support.
- Leucovorin (Folinic Acid), at least three doses, given at 42, 48 and 54 hours after start of each HD MTX

Protocol II (Re-Induction) begins two weeks after the end of Protocol M, and lasts 49 days. It can further be sub-divided into IIA, Days 1-29 and IIB, Days 36-49.

Four drugs are given during IIA:

- Dexamethasone on Days 1-21 then tapered over 9 days
- Vincristine and Doxorubicin, four doses each on Days 8, 15, 22 and 29
- Peg-Asparaginase, one dose on Day 8
- Intrathecal Methotrexate may also be given on Days 1 and 18 for CNS positive patients

Patients are required to attend the oncology clinic on Day 1 (to start the Protocol), and Days 8, 15, 18, 22 and 29 for these treatments.

Four drugs are given in IIB:

- Oral Thioguanine on Days 36-49
- Cyclophosphamide on Day 36
- Cytarabine four consecutive doses each week for two weeks (total of eight doses)
- Intrathecal Methotrexate on Days 38 and 45

Patients attend the oncology clinic on Days 36, 38, 43 and 45 to receive these treatments.

The Maintenance Phase starts two weeks after the completion of Protocol IIB, if blood counts are satisfactory and continues until the completion of treatment (24 months or 104

weeks). This equates to 18 months of maintenance if no significant delays have occurred during the other treatment phases. Two drugs are given orally throughout maintenance:

- Mercaptopurine once daily at night
- Methotrexate once a week, same day of the week

Patients attend the oncology clinic on Day 1, to start Maintenance and then every two weeks for blood tests to check blood counts. Doses of the Maintenance phase drugs are adjusted accordingly, in the same ratio, to keep the total white cell count (WCC) below 3000 per microliter. Therapy may be temporarily suspended if significant toxicities occur.

During the Maintenance Phase Intrathecal Methotrexate and cranial radiotherapy may also be given to some eligible patients that are CNS positive.

HR Treatment Phases

Like SR/MR patients, HR patients also complete Protocols IA and IB. Patients require at least six days' hospital admission for each of the HR Blocks 1, 2 and 3; however, treatments in Protocol III, Interim Maintenance and Maintenance are administered to patients as out-patients. In total 16-22 hospital admissions and 70-84 out-patient visits were expected of each HR patient to complete all treatments and procedures.

HR Block 1 starts two weeks after completion of Protocol IB and like HR Blocks 2 and 3 lasts 3-4 weeks (11 days for treatment and 10-17 days to allow for blood counts recovery).

Nine drugs are administered during HR Block 1:

- Dexamethasone on Days 1-5
- Vincristine, two doses on Days 2 and 6
- High Dose Methotrexate (HD MTX) and intrathecal Methotrexate on Day 1
- Leucovorin (Folinic Acid), at least three doses, given at 42, 48 and 54 hours after start of HD MTX
- High Dose Cytarabine (HD Ara-C), two doses 12 hours apart on Day 5
- Cyclophosphamide, five doses given 12 hours apart on Days 2-4
- Peg-Asparaginase on Day 6
- Pegfilgrastim (Peg-GCSF) on Day 11 or regular Filgrastim (GCSF) daily from Day 11 until neutrophil recovery for patients weighing less than 10kg

HR Block 2 starts four weeks after the start of HR Block 1 but can be given up to one week earlier if blood counts recover early. For the purpose of calculating delays in this study, the full four-week period was allowed between the starting points of the HR blocks.

Nine drugs are also given in HR block 2:

- Dexamethasone on Days 1-5
- Vindesine, two doses on Days 2 and 6
- HD MTX and intrathecal Methotrexate on Day 1
- Leucovorin (Folinic Acid), at least three doses, given at 42, 48 and 54 hours after start of HD MTX
- Ifosfamide, five doses given 12 hours apart on Days 2-4
- Daunorubicin on Day 5
- Peg-Asparaginase on Day 6
- Peg-GCSF on Day 11 or regular GCSF daily from Day 11 until neutrophil recovery for patients weighing less than 10kg

In HR Block 3, six drugs are administered, namely:

- Dexamethasone on Days 1-5
- Intrathecal Methotrexate on Day 1
- High Dose Cytarabine (HD Ara-C), four doses administered 12 hours apart on Days 1-2
- Etoposide (as Phosphate), five doses administered 12 hours apart on Days 3-5
- Peg-Asparaginase on Day 6
- Peg-GCSF on Day 11 or regular GCSF daily from Day 11 until neutrophil recovery for patients weighing less than 10kg

Protocol III (Re-Intensification) is a re-intensification treatment phase repeated three times as cycles 1-3 with Interim Maintenance phases between them. Cycle 1 commences four weeks after the start of HR Block 3. Each Protocol III cycle lasts four weeks. Days 1-14 are referred to as III A and Days 15-28 as III B.

A total of eight drugs are given during each cycle of Protocol III:

- Dexamethasone on Days 1-14 then tapered over 9 days

- Vincristine and Doxorubicin, two doses each on Days 1 and 8
- Peg-Asparaginase on Day 1
- Cyclophosphamide on Day 15
- Cytarabine, eight doses on Days 15-18 and 22-25
- Thioguanine, orally on Days 15-28
- Intrathecal Methotrexate on Days 17 and 24; and an extra dose on Day 1 for CNS positive patients.

Patients have to attend the oncology clinic on Day 1 to start the cycle, then on Days 8, 15, 17, 22 and 24 for treatments.

Interim Maintenance phase starts one week after the end of Cycles 1 and 2 of Protocol III if blood counts have recovered and lasts a maximum of four weeks. It may be given for a shorter duration if blood counts are slow to recover; or not at all if blood count recovery has not fully occurred during the four weeks that the Interim Maintenance is due. A one-week treatment break is given between the completion of Interim Maintenance and the start of the subsequent cycle of Protocol III. For the purposes of calculating delays in this study, a six-week interval was allowed between the cycles of Protocol III.

The two oral drugs given here are:

- Mercaptopurine once daily at night
- Methotrexate once weekly

Cranial radiotherapy is also scheduled during this period for eligible patients who are CNS positive.

Maintenance phase starts two weeks after completion of Cycle 3 Protocol III and is similar to SR/MR Maintenance, except that it is 12 months in duration. And like SR/MR patients, the total duration of active treatment for HR patients is 24 months or 104 weeks (728 days).

2.4 Procedures

Data on patient demographics; treatment dates; and supportive care (e.g. unplanned hospital admissions) for patients in the study sample were extracted via an in-depth retrospective audit of clinical information systems and paper records. Table 3 shows the different sources of data extracted.

Table 3.

Sources of data and data elements extracted

Data source	**Data extracted**
Paper chemotherapy drug charts	• Dates chemotherapy treatments were administered
Oncology Department electronic records	• Patient gender • Age at diagnosis • Immunophenotype • White cell count at diagnosis • Risk stratification • Day 15 minimal residual disease (MRD) • Day 33 remission status
Electronic medical record (Powerchart/Cerner)*	• Date of presentation • Date of start of steroids (treatment) • Reasons for treatment delays • Number of hospital admissions • Number of oncology clinic attendances • Number of PICU admissions
Hospital Blood Bank	• Number of transfusions (platelets, red cells, albumin, fresh frozen plasma etc.)

*Includes imaged/scanned documents (in-patient medication charts; clinical notes); pathology results; etc.

Extraction of the data was difficult and time-consuming, and assistance was sought from relevant staff working in the hospital blood bank, medical records department and oncology department. On average, it took 5.5 hours to extract the required data for each standard risk or medium risk patient and approximately 6.5 hours for each high risk patient.

Based on the six key phases for SR/MR patients and eleven phases for HR patients (please see Figure 1 and Table 2), the number of expected treatment visits to the hospital were calculated. In total SR/MR patients were expected to visit 21 times and HR patients 26 times up to the start of the Maintenance Phase. This excluded: the two-weekly visits during the Maintenance Phase; visits for bone marrow procedures; intrathecal therapies; cranial radiotherapy and extra treatments for selected patients because of clinical trial randomisations.

In order to complete all treatments and procedures during the entire two-year treatment period, SR/MR patients were expected to have 12-18 admissions and 64-85 oncology clinic visits, whilst HR patients expected 16-22 admissions and 70-84 oncology clinic visits. Any admissions/visits above these figures were for supportive care.

The start date of treatment was verified from two sources (paper chemotherapy drug chart and scanned in-patient medication chart in electronic clinical records). Once this start date was determined, treatment-date-tracking "roadmaps" (used by oncology clinicians) were used to determine the expected (intended) due date for each subsequent treatment visit, that is, 21 and 26 visits for SR/MR patients and HR patients respectively. Some treatments were administered at home orally by a parent or intravenously by an oncology outreach nurse and, as such, did not require the patient to visit the hospital. The oncology clinic at the hospital is closed on weekends and public holidays, and as such, out-patient treatment due dates that fell on weekends/public holidays were moved to the next available working day.

Delays in treatment were calculated as the difference between actual date a treatment was administered and the intended (expected) date of treatment. When a delay occurred, the expected due dates for the subsequent treatment visits were adjusted so that the delays at each treatment visit as well as the cumulative delays were recorded for each patient. A treatment visit delay of 1-2 days' duration (and a total cumulative delay of less than three days duration over the entire treatment journey) was not considered clinically important, so it was excluded as a delay in this study. Total cumulative delays which exceed 6-8 weeks (42-56 days) for the entire 24-months treatment period are considered clinically significant at the study hospital. To identify the reasons for each delay, a thorough search of documentation in the electronic clinical records was undertaken. Where the reason for a delay could not be identified (approximately five situations), the case was discussed with the treating clinician. Delay reasons were classified as Low Counts (LC), other ToxiCities (TC), Patient (patient and family social) Factors (PF), and System (hospital or organisational) Factors (SF). Please refer to Table 4. Some of the treatment visits in the Study 9 Protocol that have no blood counts requirements (e.g. Protocol I A Day 1-29 – Induction phase) would usually proceed even when blood counts were low provided the patient was clinically well. Delays in such visits were generally minimum and were never as a result of low counts. Low counts, other toxicities and patient factors were clearly documented in the patients' clinical notes. However, system factors were not always clearly documented. Where a delay longer than two days' duration occurred and there was no documented reason for it and a discussion with the clinician failed to classify it otherwise, such a delay was then classified as system related.

Table 4.

Delay reasons classification, codes, definitions and examples

Delay reasons	**Delay codes**	**Definitions and examples**
Low counts	LC	Less severe form of toxicity, e.g. low blood cells counts (white cells, neutrophils, red cells, platelets etc.). Usually no admission required as patients are managed as out-patient.
Other toxicities	TC	Hospital or PICU admission for treatment- related adverse effects e.g. febrile neutropenia, pancreatitis, mucositis etc.
Patient factors (=patient and family social factors)	PF	Patient/family did not attend appointment; regional patient given time to visit home; social/school reason (e.g. birthday, graduation, school function, exam); family concern related to parent or sibling or other family member; and financial reason (e.g. patient/parent cannot afford to come to hospital for treatment or review)
System factors (=hospital or organisational factors)	SF	Bookings not done, no bed available, chemotherapy not ordered or prepared, results not available, no documented reason for the delay longer than two days' duration
Low counts/ other toxicities or vice versa	LC/TC or TC/LC	Low blood counts cause initial delay and other toxicities further extend that delay resulting in admission OR vice versa

The extracted data were de-identified, entered into an excel spreadsheet, collated, checked and analysed. Patients were grouped into two groups according to their risk classification, i.e. standard risk/medium risk (SR/MR) and high risk (HR).

Descriptive statistics were undertaken on all variables to provide a profile of patients in the study. To test the significance differences in treatment delays, IBM SPSS Statistics 23 software was used to make the following comparisons between:

1. Males and females in the SR/MR group at Day 36 Protocol I B, Day 64 Protocol I B, Day 50 Protocol M, Day 43 Protocol II B and start of Maintenance Phase.
2. SR/MR and HR patient groups at Days 36 and 64 Protocol I B when both groups were still receiving the same treatments.

2.5 Ethics

Ethics approval was obtained from the Hospital's Network Human Research Ethics Committee (LNR/16/SCHN/101) and ratified by Macquarie University Human Research Ethics Committee (MQ ethics ref. no. 5201600326).

Chapter Three: Results

3.1 Patients' characteristics

The study sample consisted of 30 patients of whom 63% (n=19) were male and 37% (n=11) were female. The characteristics of the patients included in the study and their risk classification are summarised in Table 5. The median patient age at diagnosis was 4.8 years (range = 1.4-17). Seventy-seven percent (n=23) of the patients were under the age of ten at diagnosis, while 23% (n=7) were aged ten and older. Three of these seven patients that were over the age of ten were classified as high risk.

Table 5.

Patient characteristics and risk classification

Patient characteristics	No. of patients	Percentage
SR/MR	**24**	
Female	**9**	**37.5**
Pre B	9	37.5
T-ALL	0	0
Male	**15**	**62.5**
Pre B	12	50
T-ALL	3	12.5
HR	**6**	
Female	**2**	**33.3**
Pre B	2	33.3
T-ALL	0	0
Male	**4**	**66.7**
Pre B	2	33.3
T-ALL	2	33.3

Key: SR = standard risk
MR = medium risk
HR = high risk
Pre-B = precursor B-ALL
T-ALL = T-cell ALL

Patients were classified as standard risk (SR; n=11), medium risk (MR; n=13) and high risk (HR; n=6). Fifty percent (n=3) of the HR patients were over the age of ten. Eighty-three percent (n=25) of patients had Precursor B (Pre B) ALL and 17% (n=5) had T-cell ALL (T-ALL). All the T-ALL patients were male. Sixty-seven percent (n=20) of patients had a white cell count (WCC) lower than $20x10^9$/L at diagnosis and 87% (n=26) were lower than $50x10^9$/L.

3.2 Time from presentation to diagnosis and start of treatment

From the time a patient presented at the hospital it took on average 1.4 days (range = 0-4) for a diagnosis of ALL to be confirmed. Seventy percent (n=21) of the patients were diagnosed within 24 hours of presentation and 13% (n=4) within 12 hours. The timely diagnosis may have been due to the fact that patients presented at the tertiary study hospital with a suspected leukaemia diagnosis following preliminary investigations at a smaller hospital or general practitioner. Time of presentation seemed to also play a role as patients who presented by 12 midday Monday to Friday tended to be diagnosed within 12 hours of presentation, while weekend and public holiday presentations resulted in delays in confirmation of diagnosis.

It took on average one (0.97) day (range = 0-3) for patients to be commenced on treatment from the time they were diagnosed. Seventy-three percent (n=22) of patients commenced treatment within 24 hours of diagnosis, while 17% (n=5) commenced after two days and the remaining 10% (n=3) commenced treatment three days after diagnosis.

Thus, it took on average 2.4 days for patients to commence treatment from the time they presented at the hospital. Twenty-three percent (n=7) of patients were commenced on treatment within 24 hours of presentation, 33% (n=10) after two days, 27% (n=8) after three days, and the remaining 17% (n=5) were commenced on treatment four days after presentation.

3.3 Completion of key treatment milestones

All SR/MR patients completed the key milestones of the treatment journey. One HR patient (Patient number 2) could not complete all the milestones because of toxicities. This patient missed ten cycles of treatments but had their Maintenance phase started 49 days earlier and continued for an extra 174 days.

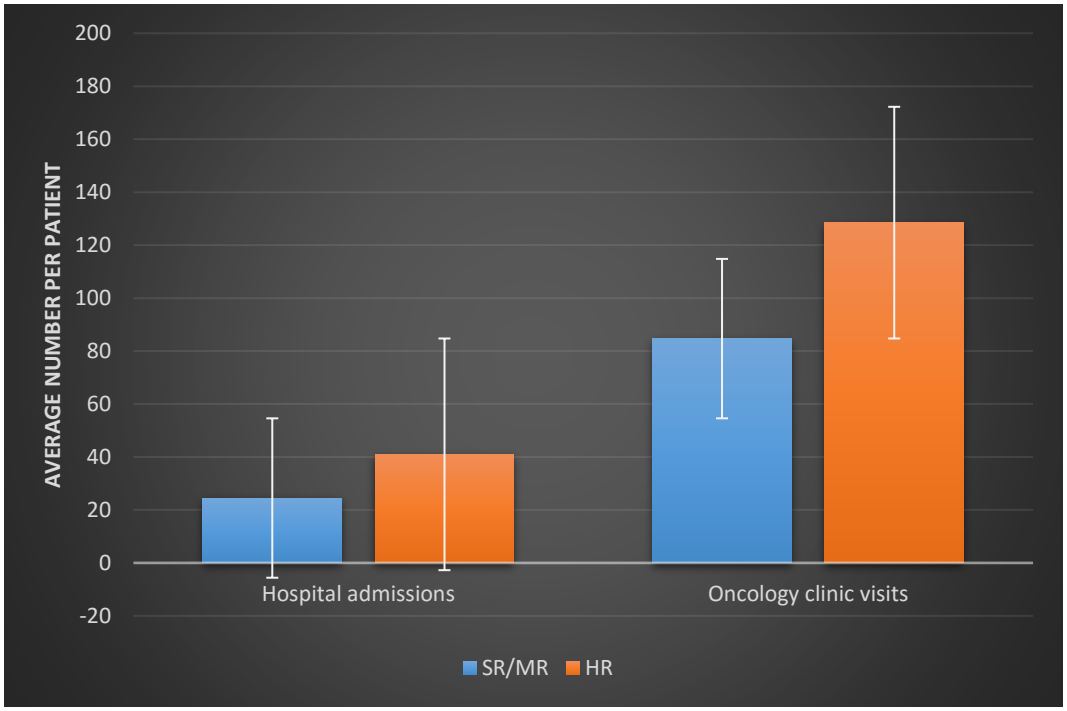
3.4 Total hospital admissions and oncology clinic visits

The average number of hospital admissions and average number of oncology clinic visits for both SR/MR and HR patients over the course of their entire treatment period are shown in Figure 2. HR patients had more admissions and clinic visits than SR/MR patients. The number of hospital admissions for SR/MR patients ranged from 17-36 and for HR patients ranged from 30-71, while the number of clinic visits for SR/MR and HR patients ranged from 53-117 and 77-169 respectively.

In order to complete all treatments and procedures during the entire two-year treatment period, SR/MR patients were anticipated to have 12-18 admissions and 64-85 clinic visits, whilst HR patients anticipated 16-22 admissions and 70-84 clinic visits. Any admissions/visits above these anticipated figures were for supportive care.

Figure 2.

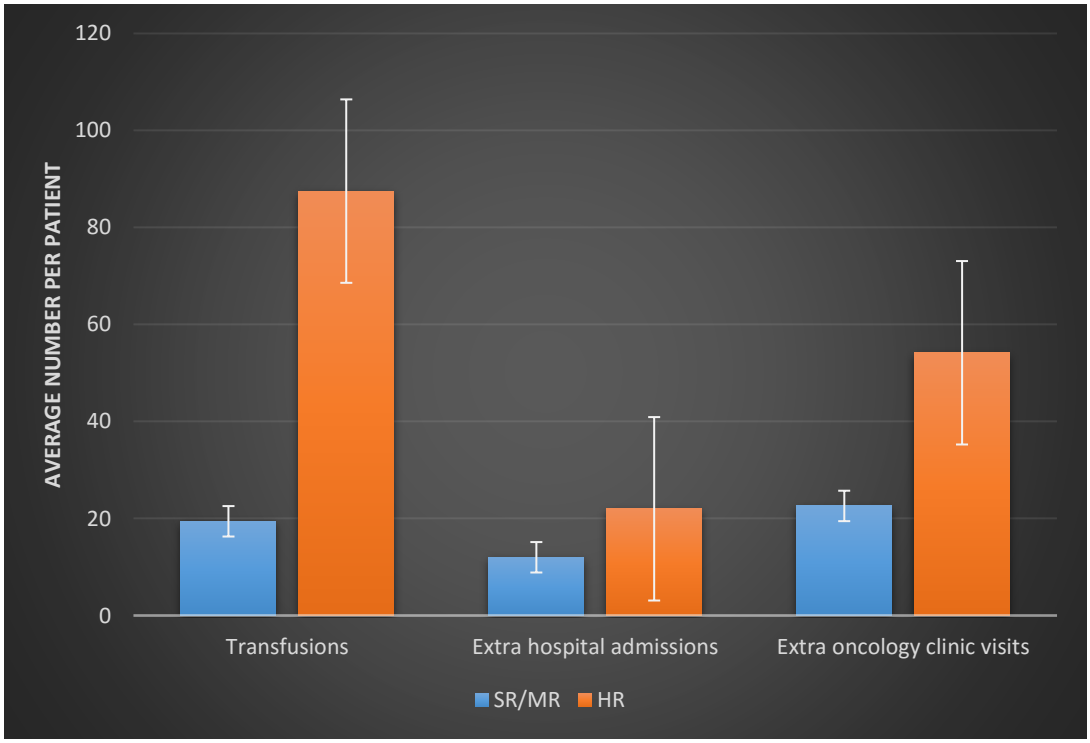
Average number of hospital admissions and oncology clinic visits for SR/MR (n=24) and HR (n=6) patients



A large number of hospital admissions and oncology clinic visits were for supportive care. Supportive care was provided to all patients for management of treatment related toxicities. This care was in the form of extra (more than anticipated) hospital admissions, extra oncology clinic visits, blood product transfusions, and paediatric intensive care unit (PICU) admissions for those patients that experienced severe toxicities. Each SR/MR patient in the study sample had on average 12 extra admissions (range = 5-24), 23 extra clinic visits (range = 2-44) and 19 transfusions (range = 4-61). Each HR patient had on average 22 extra hospital admissions (range = 9-55), 54 extra clinic visits (range = 7-95) and 88 transfusions (range = 61-139). Seventeen percent (n=4) of SR/MR patients had a PICU admission and 33% (n=2) of HR patients had a PICU admission. Figure 3 shows a summary of some of the supportive care provided to the SR/MR and HR patients.

Figure 3.

Some of the supportive care provided to SR/MR (n=24) and HR (n=6) patients during their treatment journey



As shown in Figure 3, HR patients received more transfusions, more hospital admissions and additional oncology clinic visits than the SR/MR patients.

3.5 Treatment delays

3.5.1 SR/MR treatment delays

By the start of the Maintenance phase, 96% (n=23) of SR/MR patients had experienced at least one treatment delay. Patients experienced on average 4.3 treatment delays during their 21 treatment visits. This equated to an average of 33 days of treatment delay per patient (median 28 days; range = 7-115). Only one patient (Patient no. 17) in the SR/MR group experienced no delay throughout the entire journey.

Figure 4a shows the delays experienced by SR/MR patients as well as the cumulative delays across their treatment journey. During the initial 29 days of treatment (induction), there were virtually no delays experienced by patients. However, Day 36 of Protocol II B was associated with the longest average delay (8.5 days of treatment delay per patient), while there were no delays experienced by any patient at Day 15 of Protocol II A.

Figure 4b shows the treatment journey of a single patient (Patient number 14) who experienced the longest cumulative delay in the SR/MR treatment group.

Figure 4a.
The average length of delays (raw and cumulative) experienced by SR/MR patients across their treatment journey (n=23)

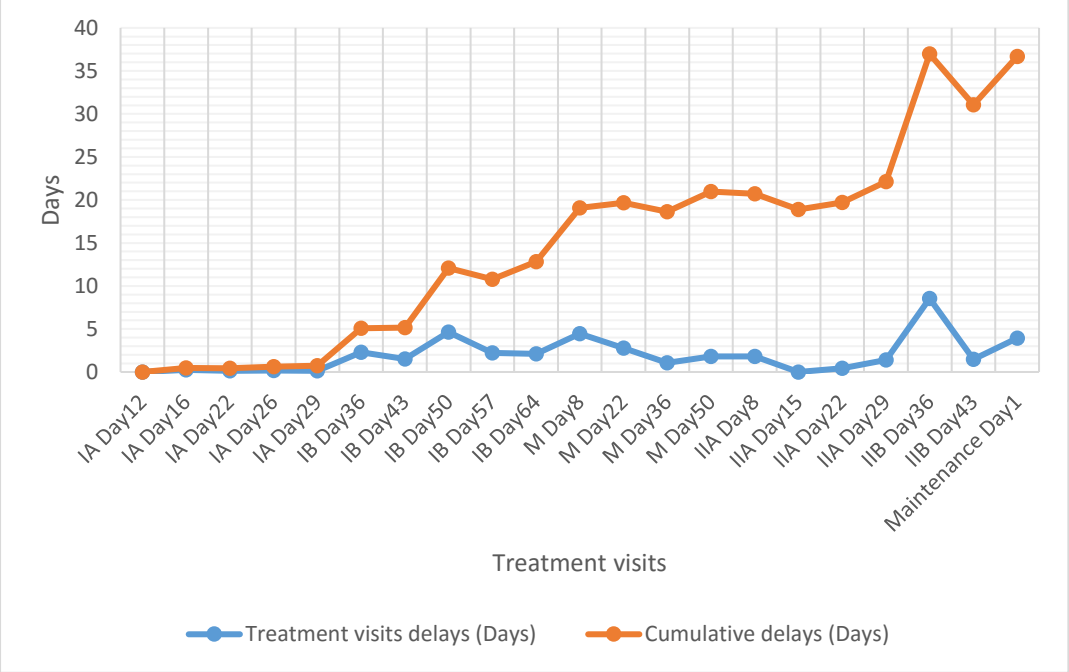
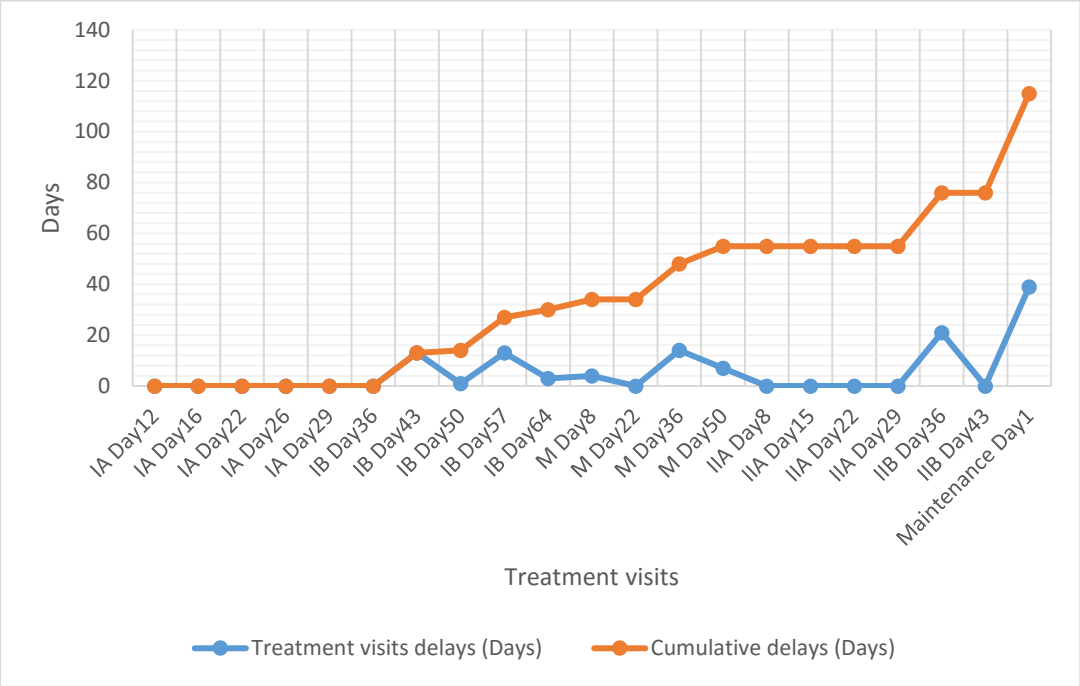


Figure 4b.

The treatment journey of a single patient who experienced the longest cumulative delay in the SR/MR treatment group (Patient no. 14)



The number and percentage of treatment visit delays for SR/MR patients are shown in Table 6. On average SR/MR patients experienced delays four times during the 21 visit journey (range = 0-9 visits delays).

Table 6.

The number and percentage of treatment visit delays for the SR/MR patient group (n=24)

Individual SR/MR Patients I.D.	No. of treatment visits delayed	Percentage of treatment visits which were delayed (out of 21)
6	9	43
7	8	38
14	8	38
5	6	29
1	5	24
9	5	24
13	5	24
19	5	24
27	5	24
10	4	19
12	4	19
20	4	19
24	4	19
25	4	19
26	4	19
3	3	14
15	3	14
16	3	14
23	3	14
28	3	14
29	2	10
30	2	10
22	1	5
17	0	0

Total number of treatment visits = 21

SR/MR males versus females

Male patients initially experienced more delays than female patients, although this difference diminished over time. At Day 36 Protocol I B, male patients had experienced significantly more delays (mean=33.8 days, SD=15.3) than females (mean=19.4 days, SD=10.9); t(22)=-2.46, p=0.022). However, the difference between males and females was not statistically significant at Day 64 Protocol I B (t= -0.37, p=0.712); Day 50 Protocol M (t= -

1.60, p=0.123); Day 43 Protocol II B (t= -1.96, p=0.063); or the start of Maintenance Phase (t= -2.68, p=0.107).

Reasons for treatment delays in SR/MR patients

Eighty-eight percent of SR/MR patients' treatment delays were due to, low counts (LC), other toxicities (TC) or to a combination of these factors. Ten percent of delays were due to system factors (SF) and 2% due to patient factors (PF).

Table 7 shows a summary of the numbers and reasons for delays for patients in the SR/MR group by treatment phase, and Table 8 shows the distribution of treatment delays by reason and the average length of delays for each patient in the SR/MR group.

Table 7.

Number of SR/MR patients experiencing delays in treatment phases by reason for delay

SR/MR treatment phases	Reasons for treatment delays					
	Other toxicities	Low counts	Other toxicities/ Low counts and vice versa	System factors	Patient factors	Total
IA	2	0	0	0	0	2
IB	12	11	5	2	0	30
M	11	11	1	6	1	30
IIA	6	3	2	1	1	13
IIB	11	6	4	0	0	21
Maintenance Day1	0	2	1	1	0	4
Total	**42 (42%)**	**33 (33%)**	**13 (13%)**	**10 (10%)**	**2 (2%)**	**100 (100%)**

Key: TC = Other toxicities
LC = Low counts
SF = System factors (Hospital or organisational factors)
PF = Patient factors (patient and family social factors)

Table 8.

Distribution of treatment delays by reasons and average length of each delay experienced by SR/MR patients (n=24)

Individual SR/MR Patients I.D. (n=24)	Reasons for treatment delays					No. of treatment visits delayed	Average delay length (days)	Journey Cum. Delays (days)
	Other toxicities	Low counts	Other toxicities/ low counts and vice versa	System factors	Patient factors			
1	1	3	0	1	0	5	7	35
3	2	1	0	0	0	3	8	24
5	0	4	1	0	1	6	8.5	51
6	5	2	0	2	0	9	6.2	56
7	3	0	1	4	0	8	5	40
9	3	0	2	0	0	5	9.4	47
10	3	1	0	0	0	4	3.5	14
12	2	2	0	0	0	4	5.5	22
13	2	2	0	1	0	5	5.6	28
14	2	3	2	1	0	8	14.4	115
15	2	1	0	0	0	3	6.7	20
16	2	0	1	0	0	3	10	30
17	0	0	0	0	0	0	0	-4*
19	2	1	1	1	0	5	5	25
20	1	3	0	0	0	4	9.3	37
22	1	0	0	0	0	1	7	7
23	2	1	0	0	0	3	4.7	14
24	1	1	2	0	0	4	10.5	42
25	2	1	1	0	0	4	7	28
26	1	3	0	0	0	4	6.3	25
27	2	3	0	0	0	5	7	35
28	2	0	0	0	1	3	7.3	22
29	0	1	1	0	0	2	11.5	23
30	1	0	1	0	0	2	6.5	13
Total	**42 (42%)**	**33 (33%)**	**13 (13%)**	**10 (10%)**	**2 (2%)**	**100 (100%)**		

*Negative delay means treatments were brought forward – this patient's Maintenance phase was started four days earlier

Key: TC = Other toxicities SF = System factors (Hospital or organisational factors)
LC = Low counts PF = Patient factors (patient and family social factors)

3.5.2 HR treatment delays

One patient, who missed ten cycles of treatments prior to the Maintenance phase due to toxicities was excluded from the following analysis. This patient had their Maintenance phase started 49 days earlier because they had missed earlier treatments.

All of the remaining HR patients (n=5) experienced at least one treatment delay by the start of the Maintenance Phase. HR patients experienced an average of 94 days of treatment delay (median 101, range = 36-152). HR delays were most common at Day 15 of Protocol III Cycle 2, where there was an average of 13 days of treatment delay per patient. Figure 5a shows the average treatment visit delays and average cumulative delays for HR patients. Figure 5b shows the delays experienced by a single patient (Patient number 21) who experienced the longest delays in the HR treatment group.

Figure 5a.

The average length of treatment delays (raw and cumulative) experienced by HR patients across their treatment journey (n=5)

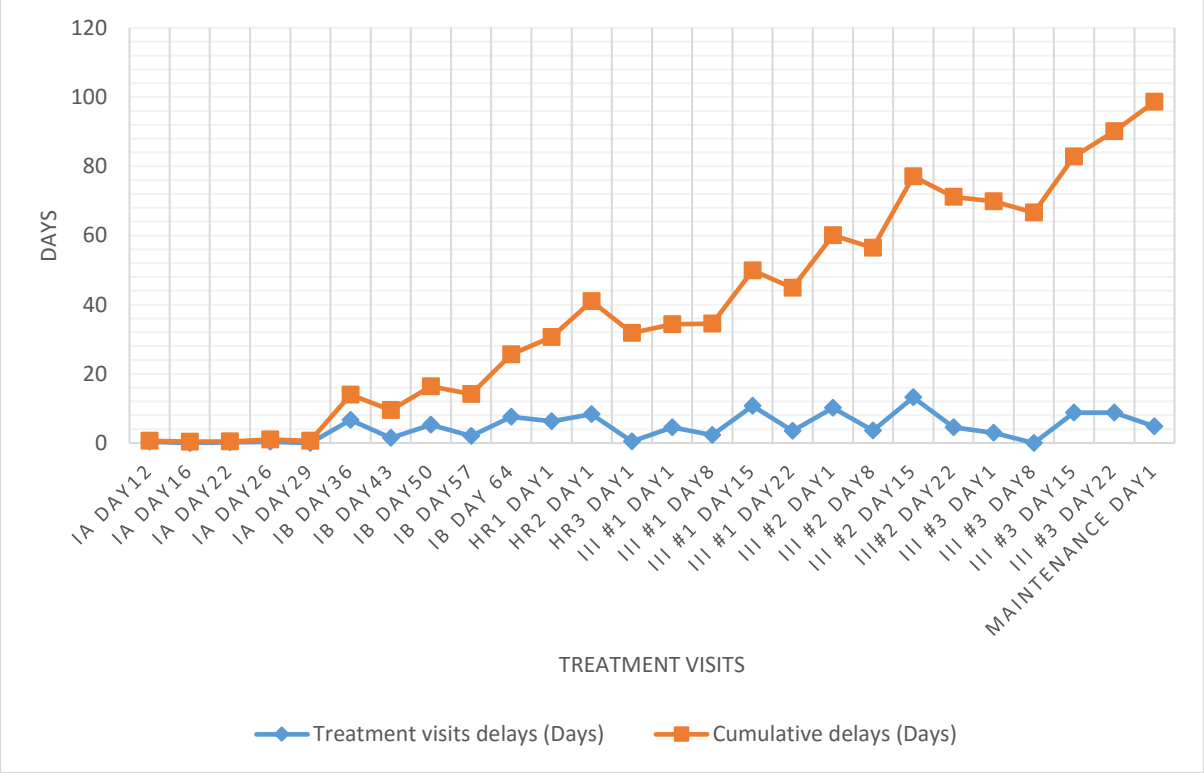
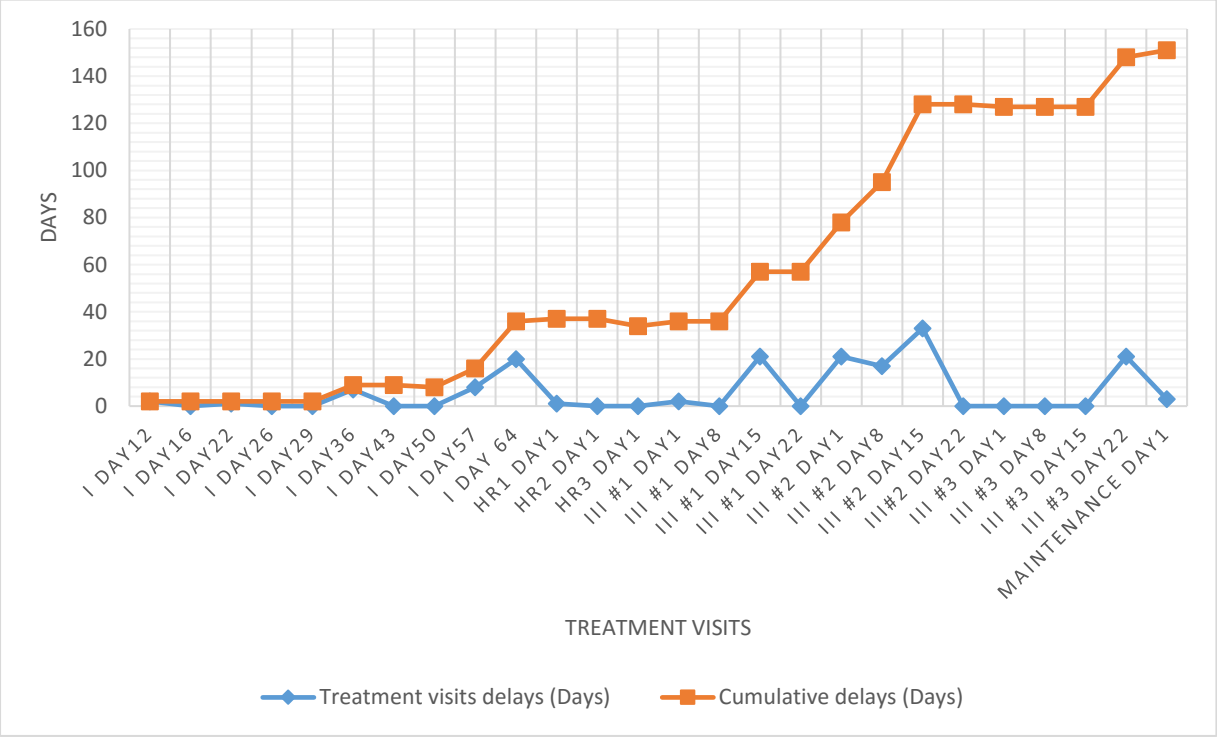


Figure 5b.

The treatment journey of a single patient who experienced the longest cumulative delays in the HR treatment group (Patient no. 21)



The number and percentage of treatment visit delays for HR patients are shown in Table 9. On average HR patients experienced delays eight times during the 26 visit journey (range = 5-9 visit delays).

Table 9.

Number and percentage of treatment visit delays for the HR patient group (n=6)

HR Patient I.D.	No. of treatment visits delayed	Percentage of treatment visits which were delayed (out of 26)
2	*	*
8	9	35
11	9	35
21	9	35
4	7	27
18	5	19

Total number of treatment visits = 26

*HR Patient no. 2 excluded because of some missed treatments due to toxicities

Reasons for treatment delays in HR patients

At the start of the Maintenance Phase, 93% of the treatment delays in HR patients were attributed to low counts (LC) and other toxicities (TC) or to a combination of these factors. Seven percent of delays were due to system factors (SF) and none were due to patient factors (PF).

Table 10 shows a summary of the numbers and reasons for delays for HR patients by treatment phase, and Table 11 shows the distribution of treatment delays by reason and the average length of delays for each patient in the HR group.

Table 10.

Number of HR patients experiencing delays in treatment phases by reasons for delay

HR treatment phases	Reasons for treatment delays					
	Other toxicities	Low counts	Other toxicities/ low counts and vice versa	System factors	Patient factors	Totals
IA	1	0	0	1	0	2
IB	4	4	2	0	0	10
HR1	1	2	1	0	0	4
HR2	2	0	0	0	0	2
HR3	0	0	0	0	0	0
III#1	1	2	2	0	0	5
III#2	4	5	0	1	0	10
III#3	2	4	0	1	0	7
Maintenance Day1	1	1	1	0	0	3
Total	**16 (37%)**	**18 (42%)**	**6 (14%)**	**3 (7%)**	**0 (0%)**	**43 (100%)**

Key: TC = Other toxicities SF = System factors (Hospital or organisational factors)
LC = Low counts PF = Patient factors (patient and family social factors)

Table 11.

Distribution of treatment delays by reasons and average length of each delay experienced by HR patients (n=6)

Individual HR Patient I.D.	Reasons for treatment delays					Total no. of patient delays	Average delay length (days)	Journey Cum. Delays (days)
	Other toxicities	Low counts	Other toxicities/ low counts and vice versa	System factors	Patient factors			
2	4	0	0	0	0	4	-12.3*	-49*
4	1	5	1	0	0	7	11.3	79
8	3	3	3	0	0	9	11.3	102
11	3	4	0	2	0	9	11.2	101
18	2	2	1	0	0	5	7.2	36
21	3	4	1	1	0	9	16.9	152
Total	**16 (37%)**	**18 (42%)**	**6 (14%)**	**3 (7%)**	**0 (0%)**	**43 (100%)**		

*Negative delays mean treatments were brought forward – this patient's Maintenance phase was brought forward by 49 days because of missed earlier treatments due to toxicities.

Key: TC = Other toxicities SF = System factors (Hospital or organisational factors)
LC = Low counts PF = Patient factors (patient and family social factors)

3.7.3 SR/MR versus HR patients

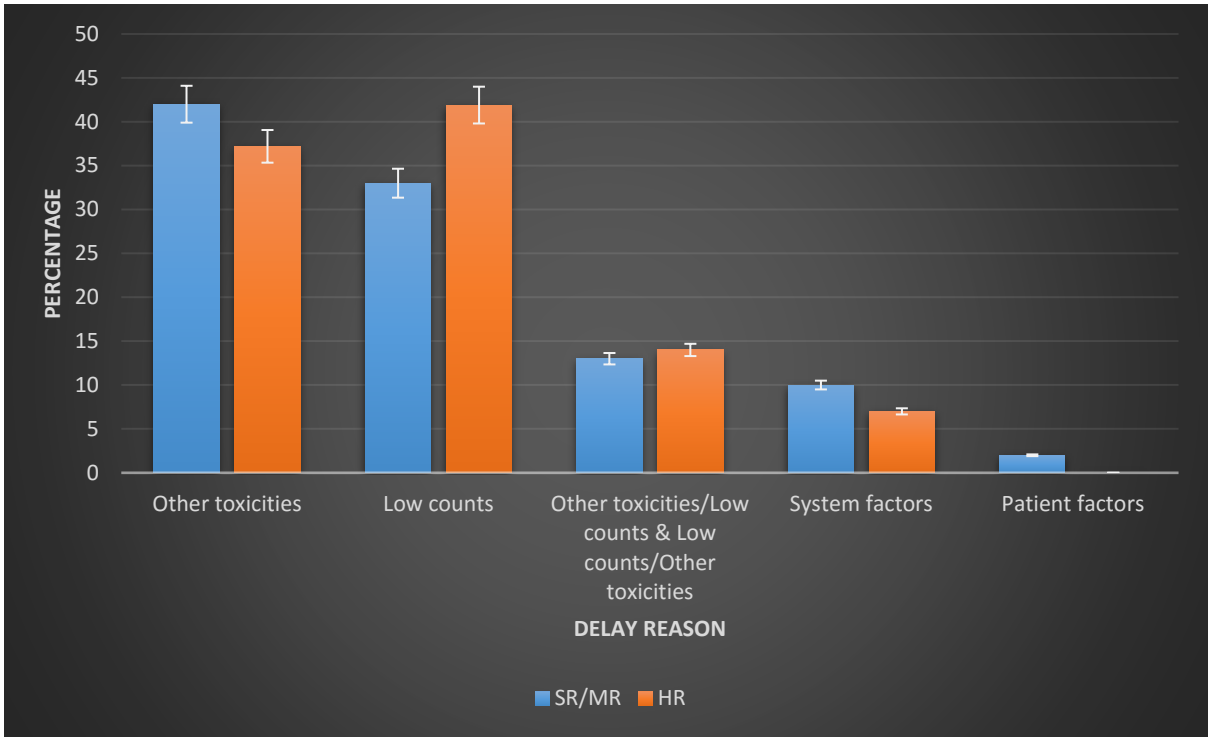
Although SR/MR and HR patients underwent the same treatment during Protocol I A and B, HR patients experienced more delays than SR/MR patients during these phases.

At Day 36 Protocol I B, HR patients had experienced significantly longer delays (mean=7.5 days, SD=6.6) than SR/MR patients (mean=2.1 days, SD=3.9); $t(28)= -2.65$, $p=0.013$. At Day 64 Protocol I B, HR patients had also experienced longer delays (mean=18.1 days, SD=11.3) than SR/MR patients (mean=10.7 days, SD=7.0); $t(28)= -2.05$, $p=0.05$. However, this difference was not significant.

The reasons for treatment delays were similar in the SR/MR and HR patient groups, with the exception that patient factors did not cause any delays in the HR group. Treatment visits that did not have blood counts requirements (e.g. Induction phase - Protocol I A Days 1-29) were associated with the least delays and any delays that occurred during these visits were never due to low counts but the other reasons. Figure 6 illustrates reasons for delays experienced by SR/MR and HR patients.

Figure 6.

Proportion of treatment delays by reason for SR/MR (n=24) and HR (n=6) patients across the treatment journey



3.6 Map of the ALL journey

Tables 12a and 12b show the key milestones of the ALL journey for both SR/MR and HR patients, the expected number of days to reach each milestone, and the average number of days each milestone was reached by patients in the study sample. Please also see Appendix B which presents a graphical display of the process map of the ALL journey showing milestone delays for both treatment groups.

Table 12a

SR/MR milestones, including expected number of days to reach each milestone and the average number of days taken to reach each milestone by patients in the study sample.

SR/MR Milestone	Expected no. of days to reach milestone	Average no. of days taken to reach milestone
PROTOCOL I A	1	1
B	36	39
PROTOCOL M	78	93
PROTOCOL II A	148	167
B	184	212
MAINTENANCE	212	245
Treatment Completion	728	728

Table 12b

HR milestones, including expected number of days to reach each milestone and the average number of days taken to reach each milestone in the study sample.

HR Milestone	Expected no. of days to reach milestone	Average no. of days taken to reach milestone
PROTOCOL I A	1	1
B	36	43
HR Block 1	78	102
HR Block 2	106	139
HR Block 3	134	165
PROTOCOL III #1 of 3	162	192
1st INTERIM MAINTENANCE	197	227
PROTOCOL III #2 of 3	232	282
2nd INTERIM MAINTENANCE	267	317
PROTOCOL III #3 of 3	302	369
MAINTENANCE	344	428
Treatment Completion	728	728

Chapter Four: Discussion

This study investigated the treatment journey of paediatric patients with ALL at a major paediatric tertiary hospital in Sydney. SR/MR patients were found to experience on average 33 days of delay and HR patients experienced 94 days of delay across their two-year treatment journey. Nearly 90% of treatment delays were due to low counts, other toxicities or a combination of these factors. Nine percent and 1% of the delays were attributed to system factors and patient factors respectively. Despite these delays, the majority of patients in the study completed all the milestones of ALL treatment.

4.1 Treatment delays

The Study 9 ALL treatment protocol has a stipulated total duration of 104 weeks (24 months), which includes an optimum Maintenance phase duration of 18 months for SR/MR patients and 12 months for HR patients if no delays occur. Treatment is discontinued after 104 weeks from commencement, thus the Maintenance phase duration is shortened by that same length of delays. Extensive delays in Maintenance treatment are managed by prolonging the duration of the Maintenance phase, but it did not happen in this cohort of patients. The decision to extend the Maintenance and duration of extension lies entirely with the treating oncologist. Total cumulative delays which exceed 6-8 weeks (42-56 days) for the entire 24-months treatment period are considered clinically significant at the study hospital. In the current study the average Maintenance duration was shortened by 33 days (range = 7-115) for SR/MR patients and by 94 days (range = 36-152 days) for HR patients. There is some evidence to suggest that shortening of the optimum duration of the Maintenance phase by six months has been associated with an increased risk of systemic relapse (or recurrence) of the disease.[55] However, it is not clear from the current literature what is the impact of shortening the Maintenance Phase by periods less than six months. Any clinically significant delay would therefore be undesirable to both the patient and the clinician. While an isolated treatment delay of 1-3 days (e.g. as a result of weekend, public

holiday or both) may not be clinically important, this study showed that over time, small delays can easily accumulate into larger delays and become clinically significant.

In exceptional cases (e.g. poor compliance with taking oral chemotherapy during Maintenance), some clinicians may decide to also extend the duration of the Maintenance phase, if it is judged to clinically benefit some individual patients. There is some evidence to suggest that lengthening the duration of the Maintenance phase beyond the optimum period may improve treatment outcomes for some patient groups (e.g. SR males), however, this benefit has also been associated with an increased risk of developing secondary malignancies such as acute myeloid leukaemia.[56]

Male patients in the SR/MR treatment group experienced more delays initially compared to female patients, however this difference appeared to diminish over time. This comparison of males versus females could not be carried out for the HR treatment group as there were only six patients in that group. This study was not powered to detect differences in delays between males and females across their treatment journey and previous studies present conflicting results on gender differences. For example, a study which compared toxicities and treatment delays in paediatric ALL patients in both HR and SR groups found that females experienced more toxicities and delays than males.[57] In contrast, studies in older (adolescent and adult) patients have shown that females experience fewer delays and toxicities than males.[57, 58] It has been suggested that this resilience in older female patients is possibly due to female hormones (e.g. oestrogen) enhancing the immune system and generating better responses to infections whereas the male hormone testosterone tends to suppress the immune function.[57, 58] The reasons why this trend tends to be reversed in younger children is difficult to explain from current literature and further research is continuing in this area.

In this study, a comparison between SR/MR and HR patients on Days 36 and 64 in Protocol I (when both groups received the same treatments) showed that HR patients experienced more delays. This difference is likely because some of the HR patients have a higher burden of disease at the start of treatment and may therefore not tolerate treatment as well as the SR/MR patients.[59] At diagnosis, such HR patients may have a higher ratio of leukaemia cells to normal blood cells in their bone marrow compared to SR/MR patients.[59] Chemotherapy would suppress their bone marrow, worsening this situation, making these HR patients

more prone to infections and low blood cell counts. The consequence is such HR patients being at risk of experiencing more delays earlier in the treatment journey than SR/MR patients.

4.2 Reasons for treatment delays

The low counts and other toxicities factors were an indication of how well patients tolerated chemotherapy treatment. The toxic side effects of chemotherapy drugs, such as bone marrow suppression, immunosuppression, osteonecrosis, emesis etc. are well documented and each patient is affected differently depending on their genetics, their disease and other unknown factors.[59] Except for the timely provision of adequate supportive care, delays due to low counts and other toxicities are difficult to avoid. When a drug (including chemotherapy drug) is administered, the body metabolises it (breaks it down), mostly in the liver then clears it out of the body through the kidneys (in urine) or in faeces.[60] The metabolism of the drug is a complex process that involves synthesis of the necessary enzymes that speed up this metabolism process. Individual patients have different capabilities to synthesise the necessary enzymes required for drug metabolism depending on their genetic make-up.[60] Traditionally, chemotherapy dosing is based on body surface area (BSA) which takes into account the size of the patient (i.e. height and body weight) but does not take into account how quickly an individual patient clears a particular drug from their body based on their genetic make-up.[59] A new approach to dosing, called pharmacogenomics, is now enabling sequencing of patients' genes to predict drug clearance. This allows adjustment of doses so that those who clear more slowly will receive lower doses and those who clear the drug more quickly will receive higher doses.[61] This approach would reduce the risk of toxicity and result in fewer treatment delays in patients with slow clearance. It would also enable more appropriate dosing for those patients with faster clearance.

One SR/MR patient (Patient no. 17) in the study sample experienced no delays in their treatment journey. Although positive, this lack of delays also raises a question of whether it was because the patient cleared their chemotherapy drugs too quickly and did not receive adequate doses to treat their disease. Such a patient would benefit from pharmacogenomic

profiling. Pharmacogenomic profiling is well established for one chemotherapy drug in particular – Mercaptopurine,[61] which is taken during a number of phases of ALL treatment, mostly during the Maintenance phase. In Australia, pharmacogenomic profiling, though still very expensive, is now available for selected non-chemotherapy drugs.[60] Patients experiencing no delays or minimum delays could also be attributed to proactive supportive care (e.g. blood products transfusions) between treatments before patients developed more severe toxicities which would result in more extended delays.

During the induction phase, i.e. Protocol IA Days 1-29, the treatment usually proceeded irrespective of blood counts provided patients were clinically well.[52] The reason for giving chemotherapy treatment irrespective of blood counts during this induction phase is that the leukaemia disease process itself decreases blood counts, and as such, chemotherapy is necessary to bring that process under control. Patients tended to experience the least treatment delays during such visits and any delays that occurred were never due to low counts, but the other causes.

The other reasons for treatment delays, (system and patient factors) are more likely to be amenable to intervention than low counts and other toxicities. Patient factors accounted for a small proportion of the overall delays and were deliberately permitted by the treating clinicians at non-critical times during the treatment journey in order to accommodate individual patient circumstances, e.g. allowing a patient from a regional area to visit their home for a few days. Like weekends and public holidays, in isolation these patient factors produce delays which are clinically insignificant. However, if added to other delays they can contribute to clinically significant delays. While it is important to consider accommodating patient social circumstances for their well-being during their long treatment journey, any resultant treatment delays should be kept to a minimum.

Some system factors which contributed to delays were identified. These included lack of a hospital bed preventing admission, chemotherapy not ready for administration for a patient visit and patients and clinicians having to wait for anaesthetic time (theatre time) to do procedures (e.g. bone marrow aspirate, lumbar puncture, central venous line insertion and administering intrathecal chemotherapy treatments). Identification of these system factors was not easy in this study as their documentation in clinical information systems was not as clear as the low counts and other toxicities factors. However, factors that rely on

communication and information flow, such as, failure to make appointments within the hospital, chemotherapy ordering being missed and late availability of test results delaying decision-making processes are possible additions to the list of system factors. It seems logical that any intervention to reduce treatment delays should target system factors as a group. While the non-availability of a bed for admission would be difficult to influence, an electronic medical record or electronic medication management (EMR or EMM) system may, for example, help ensure chemotherapy orders are available early enough for pharmacy to prepare the drugs for the times that they are required. Some drugs are required to be prepared on the day of treatment, and as such, efficient transmission of test results would enable clinicians to make timely decisions on whether a treatment should proceed or not.[51, 62] It is important to remember, however, that even with an EMM/EMR system, a doctor would still need to actually order the chemotherapy for pharmacy to prepare it. The difference though, is that the EMM/EMR systems can be built with enough decision support functions to prompt clinicians so as to assist human function, thus possibly assist in reducing chances of some processes being missed or forgotten. Information management and communication is central to effective and efficient patient care in health institutions. In the previous years the study hospital had relied on combination of paper (mostly) and computer based systems to support information management and communication. However, this year, it has started implementing a hospital-wide electronic health records system, which is expected to positively impact on patient care.

There are many potential benefits of electronic health record systems, e.g. clearer documentation; easy sharing of documentation among health care professionals; ability to coordinate patients more efficiently; reduction in errors due to use of set templates and electronic systems); ability of health care providers to access records at any time and any location inside or outside the hospital; providing electronic summaries with clearer/more accurate information; efficiency and cost saving etc.[51,62,63,64] The use of set templates and standardised documentation can significantly improve communication and the quality of documentation as all users follow the same format.[63,64]

Poor adherence to ALL treatment protocols by both patients and clinicians has been suggested to contribute to poor treatment outcomes, particularly in high income countries, such as Australia.[21, 22] All patients in the study sample were enrolled in an international

clinical trial, and as such, clinicians were vigilant in adhering to the protocol and minimising delays. The same level of adherence to timelines may not have been found if patients were not enrolled in an international clinical trial, as more flexibility is permissible, which in turn may lead to greater delays in such patients.

4.3 The ALL journey

In this study, key milestones in the ALL journey were identified through a detailed review of medical records to determine the actual dates these milestones were reached. Despite the delays experienced, all the patients in the SR/MR group completed all the key milestones of treatment and only one HR patient (Patient number 2) could not complete all the milestones because of toxicities.

In ALL treatment, getting patients to successfully complete all milestones of treatment is an achievement in itself.[21] Treatment related toxicities are common and can lead to incompletion or abandonment of treatment which in turn increases the risk of treatment failure or disease relapse.[21] Because of the toxic nature of chemotherapy treatment, supportive care of patients to enable them to complete treatment milestones is an integral part of ALL treatment. Once one treatment is administered, the next goal for clinicians is to help the patient recover from the adverse effects of that treatment so that they are clinically well enough for the next treatment.

A high level of supportive care, comprising blood product transfusions, extra (more than anticipated) hospital admissions and extra oncology clinic visits was provided to all patients for the management of treatment related toxicities. “Extra” implies that these admissions/clinic visits were in addition to the minimum required to complete all treatments and necessary procedures. Extra hospital admissions were for managing more serious toxicities while extra out-patient oncology visits were for less severe adverse effects. The level of supportive care is proportional to the intensity of chemotherapy treatment in order to prevent treatment related deaths and complications.[18] As HR patients in the study sample received more chemotherapy treatments it was not surprising that they also

received more supportive care. Vigilant proactive supportive care in ALL patients prevents early complications due to the disease itself as well as on-therapy and late complications due to treatments.[59, 18] The most common side effects of chemotherapy which often require hospital admissions are immunosuppression (resulting in infections) and bleeding which can often cause many deaths if they are not properly managed.[5, 13] Other side effects requiring supportive care include nausea and vomiting; pain; malnutrition; anaemia and other blood problems.[5, 13] Overall, adequate supportive care ensures that patients' treatments are not delayed because of toxicities. However, even with adequate supportive care treatment delays can still occur, as this study has shown. A question that may arise, though, is: how much does it cost to provide such supportive care? An evaluation of the cost of supportive care and treatment for ALL patients may warrant further study.

4.4 Delays in diagnosis and commencement of treatment

The turnaround time from presentation to diagnosis and start of treatment was relatively short, with most of patients diagnosed within 24 hours of presentation.

Timely diagnosis ensures that there are no delays in commencing treatment.[49] However, a delay (lag-time) of 3-4 days from presentation to commencement of treatment in clinically stable patients is not prognostic. Most patients presented at the study hospital (a tertiary institution) via a referral of suspected leukaemia from a smaller hospital or general practitioner. Only some specific tests were then performed at the study hospital to confirm the diagnosis of ALL. This may have contributed to timely diagnosis as some unnecessary diagnostic tests were avoided this way.

A small number of patients (n=5) started treatment four days after presentation. Delays in confirmation of diagnosis and subsequent commencement of treatment tended to be associated with weekend and public holiday presentations, when some of the hospital's departments that play key roles in ALL diagnosis, such as Haematology and Pathology, were not fully functional. Sometimes it was prudent for clinicians to wait for special flow cytometry test results to confirm diagnosis of some patients, in which case the start of

treatment would also be delayed. Time of presentation seemed to also play a role as patients who presented before midday Monday to Friday tended to be those that were diagnosed within 12 hours of presentation. Overall, delays in diagnosis and consequently the commencement of treatment can possibly be attributed to hospital system factors, since patients are already in-patient and the hospital may be able to influence how quickly patient processes happen. Patients may initially present through the Emergency Department (ED) and various other medical teams (other than Oncology) may be involved in caring for the patient in initial stages of the ALL journey before care is handed over to the Oncology Department. Delays that result from poor communication among hospital departments can possibly be mitigated by using a hospital-wide electronic medical record (EMR) system that can potentially help improve communication and information flow among different departments/medical teams and hence contribute to reducing the associated delays.[51, 62]

4.5 Effects of patient characteristics on treatment delays

Patient characteristics such as age, gender, immunophenotype and WCC at diagnosis are important in influencing overall treatment outcomes of ALL patients and to some extent treatment delays experienced by patients. Age and WCC are used for accurate risk classification of pre B ALL patients with those aged 1 to < 10 years and having WCC less than $50x10^9$/L at diagnosis classified as SR, while those aged 10 years and older and with WCC ≥ $50x10^9$/L being classified as high risk.[65] Unfortunately, age and WCC are not accurate predictors of outcome for T-ALL patients.[65]

The majority of patients (77%, n=23) in the study sample were aged less than ten years old and 23% (n=7) were aged ten years and older. Age has been consistently identified associated with treatment outcomes for ALL paediatric patients, with those aged less than one year and between 10-20 years more likely to have unfavourable clinical outcomes.[5] The median age at diagnosis for the study sample was 4.8 years, which was within the childhood ALL incidence peak age range of 2-5 years.[59] Age is an unmodifiable risk factor for treatment outcome, however, most of the patients were in the more favourable age range. Patients older than ten years have a higher chance of having high risk ALL, which tends to be less responsive to treatment and also more prone to treatment delays. In this study sample, out

of the seven patients over the age of ten years, three of them were classified as high risk (50% of all the HR patients). Comparing treatment delays experienced by patients aged less than ten to those over ten years old was not feasible because of the relatively small proportion of those over ten years old in both SR/MR (n=4) and HR (n=3) treatment groups.

There were more males (n=19) than females (n=11) in the study sample. This was expected, as the worldwide incidence of childhood ALL is higher in males than females.[59] However, females experience more favourable treatment outcomes than males.[5] At diagnosis it is difficult to predict how an individual patient will tolerate chemotherapy treatment solely based on their gender. As such, prediction of which patients will experience more treatment related delays is not always possible.

In the current study, there were 83% (n=25) patients with Pre B ALL and 17% (n=5) with T-ALL. All the T-ALL patients were male. Worldwide statistics of childhood ALL show that a diagnosis of Pre B ALL is more prevalent at around 85%, but has more favourable outcomes, compared to a diagnosis of T-ALL.[5] T-ALL also tends to be associated with the high risk classification, older age at diagnosis and poorer response to treatment compared to Pre B ALL and is more common in males.[5] Four of the five patients aged 10-17 years old in this study and 33% (n=2) of the HR patients had T-cell ALL. The small proportion of patients with T-ALL (n=5) and those aged 10-17 years (SR/MR, n=4; HR, n=3) in the study sample did not make it feasible to compare treatment delays in these categories of patients. Further research may be warranted to compare the treatment delays between T-ALL and Pre B ALL patients.

The majority (87%) of patients in the study sample (n=26) had a WCC below $50x10^9$/L and 67% (n=20) were below $20x10^9$/L at diagnosis. WCC higher than $20x10^9$/L at diagnosis is associated with an unfavourable treatment outcome, even more so if higher than $50x10^9$/L.[5, 66] For Pre B ALL patients, very high WCC at diagnosis tends to be associated with high risk classification,[65] which in turn is also associated with increased risk of treatment delays. However, high WCC at diagnosis is a poorer risk predictor for T-ALL compared to Pre-B ALL.[65]

4.6 Strengths and limitations of the study

This study used a sample size of 30, which was larger than the minimum recommended when mapping patient journeys using medical records review. This sample represented the total number of patients presenting to this tertiary paediatric referral centre with ALL over a one-year period. This sample size was a strength of the study. The recommended minimum number of patients for mapping a patient journey using medical records review is ten.[26] This large sample size in this study provides greater confidence as it is more representative.[37] Despite being time consuming, retrospective review of medical information was a relatively easy method to use, although it may sometimes not provide explanations as to why some events occurred.[26] Explanations could be sought from relevant clinicians but some explanations may never be found. For example, in this study a number of the reasons for treatment delays could not be determined due to lack of documentation. This could be potentially improved with electronic health records where reasons for delay in treatment are documented in a standardised way. Obtaining data in real time, e.g. shadowing and observing a patient as they transverse through their treatment journey, could also address such a problem but it would require more time and resources.[26, 27] While this study revealed some insight into treatment interruptions of the ALL journey by retrospectively auditing patient medical information, it would be strengthened by complementing chart review with patient and carer interviews or patient observations to explore the true patient experience of their treatment journey.

4.7 Conclusions

Children diagnosed with life threatening acute lymphoblastic leukaemia, the most common childhood cancer, transverse through a complex two-year journey of intensive chemotherapy treatment. This is one of the first studies to follow a cohort of patients on this journey and to document delays in the process and factors which may be associated with those delays. The study demonstrated that the journey of ALL patients is often interrupted by treatment delays, most frequently as a result of the toxic adverse effects of chemotherapy treatment. While the toxic effects of chemotherapy as a factor in delaying children's treatment journeys is not a surprising finding, importantly this study has

quantified that effect and identified the relative contribution of other factors in delaying treatment. Delays may also occur for social and family reasons, which are often necessary, but in concert with other factors, may be cumulative and result in substantial delays over time which may have important clinical consequences for patients.

Importantly, the study identified that some delays are due to organisational issues, such as breakdowns in communication among the care teams, including failures in making appointments, and inefficient reporting of test results, and delaying decision-making, and waiting for anaesthetic time to do procedures (such as bone marrow aspirate, lumbar puncture, central venous lines) under general anaesthesia. These types of delays are more likely to be amenable to interventions and should be a focus of attention. The greater use of electronic health records systems is one intervention which has the potential to reduce these types of delays and their subsequent impact on children's treatment by improving the coordination of care. Hospitals and healthcare organisations should tap into the many potential benefits of electronic health record systems, e.g. clearer documentation; easy sharing of documentation among health care professionals; ability to coordinate patients more efficiently; reduction in errors; ability of health care providers to access records anywhere, any time; providing electronic summaries with clearer/more accurate information; efficiency and cost saving etc.

References

1. Bhojwani D, Yang JJ, Pui C-H. Biology of childhood acute lymphoblastic leukemia. The Pediatric Clinics of North America. 2015; **62**(1): 47-60 doi: 10.1016/j.pcl.2014.09.004

2. Stanulla M, Schrappe M. Treatment of childhood acute lymphoblastic leukemia. Seminars in Hematology. 2009; **46**(1): 52-63 doi: 10.1053/j.seminhematol.2008.09.007

3. Cancer Institute of New South Wales [Internet] 2016 [cited 2016 May 9]; Available from: http://www.cancerinstitute.org.au/cancer-in-nsw/cancer-facts/childhood-cancer

4. Inaba H, Greaves M, Mullighan CG. Acute lymphoblastic leukaemia. The Lancet. 2013; **381**: 1943-1955 doi: 10.1016/S0140-6736(12)62187-4

5. Pieters R, Carroll WL. Biology and treatment of acute lymphoblastic leukemia. Pediatric Clinics of North America. 2008; **55**: 1-20 doi: 10.1016/j.pcl.2007.11.002

6. Hunger SP, Mullighan CG. Refining ALL classification: toward detecting high risk ALL and implementing precision medicine. Blood. 2015; **125**(26): 3977-3987 doi: 10.1182/blood-2015-02- 580043

7. Pui C-H, Evans WE. Treatment of acute lymphoblastic leukemia. The New England Journal of Medicine. 2006; **354**: 166-178

8. Pui C-H, Evans WE. A 50-year journey to cure childhood acute lymphoblastic leukemia. Seminars in Hematology. 2013; **50**(3): 185-196 doi: 10.1053/j.seminhematol.2013.06.007

9. Pui C-H, Mullighan CG, Evans WE, Relling MV. Pediatric acute lymphoblastic leukemia: where are we going and how do we get there? Blood. 2012; **120**(6): 1165-1174 doi: 10.1182/blood-2012-05- 378943

10. Pui C-H, Yang JJ, Hunger SP, Pieters R, Schrappe M, Biondi A, Vora A, Baruchel A, Silverman LB, Schmiegelow K, Escherich G, Horibe K, Benoit YCM, Izraeli S, Yeoh AEJ, Liang D-C, Downing JR, Evans WE, Relling MV, Mullighan CG. Childhood acute lymphoblastic leukemia: progress through collaboration. Journal of Clinical Oncology. 2015; **33**(27): 2938-2948 doi: 10.1200/jco.2014.59.1636

11. Tasian MD, Loh ML, Hunger SP. Childhood acute lymphoblastic leukemia: integrating genomics into therapy. Cancer. 2015; **121**: 3577-3590 doi: 10.1002/cncr.29573

12. Pui C-H, Carroll WL, Meshinchi S, Arceci RJ. Biology, risk stratification, and therapy of pediatric acute leukemias: an update. Journal of Clinical Oncology. 2011; **29**: 551-565 doi: 10.1200/JCO. 2010.30.7405

13. Yeoh AEJ, Tan D, Li C-K, Hori H, Tse E, Pui C-H. Management of adult and paediatric acute lymphoblastic leukaemia in Asia: resource-stratified guidelines from the Asian Oncology Summit 2013. Lancet Oncology. 2013; **14**(12): e508-e523 doi: 10.1016/S1470-2045(13)70452-2

14. Kaul S, Korgenski EK, Ying J, Ng CF, Smits-Seemann RR, Nelson RE, Andrews S, Raetz E, Fluchel M, Lemons R, Kirchhoff AC. A retrospective analysis of treatment-related hospitalization costs of pediatric, adolescent, and young adult acute lymphoblastic leukemia. Cancer Medicine. 2016; **5**(2): 221-229 doi: 10.1002/cam4.583

15. Israels T, Renner L, Hendricks M, Hesseling P, Howard S, Molyneux E. SIOP PODC: recommendations for supportive care of children with cancer in a low-income setting. Pedriatric Blood Cancer. 2013; **60**: 899-904 doi: 10.1002/pbc

16. Bhojwani D, Pui C-H. Relapsed childhood acute lymphoblastic leukaemia. Lancet Oncology. 2013; **14**: e205-217

17. World Health Organisation (WHO). WHO Guidelines on the pharmacological treatment of persisting pain in children with medical illnesses. [Internet] 2012 [cited 2016 May 12]; Available from: http://www.who.int/medicines/areas/quality_safety/guide_perspainchild/en/index.html

18. van de Wetering MD, Schouten-van Meeteren NYN. Supportive care for children with cancer. Seminars in Oncology. 2011; **38**(3): 374-379 doi: 10.1053/j.seminoncol.2011.03.006

19. Baade PD, Youlden DR, Valery PC, Hassall T, Ward L, Green AC, Aitken JF. Population-based survival estimates for childhood cancer in Australia during the period 1997-2005. British Journal of Cancer. 2010; **103**: 1663-1670 doi: 10.1038/sj.bjc.6605985

20. Hunger SP, Lu X, Devidas M, Camitta BM, Gaynon PS, Winick NJ, Reaman GH, Carroll WL. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the Children's Oncology Group. Journal of Clinical Oncology. 2012; **30**(14): 1663-1669 doi: 10.1200/JCO.2011.37.8018

21. Sitaresmi MN, Mostert S, Schook RM, Veerman S, Veerman AJP. Treatment refusal and abandonment in childhood acute lymphoblastic leukemia in Indonesia: an analysis of causes and consequences. Psycho-Oncology. 2010; **19**: 361-367 doi: 10.1002/pon.1578

22. Abboud MR, Ghanem K, Muwakkit S. Acute lymphoblastic leukemia in low and middle income countries: disease characteristics and treatment results. Current Opinion in Oncology. 2014; **26**(6): 650-655 doi: 10.1097/CCO.0000000000000125

23. Pui C-H, Pei D, Campana D, Cheng C, Sandlund JT, Bowman WP, Hudson MM, Ribeiro RC, Raimondi SC, Jeha S, Howard SC, Bhojwani D, Inaba H, Rubnitz JE, Metzger ML, Gruber TA, Coustan-Smith E, Downing JR, Leung WH, Relling MV, Evans WE. A revised definition for cure of childhood acute lymphoblastic leukemia. Leukemia. 2014; **28**: 2336-2343 doi: 10.1038/leu.2014.142

24. Kuo S, Huang KE, Davies SA, Feldman SR. The rosacea patient journey: a novel approach to conceptualizing patient experiences. CUTIS. 2015; **95**: 37-43

25. Manchaiah VKC, Stephens D. The 'patient journey' of adults with sudden-onset acquired hearing impairment: a pilot study. The Journal of Laryngology. 2012; **126**: 475-481 doi: 10.1017/ S0022215111003197

26. NHS Institute of Innovation and Improvement. A focus on the whole patient journey. [Internet] 2008 [Cited 2016 March 14]; Available from: http://www.institute.nhs.uk/quality_and_service_improvement_tools/quality_and_service_improvement_tools/process_mapping_-_an_overview.html

27. Trebble TM, Hansi N, Hydes T, Smith MA, Baker M. Process mapping the patient journey: an introduction. British Medical Journal. 2010; **341**: 394-397 doi: 10.1136/bmj.c4078

28. Ben-Tovim DI, Dougherty ML, O'Connell TJ, McGrath KM. Patient journeys: the process of clinical redesign. Medical Journal of Australia. 2008; **188**(6): S14-S17

29. Johnson JK, Farnan JM, Barach P, Hesselink G, Wollersheim H, Pijnenborg L, Kalkman C, Arora VM. Searching for the missing pieces between the hospital and primary care: mapping the patient process during care transitions. BMJ Quality & Safety. 2012; **0**: 1-9 doi:10.1136/bmjqs-2012-001215

30. Ajmi I, Zgaya H, Gammoudi L, Hammadi S, Martinot A, Beuscart R, Renard J. Mapping patient path in the Pediatric Emergency Department: a workflow model driven approach. Journal of Biomedical Informatics. 2015; **54**: 315-328 doi: 10.1016/j.jbi.2014.12.004

31. Paul C, Carey M, Anderson A, Mackenzie I, Sanson-Fisher R, Courtney R, Clinton-Mcharg T. Cancer patients' concerns regarding access to cancer care: perceived impact of waiting times along the diagnosis and treatment journey. European journal of Cancer Care. 2012; **21**: 321-329 doi: 10.1111/ j.1365-2354.2011.01311.x

32. Blair M, Gore J, Isaza F, Pajak S, Malhotra A, Islam S, Vigneswaran VT, Lachman P. Multi-method evaluation of paediatric ambulatory care unit (PACU): impact on families and staff. Archives in Disease Childhood. 2008; **93**: 681-685 doi: 10.1136/adc.2006.115386

33. Castillo H, Ramon S, Morant N. A recovery journey for people with personality disorder. International Journal of Social Psychiatry. 2013; **59**(3): 264-273 doi: 10.1177/0020764013481891

34. Firth J, Nelson A, Briggs M, Gorecki C. Experiences of healthcare provision for foot ulceration occurring in people with rheumatoid arthritis. Musculoskeletal Care. 2013; **11**: 159-167 doi: 10.1002/ msc.1036

35. Wong A, Kozan E, Sinnott M, Spencer L, Eley R. Tracking the patient journey by combining multiple hospital database systems. Australian Health Review. 2014; **38**: 332-336 doi: 10.1071/ AH13070

36. Murray M, Brown J, Hinder V, Merrie A, Hill A, Hulme-Moir M, Sharples K, Findlay M. The colorectal patients' journey: the Auckland region. The New Zealand Medical Journal. 2011; **124**(1331): 18-28

37. Sloans JA, Scott-Findlay S, Nemecek A, Blood P, Trylinski C, Whittaker H, El Sayed S, Clinch J, Khoo K. Mapping the journey of cancer patients through the health care system.

Part 2: methodological approaches and basic findings. Canadian Oncology Nursing Journal. 2004 Fall; **14**(4): 224-227 doi: 10.5737/1181912x144224227

38. Kim CS, Spahlinger DA, Kin JM, Coffey RJ, Billi JE. Implementation of lean thinking: one health system's journey. The Joint Commission Journal on Quality and Patient Safety. 2009; **35**(8): 406-413

39. Ben-Tovin DI, Bassham JE, Bennett DM, Dougherty ML, Martin MA, O'Neill SJ, Sincock JL, Szwarcbord MG. Redesigning care at Flinders Medical Centre: clinical process design using "lean thinking". Medical Journal of Australia. 2008; **188**(6): S27-S31

40. Ryan A, Hunter K, Cunningham K, Williams J, O'Shea H, Rooney P, Hickey F. STEPS: lean thinking, theory of constraints and identifying bottlenecks in an emergency department. The Irish Medical Journal. 2013; **106**(4): 105-107

41. Manchaiah VKC, Stephens D, Meredith R. The patient journey of adults with hearing impairment: patients' views. Clinical Otolaryngology. 2011; **36**: 227-234

42. Evans WK, Ung YC, Assouad N, Chyjek A, Sawka C. Improving the quality of lung cancer care in Ontario: the lung cancer disease pathway initiative. Journal of Thoracic Oncology. 2013; **8**(7): 876-882

43. Scott-Findlay S, Sloan JA, Nemecek A, Blood P, Trylinski C, Whittaker H, El Sayed S, Clinch J, Khoo K. Mapping the journey of cancer patients through the health care system. Part 3: an approach to staging. Canadian Oncology Nursing Journal. 2005; **15**(1): 4-8 doi: 10.5737/1181912x15148

44. Elliss-Brookes L, McPhail S, Ives A, Greenslade M, Shelton J, Hiom S, Richards M. Routes to diagnosis for cancer – determining the patient journey using multiple routine data sets. British Journal of Cancer. 2012; **107**: 1220-1226 doi: 10.1038/bjc.2012.408

45. Gerrand C, Francis M, Dennis N, Charman J, Lawrence G, Evans T, Grimer R. Routes to diagnosis of sarcoma – describing the sarcoma patient journey. European Journal of Surgical Oncology. 2015; **41**: 1393-1399 doi: 10.1016/j.ejso.2015.07.009

46. Crepaz M, Curry JM. Improving the cancer patient journey. Studies in Health Technology and Informatics. 2013; **188**: 14-19 doi: 10.3233/978-1-61499-266-0-14

47. Guilhot F, Coombs J, Szczudlo T, Zernovak O, Paolantonio M, Bender C, MacDonald NJ, Shapiro A. The patient journey in chronic myeloid leukemia patients on tyrosine kinase inhibitor therapies: qualitative insights using a global ethnographic approach. The Patient. 2013; **6**(2): 81-92 doi: 10.1007/s40271-013-0006-3

48. Bhatnagar S, Goyal A, Sharma A, Joshi S, Ahmed SM. Journey of patients with cancer: a systematic evaluation at Tertiary Care Center in India. American Journal of Hospice and Palliative Medicine. 2014; **31**(40): 406-413 doi: 10.1177/1049909113494091

49. Molassiotis A, Wilson B, Brunton L, Chandler C. Mapping patients' experience from initial change in health to diagnosis: a qualitative exploration of patient and system factors mediating this process. European Journal of Cancer Care. 2010; **19**: 98-109 doi: 10.1111/j.1365-2354.2008.01020.x

50. Lowe R, Bravery K, Gibson F. Navigating the maze: parents' views and influence on paediatric haematology and oncology day care service. Journal of Clinical Nursing. 2008; **17**: 3159-3167 doi: 10.1111/j.1365-2702.2008.02632.x

51. Galligioni E, Berloffa F, Caffo O, Tonazolli G, Ambrosini G, Valduga F, Eccher C, Ferro, A, Forti S. Development and daily use of an electronic oncological patient record for the total management of cancer patients: 7 years' experience. Annals of Oncology. 2009; **20**(2): 349-352 doi: 10.1093/annonc/ mdn567

52. National Institute of Health. International Collaborative Treatment Protocol for Children and Adolescents with Acute Lymphoblastic Leukemia. [Internet] 2016 [Cited 2016 Aug 25]; Available from: https://clinicaltrials.gov/ct2/show/NCT01117441

53. National Institute of Health. National Cancer Institute Dictionary of Cancer Terms. [Internet] 2016 [Cited 2016 Aug 25]; Available from: http://cancer.gov/publications/dictionaries/cancer-terms

54. Conter V, Bartram CR, Valsecchi MG, Schrauder A, Panzer-Grumayer R, Moricke A, Arico M, Zimmermann M, Mann G, De Rossi G, Stanulla M, Locatelli F, Basso G, Niggli F, Barisone E, Henze G, Ludwig W-D, Haas OA, Cazzaniga G, Koehler R, Silvestri D, Bradtke J, Parasole R, Beier R, van Dongen JJM, Biondi A, Schrappe M. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic

leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. Blood. 2010; **115**: 3206-3214 doi: 10.1182/blood-2009-10-248146

55. Moricke A, Zimmermann M, Reiter A, Henze G, Schrauder A, Gadner H, Ludwig WD, Ritter J, Harbott J, Mann G, Klingebiel T, Zintl F, Niemeyer C, Kremens B, Niggli F, Niethammer D, Welte K, Stanulla M, Odenwald E, Riehm H, Schrappe M. Long-term results of five consecutive trials in childhood acute lymphoblastic leukemia performed by the ALL-BFM study group from 1981 to 2000. Leukemia. 2010; **24**: 265-284 doi: 10.1038/leu.2009.257

56. Schmiegelow K, Al-Modhwahi I, Anderson MK, Behrendtz M, Forestier E, Hasle H, Heyman M, Kristinsson J, Nersting J, Nygaard R, Svendsen AL, Vellenranta K, Weinshilboum. Methotrexate/6-mercaptopurine maintenance therapy influences the risk of a second malignant neoplasm after childhood acute lymphoblastic leukemia: results from the NOPHO ALL-92 study. Blood. 2009; **113**: 6077-6083 doi: 10.1182/blood-2008-11-187880

57. Meeske KA, Ji L, Freyer DR, Gaynon P, Ruccione K, Butturini A, Avramis VI, Siegel S, Matloub Y, Seibel NL, Sposto R. Comparative toxicity by sex among children treated for acute lymphoblastic leukemia: a report from the Children's Oncology Group. Pediatric Blood & Cancer. 2015; **62**: 2140-2149 doi: 10.1002/pbc

58. Pennell LM, Galligan CL, Fish EN. Sex affects immunity. Journal of Autoimmunity. 2012; **38**: J282-J291

59.Pui C-H (Ed.). Childhood Leukemias. 2nd ed. Cambridge University Press, 2006

60. Meier B. Medicines and genetic testing results. Australian Pharmacist. 2016; **35**(3): 58-61

61. Biondi A, Cazzaniga G. Novel clinical trials for pediatric leukemias: lessons learned from genomic analyses. Hematology. 2013; **2013**(1): 612-619 doi: 1182/asheducation-2013.1.612

62. Hesse BW, Hanna C, Massett HA, Hesse NK. Outside the box: will information technology be a viable option to improve the quality of cancer care? Journal of the National Cancer Institute Monographs. 2010; **40**: 81-89 doi:10.1093/jncimonographs/lgq004

63. Wallace PJ. Reshaping cancer learning through the use of health information technology. Health Affairs. 2007; **26**(2): w169-w177 doi: 10.1377/hlthaff.26.2.w169

64. Hillestad R, Bigelow J, Bower A, Girosi F, Meili R, Scoville R, Taylor R. Can electronic medical records systems transform health care? Potential health benefits, savings, and costs. Health Affairs. 2005; **24**(5): 1103-1117 doi: 10.1377/hlthaff.24.5.1103

65. Teachery DT, Hunger SP. Predicting relapse risk in childhood acute lymphoblastic leukaemia. British Journal of Haematology. 2013, **162:** 606-620 doi: 10.1111/bjh.12442

66. Jastaniah W, Elimam N, Abdalla K, Iqbal BAC, Khattab TM, Felimban S, Abrar MB. Identifying causes of variability in outcomes in children with acute lymphoblastic leukaemia treated in resource-rich developing countries. Pediatric Blood & Cancer. 2015; **62**: 945-950 doi: 10.1002/pbc

Appendix A.

Phases of AIEOP-BFM ALL 2009 Including drugs, doses, routes and days given

Risk group	Drug/Administration route	Dose (mg/m^2/day	Day
SR/MR HR	**Prephase**		
	Prednisone/po or iv	60	1-7
	Methotrexate/it	Age adjusted***	1
SR/MR HR	**Induction: Protocol IA**		
	Prednisone/po-iv or	60	8-28 then tapered over 9 days
	Dexamethasone/po or iv	10	8-28 then tapered over 9 days
	Vincristine/iv	1.5 (max. 2mg)	8, 16, 22, 29
	Daunorubicin/iv 30 8, 15, 22, Peg-	30	8, 16, 22, 29
	Peg-Asparaginase/iv $	2,500IU/m^2/dose	12, 26
	Methotrexate/i.t.	Age adjusted***	15, 33
SR/MR HR	**Consolidation: Protocol IB**		
	Cyclophosphamide/iv	1,000**	36, 64
	Cytarabine/iv	75	36-39, 43-46, 50-53, 57-60
	Mercaptopurine/po	60	36-63
	Methotrexate/i.t.	Age adjusted***	45, 59
SR/MR	**Protocol M**		
	Mercaptopurine/po	25	1-56
	Methotrexate/iv	5,000^	8, 22, 36, 50
	Methotrexate/i.t.	Age adjusted***	8, 22, 36, 50
	Leucovorin rescue/iv	15mg/m^2/dose	42, 48, 54 h after start HD-MTX
SR/MR	**Protocol II: Re-Induction**		
	Dexamethasone/po or iv	10	1-21 then taper over 9 days
	Vincristine/iv	1.5 (max. 2mg)	8, 15, 22, 29
	Doxorubicin/iv	30	8, 15, 22, 29
	Peg-Asparaginase/iv $	2,500IU/m^2/dose	2,500IU/m^2/dose
	Cyclophosphamide/iv	1,000***	36
	Cytarabine/iv	75	36-39; 43-46
	6-Thioguanine/po	60	36-49
	Methotrexate/i.t.*	Age adjusted***	1, 18 (*only if CNS positive)
HR	**HR Block 1**		
	Dexamethasone/po-iv	20	1-5
	Vincristine/iv	1.5 (max. 2mg)	2, 6
	HD Cytarabine/iv	2,000 (q 12h x2)	5
	Methotrexate/iv	5,000^	1
	Leucovorin rescue/iv	15mg/m^2/dose	42, 48, 54 h after start HD MTX
	Cyclophosphamide/iv	200 q (12h x5)	2-4
	Peg-Asparaginase/iv $	2,500IU/m^2/dose	6
	Methotrexate/i.t.	Age adjusted***	1
	Peg-filgrastim/sc#	Weight adjusted	11

Abbreviations: iv = intravenous; po = per oral; i.t. = intrathecal; sc = subcutaneous

$ Maximum dose is 3,750IU

*Only given in CNS (central nervous system) positive patients

**Mesna and hydration fluids also given

*** Age adjusted doses: 1-<2years: 8mg; 2-<3years: 10mg; ≥3years: 12mg

^ Dose is infused continuously over 24 hours. Patients admitted the night before for pre-hydration overnight

#Weight adjusted: 10-<20kg: 2mg; 20-<30kg: 3mg; 30-<40kg: 4mg & ≥40kg: 6mg. <10kg: Give Filgrastim 5microgram/kg Day11 until neutrophil recovery

Appendix A cont.

HR	**HR Block 2**		
	Dexamethasone/po-iv	20	1-5
	Vindesine/iv	3 (max. 5mg)	2, 6
	Daunorubicin/iv	30	5
	Methotrexate/iv	5,000^	1
	Leucovorin rescue	15mg/m^2/dose	42, 48, 54 h after start HD MTX
	Ifosfamide/iv	800 q (12h x5)**	2-4
	Peg-Asparaginase/iv $	2,500IU/m^2/dose	6
	Methotrexate/i.t.	Age adjusted***	1
	Peg-filgrastim/sc#	Weight adjusted	11
HR	**HR Block 3**		
	Dexamethasone/po-iv	20	1-5
	HD Cytarabine/iv	2,000 (q 12h x4)	1-2
	Etoposide as Phosphate/iv	100 (q 12 x5)	3-5
	Peg-Asparaginase/iv $	2,500IU/m^2/dose	6
	Methotrexate/i.t.	Age adjusted***	1
	Peg-filgrastim/sc#	Weight adjusted	11
HR	**Protocol III: Re-Intensification x3 Cycles**		
	Dexamethasone/po-iv	10	1-14 then taper over 9 days
	Vincristine/iv	1.5 (max. 2mg)	1, 8
	Doxorubicin/iv	30	1, 8
	Peg-Asparaginase/iv $	2,500IU/m^2/dose	1
	Cyclophosphamide/iv	500	15
	Cyatarabine/iv	75	15-18, 22-25
	6-Thioguanine/po	60	15-28
	Methotrexate/i.t.	Age adjusted***	17, 24
HR	**Interim Maintenance**		
	Mercaptopurine/po	50	1-28 (Daily)
	Methotrexate/po	20	1-28 (Weekly)
SR/MR HR	**Maintenance x18mths for SR/MR x12mths for HR**		
	Mercaptopurine/po	50	Daily
	Methotrexate/po	20	Weekly

Abbreviations: iv = intravenous; po = per oral; i.t. = intrathecal; sc = subcutaneous

$ Maximum dose is 3,750IU

*Only given in CNS (central nervous system) positive patients

**Mesna and hydration fluids also given

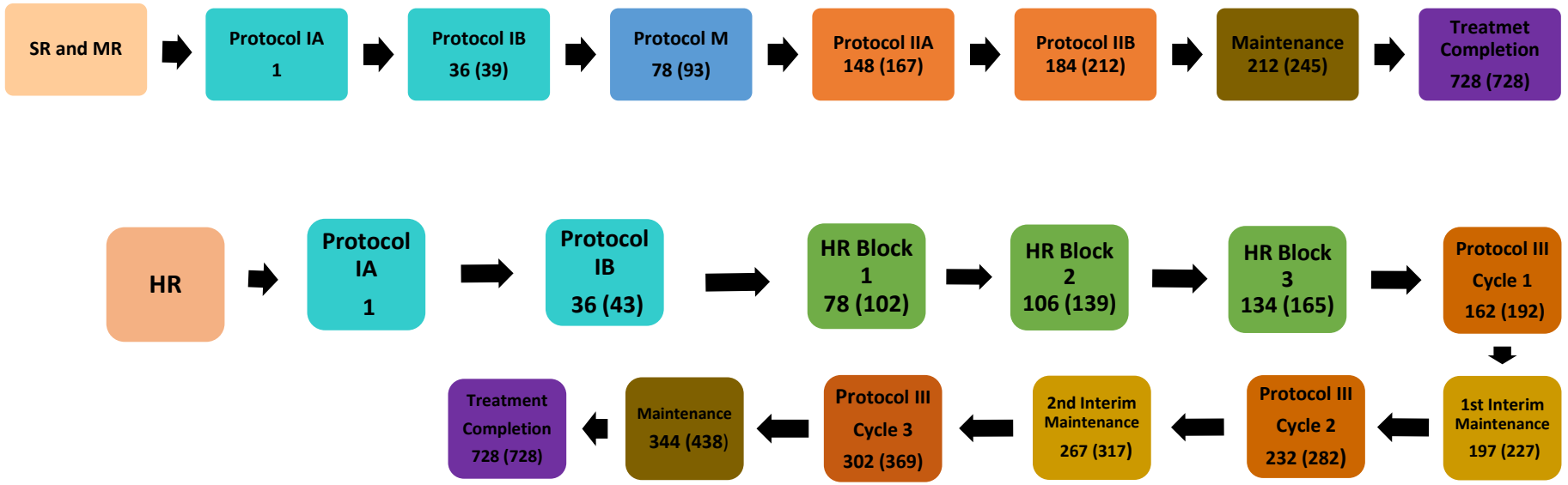
*** Age adjusted doses: 1-<2years: 8mg; 2-<3years: 10mg; ≥3years: 12mg

^ Dose is infused continuously over 24 hours. Patients admitted the night before for pre-hydration overnight

#Weight adjusted: 10-<20kg: 2mg; 20-<30kg: 3mg; 30-<40kg: 4mg & ≥40kg: 6mg. <10kg: Give Filgrastim 5microgram/kg Day11 until neutrophil recovery

Appendix B.

ALL Patient Journey including expected no. of days to reach milestones (& average no. of days taken to reach milestones)



SR = standard risk; MR = medium risk; HR = high risk

Numbers outside bracket = Expected number of days to reach milestone without delays

Numbers in bracket = Average number of days taken to reach milestone (when average cumulative delays were added)

Appendix C.
Ethics Approval Letter

The Sydney children's Hospitals Network
care, advocacy, research, education

Contact for this correspondence:
Research Ethics Office
Research Ethics Administration Assistant
Phone: (02) 9845 1253
Facsimile: (02) 9845 1317
Email: [redacted]

Corner Hawkesbury Road
and Hainsworth Street
Locked Bag 4001
Westmead NSW 2145
Sydney Australia
DX 8213 Parramatta
Tel +61 2 9845 0000
Fax +61 2 9845 3489
http://www.schn.health.nsw.gov.au/
ABN 53 188 579 090

23 March 2016

Professor Johanna Westbrook
Centre for Health Systems and Safety Research
Australian Institute of Health
Macquarie University

Dear Professor Westbrook,

HREC Reference: **LNR/16/SCHN/101**

Project title: **An investigation of the treatment journey of Acute Lymphoblastic Leukaemia patients at a paediatric tertiary hospital**

Sites: **The Children's Hospital at Westmead**

Thank you for submitting the above project for single ethical and scientific review. This project was considered by the Sydney Children's Hospitals Network Human Research Ethics Committee's Executive Committee ("the Committee") at its meeting **21 March 2016**.

This HREC has been accredited by the NSW Department of Health as a lead HREC under the model for single ethical and scientific review, and by the National Health and Medical Research Council as a certified committee in the review of multi-centre clinical research projects.

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and *CPMP/ICH Note for Guidance on Good Clinical Practice*.

I am pleased to advise that the Committee has granted ethical approval of this research project. Your approval is valid for one (1) year, effective the date of this letter.

This application has been assessed in accordance with, and meets the requirements of the National Statement on Ethical Conduct in Human Research (2007).

The documents reviewed and approved by the Committee are:

Document Reviewed	*Version*	*Date*
LNR Submission Code, AU/6/4CB4212		11 March 2016
Research Proposal	V2	Received 17 March 2016

J:\PROJECT FILES - Ethics & Governance\Ethics\LNR\2016\LNR.16.SCHN.101 - TRIM E16.0108\6. Correspondence Out\2016-03-23 - Executive Officer 21-03-2016 - Ethics approval letter.docx

The Sydney children's Hospitals Network
care, advocacy, research, education

The documents noted by the Committee are:

Document Reviewed	*Version*	*Date*
CV of Dudzayi Nhiwatiwa		Received 17 March 2016

Please note the following conditions of approval:

1. This approval is restricted to research being conducted in accordance with the approved documents, and the review of the medical records you have nominated. There is to be no contact with patients, parents/guardians or other family members.

2. The Coordinating Investigator will immediately report anything which may warrant review of ethical approval of the project in accordance with the SCHN adverse event reporting policy.

3. All proposed changes to the research protocol, including the conduct of the research, changes to site or personnel, or an extension to HREC approval, are to be provided to the HREC or its delegate for review before those changes can take effect.

4. The HREC will be notified, giving reasons, if the project is discontinued at a site before the expected date of completion.

5. The co-ordinating investigator will provide a final report to the HREC on completion of the study.

6. Your approval is valid for one (1) year from the date of the final approval letter. If your project extends beyond that one year period please submit an application for amendment to extend the approval period. Ethics approval can be extended for a period of twelve (12) months at a time.

7. In the event of a project **not having commenced** within 12 months of its approval, the approval will lapse and reapplication to the HREC will be required.

Should you have any queries about the HREC's consideration of your project please contact the Research Ethics Administration Assistant on (02) 9845 1253.

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a site until separate authorisation from the Chief Executive or delegate of that site has been obtained. A copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

The HREC wishes you every success in your research.

Yours faithfully

[redacted]

Dr Peter Cooper
Chair, Sydney Children's Hospitals Network Human Research Ethics Committee
Sydney Children's Hospitals Network Human Research Ethics Committee
Cc Mr Dudzayi Nhiwatiwa

J:\PROJECT FILES - Ethics & Governance\Ethics\LNR\2016\LNR.16.SCHN.101 - TRIM E16.0108\6. Correspondence Out\2016-03-23 - Executive Officer 21-03-2016 - Ethics approval letter.docx