Generating evidence to improve childhood cancer health outcomes and resource use in Egypt



Ranin M. Soliman

Kellogg College

University of Oxford

A thesis submitted for the degree of

Doctor of Philosophy in Evidence-based Healthcare

Hilary Term 2023

"*No child should die in the dawn of life*."

This thesis is dedicated to children with cancer worldwide.

Acknowledgements

I would like to express my gratitude to all those who helped make my DPhil journey an enlightening and insightful experience. First and foremost, I would like to thank my supervisors at the Nuffield Department of Primary Care Health Sciences, Professor Carl Heneghan, Dr. Jason Oke, and Dr. Anne-Marie Boylan, for their guidance and support.

Professor Carl Heneghan, I thank you for your mentorship and intellectual guidance throughout my DPhil. You have opened up for me new horizons of thinking that I did not know existed, and you have encouraged me to reach my full potential. I thank you for believing in me and giving me the space to develop and articulate my critical thinking skills, which enabled me to develop the conceptual framework underpinning this thesis and to become an independent researcher under your supervision and guidance. Dr. Jason, I would like to thank you for overseeing all statistical analyses conducted in this thesis. You provided insightful answers to all of my statistical analysis queries, and helped me through when my Cox model was not fitting properly. Dr. Anne-Marie, I thank you for supervising the qualitative component in the last chapter of my thesis. You have helped me realise the importance of understanding the research context, concepts and beliefs, to help translate knowledge into practice. It has been my absolute pleasure and inspiration to have worked with you all. Moreover, I would like to express my gratitude and appreciation to Professor Sir Muir Gray and Dr. Anant Jani for their unconditional support throughout my DPhil and for teaching me about value-based healthcare.

Although my DPhil journey has been an amazing experience, it has also been challenging at times. This was caused by some distractions during the COVID–19 pandemic, my difficult pregnancy with twins, and throughout the first year of my twins' lives while completing my

DPhil thesis. During these times, I have had the greatest support from my supervisors, for whom I am extremely grateful, and from Jamie Hartmann-Boyce, the director of the EBHC programme, who has helped me get through these times with her kindness and advice.

Second, I would like to express my appreciation and gratitude to Professor Alaa Elhaddad, head of the paediatric oncology department at the Children's Cancer Hospital Egypt (CCHE) and former dean of the National Cancer Institute, Cairo University. He taught me a lot about the various approaches to childhood cancer treatment, and the most recent developments in the field. Also, I would like to thank Dr Wael Eweida, CCHE's chief operating officer and strategic consultant, for his advice on the economic and policy aspects of this thesis. In addition, I want to thank all the paediatric oncologists at CCHE who provided advice on current childhood cancer care, and the senior clinicians who participated in the qualitative interview study in my thesis.

Definitely, I would like to thank Egypt Cancer Network USA for funding me to undertake this research, and Professor Sherif Abouelnaga, founder and CEO of CCHE, for his inspiration and support, without whom the hospital would not have existed and thousands of children with cancer in Egypt could not have received high-quality childhood cancer care.

Finally, I am grateful for my family; my kind husband (Abdelrahman), who encouraged me to apply for this DPhil in the first place and who gave me emotional support throughout the DPhil; my girls, Kenzy (6 years) and the twins (Leen & Layan, 1 year); my mother (Eman), who took care of my daughters while I was working on my thesis; and my father (Magdi) and brothers (Ahmed and Youssef), who believed in me. To my family, I hope I make you proud of me.

Funding: This work is funded by Egypt Cancer Network (ECN), USA.

Abstract

The aim of this thesis was to generate evidence to improve childhood cancer health outcomes and resource use in Egypt. Childhood cancer is an urgent priority in Egypt, owing to the large numbers of children with cancer, limited resources, and inferior survival. Therefore, there is a need to improve childhood cancer health outcomes (survival) with optimal resource use. The thesis generates three types of evidence using hybrid research methods: (1) Real-world evidence through conducting observational cohort studies in a local setting in Egypt (Chapters 3–5); (2) systematic evidence from the literature through conducting a systematic review study (Chapter 6); and (3) qualitative evidence from experts' opinions in the local context through conducting a qualitative interview study (Chapter 7). In Chapter 3, I determined the survival rates and temporal trends in survival for 14,808 children with cancer treated at Children's Cancer Hospital Egypt (CCHE) between 2007 and 2017, and identified cancers with inferior survival compared to international benchmarks. In Chapter 4, I determined childhood cancer hospital resource use and associated costs for 8,886 children with cancer treated between 2013 and 2017, and identified cancers with the highest resource use/costs. In Chapter 5, I estimated treatment cost-effectiveness at CCHE and found that it was not cost-effective for children with relapsed/refractory acute leukaemia. Accordingly, In Chapter 6, I conducted a systematic review on costs/cost-effectiveness of treatment for relapsed/refractory paediatric acute leukaemia. In Chapter 7, I conducted interviews to determine the clinicians' perceptions of barriers and facilitators to implementing cost-effective evidence-based treatment at CCHE. Overall, I have reported that the 5-year overall survival rate for children with cancer at CCHE was 72.1%, where 12 (out of 18) cancer types had inferior survival compared to international benchmarks, and that children with

acute myeloid leukaemia had the highest costs/resource use. Also, I found that treatment of relapsed/refractory acute leukemia was not cost-effective at CCHE, and the systematic review findings have shown that CAR–T cell therapy was a cost-effective treatment option, besides other novel therapies. I have identified four themes of barriers and facilitators to implementing cost-effective evidence-based treatment at CCHE. In conclusion, the thesis provides evidence-based recommendations for improving childhood cancer survival, resource use/costs, and treatment cost-effectiveness, addressing the implementation gaps at CCHE/Egypt. In Chapter 8, I discuss the implications of my thesis, and I propose a context-specific conceptual framework of evidence synthesis to improve childhood cancer health outcomes and resource use in Egypt.

Statement of Contributions

I certify that the conceptual framework that underpins this thesis and the underlying research are all my original work, of which I am the sole author. This thesis was completed under the supervision of Professor Carl Heneghan, who contributed intellectual guidance on the overall thesis structure, analyses, and presentation of results; Dr Jason Oke, who provided technical guidance on the statistical analyses methods and interpretation of results; and Dr Anne-Marie Boylan, who provided advice on the qualitative component of the thesis.

Other individuals have made the following contributions:

Nourhan Tarek (NT): researcher at Children's Cancer Hospital Egypt, helped in tabulation of part of the study results in Chapters 3 and 4.

Mahmoud Hamza (MH): data scientist at Children's Cancer Hospital Egypt, assisted with merging the resource use and costs data and making data adjustments in Chapter 4.

Nickhill Bhakta (NB): Associate Professor, Global Paediatric Medicine Department at St. Jude Children's Research Hospital, USA, provided technical advice on the cost-effectiveness model in Chapter 5.

Nancy S. Bolous (NSB): Faculty member, Global Paediatric Medicine Department at St. Jude Children's Research Hospital, USA, helped in full-text screening, data extraction, and quality appraisal of studies included in the systematic review in Chapter 6.

Nia Roberts (NR): Outreach librarian at the Bodleian Libraries, University of Oxford, helped in developing the search strategy for the systematic review in Chapter 6.

Table of Contents

Acknowledgements 4

Abstract 6

Statement of Contributions 8

List of Figures 17

List of Tables 18

List of Panels 21

List of Abbreviations 22

Chapter One: Introduction 25

1.1. Thesis overview 25

1.1.1. Aim of thesis 25

1.1.2. Thesis hypothesis 25

1.1.3. Setting and context 25

1.1.4. Research objectives 25

1.2 Thesis conceptual framework of evidence synthesis 26

1.3 Thesis structure 30

1.3.1. Chapter 2: Background 30

1.3.2. Chapter 3: Survival rates and temporal trends in survival 30

1.3.3. Chapter 4: Hospital resource use and costs of care 30

1.3.4. Chapter 5: Cost-effectiveness of childhood cancer treatment 31

1.3.5. Chapter 6: Systematic review of costs and cost-effectiveness of treatment for relapsed/refractory (r/r) acute leukaemia in children 31

1.3.6. Chapter 7: Barriers and facilitators to implementing cost-effective evidence-based treatment for children with cancer 32

1.3.7. Chapter 8: Discussion 32

1.4 Key Accomplishments 33

1.4.1. Publications 33
1.4.2. Other achievements (not related to my DPhil thesis) 33
1.4.3. Teaching 34
1.5 Personal motivation 34
Chapter One references 36
Chapter Two: Background 38
2.1 Chapter aim 38
2.2 Chapter methods 38
2.3 Burden of childhood cancer 39
2.4 Treatment of childhood cancer 44
2.5 Childhood cancer health outcomes 48
2.6 Childhood cancer resource use and costs 52
2.7 Cost-effectiveness of childhood cancer treatment 55
2.8 Barriers and facilitators to childhood cancer care 57
2.9 Gaps in the literature and the need for future research 59
Chapter Two References 61
Chapter Three: Childhood cancer survival rates and temporal trends in survival in Egypt 74
3.1 Publication statement 74
3.2 Introduction 74
3.3 Aim of work 75
3.4 Objectives 75
3.5 Methods 76
3.5.1 Study design and population 76
3.5.2 Data collection and validation 79
3.5.3 Statistical analysis 79
3.5.4 Comparison to international benchmarks 80

3.6 Results 81
3.6.1 Patient characteristics 81
3.6.2 Survival rates 83
3.6.3 Temporal trends in survival 87
3.6.4 Survival stratification by stage at diagnosis, risk, and subtype 93
3.6.5 Comparing age-standardised survival with international benchmarks 93
3.7 Discussion 99
3.7.1 Summary and interpretation of findings 99
3.7.2 Comparison with other published literature 100
3.7.3 Strengths and limitations 101
3.7.4 Implications 104
3.7.5 Evidence-based recommendations for improvement 106
3.8 Conclusions 106
3.9 Chapter How this study fits with my overall thesis 107
3.10 Chapter summary 107
Chapter Three References 108
Chapter Four: Childhood cancer hospital resoucre use and costs in Egypt 115
4.1 Publication statement 115
4.2 Introduction 115
4.3 Aim of work 116
4.4 Study Objectives 116
4.5 Methods 117
4.5.1 Population and setting 117
4.5.2 Data collection and validation 118
4.5.3 Costing approach 122
4.5.4 Statistical analysis 123

4.6 Results 124
4.6.1 Patient characteristics 124
4.6.2 Hospital resource use 126
4.6.3 Costs of childhood cancer care 135
4.7 Discussion 143
4.7.1 Summary and interpretaton of findings 143
4.7.2 Comparison with other published literature 144
4.7.3 Strengths and limitations 146
4.7.4 Implications 148
4.7.5 Evidence-based recommendations for improvement 149
4.8 Conclusion 150
4.9 How this chapter relates to the overall thesis 150
4.10 Chapter summary 150
Chapter Four References 152
Chapter Five: Cost-effectiveenss of childhood cancer treatment in Egypt 157
5.1 Publication statement 157
5.2 Introduction 157
5.3 Aim of work 158
5.4 Objectives 158
5.5 Methods 159
5.5.1 Patients and setting 159
5.5.2 Data collection and validation 161
5.5.3 Cost-effectiveness analysis 162
5.5.4 Statistical analysis 165
5.6 Results 166
5.6.1 Patient characteristics 166

5.6.2 Cost-effectiveness analysis 168
5.6.3 Association between costs and survival 177
5.7 Discussion 180
5.7.1 Summary and interpretation of findings 180
5.7.2 Comparison with other published literature 181
5.7.3 Strengths and limitations 182
5.7.4 Implications 185
5.7.5 Evidence-based recommendations for improvement 187
5.8 Conclusion 187
5.9 How this chapter relates to the overall thesis 188
5.10 Chapter summary 188
Chapter Five References 190
Chapter Six: Systematic review of costs and cost-effectiveness of treatment for relapsed/refractory acute leukaemia in children 196
6.1 Publication statement 196
6.2 Introduction 196
6.3 Aim of work 197
6.4 Objectives 197
6.5 Methods 198
6.5.1 Protocol 198
6.5.2 Search strategy 198
6.5.3 Eligibility criteria 199
6.5.4 Study selection and data extraction 200
6.5.5 Quality assessment of included studies 201
6.5.6 Data synthesis and analysis 201
6.6 Results 202
6.6.1 Search results and characteristics of included studies 202

6.6.2 Quality of included studies 206
6.6.3 Approach to cost-effectiveness analyses 206
6.6.4 Costs, benefits, and cost-effectiveness estimates 212
6.7 Discussion 217
6.7.1 Summary and interpretation of findings 217
6.7.2 Sources of variability and addressing uncertainty 219
6.7.3 Comparison with other studies in the literature 220
6.7.4 Strengths and limitations 222
6.7.5 Implications 223
6.7.6 Evidence-based recomemndations for improvement 225
6.8 Conclusion 226
6.9 How this chapter relates to the overall thesis 226
6.10 Chapter summary 227
Chapter Six References 228
Chapter Seven: Barriers and facilitators to implementing cost-effective evidence-based childhood cancer treatment in Egypt 234
7.1 Publication statement 234
7.2 Introduction 234
7.3 Aim of work 235
7.4 Objectives 236
7.5 Methods 236
7.5.1 Design, setting, and scope 236
7.5.2 Ethical considerations 237
7.5.3 Participants and recruitment 237
7.5.4 Data collection 238
7.5.5 Thematic data analysis 239
7.6 Results 239

7.6.1 Participant characteristics 239
7.6.2 Themes of barriers and facilitators 241
7.6.3 Participants' suggestions 252
7.7 Discussion 255
7.7.1 Summary and interpretation of findings 255
7.7.2 Comparison with other published literature 256
7.7.3 Strengths and limitations 256
7.7.4 Implications 258
7.7.5 Evidence-based recommendations for improvement 259
7.8 Conclusion 260
7.9 How this chapter relates to the overall thesis 260
7.10 Chapter summary 260
Chapter Seven References 262
Chapter Eight: Discussion 265
8.1. Chapter aim 265
8.2. Introduction 265
8.3. Summary of findings 265
8.4. Strengths and limitations 268
8.4.1 Strengths 268
8.4.2 Limitations 271
8.5. Implications of my DPhil thesis 275
8.5.1. Implications for policy and practice 275
8.5.2. Implications for future research 284
8.5.3. Implications for patients 286
8.6 Personal aspirations after my DPhil 287
8.7 Conclusion 287

Chapter Eight references 289

Appendix Chapter 1 293

Appendix Chapter 3 294

Appendix Chapter 4 325

Appendix Chapter 5 344

Appendix Chapter 6 359

Appendix Chapter 7 379

List of Figures

Figure 1.1. Context-specific conceptual framework of evidence synthesis to improve childhood cancer health outcomes and resource in Egypt/CCHE……....28

Figure 2.1. Egypt's geographical map, age structure, and population density……...….42

Figure 2.2. Children's Cancer Hospital Egypt – 57357……...47

Figure 3.1. Flowchart of included/excluded patients in survival analysis……...77

Figure 3.2. Five-year overall survival of childhood cancers, ranked ascendingly……...85

Figure 3.3. Trends in survival for all childhood cancers combined, over 2 and 3 diagnosis periods……..87

Figure 3.4. Change in 5-year overall survival for childhood cancers over 2 diagnosis periods…….…….88

Figure 3.5. Comparing 5-year childhood cancer age-standardised survival (aged 0–14 years) at CCHE/Egypt with international benchmarks from England and the US (n= 13,835)…….94

Figure 4.1. Trends in resource use over time at one-year post-diagnosis, per ICCC-3 groups…….131

Figure 4.2. Proportion (%) of total cost (USD) by childhood cancer type from the total…….136

Figure 5.1. Flowchart of included/excluded patients in survival/cost-effectiveness analyses……..159

Figure 5. 2. Cost per DALY averted for childhood cancers, stratified by stage/risk, subtype……..171

Figure 5.3. Cost per DALY averted, stratified by relapse/refractory or progressive disease (PD) status at 3-years post-diagnosis……174

Figure 6.1. PRISMA flow diagram……202

Figure 6.2. QALYs gained for CAR-T cell therapy versus alternative interventions to treat relapsed/refractory paediatric ALL……213

Figure 6.3. Costs of CAR–T cell therapy (USD 2019) for relapsed/refractory ALL……215

Figure 7.1. Thematic framework of interrelated themes of barriers and facilitators…….241

Figure 8.1. Context-specific conceptual framework of evidence synthesis…….....275

List of Tables

Table 2.1. MEDLINE search strategy……..…37

Table 2.2. Comparison of global childhood cancer burden approaches and estimates……40

Table 3.1. Demographic characteristics of children with cancer at CCHE/Egypt (N= 15,779)……..81

Table 3.2. 1-, 3- and 5-year overall survival of children with cancer at CCHE (2007–2017) with median survival time, (n=14,808)…….....83

Table 3.3 Trends in 3-year and 5-year overall survival of children with cancer at CCHE, by periods of diagnosis and single year of diagnosis, grouped by ICCC-3 diagnostic groups (n=14,808)……..…….90

Table 3.4. Comparing 5-year age-standardized survival rates for children with cancer (aged, 0–14 years) at CCHE/Egypt [2007–2017] with survival in England [2001–2015] and the US [2008–2014], by ICCC-3 diagnostic groups…….93

Table 3.5. Cause-specific mortality for childhood cancers with inferior survival at CCHE/Egypt…….96

Table 3.6. Adverse events for childhood cancers with inferior survival at CCHE/Egypt……...…97

Table 4.1. Description of resource use measures and cost categories/sub-categories, definitions and methods of measurement/allocation…….……..119

Table 4.2. Patient-related and disease-related characteristics at CCHE/Egypt, (N=8,886)……...……124

Table 4.3. Main resource use measures at 1-year post diagnosis, by ICCC-3 groups (N=8 886)……..…126

Table 4.4. In-patient hospital admission, PICU admission, and BMT rates, by 4 main childhood cancer types, during the first-year post-diagnosis (N=8,886)…….....127

Table 4.5. Resource use measures of investigations and treatment interventions at 1-year post diagnosis, (N=8,886)……..……..…129

Table 4.6. Factors associated with length of inpatient stay (in weeks) during first year post-diagnosis, using univariate and multi-variate analysis (N=8,886)……..133

Table 4.7. Median total costs (in USD) for childhood cancers at 1 -and 3- years post-diagnosis, by ICCC-3 diagnostic groups (N=8,886)……...…135

Table 4.8. Main cost categories and sub-categories (USD) at 1-year post-diagnosis, per ICCC-3 groups (N=8,886)……..…....137

Table 4.9. Trends in total costs (USD) at 1-year post diagnosis, for the ICCC-3 groups, by year of diagnosis (N=8,886)……...139

Table 4.10. Factors associated with total costs (USD) during first year post-diagnosis, using univariate and multivariate analysis (N=8,886)……..141

Table 5.1. Patient and disease characteristics at initial diagnosis, and survival/disease status at 3-years post-diagnosis, (N=8,886)…….....166

Table 5.2. Cost per DALY averted for childhood cancers, by ICCC-3 groups, diagnosed between 2013–2017……..…..168

Table 5.3. Base-case and sensitivity analysis for Cost per DALY averted, (N=8,886)…….169

Table 5.4. Hazard ratio (95% CI) estimated in Cox regression model for the association between costs and risk of mortality controlling for confounders…….177

Table 6.1. Characteristics of included studies……203

Table 6.2. Costs, clinical outcomes, and cost-effectiveness estimates to treat relapsed/refractory acute leukaemia……..…….207

Table 6.3. Costs (USD 2019) and QALYs gained of CAR–T cell therapy and comparator(s) to treat relapsed/refractory ALL……..……212

Table 7.1. Characteristics of interview participants (N=14)……..240

Table 7.2. Themes and domains of Barriers and facilitators to implement cost-effective evidence-based treatment for children with cancer at CCHE/Egypt……...242

Table 7.3. Sub-group analysis of themes of barriers and facilitators to implement cost-effective evidence-based childhood cancer treatment at CCHE/Egypt, by health professions….....248

Table 7.4. Sub-group analysis of themes of barriers and facilitators to implement cost-effective evidence-based childhood cancer treatment at CCHE/Egypt, by level of decision-making…….249

Table 7.5. Participants' Suggestions to implement cost-effective evidence-based treatment for children with cancer at CCHE/Egypt……..……..252

Table 8.1. Implications of each type of evidence in the conceptual framework……...….276

Table 8.2. Table 8.2. Advantages and disadvantages of research methods used in the conceptual framework……..……..……....…….278

List of Panels

Panel 3.1 Recommendations to improve survival of children with cancer at CCHE……...….105

Panel 4.1 Recommendations to optimise resource use and manage costs effectively at CCHE……..….148

Panel 5.1 Recommendations to increase cost-effectiveness and promote high-value care at CCHE…....186

Panel 6.1 Key recommendations to deliver cost-effective treatment for relapsed/refractory paediatric acute leukaemia in children…….224

Panel 7.1 Recommendations to implement cost-effective evidence-based childhood cancer treatment in Egypt, addressing the implementation gaps at CCHE/Egypt……...….258

List of Abbreviations

Abbreviation	Meaning
ALL	Acute Lymphoblastic Leukaemia
AML	Acute Myeloid Leukaemia
ASRs	Age-Standardized Rates
BMT	Bone Marrow Transplant
BENCHISTA	International Benchmarking of Childhood Cancer Survival by Stage
Blina	Blinatumomab
CAR	Chimeric Antigen Receptors
CCHE	Children's Cancer Hospital Egypt
CCEMG	Campbell and Cochrane Economic Methods Group
CE	Cost-Effectiveness
CEA	Cost-effectiveness analysis
CEBM	Centre for Evidence-based Medicine
CML	Chronic Myeloid leukaemia
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CHOICE	Choosing Interventions that are Cost-Effective
CI	Confidence Interval
CNS	Central Nervous System
COG	Children's Oncology Group
COREQ	Consolidated Criteria for Reporting Qualitative Research
Clo–C	Clofarabine combination therapy
Clo–M	Clofarabine monotherapy therapy
COVID-19	COronaVIrus Disease of 2019
CRD	Centre for Reviews and Dissemination
DALYs	Disability-Adjusted Life Years
DARE	Database of Abstracts of Reviews of Effects
DDI	Double Delayed Intensification
DI	Double intensification
DLBCL	Diffuse Large B-cell Lymphoma
EC3T	Evidence on Cost-effective Childhood Cancer Treatment
EGP	Egyptian Pound
EFS	Event-free survival
EMR	Eastern Mediterranean Region
EMR	Electronic Medical Record
EBRT	External Beam Radiation Therapy
ED	Emergency Department
EU	European Union
EBM	Evidence-based Medicine
EBP	Evidence-based practice

FDA	Food and Drug Administration
FU	Follow-up
GBD	Global Burden of Disease
GCC	Global Childhood Cancer
GCT	Germ Cell Tumours
GICC	Global Initiative for Childhood Cancer
G-CSF	Granulocyte colony-stimulating factor
GDP	Gross Domestic Product
HCUP	Healthcare Cost and Utilization Project
HR–QOL	Health-Related Quality of Life
HSCT	Haematopoietic Stem-Cell Transplantation
HTA	Health Technology Assessment
HICs	High-Income Countries
HLA	Human Leukocyte Antigens
HR	Hazard Ratio
IARC	International Agency for Research on Cancer
ICCC-3	International Childhood Cancer Classification – third edition
ICD-10	International Classification of Disease – tenth edition
ICD-O-3	International Classification of Diseases for Oncology – third edition
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
ICUR	Incremental Cost Utility Ratio
IICC-3	International Incidence of Childhood Cancer
IQR	Interquartile Range
IHME	Institute for Health Metrics and Evaluation
IRB	Institutional Review Board
IV	Intravenous
JMML	Juvenile Myelomonocytic Leukaemia
KT	Knowledge Translation
LCH	Langerhans Cell Histiocytosis
LE	Life Expectancy
LMICs	Low- and Middle-Income Countries
LICs	Low-Income Countries
LY	Life Year
LYG	Life Year Gained
MICs	Middle-Income Countries
MDS	Myelodysplastic Syndrome
NCCN	National Comprehensive Cancer Network
NFT	No-Further-Treatment
NGOs	Non-Governmental Organisations
NHL	Non-Hodgkin Lymphoma
NHS	National Health System

NHS–EED	NHS Economic Evaluation Database
OLS	Ordinary Least Squares
OMRU	Ottawa Model of Research Use
OR	Operating Room
OS	Overall Survival
OxTREC	Oxford Tropical Research Ethics Committee
PBT	Proton Beam Therapy
PBSCT	peripheral blood stem cell transplant
PICU	Paediatric Intensive Care Units
PD	Progressive Disease
PH	Proportional Hazards
QALY	Quality-Adjusted Life Year
QOL	Quality of Life
RFS	Relapse-free survival
R/R	Relapsed/Refractory
RTH	Radiotherapy
RWD	Real-World Data
RWE	Real-World Evidence
REDCap	Research Electronic Data Capture
SIOP	International Society of Paediatric Oncology
SD	Standard Deviation
SEER	Surveillance, Epidemiology, and End Results program
SCT	Stem Cell Transplant
SMAC	Scientific Medical Advisory Committee
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
Tisa-cel	Tisagenlecleucel
TRMs	Treatment-Related Mortalities
UHIP	Universal Health Insurance Project
UI	Uncertainty Intervals
US	United States
USD	United States Dollar
WHO	World Health Organization
WTP	Willingness-to-Pay
YLL	Years of Life Lost
YLD	Years Lived with Disability

Chapter One: Introduction

1.1. Thesis overview

1.1.1. Aim of thesis

This DPhil thesis aims to generate evidence that will help improve childhood cancer health outcomes and resource use in Egypt.

1.1.2. Thesis hypothesis

The overarching hypothesis of this thesis was that childhood cancer health outcomes (survival outcomes) and resource use are sub-optimal in Egypt.

1.1.3. Setting and context

The research work for this thesis was conducted at the Children's Cancer Hospital Egypt (CCHE). CCHE is a large paediatric oncology centre in Egypt with a 320-inpatient bed capacity that treats annually around 2,500–3,000 newly diagnosed children with cancer, aged 0–18 years, representing around 40% of all children with cancer across Egypt.[1] CCHE is a non-profit charity hospital that treats children with cancer for free based on philanthropic donations.[1]

1.1.4. Research objectives

The research objectives of this thesis included:

1. Determine survival rates and temporal trends in survival for children with cancer at CCHE/Egypt.
2. Assess childhood cancer hospital resource use and costs of care at CCHE/Egypt.

3. Estimate the cost-effectiveness of childhood cancer treatment at CCHE/Egypt.
4. Summarise systematic evidence from the literature about the costs and cost-effectiveness of treatment for relapsed/refractory acute leukaemia in children.
5. Understand the clinicians' perceptions of barriers and facilitators to implementing cost-effective evidence-based treatment for children with cancer at CCHE/Egypt.

1.2 Thesis conceptual framework of evidence synthesis

1.2.1. Publication statement

Features of the conceptual framework underpinning this DPhil thesis are accepted for publication in the following peer-reviewed journal:

Soliman R. A context-specific conceptual framework of evidence synthesis to improve childhood cancer health outcomes and resource use in Egypt: Using real-world data and addressing the implementation gaps. *Cochrane Evidence Synthesis and Methods* journal. DOI:10.1002/cesm.12010

In this thesis, I propose a context-specific conceptual framework of evidence synthesis to improve childhood cancer health outcomes and resource use in Egypt, using real-world data and addressing the implementation gaps. The conceptual framework underpinning my DPhil thesis illustrates the thesis structure, research studies included, and research methods used, as presented in Figure 1.1.

A conceptual framework is a set of interlinked key concepts, factors, or variables that together provide a comprehensive understanding of a phenomenon of interest, where each concept plays an integral role.[2] Real-world data (RWD) is defined as data relating to patient health status

and/or the delivery of health services routinely collected (outside the context of randomised trials) from various data sources, including electronic health records, disease registries, or administrative/costing database.[3] Real-world data can be used to conduct observational cohort research studies, either prospectively or retrospectively.[3]

The conceptual framework builds upon three key concepts to address this context-specific problem: conducting primary research from local context to address the gap in literature; conducting systematic review as the main gold standard for evidence synthesis; and addressing the implementation gaps. The conceptual framework was also inspired by key concepts[4,5,6] in evidence-based medicine (EBM) (Box 1.1).

Box 1.1 Key EBM Concepts that inspired the Conceptual Framework

- Different types of research questions require different types of evidence.[4]
- Generating evidence that is relevant to clinical practice and applies to our patients.[5]
- EBM is about integrating individual clinical expertise and the best external evidence.[6]
- Irrespective of the type of research, systematic reviews are necessary.[4]

In light with the above, the conceptual framework of evidence synthesis (Figure 1.1) proposes to generate three types of evidence using hybrid research methods:

1. Real-world evidence (RWE) from local context in Egypt/CCHE, through conducting observational cohort studies based on routinely collected data from the local setting. This would help assess the current situation, and identify key priority areas from local context. Accordingly, provide evidence-based recommendations for improvement.

2. Systematic evidence from the literature through conducting a systematic review. This would provide currently best available external evidence about a local priority area.
3. Qualitative evidence based on experts' opinions from local context, through conducting qualitative interview study. This would help address the implementation gaps and translate the generated evidence into practice.

According to the Royal Society, '*evidence synthesis*' refers to the process of bringing together information from a range of sources and disciplines to inform debates and decisions on specific issues.[7] In this context-specific conceptual framework, the term '*evidence synthesis*' refers to generating the three different types of evidence altogether, rather than the more commonly used/known term that only refers to systematic reviews. Implications of implementing this conceptual framework are discussed in Chapter 8.

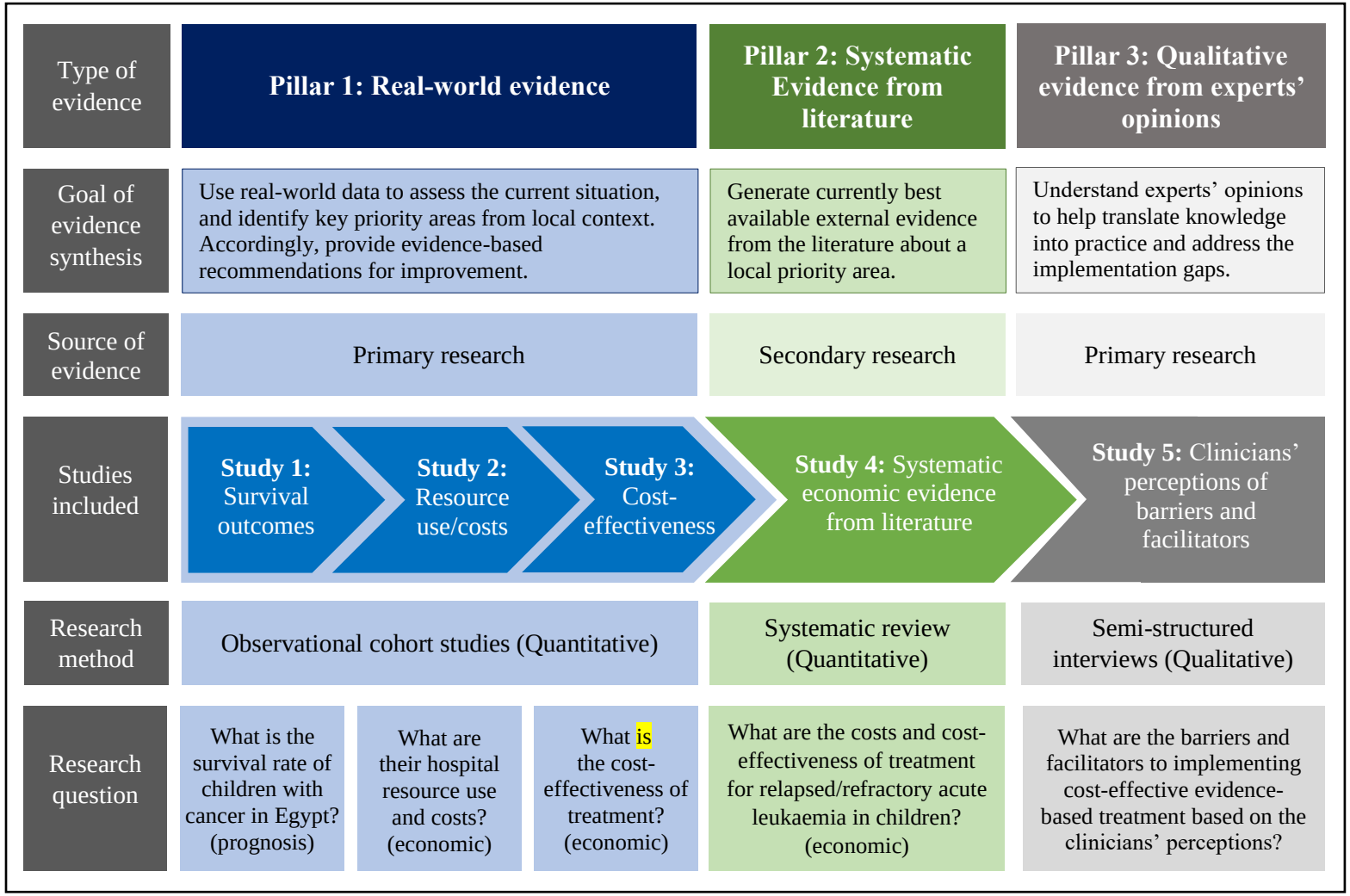


Figure 1.1. Context-specific conceptual framework of evidence synthesis to improve childhood cancer health outcomes and resource in Egypt/CCHE

1.3 Thesis structure

1.3.1. Chapter 2: Background

In Chapter 2, I summarise the published literature on the disease burden of childhood cancers on the global, LMIC contexts, and national level in Egypt. I reflect on the recent advances in childhood cancer care, and describe the disparties in survival outcomes. Then, I outline the resources utilised during childhood cancer treatment, and their associated costs and cost-effectiveness estimates. Finally, I discuss the main barriers and facilitators to paediatric oncology care, highlighting the main issues in Egypt. I identify the gaps in the litearture and the need for futture research, explaining how my thesis research work helps address some of these gaps.

1.3.2. Chapter 3: Survival rates and temporal trends in survival

In Chapter 3, I conducted a retrospective observational cohort study (inception cohort), to determine the 5-year overall survival (OS) and temporal trends in childhood cancer survival at CCHE. I compared the age-standardised survival rates at CCHE with international benchmarks from England and the US. This helped identify which childhood cancer types had inferior 5-year OS relative to the international benchmarks, and identify the cancers with inferior/steady survival trends over time. Finally, I present evidence-based recommendations to improve the survival outcomes of children with cancer at CCHE.

1.3.3. Chapter 4: Hospital resource use and costs of care

In Chapter 4, I conducted a retrospective observational cohort study analysing childhood cancer hospital resource use and costs-of-care (from a health system perspective) at one- and three-years post-diagnosis. I determined the resource use/costs patterns, trends and their associated factors.

Furthermore, I identified the cancers with highest resource use/costs patterns and trends over time, and highlighted the main cost drivers and the high-resource use categories. Finally, I present evidence-based recommendations to optimise childhood cancer resource use and manage costs effectively.

1.3.4. Chapter 5: Cost-effectiveness of childhood cancer treatment

In Chapter 5, I conducted retrospective analysis of the cost-effectiveness (CE) of childhood cancer treatment at CCHE, using the survival outcomes (using updated survival rates from Chapter 3) and the costs of treatment (obtained from Chapter 4). Cost-effectiveness was estimated in terms of cost per disability-adjusted life years (cost/DALYs) averted, using the WHO–CHOICE criteria thresholds at 1–3 times the country's GDP (gross domestic product) per capita. I calculated the cost-effectiveness estimates stratified by cancer type/subtype, stage at diagnosis, risk group, and disease status (relapse, refractory, or progressive). Accordingly, I identified specific childhood cancer groups whose treatment was not cost-effective (e.g.: relapsed/refractory acute leukaemia) as a key priority area. Also, I determined the association between costs-of-care and survival outcomes, accounting for potential confounders. Finally, I present evidence-based recommendations to promote the cost-effectiveness of treatment at CCHE/Egypt.

1.3.5. Chapter 6: Systematic review of costs and cost-effectiveness of treatment for relapsed/refractory (r/r) acute leukaemia in children

In Chapter 6, I conducted a systematic review of the costs and cost-effectiveness of treatment for relapsed/refractory acute leukaemia in children, for whom the existing treatment at CCHE was not cost-effective, focusing on a key priority issue as outlined in Chapter 5. I summarised the

available economic evidence about the alternative treatment strategies to treat relapsed/refractory acute leukemia, to determine the most cost-effective therapies, based on the best external evidence from the literature. I assessed the quality of evidence generated from the included health economic evaluation studies.

1.3.6. Chapter 7: Barriers and facilitators to implementing cost-effective evidence-based treatment for children with cancer

In Chapter 7, I conducted a semi-structured interview study to determine the clinicians' perceptions of the barriers and facilitators to implementing cost-effective evidence-based treatment for children with cancer at CCHE/Egypt. I conducted thematic analysis of the qualitative data, where I categorized the related concepts into themes and domains of barriers, facilitators and suggestions. Then, I developed a thematic framework of inter-related themes of barriers and facilitators. This chapter provided qualitative evidence based on clinical expertise (clinicians) to help translate the generated evidence in the previous chapters (chapters 3–6) into practice and address the implementation gaps.

1.3.7. Chapter 8: Discussion

In Chapter 8, I summarise the main results of my DPhil research work, compare my findings with relevant studies in the literature, and reflect on the methodological strengths and limitations of my research work. Additionally, I provide the implications of my research on the clinical practice, policy and research frontiers.

1.4 Key Accomplishments

1.4.1. Publications

At the time of thesis submission, I have published four papers from my DPhil research work in peer-reviewed journals,[8,9,10,11] of which one study was published in one of *The Lancet* journals.[9] The fifth study of my DPhil research was accepted for publication in a peer-reviewed journal and was in the final production stage. Besides, the conceptual framework underpinning this thesis was accepted for publication as an invited commentary article in the *Cochrane Evidence Synthesis and Methods* journal.

1.4.2. Other achievements (not related to my DPhil thesis)

1. Acted as a temporary advisor (between 2020–2022) to the WHO Global Initiative for Childhood Cancer (GICC) for the Eastern Mediterranean Region (EMR), whereby:
    a. I contributed to a book chapter about childhood cancer control in the EMR.[12]
    b. I published a manuscript as a co-first author about childhood cancer disease burden in the EMR in The *Lancet Child & Adolescent Health* journal.[13]
2. Invited to participate in the *St. Jude Global Alliance Convening* 2022, representing CCHE and Egypt, in recognition of the collaborative efforts in childhood cancer research with the Department of Global Paediatric Medicine (Disease Burden and Modelling Team) at the St. Jude Children's Research Hospital in Memphis, Tennessee, US.
3. Acted as the student representative for the DPhil in EBHC programme (between 2020–2022), whereby, I launched the "Evidence Resonates" initiative to communicate research evidence with other DPhil students, and wrote several related blogs on the website of the Centre for Evidence-based Medicine (CEBM) (Appendix 1).

1.4.3. Teaching

In 2021 and 2022, I was involved in teaching two modules, “Introduction to Evidence-based Healthcare” and “Critical Appraisal”, in the Paediatric Oncology Fellowship, which is a joint program between Boston’s Children’s Hospital/Harvard Medical School and CCHE/Egypt. In 2023, I additionally taught a course on “Health Economic Evaluation” within the same fellowship programme.

1.5 Personal motivation

Rarely would one mention their school in a DPhil thesis, but mine was a one-of-a-kind experience that helped shape who I am today. I attended *Ramses College for Girls* (RCG) (former *American College for Girls*), which has inspired me to have a sense of commitment to make a positive impact in the world and serve the community, following the school’s motto, “*Enter ye to learn. Leave ye to serve*”. On the school’s inaguration in 1910 by the former U.S. president Theodore Roosevelt, he said, "*I do not believe that any nation can rise to permanent greatness unless its women are fitted to play their part as man should play his*.” At RCG, they taught us to follow our paths in life as passionate, dedicated, and committed young ladies.

After my graduation from university, I followed my passion to help children with cancer by joining CCHE as a clinical researcher in 2010, where I was interested in conducting health outcomes research as a maens to potentially improve their outcomes and alleviate their suffering. In 2017, I became interested in health economics and outcomes research and established the Health Economics and Value Unit at CCHE to help improve patients’ health outcomes while optimising the use of hospital resources.

Once again, I followed my passion to Oxford to pursue a DPhil in Evidence-based Healthcare. Throughout my DPhil journey, I was eager to enhance my research skills and gain as much knowledge as possible as I could so that I would undertake research that could potentially help improve the health outcomes and resource use for children with cancer in Egypt/CCHE.

With this in mind, I attended several training courses to improve my research skills and knowledge in a variety of areas, including statistical analysis using R software, conducting systematic reviews, health economic evaluation, decision analytic modelling for health economic evaluation, qualitative research methods, and knowledge translation strategies. This thesis is the result of previous research experience at CCHE and five years of study in evidence-based healthcare at the Uniersity of Oxford, coupled with a passion to help children with cancer.

Chapter One references

1. Children's Cancer Hospital Egypt (CCHE). Our Vision [Internet]. Cairo: CCHE 57357; 2023 [updated 2023; cited 2023 Sep 12]. Available from: https://www.57357.org/en/home-page/
2. Jabareen, Y. Building a conceptual framework: Philosophy, definitions, and procedure. *Int. J. Qual. Methods*. 2009. 8(4):49-62.
3. Food and Drug Administration (FDA). Real-World Evidence [Internet]. FDA. 2023 [cited 2023 Mar]. Available from: https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence
4. Glasziou P, Vandenbroucke JP, Chalmers I. Assessing the quality of research. *BMJ*. 2004;328(7430):39-41.
5. Heneghan C, Brassey J, Aronson J, O'Sullivan JW. Introducing the EBM Verdict: research evidence relevant to clinical practice. *BMJ Evid Based Med*. 2019;24(3):85-6.
6. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ*. 1996;312(7023):71-2.
7. The Royal Society. Evidence synthesis [internet]. The Royal Society. 2018 Sep [cited 2023 April 6]. Available from: https://royalsociety.org/topics-policy/projects/evidence-synthesis/
8. **Soliman R**, Elhaddad A, Oke J, Eweida W, Sidhom I, Ahmed S, *et al.* Temporal trends in childhood cancer survival in Egypt, 2007 to 2017: A large retrospective study of 14 808 children with cancer from the Children's Cancer Hospital Egypt. *Int J Cancer*. 2021;148(7):1562-74.
9. **Soliman R**, Elhaddad A, Oke J, Eweida W, Tarek N, Hamza M, *et al.* Childhood cancer hospital resource utilization and costs in Egypt, 2013-2017; patterns, trends, and associated

factors for 8886 patients from Children's Cancer Hospital, Egypt. *Pediatr Blood Cancer*. 2021;68(11):e29347.

10. **Soliman R**, Oke J, Sidhom I, Bhakta N, Bolous NS, Tarek N, *et al*. Cost-effectiveness of childhood cancer treatment in Egypt: Lessons to promote high-value care in a resource-limited setting based on real-world evidence. *EClinicalMedicine – Part of The Lancet Discovery Science*. 2023;55:101729.
11. **Soliman R**, Heneghan C, Bolous NS, Sidhom I, Ahmed S, Roberts N, *et al*. Systematic review of costs and cost-effectiveness of treatment for relapsed/refractory acute leukemia in children and young adults. *Expert Rev Hematol*. 2022;15(4):345-57.
12. Saab, R., **Soliman, R**, Belgaumi, A., Hessissen, L., Kutluk, T., Konig, L., *et al*. Chapter 7: In: Childhood cancer in the Eastern Mediterranean region. Cancer Control Eastern Mediterranean Region Special Report. *Global Health Dynamics*; 2022. p. 72-81. Available from: http://www.cancercontrol.info/wp-content/uploads/2022/05/72-chapter-7.pdf
13. Fadhil I, **Soliman R**, Jaffar S, Al Madhi S, Saab R, Belgaumi A, *et al*. Estimated incidence, prevalence, mortality, and registration of childhood cancer (ages 0-14 years) in the WHO Eastern Mediterranean region: an analysis of GLOBOCAN 2020 data. *Lancet Child Adolesc Health*. 2022;6(7):466-73.

Chapter Two: Background

2.1 Chapter aim

The aim of this chapter is to provide the rationale for this thesis, discuss the relevant published literature, and address the identified gaps in the literature. Hereby, I discuss the disease burden, management and health outcomes of childhood cancers. I highlight the resources used in childhood cancer care, their costs, and cost-effectiveness estimates, and factors affecting paediatric oncology care.

2.2 Chapter methods

The search strategy for this chapter was based on the following sources:

1. A structured search of the MEDLINE database through the PubMed interface (Table 2.1).
2. The literature collected throughout my DPhil years, corresponding to each chapter.
3. Forward and backward citation to identify all the pertinent literature on my topic.
4. Grey literature search of key organizations including the World Health Organization (WHO), and the International Agency for Research on Cancer (IARC).

Table 2.1. MEDLINE search strategy

Topic	Search strategy
Childhood cancer burden and outcomes; disease burden; survival	"burden" OR "incidence" OR "mortality" OR "survival" AND "childhood cancer"
Childhood cancer treatment; resources; costs; cost-effectiveness	"treatment" OR "management" OR "resource" OR "costs" OR "cost-effectiveness" AND "childhood cancers"
Barriers and facilitators to paediatric oncology care	"barriers" OR "facilitators" AND "paediatric oncology"

2.3 Burden of childhood cancer

The term ‘disease burden’ reflects the impact of a health problem or a medical condition in a given population, showing the magnitude, severity and cumulative consequences of a disease.[1] Estimating the childhood cancer burden is crucial for developing cancer control plans, making evidence-informed policies and priority setting, and ensuring appropriate resource planning.[2–5] Disease burden measures include estimates of incidence, prevalence, mortality, and disability-adjusted life-years (DALYs).[2] DALYs is a composite measure that includes years of life lost (YLL) due to premature mortality from childhood cancer, and years lived with disability (YLD) as a consequence of the disease and/or its treatment.[3] The burden of childhood cancer varies at global, regional, and national levels,[2] and by countries’ income levels.

2.3.1 Global Burden

Childhood cancer is a main cause of cancer disease burden, where it ranks the sixth in terms of global cancer burden, and is the ninth leading cause of death in children.[2,3,4] It has been estimated that around 400,000 children and adolescents (aged 0–19 years) develop cancer each year.[6,7]

Around 80% of the global childhood cancer burden occurs in low- and middle- income countries (LMICs),[3,4] classified by the World Bank groups,[8] where the majority (90%) of the world’s children reside with limited access to resources.[9,10,11] Accurately quantifying the global burden of childhood cancer is challenging owing to the variation in childhood cancer registration around the world, and the paucity of high-quality data from population-based cancer registries in LMICs.[4,12] That is why, the global burden varies based on the estimation methods, data sources, and the modelling/simulation-based approaches.[4] Hence, the reported estimates should be interpreted with caution.

For this reason, various programmes and research projects attempted to estimate the global and regional childhood cancer burden within the last decade, yielding rather different estimates.[4,12,13,14] These initiatives include: the Global Burden of Disease (GBD) project (2019);[13] the WHO GLOBOCAN project (2018);[14] the Baseline Model (2015);[12] and the Global Childhood Cancer (GCC) microsimulation model.[5] A comparison of the different childhood cancer global burden calculation approaches and estimates are presented in Table 2.2.

There is potential underestimation of the true burden of childhood cancer globally, owing to the under-reporting and under-diagnosis in LMICs.[2,3] The GBD study (2019) and the GLOBOCAN (2018) yielded the lowest estimates of incident cases and age-standardized incidence rates (ASRs), as they mostly relied on data from local cancer registries.[13,14] Yet, the global occurrence of childhood cancer is thought to be higher than previously estimated.[5] Notably, the GCC model by Ward *et al.* (2019) estimated the highest incident cases after accounting for the proportion of undiagnosed children with cancer globally, where only 57% were previously diagnosed.[5]

DALY estimates provide a more accurate picture of the significant global burden of childhood cancer, as they reflect the large numbers of YLL and YLD as a result of the disease, rather than the relatively small absolute numbers provided by the other disease burden measures.[3]

The global burden of childhood cancer differs by world regions, where the highest incidence rates (ASRs) are in Western Europe and North America, while Africa has the lowest incidence rates, despite having the highest mortality (ASRs) worldwide.[13,14] Cancer in children (aged 5–14 years) is the third leading cause of death in the Eastern Mediterranean region (EMR), after injuries and violence.[15,16]

Table 2.2. Comparison of global childhood cancer burden approaches and estimates

Program/project	**GBD 2019** [13]	**GLOBOCAN 2018** [14]	**Baseline Model 2015** [12]	**GCC model 2015** [5]
Global childhood cancer burden estimation approaches				
Year of publication	2022	2021	2021	2019
Years of study included	1990–2019	2018	2015	2015
Organization	IHME	WHO/IARC	Research group	Research group
Disease burden measures	Incidence, prevalence, mortality, DALYs	Incidence, mortality	Incidence	Incidence
Classification	ICD–10	ICD–10	ICCC-3	ICCC-3
Data source	Individual population-based cancer registries	Individual population-based cancer registries	SEER 2015, accounting for the role of P. falciparum exposure; IICC-3	Data from IICC-3 adjusted for health system parameters
Number of registries included	7,333	468	Not applicable	>300
Countries/territories covered	204	183	Not applicable	81
Childhood cancers included	22 cancer types/subtypes	33 cancers, by site/sub-site	ICCC-3 groups	48 cancer subcategories
Age-group(s)	0–14 years	<15 years; (<5, 5–9 and 10–14)	0–14 years	<15 years; (<1, 1–4, 5–9 and 10–14)
Global childhood cancer estimates				
Incident cases	291,319 (95% UI: 254,239 – 331,993)	200,166	360,114	397,000 total (95% UI: 377,000–426,000); only 224,000 (57%) diagnosed
Incidence rate (ASR)	14.8 per 100,000	10.3 per 100,000	18.6 per 100,000	Not applicable
Prevalent cases	1,806,630 (95% UI: 1,567,808–2,089,668)	Not applicable	Not applicable	Not applicable
Deaths	98,834 (95% UI: 86,124 – 113,581)	74,956	Not applicable	Not applicable
Mortality rate (ASR)	5.04 per100,000	3.8 per 100,000	Not applicable	Not applicable
DALYs	8,302,464 (95% UI: 7,230,447–9,555,118)	Not applicable	Not applicable	Not applicable

Abbreviations: GBD: Global Burden of Disease; GCC: Global Childhood Cancer Model; IHME: Institute for Health Metrics and Evaluation; IARC: International Agency for Research on Cancer; ICD-10: International Classification of Disease – tenth edition; ICCC-3: International Childhood Cancer Classification; SEER: Surveillance, Epidemiology, and End Results program; IICC-3: International Incidence of Childhood Cancer; ASR: Age-standardized rates; UI: Uncertainty Intervals.

Childhood leukaemia contribute the most to the global childhood cancer burden (34.1% of global DALYs) in the 0-14 age group,[3,6,12] followed by brain/CNS tumours (18.1% of global DALYs), and then lymphomas and neuroblastoma.[3,17] Children with leukaemia and brain/CNS tumours altogether account for 45% of incident cases and 57% of deaths.[14] While, for children aged 15–19 years, brain/CNS tumours are the most common cancers, followed by lymphomas.[17]

2.3.2 Burden in LMICs

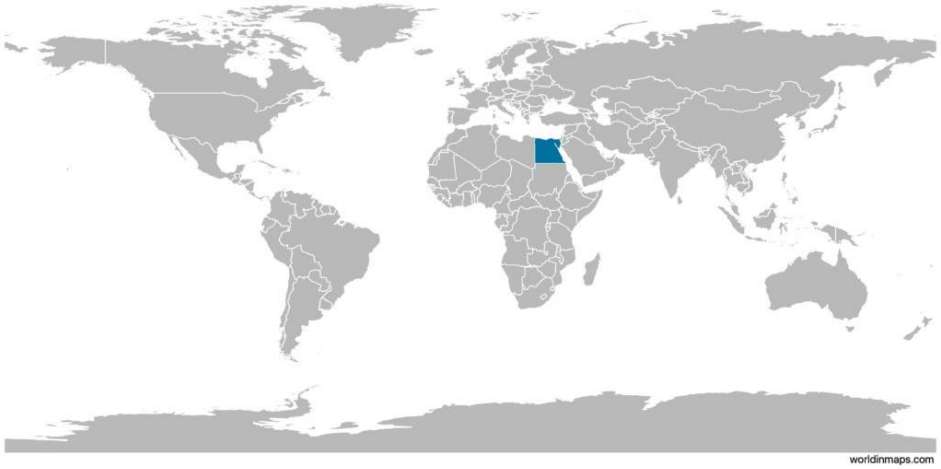
The global burden of childhood cancer differs substantially by income levels of countries.[12,13,14] Childhood cancer is considered a global child health priority in LMICs,[18] as 82.2% (95% CI: 82.1–82.2%) of global childhood cancer DALYs occur in LMIC contexts with limited access to resources (only 5% of the global resources for cancer care) and inferior survival.[2,3]

The estimated incidence rates (ASRs) of childhood cancers were lower in LMICs compared to those in high-income countries (HICs).[12,13,14] Whereas, the mortality rates (ASRs) were considerably higher in LMICs.[12,13,14] Despite the lower incidence rates in LMICs, Ward *et al*. (2019) estimated that 92% (366,000 out of 397,000) of the total incident childhood cancer cases occur in LMICs, owing to the large numbers of children with cancer in LMIC contexts.[5] Similar to global estimates, leukaemia and brain/CNS tumours were the most common in LMICs.

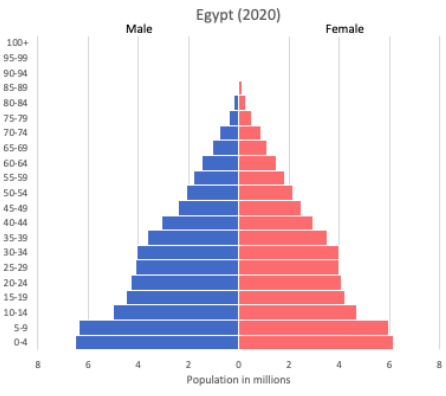
According to a *Lancet Oncology Commission* by Atun *et al.* (2020), projections based on current population growth estimate that there will be around 13.7 million (95% UI 12.5–15.0 million) new childhood cancer cases worldwide between 2020 and 2050, of which around 10.3 million (8.9–11.8 million) will be in LMICs.[2] They also estimated that 11.1 million children will die from cancer (out of 13.7 million) if no investments are made to improve access to services and treatment, with LMICs accounting for 84.1% of these deaths (9.3 million children with cancer).[2]

2.3.3 Burden in Egypt

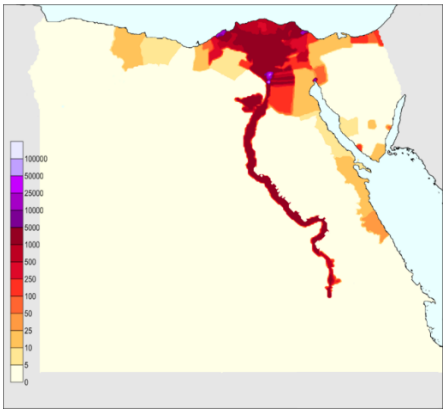
Egypt is a lower-middle income country,[19] geographically located in North Africa, and lies within the EMR.[20] Egypt ranks the tenth country globally and the second regionally (EMR) with the largest number of incident childhood cancer cases.[20,21] The WHO estimated in 2020 that the annual number of new childhood cancer cases in Egypt, aged 0-14 years, was 6,803 (20% of the total number of cases in the region).[22,23] This is attributed to the relatively large population of Egypt (102.3 million in 2020),[24] with 33.9% of the population under the age of 15.[25] Figure 2.1. shows Egypt's geographical location, age structure, and population density.



Source: World Maps. 2021.



Source: World Maps. 2021.



Source: Vivid Maps. 2021.

Figure 2.1. Egypt's geographical map, age structure, and population density

Based on GLOBOCAN 2020 estimates, childhood cancer incidence rate (ASRs) was 12.1 per 100,000 children at risk in Egypt. [20,21] Egypt had the greatest number of annual childhood cancer deaths (n=1,581) in the EMR, with mortality rate (ASRs) of 4.6 per 100,000 children at risk.[20,21] Childhood leukaemia accounted for 21.6% of total childhood cancer deaths in Egypt, followed by brain/CNS tumours (20.5%), and non-Hodgkin lymphoma (NHL) (12.4%).[20,21]

Similar to other LMIC contexts, it is difficult to accurately estimate the burden of childhood cancer in Egypt, due to the limited capacity of the cancer registration system.[26,27] To date, only one study by Ibrahim *et al.* (2014) reported cancer incidence rates in Egypt between 2008 and 2011 using data from the population-based cancer registry. [28] However, this data is outdated, and no recent data has existed since then.[28]

2.4 Treatment of childhood cancer

The most effective solution to reduce the burden of cancer in children and improve their health outcomes is to encourage early diagnosis, and provide evidence-based treatment protocols with adequate supportive care measures.[7,10,29,30]

2.4.1 Progress in global childhood cancer treatment

Over the years, there has been significant progress in the treatment of children with cancer, and today, more than 80% can be successfully cured.[31,32,33] Key advances in treatment include adopting multi-modality approaches, risk-adapted therapies, treatment intensification (mainly for the high-risk groups), and adequate supportive care.[31,32,33] Nowadays, novel therapies, such as molecular targeted drugs and immunotherapy, are used to treat some childhood cancer types that were previously incurable with conventional chemotherapy.[31,32] The main pillars of treatment may include: multi-agent chemotherapy, surgery, radiation therapy, stem cell transplant (SCT) or

bone marrow transplant (BMT), targeted therapy, and/or immunotherapy, depending on the type, risk and stage of cancer. [34,35]

Evidence-based treatment protocols and supportive care guidelines are now available for the different childhood cancer types based on the collaborative efforts of multicentre clinical trials conducted by dedicated groups.[31,32,36] The two main groups are the Children's Oncology Group (COG),[37] and the International Society of Paediatric Oncology (SIOP),[38] among many others.[39–42] Besides, the St. Jude Children's Research Hospital developed the Total Therapy studies I–XVII (and protocols) for treating childhood acute lymphoblastic leukaemia (ALL).[43]

2.4.1.1 Treatment of haematological malignancies

The treatment of childhood acute leukaemia such as ALL mainly depends on risk-stratified chemotherapy-based protocols with response-based therapy; radiotherapy for CNS involvement; and SCT/BMT for the high-risk relapsing patients.[32,44] Novel therapies currently exist to treat children with relapsed or refractory (*i.e.*, not responding to treatment) (r/r) ALL whose survival outcomes remain poor with traditional chemotherapy. These novel treatments include immunotherapy (such as chimeric antigen receptor, CAR–T cell therapy) and other targeted therapies (such as Blinatumomab, a monoclonal antibody).[31,32,44,45] Children with acute myeloid leukaemia (AML) are also treated based on risk-stratified chemotherapy regimens with/without SCT/BMT, and targeted therapies.[31–34] Treatment of children with relapsed/refractory AML patients involves intensive salvage chemotherapy followed by SCT/BMT, as well as other novel targeted therapies.[31] It is crucial to provide adequate supportive care for AML patients who receive intensive treatment in order to avoid the preventable treatment-related mortalities (TRMs) due to complications of treatment.[33,36]

On the other hand, treatment of lymphomas (Hodgkin lymphoma and NHL) is less intensive; chemotherapy, with/without radiotherapy, and some novel drugs.[31]

2.4.1.2 Treatment of brain/CNS and other solid tumours

The treatment of brain/CNS tumours may include surgery (in case of operable tumours), radiation therapy, chemotherapy, and targeted therapy, depending on the type, location, and size of the tumour.[32,34] Other solid tumours are also treated using the same approaches, based on the histological subtype, risk, and initial stage of the disease. [34] Novel targeted drugs also exist for some types of solid tumours, such as high-risk neuroblastoma and some sarcomas.[33,34] Additionally, the proton beam therapy (PBT) showed promising results in treating some solid tumours such as brain/CNS tumours, soft tissue sarcoma, bone sarcomas, and retinoblastoma, by targeting the tumour cells without adversely affecting the nearby healthy tissues.[46]

2.4.2 Treatment approaches in LMICs

The recent advances in childhood cancer treatment were poorly translated to LMIC settings, compromising equity in care delivery.[10,29,47] The evidence-based treatment protocols developed on clinical trials conducted in HICs could not be directly translated to LMICs, due to the inadequate diagnostic and treatment capacities.[10] The most reasonable solution is to make adaptation of the international treatment protocols and/or provide less intensive therapies to meet the available resource and health system capabilities.[10]

The WHO List of Essential Medicines for Children includes the essential medicines (chemotherapy, targeted treatments, and supportive care pharmaceuticals) that should be used to treat children with cancer based on standard treatment protocols.[48,49,50] Nevertheless, there is poor availability of some of these essential medicines in LMICs, especially in low-income

countries (LICs) due to unaffordability to pay, or in some middle-income countries (MICs) due to difficulty in access because of political disputes and restrictions, jeopardising effective childhood cancer treatment.[27,50,51] Other treatment barriers include: limited access to radiation therapy, adequate supportive care drugs, and opioids used in palliative care; abandonment of treatment; and loss of follow-up. [49,50]

Despite the limited resources in most paediatric oncology settings in LMICs, some centres of excellence exist that provide high-quality childhood cancer care and achieve good survival outcomes.[27,51] Advancements in treatment in these centres were facilitated by twining programs with institutions in HICs, regional and international collaborative networks, and dedicated non-governmental organisations (NGOs) with innovative funding models.[2, 29,51]

2.4.3 Treatment approaches in Egypt

In Egypt, there are approximately twenty paediatric oncology units/centres for the treatment of children with cancer, with limited to adequate diagnostic services, and adequate availability of medications and radiotherapy.[52] Treatment is either based on implementing intensity-regulated protocols (starting with low-intensity and gradually intensifying based on patient tolerability), or following international protocols with/without adaptations to local contexts.[16,27,51]

The Children's Cancer Hospital Egypt (CCHE) –known as *57357* hospital– is a large paediatric oncology centre in Egypt with 320 inpatient beds that treats annually around 2,500–3,000 newly diagnosed children with cancer, aged 0–18 years, representing around 40% of all children with cancer across Egypt.[27,53] CCHE (shown in Figure 2.2) is a non-profit charity hospital that treats children with cancer for free based on philanthropic donations.[53]



Figure 2.2. Children's Cancer Hospital Egypt – 57357

Childhood cancer treatment at CCHE follows international treatment protocols such as: COG, SIOP, and the St. Jude Total XV for ALL.[16,51,53] The hospital provides comprehensive childhood cancer care with state-of-the-art diagnostic and therapeutic services, offering multimodal treatment that includes chemotherapy regimens, specialised surgeries (neurosurgery, orthopaedic surgery, surgical oncology) BMT, external beam radiation therapy (EBRT); Cyberknife radiosurgery, and is currently installing proton beam therapy (PBT).[53]

2.5 Childhood cancer health outcomes

Health outcomes of childhood cancer treatment can be measured in terms of survival rate, health-related quality of life (HR–QOL), relapse rate, treatment-related mortality (TRM), and late-effects of treatment.[31,33,54–57] In this thesis, I focused on survival rate as the primary health

outcome, reflecting on disease relapse and TRMs as unfavourable events affecting survival rates as these are the most commonly reported health outcomes in LMICs. Whereas, HR–QOL and late-effects of treatment are not commonly reported or evaluated in LMICs, including Egypt.

2.5.1 Survival outcomes

Survival outcomes are the most commonly used measures to determine cancer prognosis, as they provide valuable insights about how likely the course of the disease would be, reflecting the health consequences/outcomes of treatment.[58] Overall survival (OS), is defined as, "the percentage of people with a specific cancer who have not died from any cause during a certain period of time after diagnosis or since starting of treatment", with 5 years being the most commonly used time period (5-year OS).[59] Survival estimates may be prone to lead-time bias as early diagnosis can improve survival.[60] Nevertheless, this is more common in adult cancers where cancer screening can lead to early diagnosis, while childhood cancers do not usually have screening programs.

2.5.1.1 Global survival rates

Advancements in childhood cancer diagnosis and treatment have been reflected on considerable improvements in the 5-year survival rates, exceeding 80% in some HICs.[2,61,62,63] Nevertheless, given the existing disparities in childhood cancer care worldwide, survival outcomes are still poor in LMICs. Globally, the 5-year net survival for childhood cancers has been estimated to be 37.4% (95% UI: 34.7%–39.8%).[63] In 2018, the WHO launched the Global Initiative for Childhood Cancer (GICC) aiming to increase the global survival rate of children with cancer to at least 60% by 2030.[64] The ultimate goal of the initiative is to focus on improving the much lower survival in the less developed countries (LMICs).[64]

The CONCORD programme estimates global cancer survival based on data from population-based registries worldwide.[65] The CONCORD–3 study conducted by Allemani *et al.* (2018) estimated that the global 5-year net survival for ALL ranged from 50% to more than 90%, for brain/CNS tumours was 40–80%, and for lymphomas was 80–95% for lymphomas.[61] Survival trends were mostly stable or increasing over the last 15 years.[61] Another study by Ward *et al.* (2019) estimated global survival based on a simulation-based model (accounting for treatment variables worldwide).[63] The highest global 5-year net survival was for ALL at 56.1%, while it ranged between 30–50% for Hodgkin lymphoma, NHL, AML, neuroblastoma, hepatoblastoma, and some brain tumours' subtypes.[63] The most inferior survival (<30%) was estimated for Ewing sarcoma, osteosarcoma, Wilms tumours, retinoblastoma, and hepatic carcinoma.[63]

Although survival outcomes are greatly affected by cancer stage at diagnosis,[33] limited staging data exist in most population-based cancer registries worldwide.[33] That is why the International Benchmarking of Childhood Cancer Survival by Stage (BENCHISTA) project was launched to study differences in survival by stage at diagnosis across Europe and the UK.[66]

2.5.1.2 Survival rates in LMICs

The 5-year survival rate of children with cancer in LMICs is only up to 30–40%.[2,4,61,63] Childhood cancer survival differs considerably based on world regions and countries' income levels.[61,63] Between 2015–2019, the 5-year net survival was 11.6% in LMIC contexts in Africa, compared to over 80% in HIC contexts (81% in Europe and 83.0% in North America).[2,63,67]

A literature review article by van Heerden *et al.* (2022) summarised the baseline survival outcomes of the six GICC index cancers in Africa.[68] There was a wide range of survival variation between LICs and upper MICs as follows: from18% to 82.3% for ALL, 26.9% to

77.9% for Wilms tumour, 23% to 100% for retinoblastoma, 45% to 95% for Hodgkin lymphoma, 28% to 76% for Burkitt lymphoma, and from 86.8% to 87.3% for low grade glioma.[68] Survival estimates were mainly reported from institution-based registries, due to the paucity of survival data in the national cancer registries in most LMICs.[2,68]

2.5.1.3 Survival rates in Egypt

Similar to LMIC contexts, childhood cancer survival cannot be evaluated on a national level in Egypt, due to the absence of survival data in the population-based cancer registry.[20,27] A baseline assessment of paediatric oncology care in Egypt estimated a 5-year survival for children with cancer of around 40–60% based on modelled data.[52] A review article conducted by Basbous *et al.* (2021) summarised the existing literature and abstracts about childhood cancer survival in Egypt, which ranged from 45% to 70% depending on cancer type, availability of resources, quality of care, and adopted treatment protocols, which varied across centres/units in Egypt.[27]

The 5-year overall survival ranged from 50% to >80% for ALL, and 50–65% for solid tumours.[27] Highest survival estimates (>90%) were achieved in some centres in Egypt for Hodgkin lymphoma and retinoblastoma.[27] However, the reported survival rates in Egypt were obtained from nine published studies and seventeen SIOP abstracts, estimated for a few cancers using a small sample size, limiting the confidence in quality and generalisability of evidence.[27] Moreover, there were no published studies that reported survival rates for all childhood cancer combined and/or categorised patients by cancer type, severity, or stage.[27] Therefore, there is a gap in evidence about childhood cancer survival in Egypt for all cancer combined and stratified by cancer types/subtypes, risk, and stage at diagnosis, using large cohorts of children with cancer.

2.5.2 Disease relapse and TRMs

Disease relapse remains a major challenge to improving childhood cancer survival outcomes, as survival after relapse remains generally poor.[55] Relapse is the most common cause of treatment failure in paediatric ALL, where around 15–20% of ALL patients relapse; thus relapsed ALL is considered the fourth most common childhood cancer.[55,69] Besides, around 2% of ALL patients show refractory disease (i.e., do not respond to treatment).[69,70] Relapsed/refractory acute lymphoblastic leukaemia (ALL) is a leading cause of death by cancer in children.[71] Whereas around 30% of children with AML relapse.[72] The survival outcomes of children with relapsed/refractory (r/r) acute leukaemia (ALL and AML) remain poor (approximately 40%),[69] requiring intensive treatment using novel drugs, as previously discussed in section 2.4.1.1.

Treatment-related mortality (TRM) is becoming an important area for improving overall survival, especially in LMICs, since more children with cancer die from treatment-related complications, and fewer die from the disease.[56] TRMs are defined as, "death occurring in the absence of progressive cancer".[56] TRMs are more common in haematological malignancies, and are much higher in LMICs contexts with suboptimal supportive care.[56,73] In Africa, almost 90% of early deaths (within the first 3 months post-diagnosis) in ALL patients are treatment-related.[73] In Egypt, early deaths and TRMs are a key concern during intensive induction therapy in paediatric acute leukaemia (ALL and AML), where 47.3% of all deaths occur.[74] The majority of the early deaths (65%) are caused by infection.[75]

2.6 Childhood cancer resource use and costs

Worldwide, unfair disparities exist in access to childhood cancer care as only 5% of the global childhood cancer resources are allocated to LMICs, where 80% of the global childhood cancer

burden exists.[2] This unacceptable inequality in the distribution of resources is one of the main reasons behind inferior survival in LMICs.[2]

Health care resources are defined as, "all materials, personnel, facilities, funds that can be used for providing health care services",[76] and a resource use measure quantifies the frequency with which specific resources are utilised in a healthcare system.[77] In paediatric oncology care, examples of resource use measures include number of hospital admissions, length of in-hospital stays, number of tests (laboratory, pathology and imaging), and number of treatment interventions received (drug doses, surgeries, radiotherapy sessions).[78]

From a healthcare system perspective, costs of childhood cancer care include the total costs (direct and indirect) of all the resources utilised over the course of treatment.[78,79] From a societal perspective, childhood cancer costs include the direct costs incurred by the family, and indirect costs associated with lost productivity due to premature cancer-related deaths in children.[79] This literature review only addresses childhood cancer costs from the health system perspective, which is the primary focus of my DPhil research work.

2.6.1 Resource use and costs globally

Childhood cancer treatment is complex and resource intensive, that is why, it is important to assess the resource use patterns and trends over time, to highlight any existing variations and plan future capacities accordingly.[79,80] Hospital resource use patterns vary greatly among different childhood cancer types.[78] Childhood leukaemia and brain/CNS tumours account for the highest numbers of hospitalizations, while lymphomas account for the fewest.[81] In particular, children with AML have the highest utilisation patterns in terms of hospital admissions, and length of inpatient stays.[78,81] Most hospital admissions occur during the first-year of treatment.[82]

While hospitalisation is the greatest contributor to costs,[81] other factors include: admission to paediatric intensive care units (PICU), undergoing SCT/BMT, and death within 3 years of diagnosis.[78,83]

Childhood cancer treatment is expensive, [79] where costs vary considerably by cancer type depending on the treatment modality, intensity, and duration. [78,82,83] A systematic review of the economic burden of childhood cancers across Europe (2017) reported that highest costs of treatment were attributed to leukaemia (USD $145,505) and neuroblastoma (USD $104,813), while lower costs were reported for brain/CNS tumours (USD $76,416) and lymphomas. [79] Children with AML incur the highest costs per patient, due to long hospitalisations with intensive treatment and supportive care.[78,81] However, costs varied among the different studies owing to differences in study design, source of data, costing approach, and cost items included.[79]

2.6.2 Resource use and costs in LMICs

Since LMICs have limited capacity for paediatric cancer care, resource use patterns and their associated costs are substantially lower than in HIC settings.[2,79] Shortage in essential anticancer drugs, limited access to modern diagnostic and treatment technologies, and the inadequate supply of supportive care and palliative care drugs are all examples of limited resource availability, as previously discussed in Section 2.4.2.[29,84] There are no published studies in the literature on resource use patterns or trends for children with cancer in LMIC settings.

Whereas, some published studies estimated the costs of childhood cancer treatment in LMIC contexts. Costs varied among studies based on the adopted treatment protocol, the included cost elements, and the country's income-level.[85] The treatment costs of a newly diagnosed child with cancer range from $10,540 (USD 2018) in Ghana to $30,035 in El-Salvador.[85] The costs of ALL

treatment range from $5,684 in Bangladesh to $27,209 in China, while Wilms tumour treatment costs can be as low as $122 in Malawi and up to $1,110 in Ghana.[85]

2.6.3 Resource use and costs in Egypt

Given the large numbers of children with cancer in Egypt, there is a high need and demand for paediatric oncology services, despite the limited resources and funds. It is therefore essential to maximise the use of the available resources and manage costs effectively to accommodate the need for services. However, this is challenging owing to the gap in knowledge about the resources used and the costs of childhood cancer treatment in Egypt, since no data exist from local contexts.[16,27,51,52] The available resources for childhood cancer care in Egypt were previously discussed in Section 2.4.3.

2.7 Cost-effectiveness of childhood cancer treatment

Although childhood cancer treatment is resource-intensive and expensive, it significantly improves survival outcomes and is perceived as a cost-effective strategy.[83] Generating economic evidence from cost-effectiveness studies helps make informed decisions to achieve the best possible health outcomes at a reasonable cost. [16] Cost-effectiveness analysis (CEA) is a type of health economic evaluation that evaluates the costs and health outcomes of healthcare interventions, compared to a comparator or no intervention.[79]

2.7.1 Cost-effectiveness estimates from HICs

A systematic review conducted by Russell *et al.* (2013) summarised the economic evidence of various interventions used to treat childhood cancers in HICs, including: chemotherapy, surgery, radiation, BMT/SCT, and some supportive care measures.[86] Yet, comparisons between studies

were difficult due to wide variety of topics and methodological limitations.[86] Recently, economic evaluation studies conducted in HICs focus on evaluating the cost-effectiveness of novel expensive drugs to treat childhood cancers with inferior outcomes, such as relapsed/refractory acute leukaemia. .[87] Yet, no systematic evidence exists about which treatment interventions are the most cost-effective for relapsed/refractory acute leukaemia.

2.7.2 Cost-effectiveness estimates from LMICs

While the generated economic evidence about childhood cancer treatment in HICs is valuable, yet, it cannot be directly translated to LMIC contexts, given the differences in resource availability and the variations in costs of care.[2] That is why, it is essential to generate economic evidence from local contexts to obtain context-specific insights based on the available resources and affordability to pay.[16]

A systematic review by Fung *et al.* (2019) summarised the available economic evidence about the cost-effectiveness of childhood cancer treatment (compared to no treatment) in LMICs, in terms of cost per DALYs averted.[85] Findings from this review highlighted that childhood cancer treatment was either 'very cost-effective' or 'cost-effective' for majority of cancer types, based on the WHO Choosing Interventions that are Cost-Effective (CHOICE) thresholds.[85] The WHO–CHOICE threshold is a gross domestic product (GDP)-based threshold for policy and priority setting in countries that lack nationally developed thresholds.[88] Based on the WHO–CHOICE threshold, interventions that cost <1 time the GDP per capita are 'very cost-effective', whereas, those <3 times the GDP per capita are 'cost-effective'.[88]

2.7.3 Cost-effectiveness estimates from Egypt

Costing studies using local costs data serve as the scientific basis for accurate and reliable inputs for determining the cost-effectiveness of childhood cancer treatment.[83] Since no cost data exist about childhood cancer treatment in Egypt, there is a lack of evidence about the cost-effectiveness of childhood cancer treatment.[85] To address the gap in the literature, it is therefore crucial to collect and analyse reliable survival and cost data from the local context in Egypt in order to evaluate the cost-effectiveness of childhood cancer treatment.[61]

2.8 Barriers and facilitators to childhood cancer care

2.8.1. Barriers and facilitators in HICs

Despite the progress in childhood cancer care and the improvements in long-term survival rates in developed countries, two key problems still exist; (1) the outcomes of relapsing patients remain poor; [89] (2) the morbidities and long-term effects of treatment in childhood cancer survivors.[89,90] Existing facilitators include the adoption of evidence-based treatment protocols, and availability of novel targeted therapies.[89]

2.8.2. Barriers and facilitators in LMICs

Multiple barriers still exist in most developing countries at every stage of childhood cancer care; diagnosis, referral, treatment, follow-up and palliative care.[2] Delays in childhood cancer diagnosis are a major obstacle in most LMICs, which are attributed to geographical, financial, and health system barriers (weak referral networks).[2,91] As discussed earlier in section 2.3.2, the main treatment barriers include: limited access to essential anticancer drugs and radiotherapy services, abandonment of treatment, and loss of follow-up.[49,50] A systematic literature review by

Brand *et al.* (2019) identified that health illiteracy, misdiagnosis, financial constraints, and socio-cultural factors were the most commonly reported barriers to childhood cancer care in LMICs.[92] Other significant barriers include: research gaps in LMICs based on locally relevant data, gaps between evidence and practice, and lack of well-conducted implementation research in LMICs.[93]

Several efforts have been made over the years to address these obstacles and reduce dipartites in childhood cancer care and outcomes worldwide, supported by several WHO initiatives. [29,64,65] As previously mentioned in section 2.3.2., current facilitators include: following multimodal treatment based on standard protocols, twinning programmes, regional and international collaborative networks, and dedicated NGOs with innovative funding models.[2.29,51]

2.8.3. Barriers and facilitators in Egypt

Many of the barriers that exist in LMICs also exist in Egypt. The top three barriers to childhood cancer care in Egypt include: delays in diagnosis leading to advanced stage at presentation, deaths due to infections and treatment-related toxicities, and non-adherence to therapy. [27,94] Around 50% of children with cancer in Egypt experience delays in diagnosis, with median delay of around 37–49 days from start of symptoms until initiation of treatment.[95,96] However, no research exists about the barriers and facilitators to provide cost-effective evidence-based treatment based on experts' opinions from local contexts, creating a gap between evidence and practice similar to other LMIC contexts.[93] In addition to the facilitators in LMICs, the establishment of CCHE in 2007 has facilitated the provision of comprehensive pediatric oncology care in one place, with dedicated multi-disciplinary teams.[53] Since CCHE treats children with cancer free of charge, this reduced treatment abandonment due to financial hardships and unaffordability to pay.[27]

2.9 Gaps in the literature and the need for future research

The large numbers of incident childhood cancer cases in Egypt significantly contribute to childhood cancer burden globally (ranked tenth) and regionally (ranked second). Yet, there is a paucity of data about the survival outcomes of children with cancer in Egypt. A literature review by Basbous *et al.* (2021) provided a summary of the existing literature on childhood cancer survival in Egypt, showing that survival was only reported for a few cancers without subtype, risk, or stage stratification, and no trends in survival were reported, identifying a gap in evidence in these areas, as discussed in Section 2.5.1.3. Besides, there is a gap in knowledge about childhood cancer resource use, costs, and treatment cost-effectiveness in Egypt, due to the absence of published studies in the literature based on local data in Egypt, as discussed in Sections 2.6.3 and 2.7.3.

Economic evaluation studies conducted in HICs currently focus on estimating the cost-effectiveness of novel expensive drugs to relapsed/refractory acute leukaemia in children. However, no systematic evidence exists about which treatment interventions are the most cost-effective, as discussed in Section 2.7.1. Furthermore, no research from Egypt has determined the perceptions of the clinicians to adopt cost-effective treatment strategies for children with cancer in Egypt, creating a gap between evidence and practice, as discussed in Section 2.8.3.

My DPhil research work addresses these gaps in the literature using hybrid research methods in Chapters 3–7. In Chapter 3, I conducted a retrospective cohort study using hospital-based registry data from CCHE to determine the survival of all childhood cancers combined, and stratified by cancer type/subtype (ICCC–3 groups), risk, and stage at diagnosis.

In Chapter 4, I conducted other two studies using local data from CCHE. First, I conducted a retrospective cohort study to assess the patterns and trends in resource use and costs of childhood cancer treatment, and the associated factors. In Chapter 5, I conducted a retrospective cohort study to estimate the cost-effectiveness of childhood cancer treatment for all cancers combined, and stratified by ICCC–3 groups, risk/stage at diagnosis, and disease status (relapsed, refractory, or progressive).

Findings from the cost-effectiveness study (in Chapter 5) identified a key priority area from local context; treatment of relapsed/refractory (r/r) childhood acute leukaemia is not cost-effective at CCHE. Consequently, in Chapter 6, I conducted a systematic review of the costs and cost-effectiveness of treatment for r/r childhood acute leukaemia to address the gap in systematic evidence from the literature.

Lastly, in Chapter 7, I conducted a qualitative study using semi-structured interviews to understand the clinicians' perceptions of barriers and facilitators to implement cost-effective evidence-based treatment for children with cancer in Egypt.

Chapter Two References

1. Hessel F. Burden of Disease Burden of disease(s). Encyclopaedia of Public Health. Dordrecht: Springer Netherlands; 2008. p. 94-6.
2. Atun R, Bhakta N, Denburg A, Frazier AL, Friedrich P, Gupta S, *et al*. Sustainable care for children with cancer: a Lancet Oncology Commission. *Lancet Oncol*. 2020;21(4):e185-e224.
3. Collaborators GBDCC. The global burden of childhood and adolescent cancer in 2017: an analysis of the Global Burden of Disease Study 2017. *Lancet Oncol*. 2019;20(9):1211-25.
4. Bhakta N, Force LM, Allemani C, Atun R, Bray F, Coleman MP, *et al.* Childhood cancer burden: a review of global estimates. *Lancet Oncol*. 2019;20(1):e42-e53.
5. Ward ZJ, Yeh JM, Bhakta N, Frazier AL, Atun R. Estimating the total incidence of global childhood cancer: a simulation-based analysis. *Lancet Oncol*. 2019;20(4):483-93.
6. Steliarova-Foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Bray F, *et al.* International incidence of childhood cancer, 2001-10: a population-based registry study. *Lancet Oncol*. 2017;18(6):719-31.
7. World Health Organization (WHO). Childhood Cancer: key facts [Internet]. WHO. 2022 [cited 2022 Dec]. Available from: https://www.who.int/news-room/fact-sheets/detail/cancer-in-children
8. The World Bank. World Bank Country and Lending Groups [Internet]. World Bank. 2022 [cited 2022 Dec]. Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups

9. Magrath I, Steliarova-Foucher E, Epelman S, Ribeiro RC, Harif M, Li CK, *et al.* Paediatric cancer in low-income and middle-income countries. *Lancet Oncol*. 2013;14(3):e104-16.
10. Rodriguez-Galindo C, Friedrich P, Alcasabas P, Antillon F, Banavali S, Castillo L, *et al.* Toward the Cure of All Children with Cancer Through Collaborative Efforts: Pediatric Oncology as a Global Challenge. *J Clin Oncol*. 2015;33(27):3065-73.
11. Farmer P, Frenk J, Knaul FM, Shulman LN, Alleyne G, Armstrong L, *et al.* Expansion of cancer care and control in countries of low and middle income: a call to action. *Lancet*. 2010;376(9747):1186-93.
12. Johnston WT, Erdmann F, Newton R, Steliarova-Foucher E, Schuz J, Roman E. Childhood cancer: Estimating regional and global incidence. *Cancer Epidemiol*. 2021;71(Pt B):101662.
13. Wu Y, Deng Y, Wei B, Xiang D, Hu J, Zhao P, *et al.* Global, regional, and national childhood cancer burden, 1990-2019: An analysis based on the Global Burden of Disease Study 2019. *J Adv Res*. 2022;40:233-47.
14. Sharma R. A Systematic Examination of Burden of Childhood Cancers in 183 Countries: Estimates from GLOBOCAN 2018. *Eur J Cancer Care* (Engl). 2021;30(5):e13438.
15. Institute for Health Metrics and Evaluation (IHME). University of Washington: GBD Results Tool [Internet]. IHME. 2023 [cited 2023 Jan]. Available from: http://ghdx.healthdata.org/gbd-results-tool
16. Gheorghe A, Chalkidou K, Shamieh O, Kutluk T, Fouad F, Sultan I, *et al.* Economics of Pediatric Cancer in Four Eastern Mediterranean Countries: A Comparative Assessment. *JCO Glob Oncol*. 2020;6:1155-70.

17. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA Cancer J Clin*. 2021;71(1):7-33.

18. Gupta S, Rivera-Luna R, Ribeiro RC, Howard SC. Pediatric oncology as the next global child health priority: the need for national childhood cancer strategies in low- and middle-income countries. *PLoS Med*. 2014 Jun 17;11(6):e1001656.

19. The World Bank Group. Arab Republic of Egypt [Internet]. The World Bank Group. 2023 [cited 2023 Feb]. Available from: https://data.worldbank.org/country/EG

20. Fadhil I, Soliman R, Jaffar S, Al Madhi S, Saab R, Belgaumi A, *et al*. Estimated incidence, prevalence, mortality, and registration of childhood cancer (ages 0-14 years) in the WHO Eastern Mediterranean region: an analysis of GLOBOCAN 2020 data. *Lancet Child Adolesc Health*. 2022;6(7):466-73.

21. WHO/International Agency for Research on Cancer (IARC). Global Cancer Observatory (GCO). Cancer today 2020 [Internet]. WHO/IARC 2023 [cited 2023 Jan]. Available from: https://gco.iarc.fr/today/home

22. World Health Organization (WHO). Burden of Cancer. Cancer Country Profile 2020: Egypt [Internet]. WHO. 2023 [cited 2023 Jan]. Available from: https://cdn.who.int/media/docs/default-source/country-profiles/cancer/cancer-egy-2020.pdf?sfvrsn=bb7d0d08_4&download=true

23. World Health Organization (WHO). Burden of Cancer. WHO cancer regional profiles 2020: EMRO Eastern Mediterranean Region [Internet]. WHO. 2023 [cited 2023 Jan]. Available from: https://cdn.who.int/media/docs/default-source/ncds/ncd-surveillance/cancer-profiles-2020/emro-cancer-profile-2020.pdf?sfvrsn=533e7d92_3

24. Worldometer. Egypt population. Population of Egypt (2020 and historical) [Internet]. Worldometer. 2023 [cited 2023 Jan]. Available from: https://www.worldometers.info/world-population/egypt-population/#:~:text=Egypt%202020%20population%20is%20estimated,year%20according%20to%20UN%20data.

25. Statista. Egypt: Age structure from 2011 to 2021 [Internet]. Statista. 2022 [cited 2023 Feb]. Available from: https://www.statista.com/statistics/377306/age-structure-in-egypt/#statisticContainer

26. Institute for Health Metrics and Evaluation (IHME). National Cancer Registry Program of Egypt. Global Health Data Exchange [Internet]. IHME. 2023 [cited 2023 Jan]. Available from: http://ghdx.healthdata.org/organizations/national-cancer-registry-program-egypt

27. Basbous M, Al-Jadiry M, Belgaumi A, Sultan I, Al-Haddad A, Jeha S, *et al*. Childhood cancer care in the Middle East, North Africa, and West/Central Asia: A snapshot across five countries from the POEM network. *Cancer Epidemiol*. 2021;71(Pt B):101727.

28. Ibrahim AS, Khaled HM, Mikhail NN, Baraka H, Kamel H. Cancer incidence in Egypt: results of the national population-based cancer registry program. *J Cancer Epidemiol*. 2014;2014:437971.

29. Gupta S, Howard SC, Hunger SP, Antillon FG, Metzger ML, Israels T, *et al*. Treating Childhood Cancer in Low- and Middle-Income Countries. In: Gelband H, Jha P, Sankaranarayanan R, Horton S, editors. *Cancer: Disease Control Priorities, Third Edition* (Volume 3). Washington (DC)2015.

30. International Cancer Control Partnership (ICCP). Early Diagnosis of Childhood Cancer Manual [Internet]. ICCP. 2023 [cited 2023 Feb]. Available from: https://www.iccp-portal.org/resources/early-diagnosis-childhood-cancer-manual

31. Butler E, Ludwig K, Pacenta HL, Klesse LJ, Watt TC, Laetsch TW. Recent progress in the treatment of cancer in children. *CA Cancer J Clin*. 2021;71(4):315-32.

32. Saletta F, Seng MS, Lau LM. Advances in paediatric cancer treatment. *Transl Pediatr*. 2014;3(2):156-82.

33. Erdmann F, Frederiksen LE, Bonaventure A, Mader L, Hasle H, Robison LL, *et al*. Childhood cancer: Survival, treatment modalities, late effects and improvements over time. *Cancer Epidemiol*. 2021;71(Pt B):101733.

34. Zahnreich S, Schmidberger H. Childhood Cancer: Occurrence, Treatment and Risk of Second Primary Malignancies. *Cancers (Basel)*. 2021;13(11).

35. Lavasidis G, Markozannes G, Panagiotou OA, Trikalinos NA, Petridou ET, Voorhies K, *et al*. Therapeutic interventions for childhood cancer: An umbrella review of randomized evidence**.** *Crit Rev Oncol Hematol*. 2021;164:103414.

36. Loeffen EAH, Kremer LCM, Mulder RL, Font-Gonzalez A, Dupuis LL, Sung L, *et al.* The importance of evidence-based supportive care practice guidelines in childhood cancer-a plea for their development and implementation. *Support Care Cancer*. 2017;25(4):1121-5.

37. Children's Oncology Groups (COG). Children's Oncology Group Homepage [Internet]. COG. 2023 [cited 2023 Jan]. Available from: https://childrensoncologygroup.org/

38. International Society of Paediatric Oncology (SIOP). SIOP Homepage [Internet]. SIOP. 2023 [cited 2023 Jan]. Available from: https://siop-online.org/

39. Children's Cancer and Leukaemia Group (CCLG). CCLG Homepage [Internet]. CCLG. 2023 [cited 2023 Jan] Available from: https://www.cclg.org.uk/

40. D'Angio GJ. The National Wilms Tumor Study: a 40-year perspective. *Lifetime Data Anal*. 2007;13(4):463-70.

41. Raney RB, Maurer HM, Anderson JR, Andrassy RJ, Donaldson SS, Qualman SJ, *et al*. The Intergroup Rhabdomyosarcoma Study Group (IRSG): Major Lessons from the IRS-I Through IRS-IV Studies as Background for the Current IRS-V Treatment Protocols. *Sarcoma.* 2001;5(1):9-15.

42. The Paediatric Brain Tumour Consortium (PBTC). PBTC Homepage [Internet]. PBTC. 2023 [cited 2023 Jan]. Available from: https://www.pbtc.org/

43. Omar AA, Basiouny L, Elnoby AS, Zaki A, Abouzid M. St. Jude Total Therapy studies from I to XVII for childhood acute lymphoblastic leukemia: a brief review. *J Egypt Natl Canc Inst*. 2022;34(1):25.

44. Malczewska M, Kosmider K, Bednarz K, Ostapinska K, Lejman M, Zawitkowska J. Recent Advances in Treatment Options for Childhood Acute Lymphoblastic Leukemia. *Cancers (Basel).* 2022;14(8).

45. Inaba H, Pui CH. Advances in the Diagnosis and Treatment of Pediatric Acute Lymphoblastic Leukemia. *J Clin Med*. 2021;10(9).

46. Thomas H, Timmermann B. Paediatric proton therapy. *Br J Radiol*. 2020;93(1107):20190601.

47. Hughes TM, Empringham B, Wagner AK, Ward ZJ, Yeh J, Gupta S, *et al*. Forecasting essential childhood cancer drug need: An innovative model-based approach. *Cancer*. 2021;127(16):2990-3001.

48. World Health Organization (WHO). World Health Organization model list of essential medicines for children: 7th list 2019 [Internet]. WHO. 2019 [cited 2023 Apr]. Available from: https://apps.who.int/iris/handle/10665/325772

49. Mehta PS, Wiernikowski JT, Petrilli JA, Barr RD. Working Group on Essential Medicines of the Pediatric Oncology in Developing Countries committee of S. Essential medicines for pediatric oncology in developing countries. *Pediatr Blood Cancer*. 2013;60(5):889-91.

50. Chagaluka G, Afungchwi GM, Landman L, Njuguna F, Hesseling P, Tchintseme F, *et al.* Treatment abandonment: A report from the collaborative African network for childhood cancer care research-CANCaRe Africa. *Pediatr Blood Cancer*. 2021 Dec;68(12):e29367.

51. Saab, R., Soliman, R., Belgaumi, A., Hessissen, L., Kutluk, T., Konig, L., *et al*. Childhood cancer in the Eastern Mediterranean region. Cancer Control Eastern Mediterranean Region Special Report, 72-81. Global Health Dynamics; 2022. Available from: http://www.cancercontrol.info/wp-content/uploads/2022/05/72-chapter-7.pdf

52. Ribeiro RC, Steliarova-Foucher E, Magrath I, Lemerle J, Eden T, Forget C, *et al.* Baseline status of paediatric oncology care in ten low-income or mid-income countries receiving My Child Matters support: a descriptive study. *Lancet Oncol*. 2008;9(8):721-9.

53. Children's Cancer Hospital Egypt (CCHE). CCHE Homepage [Internet]. 2023 [cited 2023 Feb]. Available from: https://www.57357.org/en/home-page/

54. Vlachioti E, Matziou V, Perdikaris P, Mitsiou M, Stylianou C, Tsoumakas K, *et al*. Assessment of quality of life of children and adolescents with cancer during their treatment. *Jpn. J. Clin. Oncol*. 2016;46(5):453-61.

55. Jensen KS, Oskarsson T, Lahteenmaki PM, Flaegstad T, Jonsson OG, Svenberg P, *et al*. Temporal changes in incidence of relapse and outcome after relapse of childhood acute

lymphoblastic leukemia over three decades; a Nordic population-based cohort study. *Leukemia*. 2022;36(5):1274-82.

56. Loeffen EAH, Knops RRG, Boerhof J, Feijen EAM, Merks JHM, Reedijk AMJ, *et al.* Treatment-related mortality in children with cancer: Prevalence and risk factors. *Eur. J. Cancer*. 2019;121:113-22.

57. Norsker FN, Pedersen C, Armstrong GT, Robison LL, McBride ML, Hawkins M, *et al*. Late Effects in Childhood Cancer Survivors: Early Studies, Survivor Cohorts, and Significant Contributions to the Field of Late Effects. *Pediatr Clin North Am*. 2020;67(6):1033-49.

58. Mariotto AB, Noone AM, Howlader N, Cho H, Keel GE, Garshell J, *et al*. Cancer survival: an overview of measures, uses, and interpretation. *J Natl Cancer Inst Monogr*. 2014;2014(49):145-86.

59. National Cancer Institute (NCI). Understanding Statistics About Survival [Internet]. NCI. 2019 [cited 2023 Jan]. Available from: https://www.cancer.gov/about-cancer/diagnosis-staging/prognosis

60. Oke J, Fanshawe T. Cancer Statistics A Survival Guide. *Significance*. 2020;17(1):26.

61. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Niksic M, *et al.* Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet*. 2018;391(10125):1023-75.

62. Gatta G, Botta L, Rossi S, Aareleid T, Bielska-Lasota M, Clavel J, *et al.* Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5--a population-based study. *Lancet Oncol*. 2014;15(1):35-47.

63. Ward ZJ, Yeh JM, Bhakta N, Frazier AL, Girardi F, Atun R. Global childhood cancer survival estimates and priority-setting: a simulation-based analysis. *Lancet Oncol*. 2019;20(7):972-83.

64. World Health Organization (WHO). The Global Initiative for Childhood Cancer (GICC) Increasing access, advancing quality, saving lives [Internet]. WHO. 2023 [cited 2023 Jan]. Available from: https://www.who.int/initiatives/the-global-initiative-for-childhood-cancer

65. London School of Hygiene & Tropical Medicine. CONCORD Programme: Global surveillance of cancer survival [Internet]. 2023 [cited 2023 Jan]. Available from: https://csg.lshtm.ac.uk/research/themes/concord-programme/

66. University College London (UCL). The BENCHISTA Project: The International Benchmarking of Childhood Cancer Survival by Stage Project [Internet]. UCL. 2023 [cited 2023 Jan]. Available from: https://www.ucl.ac.uk/child-health/research/developmental-biology-and-cancer/benchista-project

67. Botta L, Gatta G, Capocaccia R, Stiller C, Canete A, Dal Maso L, *et al*. Long-term survival and cure fraction estimates for childhood cancer in Europe (EUROCARE-6): results from a population-based study. *Lancet Oncol*. 2022;23(12):1525-36.

68. van Heerden J, Balagadde-Kambugu J, Angom R, Lusobya RC, Chantada G, Desjardins L, *et al*. Evaluating the baseline survival outcomes of the "six Global Initiative for Childhood Cancer index cancers" in Africa. *Pediatr Hematol Oncol*. 2022:1-21.

69. Locatelli F, Schrappe M, Bernardo ME, Rutella S. How I treat relapsed childhood acute lymphoblastic leukemia. *Blood*. 2012 Oct 4;120(14):2807-16.

70. Martin A, Morgan E, Hijiya N. Relapsed or refractory pediatric acute lymphoblastic leukemia: current and emerging treatments. *Paediatr Drugs*. 1;14(6):377-87 (2012).

71. Ceppi F, Duval M, Leclerc JM, Laverdiere C, Delva YL, Cellot S, *et al*. Improvement of the Outcome of Relapsed or Refractory Acute Lymphoblastic Leukemia in Children Using a Risk-Based Treatment Strategy. *PLoS One*. 2016 Sep 15;11(9):e0160310.

72. Rasche M, Steidel E, Zimmermann M, *et al*. Second relapse of pediatric patients with acute myeloid leukemia: a report on current treatment strategies and outcome of the AML-BFM study group. *Cancers (Basel).* 2021;13(4):789.

73. Israels T, Afungchwi GM, Chagaluka G, Hesseling P, Kouya F, Paintsil V, *et al.* Early death and treatment-related mortality: A report from SUCCOUR - Supportive Care for Children with Cancer in Africa. *Pediatr Blood Cancer*. 2021;68(9):e29230.

74. Hafez HA, Soliaman RM, Bilal D, Hashem M, Shalaby LM. Early Deaths in Pediatric Acute Leukemia: A Major Challenge in Developing Countries. *J Pediatr Hematol Oncol*. 2019;41(4):261-6.

75. Hafez H, Nazih S, Eldin DN, Elgammal A. ALL-204 Barriers to Improving Outcomes of Children with Acute Lymphoblastic Leukemia in Low- to Middle-Income Countries. *Clin. Lymphoma Myeloma Leuk.* 2022;22:S195.

76. Ransom H, Olsson JM. Allocation of Health Care Resources: Principles for Decision-making. *Pediatr Rev*. 2017;38(7):320-9.

77. Centers for Medicare & Medicaid Services (CMS). Cost and Resource Use Measures. Measures Management System Hub [Internet]. CMS. 2023 [cited 2023 Jan]. Available from: https://mmshub.cms.gov/sites/default/files/Cost-and-Resource-Use-Measures.pdf

78. Rosenman MB, Vik T, Hui SL, Breitfeld PP. Hospital resource utilization in childhood cancer. *J Pediatr Hematol Oncol*. 2005;27(6):295-300.

79. European Expert Paediatric Oncology Reference Network (ExPOr-Net). Deliverable 4: an analysis of economic impact of childhood cancers based on systematic review of data to inform national and regional policymakers across the EU. Final Report ICP (ECRMF) and Birmingham University. June 2017.

80. Carrasquillo O. Health Care Utilization. In: Gellman MD, Turner JR, editors. Encyclopedia of Behavioral Medicine. New York, NY: Springer New York; 2013. p. 909-10.

81. Price RA, Stranges E, Elixhauser A. Pediatric Cancer Hospitalizations, 2009. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Rockville (MD)2006.

82. Tan O, Schofield DJ, Shrestha R. An Analysis of Hospital Costs for Childhood Cancer Care. *J Natl Compr Canc Netw*. 2021;20(2):126-35.

83. de Oliveira C, Bremner KE, Liu N, Greenberg ML, Nathan PC, McBride ML, *et al.* Costs for Childhood and Adolescent Cancer, 90 Days Prediagnosis and 1 Year Postdiagnosis: A Population-Based Study in Ontario, Canada. *Value Health*. 2017;20(3):345-56.

84. Stefan DC. Childhood cancer in Africa: an overview of resources. *J Pediatr Hematol Oncol*. 2015;37(2):104-8.

85. Fung A, Horton S, Zabih V, Denburg A, Gupta S. Cost and cost-effectiveness of childhood cancer treatment in low-income and middle-income countries: a systematic review. *BMJ Glob Health.* 2019;4(5):e001825.

86. Russell HV, Panchal J, Vonville H, Franzini L, Swint JM. Economic evaluation of pediatric cancer treatment: a systematic literature review. *Pediatrics*. 2013;131(1):e273-87.

87. Sarkar RR, Gloude NJ, Schiff D, Murphy JD. Cost-Effectiveness of Chimeric Antigen Receptor T-Cell Therapy in Pediatric Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia. *J Natl Cancer Inst.* 2019;111(7):719-26.

88. WHO. New cost-effectiveness updates from WHO-CHOICE [Internet]. WHO. 2021 [updated 2021 Oct; cited 2022 May]. Available from: https://www.who.int/news-room/feature-stories/detail/new-cost-effectiveness-updates-from-who-choice

89. Cahaney C, Dhir A, Ghosh T. Role of Precision Medicine in Pediatric Oncology. *Pediatr Ann*. 2022;51(1):e8-e14.

90. Chang WH, Katsoulis M, Tan YY, Mueller SH, Green K, Lai AG. Late effects of cancer in children, teenagers and young adults: Population-based study on the burden of 183 conditions, in-patient and critical care admissions and years of life lost. *Lancet Reg Health Eur*. 2022;12:100248.

91. Cotache-Condor C, Kantety V, Grimm A, Williamson J, Landrum KR, Schroeder K, *et al.* Determinants of delayed childhood cancer care in low- and middle-income countries: A systematic review. *Pediatr Blood Cancer*. 2023;70(3):e30175.

92. Brand NR, Qu LG, Chao A, Ilbawi AM. Delays and Barriers to Cancer Care in Low- and Middle-Income Countries: A Systematic Review. *Oncologist.* 2019;24(12):e1371-e80.

93. Pramesh CS, Badwe RA, Bhoo-Pathy N, Booth CM, Chinnaswamy G, Dare AJ, *et al*. Priorities for cancer research in low- and middle-income countries: a global perspective. *Nat Med*. 2022;28(4):649-657.

94. Khalek ER, Sherif LM, Kamal NM, Gharib AF, Shawky HM. Acute lymphoblastic leukemia: are Egyptian children adherent to maintenance therapy? *J Cancer Res Ther*. 2015;11(1):54-8.

95. Abdelkhalek E, Sherief L, Kamal N, Soliman R. Factors associated with delayed cancer diagnosis in Egyptian children. *Clin Med Insights Pediatr*. 2014;8:39-44.

96. Abdelmabood S, Kandil S, Megahed A, Fouda A. Delays in diagnosis and treatment among children with cancer: Egyptian perspective. *East Mediterr Health J*. 2017;23(6):422-9.

Chapter Three: Childhood cancer survival rates and temporal trends in survival in Egypt

"We cannot improve what we cannot measure." — Peter Drucker, Change management expert

The first step towards improving childhood cancer survival in Egypt is to measure where we are now (current survival rates) and how far we have come (trends over time), and make improvements accordingly; generate real-world evidence from the local context about childhood cancer survival and temporal trends in survival.

3.1. Publication statement

Features of this chapter are published in the following peer-reviewed journal:

Soliman R, Elhaddad A, Oke J, Eweida W, Sidhom I, Ahmed S, *et al.* Temporal trends in childhood cancer survival in Egypt, 2007 to 2017: A large retrospective study of 14 808 children with cancer from the Children's Cancer Hospital Egypt. *Int J Cancer*. 2021;148(7):1562-74. DOI: 10.1002/ijc.33321.

3.2 Introduction

Childhood cancer is a main cause of global disease burden, with around 84% of this burden occurring in low- and middle-income countries (LMICs).[1] That is why childhood cancer is considered a public health priority in LMICs due to the large numbers of children with cancer, limited resources, and inferior survival.[1-10] Although 5-year survival currently exceeds 80% in high-income countries (HICs),[11-14] these improvements poorly translate to LMICs.[5,9]

Egypt is a lower middle-income country[15] with a large proportion of children with cancer, as around 34% of the population are children under 15 years old (33.1 million in 2020), [16,17] and the age-standardized incidence rate is 12.1 per 100,000 children at risk.[18] The 5-year survival of childhood cancer was estimated to be 40% in Egypt based on modelled data.[19]

It is difficult to evaluate childhood cancer survival in Egypt as part of the WHO Global Initiative for Childhood Cancer,[20] due to the lack of survival data in the population-based national cancer registry,[21] and the paucity of published studies in the literature. [22] Therefore, there is a need to estimate childhood cancer survival in Egypt using data from the local context to address the identified gap in evidence, as described in the Background Chapter 2 (section 2.4.1.3).

In this chapter, I determine childhood cancer survival in a paediatric oncology setting in Egypt.

3.3 Aim of work

To determine survival rates and temporal trends in survival for children with cancer treated at the Children's Cancer Hospital Egypt (CCHE) between 2007 and 2017.

3.4 Objectives

1. To determine survival rates for all childhood cancers combined, and startified by cancer type/subtype, risk, and stage at diagnosis.
2. To estimate temporal trends in childhood cancer survival.
3. To compare age-standardised childhood cancer survival in Egypt/CCHE with international benchmarks from England and the US, and identify cancers with inferior survival.
4. To determine cause-specific mortality for childhood cancers with inferior survival.
5. To provide evidence-based recommendations to improve survival outcomes.

3.5 Methods

This chapter was conducted following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist [23] (Appendix 3.1).

3.5.1 Study design and population

This study included a retrospective cohort of children with cancer (aged 0–18 years) diagnosed and treated at the Children's Cancer Hospital–57357 Egypt (CCHE) between July 7th, 2007 and December 31st, 2017. Patients were monitored with active follow-up until 31st July 2018. CCHE is a large comprehensive paediatric oncology centre in Egypt (with 320 beds) that treats around 40% of all children with cancer across Egypt.[24] Childhood cancers were categorized according to the *International Classification of Childhood Cancer, 3rd edition* (ICCC-3),[25] (Appendix 3.2) using data codes of the *International Classification of Diseases for Oncology,3rd edition* (ICD-O-3).[26]

The full study cohort (n=15,779) was included in the analysis of patient demographics and characteristics at initial diagnosis. The following ICCC-3 sub-groups of rare childhood cancer subtypes (n=513) were not included in survival analysis as their disease- and survival-related data collection forms were still under revision and data was not readily available: (Ia. 1) Lymphoid leukaemia, aged <1 year; (Ie) unspecified and other specified leukaemia; (VIIb) hepatic carcinomas; and (IX) other malignant epithelial neoplasms. Other 458 patients (2.9% of initial study cohort) were deemed not evaluable for survival estimation and were excluded from survival analysis. Figure 3.1 shows a flowchart for inclusion/exclusion criteria.

Children with cancer are treated based on CCHE standard treatment protocols adopted from international protocols; the Children's Oncology Group (COG) protocol for the majority of cancers, and the St. Jude Total XV protocol for acute lymphoblastic leukaemia (ALL). A list of standard treatment protocols implemented at CCHE for each cancer type is available in Appendix 3.3. Survival was evaluated for children with a confirmed cancer diagnosis who received any protocol treatment at CCHE,[27] including patients with early deaths who died before or early on treatment (within 30 days of diagnosis).[28]

Included patients were followed-up since confirmation of their diagnosis at CCHE at a uniform time-point at initial presentation, allowing the conduct of an inception cohort. This provides higher-level evidence for prognostic studies, based on the Oxford Centre for Evidence-based Medicine (CEBM) – Levels of Evidence 2011.[29]

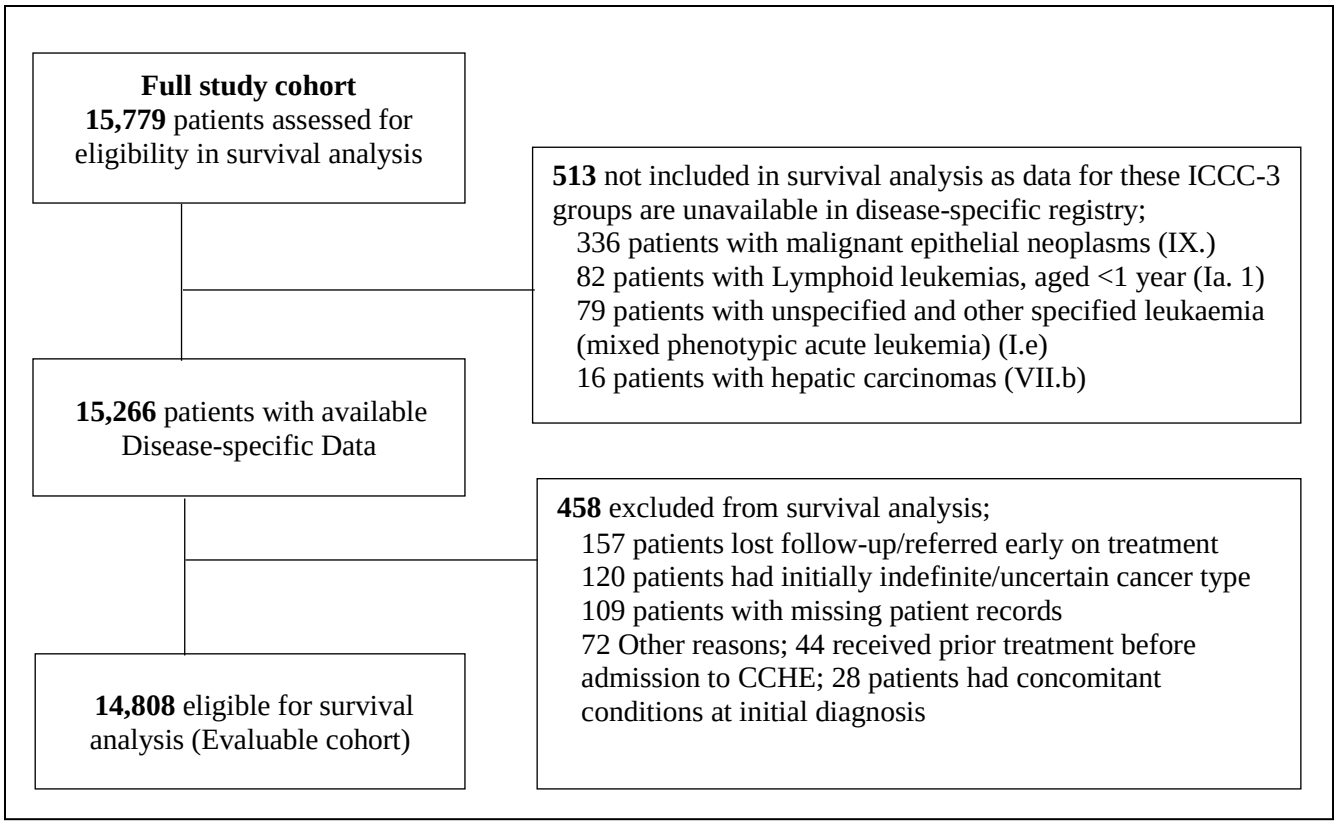


Figure 3.1. Flowchart of included/excluded patients in survival analysis

3.5.2 Data collection and validation

Real-world data (i.e., routinely collected data during clinical practice outside the context of clinical trials) [30] were extracted from the hospital-based cancer registry and disease-specific registries at CCHE available on the Research Electronic Data Capture (REDCap) online platform.[31] Data variables included: age, gender, country of origin, place of residence, cancer type/subtype, stage at diagnosis, disease risk, survival status, last date of contact, cause-specific mortality, and adverse events. Approval for data release was granted by the Scientific Medical Advisory Committee (SMAC) at CCHE. Ethics approval was not required by the institutional review board (IRB), as this study involves secondary use of routinely collected data with de-identified patients' records.

Data quality checks were done every six months over the ten years [2007–2017] by the research department and lead paediatric oncologists at CCHE through continual monitoring and validation of the cancer registry and disease-specific registries. Data was regularly checked for accuracy, completeness and consistency. Disease-related and survival data were also reviewed at the time of study initiation and validated for integrity, completeness, and accuracy.

3.5.3 Statistical analysis

I estimated overall survival (OS) using the Kaplan–Meier method for all childhood cancers combined and the main ICCC-3 diagnostic groups/sub-groups at 1, 3, and 5-years post-diagnosis, with 95% confidence intervals (95% CI). Observed survival was calculated rather than relative survival since competing risks of death are negligible in children and differences between them are quite small.[14,32] Temporal trends in survival were estimated by single year of diagnosis using Cox regression and tested by the Chi-square test.[33] A trend was defined as statistically significant

at $P<0.05$. I tested the assumption of proportional hazards by looking for trends in the residuals. I determined change in survival over different calendar periods of diagnosis; 5-year survival over two diagnosis periods [2007– 2012 and 2013–2017]; and 3-year survival over three diagnosis periods [2007–2009, 2010–2013 and 2014–2017]. It was not feasible to calculate 5-year survival over 3 diagnosis periods, as the majority of patients diagnosed in the recent period [2014–2017] have not completed adequate follow-up duration at 5 years, however adequate follow-up duration was achieved for patients diagnosed in 2013–2017.

I also examined 5-year overall survival stratified by gender, age-group (0–4, 5–9, 10–14 and 15–18 years), disease stage and/or risk using log-rank test at significance level <0.05. Definitions of stage at diagnosis, risk stratification and sub-type classifications systems are listed in Appendix 3.4. Survival analysis was performed in *R* statistical package version 3.5.0 using '*survminer*' and *'gglpot2*' packages.[34]

3.5.4 Comparison to international benchmarks

The 5-year survival for children with cancer (aged, 0–14 years) at CCHE was compared to population-based 5-year survival of children with cancer (aged, 0–14 years) in England [2001–2015],[33] and the US [2008–2014].[35] I estimated age-standardized survival rates using the weighted average method by giving equal weights to all three age-groups (0–4, 5–9, and 10–14 years) for majority of cancers, using England as the reference population. For neuroblastoma, weights were adjusted for patients <1 year and 1–4 years within the 0–4 age age-groups, and for retinoblastoma weights were adjusted for 2 age-groups only (0–4 and 5–9 years), to allow for complete controlling for age.

Differences between survival at CCHE/Egypt and England were calculated using test of two-independent proportions at a significance level of 0.05, to determine inferior survival. Since survival in the US is higher/comparable with England, I assumed that inferior survival than England would also be inferior than the US. For cancers with inferior survival, I evaluated cause-specific mortality as either cancer-related mortality or treatment-related mortalities (TRMs), where TRMs were defined as deaths occurring in the absence of progressive cancers.[36] I also evaluated adverse events as either TRMs (toxic deaths), relapse (recurrence), refractory disease (not responding to treatment), disease progression, or secondary malignancy.[37] Findings were discussed with lead paediatric oncologists to advise on the potential reasons for inferior survival.

3.6 Results

3.6.1 Patient characteristics

I analysed data for 15,779 children with cancer, and the main demographic characteristics of patients are shown in Table 3.1. Almost half of the patients (47.8%) were in the youngest age group (0–4 years), 58.3% were males, and 64.5% came from rural/sub-urban areas in Egypt. The geographical distribution of children with cancer treated at CCHE is presented in Appendix 3.5. Table 3.2 shows that the most common childhood cancer types treated at CCHE were leukaemia (27.6%), brain/CNS tumours (16.9%), lymphomas (15.4%), and neuroblastoma (10.0%). Childhood cancers types (by the ICCC-3 groups) were stratified by age-groups in Appendix 3.6. The trend of newly diagnosed patients accepted for treatment at CCHE increased annually by 9% on average between July 2007 and December 2017 (Appendix 3.7). The distribution of gender (male to female ratio) and age-groups (for all children, males and females) was almost steadily uniform over the years (Appendix 3.8).

Table 3.1. Demographic characteristics of children with cancer at CCHE/Egypt (N= 15,779)

	Age group	No. of patients	Percent
Age Groups			
	0 – 4 years	7,556	47.8%
	5 – 9 years	4,213	26.7%
	10 – 14 years	2,871	18.1%
	15 – 18 years	1,139	7.40%
Gender			
	Male	9,202	58.3%
	Female	6,577	41.7%
Country of Origin			
	Egypt	15,360	97.3%
	Outside Egypt	419	2.7%
Place of Residence			
	Urban	5,622	35.6%
	Rural/Sub-urban	10,157	64.4%
Main childhood cancer types			
	Leukaemia	4,142	28.0%
	Lymphoma	2,379	15.1%
	Brain/CNS tumours	2,588	16.4%
	Other solid tumours	6,361	40.3%
	Others*	309	0.2%

*Others include Langerhans Cell Histiocytosis

3.6.2 Survival rates

A total of 14,808 patients fulfilled the inclusion criteria for survival analysis (evaluable cohort). I performed survival analysis for 14,808 patients, representing 93.8% of the original study cohort. Overall survival for all childhood cancers combined was 72.1% (95% CI: 71·3%–72·9%) at 5 years, with median survival duration of 33.1 months (Table 3.2 shows 1-,3-,5-year survival rates, by the ICCC-3 groups). I ranked the 5-year overall survival for all childhood cancer types ascendingly (from lowest to highest survival) as illustrated in Figure 3.2.

For childhood cancers combined, the 5-year overall survival was slightly higher for males (73.0%; 95% CI: 71.9%–74.1%) than females (70.9%; 95% CI: 69.7%–72.1%) ($p<0.001$). Furthermore, the youngest age-groups (0–4 years) and (5–10 years) showed better survival estimates (72.9%; 95%: CI 71.7%–74.1%) and (73.1%, 95% CI 71.5%–74.7%) respectively, than the older age-groups ($p<0.001$). Appendix 3.9 shows the 5-year survival rates for each childhood cancer type, categorized by gender and age-groups.

Table 3.2. 1-, 3- and 5-year overall survival of children with cancer at CCHE (2007–2017) with median survival time, (n=14,808)

ICCC-3 Diagnostic Group	No. of patients (%)	Diagnosis Period (2007-2017)			Median survival time (months)
		1-year Survival (%) (95% CI)	3-year Survival (%) (95% CI)	5-year Survival (%) (95% CI)	
All cancers combined *	14,808	86·7 (86·1-87·2)	75·7 (74·9-76·4)	72.1 (71·3-72·9)	33·18
I. Leukaemia and related cancers	4,142 (27.9%)	84·8 (83·8-85·9)	75·4 (74·1-76·8)	71·5 (69·9-73·)	36.18
Ia. Acute Lymphoid Leukaemia	2,914 (19.6%)	91·0 (90·0-92·1)	83·1 (81·7-84·5)	79.1 (77·4-80·7)	41·15
Ib. Acute Myeloid leukaemia	987 (6.6%)	66·3 (63·4-69·3)	53·3 (50·1-56·6)	50·1 (46·8-53·6)	19.73
Ic. Chronic Myeloid leukaemia	121 (0.8%)	97·5 (94·8-100)	93·9 (89·6-98·4)	91·2 (85·7-97·0)	53·23
Id. Myelodysplastic Syndrome	50 (0.3%)	71·7 (60·1-85·4)	50·3 (37·5-67·5)	40·2 (27·3-59·3)	18·90
Ie. Juvenile myelomonocytic leukaemia	70 (0.4%)	76·2 (66·7-87·1)	46·6 (34·8-62·3)	37·8 (25·9-55.0)	18.86
II. Lymphomas	2,379 (16.0%)	92·3 (91·2-93·4)	89·2 (87·9-90·5)	87·9 (86·5-89·3)	45.26
IIa. Hodgkin Lymphoma	1,206 (8.1%)	98·2 (97·5-99·0)	96·2 (95·0-97·3)	95·1 (93·7-96·5)	47·88
IIb. Non-Hodgkin Lymphoma	1,173 (7.9%)	86·2 (84·2-88·2)	82·2 (79·9-84·4)	80·6 (78.2-83·0)	41.36
IIIa-e Brain/CNS Tumours	2,588 (17.4%)	79·8 (78·3-81·4)	66·8 (64·8-68·8)	64·3 (62·3-66·4)	26·43
IIIa. Ependymomas/choroid plexus tumours	238 (1.6%)	92·6 (89·.2-96·0)	72·0 (65·7-78·8)	68·5 (61·7-75·9)	30.47
IIIb. Astrocytoma	742 (5.0%)	88·6 (86·3-90·9)	78·7 (75·6-82·0)	76·8 (73·4-80·3)	33.77
IIIc.1-2 Medulloblastoma/Embryonal	565 (3.8%)	81·8 (78·6-85·1)	63·4 (59·2-67·9)	60·6 (53·7-68·4)	25.97
IVa. Neuroblastoma and ganglioneuroblastoma	1,547 (10.4%)	82·8 (80·9-84·7)	62·2 (59·6-64·9)	54·7 (51·8-57·8)	23·60
V. Retinoblastoma	786 (5.3%)	96·6 (95·4-97·9)	94·2 (92·4-95·9)	92·6 (90·5-94·8)	40·00
VI. Renal Tumours	900 (6.0%)	93·1 (91·5-94·8)	83·6 (81·0-86·2)	81·7 (78·9-84·6)	39·13
VIa.1 Wilms Tumour	765 (5.1%)	95·2 (93·7-96·8)	85·7 (83·0-88·4)	83·7 (80·8-86·7)	40.30

VIIa. Hepatoblastoma**	208 (1.4%)	73·8 (68·0-80·1)	54·2 (47·1-62·4)	51·3 (43·9-59·8)	17.86
VIII. Malignant bone tumours	1,001 (6.7%)	87·6 (85·6-89·7)	65·3 (62·1-68·6)	56·3 (52·6-60·2)	26.46
VIIIa. Osteosarcoma	502 (3.3%)	82·4 (79·1-85·9)	55·7 (51·1-60·8)	48·2 (43·2-53·8)	23·90
VIIIc. Ewing sarcomas	499 (3.3%)	92·9 (90·7-95·2)	74·9 (70·7-79·3)	64·4 (59.4-70·0)	31.26
IX. Soft tissue and extra osseous sarcoma	701 (4.7%)	88·2 (85·9-90·7)	69·2 (65·5-73·1)	64·2 (60·1-68·7)	27.73
IXa. Rhabdomyosarcoma	523 (3.5%)	86·3 (83·4-89·4)	64·3 (59·8-69·0)	59.8 (55·1-64·9)	26·50
IXb-d Other soft tissue tumours	178 (1.2%)	94·2 (90·7-97·7)	84·6 (78·7-90·9)	77·5 (69·2-86·8)	31·90
X. a-c Germ Cell Tumours	247 (1.6%)	94·6 (91·8-97·5)	87·6 (83·2-92·1)	86·9 (82·4-91·6)	38·13
XII. Other Tumours (LCH)***	309 (2.0%)	95·0 (92·6-97·5)	90·8 (87·4-94·3)	90·8 (87·4-94·3)	43·27

***** For all cancers combined, only the primary tumours were included based on ICCC-3 diagnostic groups excluding (Ia.1.) Precursor cell leukaemia – aged <1); (I.e.) Unspecified and other specified leukaemia; (VII.b.) Hepatic carcinomas; (XI.) Other malignant epithelial neoplasms and malignant melanomas. ** Hepatic tumours included Hepatoblastoma only. *** XII includes LCH only. Abbreviations. 95% CI: 95% Confidence Intervals; LCH. Langerhans cell histiocytosis.

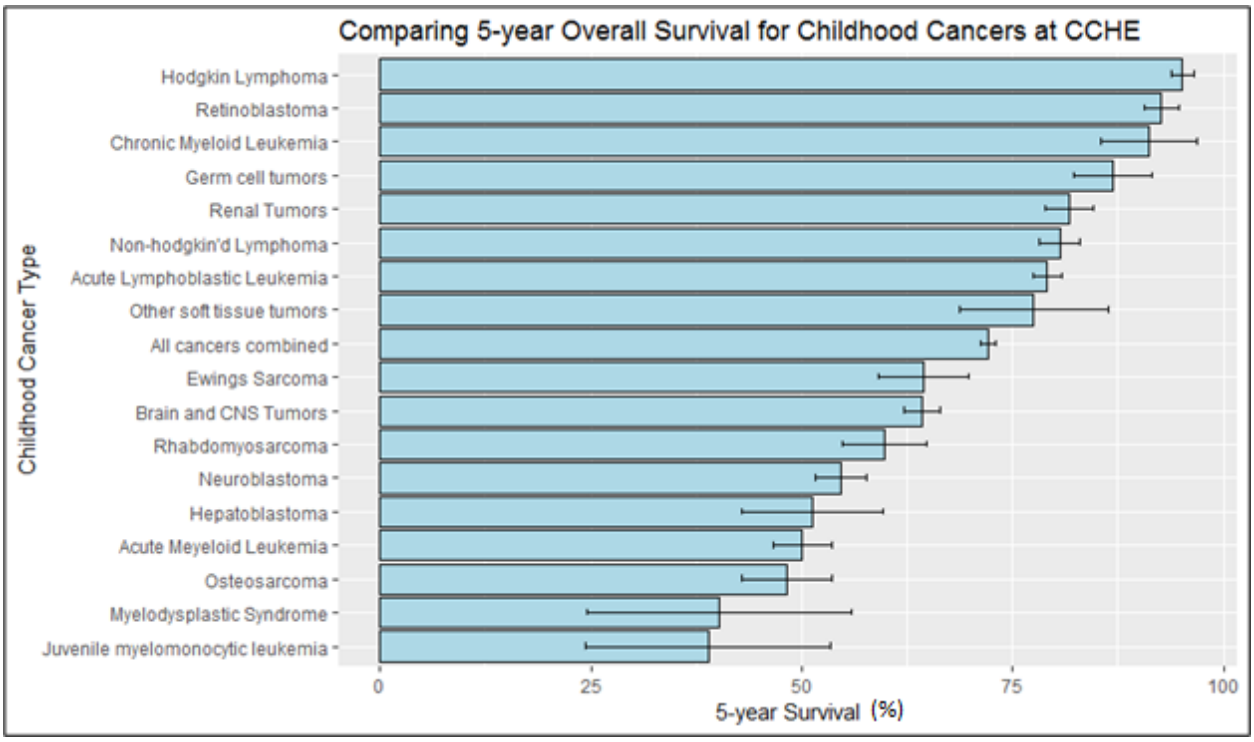


Figure 3.2. Five-year overall survival of childhood cancers, ranked ascendingly

Error bars represent 95% confidence intervals

3.6.3 Temporal trends in survival

For all childhood cancers combined, trends in survival improved over time as shown in Figure 3.3. The 5-year overall survival improved by diagnosis periods between 2007–2012 and 2013–2017, from 69.6% (95% CI: 68.4%–70.8%) to 74.2% (95% CI: 73.0%–75.4%) respectively (p<0.001) as shown in Figure 3.3(A). Also, for all childhood cancers combined, the 3-year survival improved over the 3 diagnosis periods, from 73.0% (95% CI: 71.1%–74.8%) in 2007–2009 to 73.3% (95% CI: 72.1%–74.6%) in 2010–2013 to 78.4% (95% CI 77.4%–79.5%) in 2014–2017 (p<0.001) as shown in Figure 3.3(B). Temporal trends in 5-year survival were significantly increasing by single year of diagnosis for all cancers combined (p<0.001), acute lymphoblastic leukaemia (ALL) (p<0.001), acute myeloid leukaemia (AML) (p=0.006), non-Hodgkin lymphoma (NHL) (p= 0.005), CNS tumours (p<0.001), neuroblastoma (p<0.001), hepatoblastoma (p=0.008), and Ewing sarcoma (p=0.02).

Change in 5-year survival over the two diagnosis periods showed significant improvement for ALL, AML, CNS tumours, neuroblastoma, and hepatoblastoma (as shown in Figure 3.4 and Table 3.3). Change in 3-year survival over three diagnosis periods showed significantly improving survival for ALL, AML, CNS tumours, NHL, neuroblastoma, retinoblastoma, hepatoblastoma, and Ewing sarcoma (as shown in Table 3.3, and illustrated in survival curves in Appendix 3.10). The remaining cancer types showed no significant change in survival over the different diagnosis periods.

Figure 3.3(A)

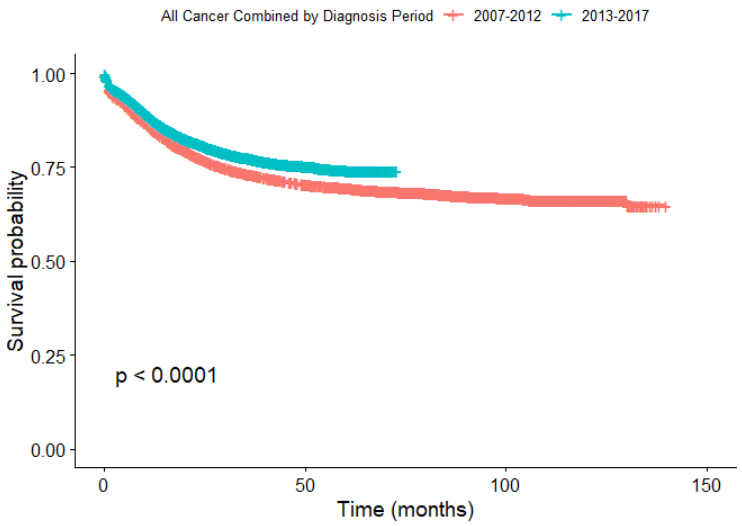


Figure 3.3(B)

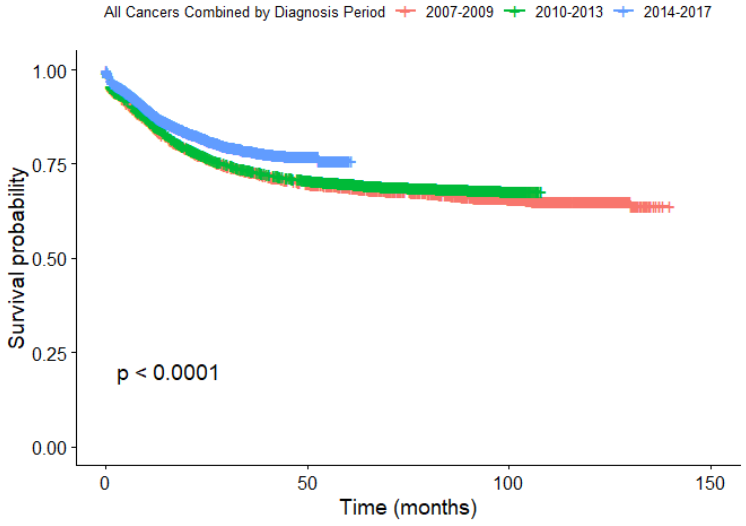


Figure 3.3. Trends in survival for all childhood cancers combined, over 2 and 3 diagnosis periods; Figure 3.3(A) Trends in survival over 2 diagnosis periods. Figure 3.3(B) Trends in survival over 3 diagnosis periods

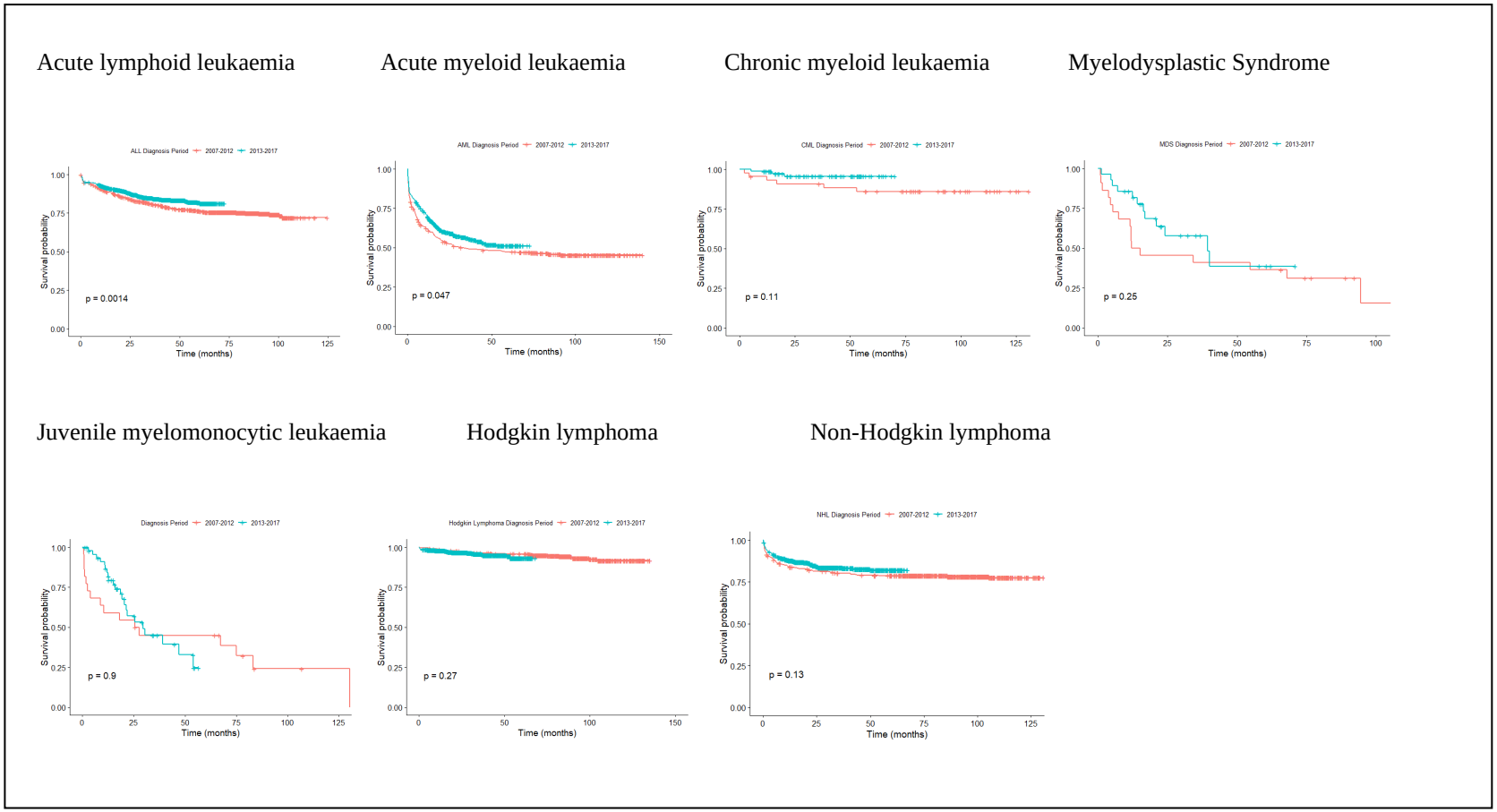


Figure 3.4. Change in 5-year overall survival for childhood cancers over 2 diagnosis periods: 2007 to 2012 and 2013 to 2017

Figure 3.4(A): Leukaemia and lymphoma.

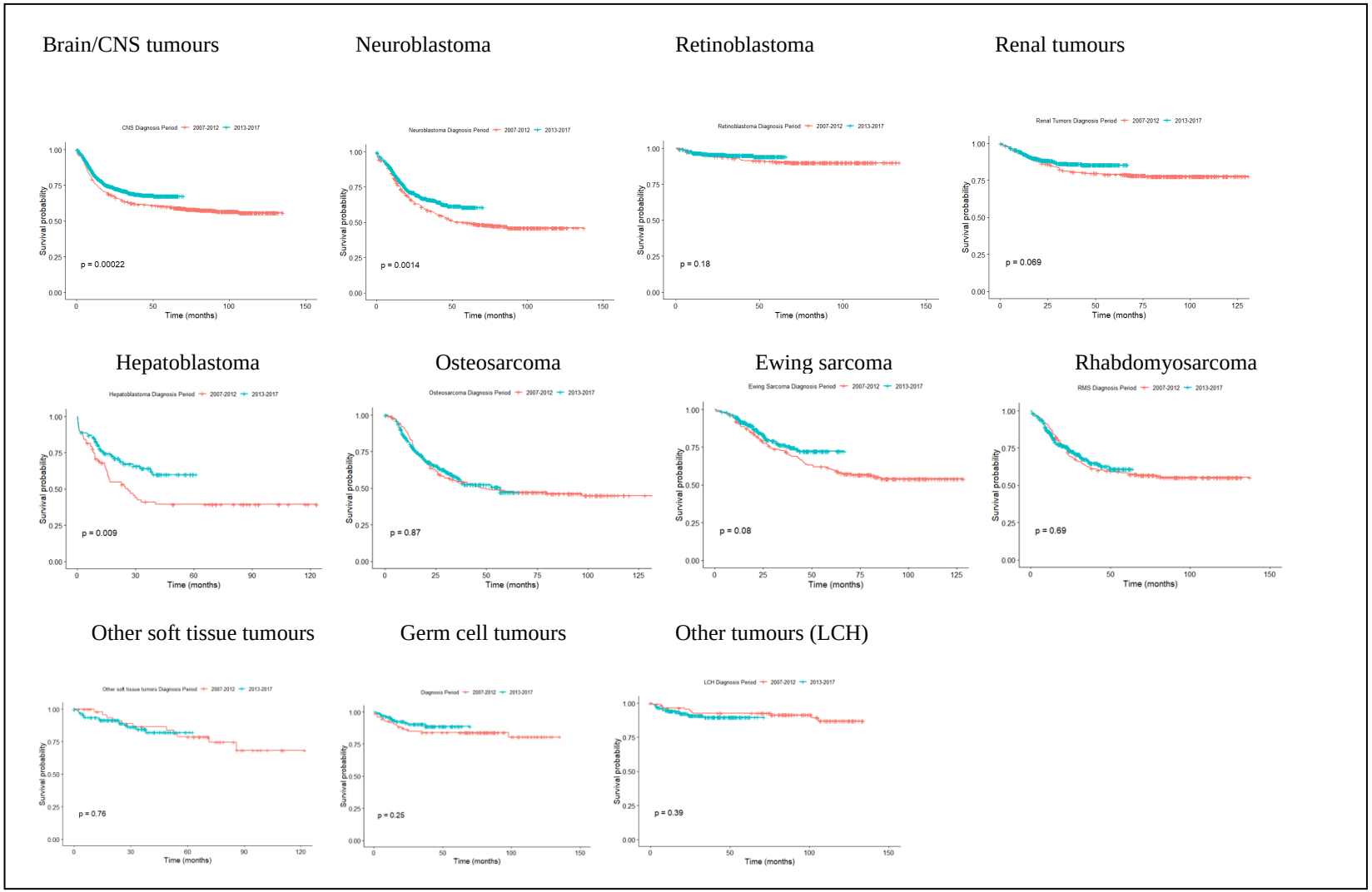


Figure 3.4. (Cont.) Change in 5-year overall survival for childhood cancers over 2 diagnosis periods: 2007-2012 and 2013-2017

Figure 3.4(B): Brain/CNS and other solid tumours

Table 3.3 Trends in 3-year and 5-year overall survival of children with cancer at CCHE, by periods of diagnosis and single year of diagnosis, grouped by ICCC-3 diagnostic groups (n=14,808)

Cancer Type by ICCC–3 diagnostic groups	**3-year Survival (%) (95% CI), by 3 diagnosis periods**				**5-year Survival (%) (95% CI), by 2 diagnosis periods**			***P*** **trend** **§** **by single year of diagnosis**
	2007–2009	**2010–2013**	**2014–2017**	***P*** **°**	**2007–2012**	**2013–2017**	***P*** **°**	
All cancers combined*	73.0 (71.1-74.8)	73.3 (72.1-74.6)	78.4 (77.4-79.5)	<0.0001˜	69.6 (68.4-70.8)	74.2 (73.0-75.4)	<0.0001˜	<0.001˜
I. Leukaemia and related cancers	71.7 (68.5-75.2)	73.4 (71.1-75.7)	78.3 (76.3-80.3)	<0.0001˜	68.9 (66.8-71.2)	73.4 (71.1-75.7)	<0.001˜	<0.001˜
Ia. Acute Lymphoid Leukaemia	80.4 (76.9-84.0)	80.9 (78.5-83.3)	85.9 (83.9-88.0)	0.0001˜	76.4 (74.0-78.8)	81.7 (79.3-84.2)	0.001˜	<0.001˜
Ib. Acute Myeloid Leukaemia	49.3 (42.4-57.5)	49.6 (44.4-55.4)	57.1 (52.5-62.1)	0.03˜	47.3 (42.6-52.5)	51.2 (46.5-56.4)	0.047˜	0.006˜
Ic. Chronic Myeloid Leukaemia	93.7 (82.6-100)	87.6 (78.0-98.3)	98.4 (95.4-100)	0.08	86.0 (76.2-97.1)	95.6 (90.0-100)	0.11	0.227
Id. Myelodysplastic Syndrome	35.7 (17.7-72.1)	50.0 (30.681.6)	63.8 (43.7-93.1)	0.3	36.4 (20.9-63.2)	38.6 (19.8-75.4)	0.25	0.115
Ie. Juvenile myelomonocytic leukaemia	43.6 (21.8-87.4)	59.2 (39.9-87.8)	34.5 (19.2-62.0)	0.46	45.0 (28.2-71.7)	---	0.90	0.967^
II. Lymphomas	87.4 (84.2-90.7)	87.7 (85.5-89.9)	91.1 (89.3-93.0)	0.019˜	87.0 (84.9-89.1)	88.0 (85.7-90.4)	0.20	0.015˜
IIa. Hodgkin Lymphoma	97.8 (95.7-100)	95.7 (93.7-97.6)	96.0 (94.2-97.9)	0.09	95.8 (94.0-97.6)	93.4 (90.3-96.5)	0.27	0.177
IIb. Non-Hodgkin Lymphoma	78.6 (73.3-84.3)	80.0 (76.4-83.9)	85.5 (82.3-88.8)	0.02˜	78.7 (75.3-82.3)	82.0 (78.6-85.7)	0.13	0.005˜
IIIa-e CNS Tumours	61.7 (56.7-67.2)	63.0 (59.8-66.5)	70.6 (67.9-73.4)	<0.0001˜	60.0 (56.9-63.4)	67.4 (64.7-70.3)	<0.001˜	<0.001˜
IIIa. Ependymomas/choroid plexus	67.7 (53.1-86.4)	65.6 (56.1-76.8)	80.8 (71.8-90.8)	0.23	63.7 (54.5-74.6)	72.4 (62.9-83.3)	0.13	0.039˜
IIIb Astrocytoma	73.1 (65.5-81.5)	81.4 (76.2-86.9)	79.3 (74.9-83.9)	0.34	76.2 (71.2-81.6)	78.3 (74.1-82.7)	0.76	0.378
IIIc.1-2 Medulloblastoma and Embryonal	55.3 (44.5-68.8)	63.7 (57.3-70.9)	64.0 (57.5-71.3)	0.35	59.1 (54.6-64.0)	56.5 (50.1-63.7)	0.28	0.075
IV.a Neuroblastoma	57.8 (51.6-64.8)	60.3 (56.1-64.7)	65.8 (61.8-69.9)	0.014˜	49.6 (45.5-54.0)	60.5 (56.3-65.0)	0.001˜	<0.001˜ ^
V. Retinoblastoma	91.3 (85.7-97.2)	93.6 (90.5-96.8)	95.2 (93.0-97.5)	0.031˜	90.8 (87.2-94.5)	94.1 (91.6-96.7)	0.18	0.060 ^
VI. Renal Tumours	86.1 (80.3-92.5)	81.3 (77.1-85.7)	85.3 (81.6-89.1)	0.25	78.9 (74.8-83.2)	85.4 (82.0-89.0)	0.069	0.461
VIa.1 Wilms Tumour	85.9 (79.6-92.8)	83.5 (79.2-88.0)	88.0 (84.3-91.9)	0.29	80.7 (76.4-85.2)	87.6 (84.0-91.2)	0.050	0.164

VII.a Hepatoblastoma**	39.0 (23.4-64.9)	45.9 (35.4-59.5)	68.2 (59.0-78.9)	0.005~	39.5 (29.4-52.9)	59.8 (50.2-71.3)	0.009~	0.008~
VIII. Malignant bone tumours	65.2 (58.4-73.0)	59.9 (54.7-65.7)	70.0 (65.2-75.1)	0.053	54.1 (49.2-59.4)	59.0 (52.7-66.1)	0.24	0.077^
VIIIa Osteosarcoma	57.0 (46.9-69.2)	50.4 (43.2-58.7)	60.9 (54.0-68.7)	0.40	47.7 (41.0-55.5)	47.2 (38.4-58.0)	0.87	0.648 ^
VIIIc Ewing sarcomas	72.5 (63.7-82.5)	70.5 (63.4-78.3)	79.0 (72.8-85.7)	0.032~	62.0 (55.4-69.4)	72.3 (65.8-79.5)	0.087	0.026~
IX. Soft tissue and extra osseous sarcoma	67.7 (59.1-77.6)	67.0 (60.7-73.9)	71.7 (66.4-77.5)	0.65	62.2 (56.3-68.7)	66.7 (60.9-73.0)	0.47	0.257
IXa. Rhabdomyosarcoma	65.9 (56.7-76.6)	61.0 (53.8-69.1)	66.7 (59.9-74.3)	0.73	58.4 (51.9-65.8)	60.8 (53.7-68.9)	0.69	0.377
IXb-d Other soft tissue tumours	81.8 (61.9-100)	89.9 (80.9-99.8)	82.4 (74.5-91.1)	0.48	78.7 (67.2-92.1)	81.4 (73.1-90.7)	0.69	0.365
X.a-c Germ Cell Tumours	83.6 (72.4-96.5)	84.7 (77.1-93.0)	92.1 (87.2-97.2)	0.26	84.0 (76.9-91.8)	88.8 (83.0-95.0)	0.25	0.143
XII. Other Tumours (LCH)****	95.8 (90.3-100)	88.7 (82.1-95.9)	90.0 (84.9-95.4)	0.66	92.5 (87.7-97.6)	89.6 (84.9-94.6)	0.39	0.313

***** For all cancers combined, only the primary tumors were included based on ICCC-3 diagnostic groups excluding (Ia.1.) Precursor cell leukemia – aged <1; (I.e.) Unspecified and other specified leukemia; (VII.b.) Hepatic carcinomas; (XI.) Other malignant epithelial neoplasms and malignant melanomas. ** Hepatic tumours included Hepatoblastoma only. *** XII includes LCH only. ° *P* obtained from log-rank test. § P *trend* obtained from Cox regression test for trend by single year of diagnosis. ~ indicates significant trend at p *P*<0.05. -- Trend not reported because fewer than 10 deaths. ^ Trend accepts Cox proportional hazards assumption, and so trend significance is not considered. Five-year survival could not be calculated divided on 3 diagnostic periods only, as most patients in the latest diagnostic period have not completed 5-year follow-up duration. Abbreviations. 95% CI: 95% Confidence Intervals; LCH. Langerhans cell histiocytosis.

3.6.4 Survival stratification by stage at diagnosis, risk, and subtype

The 5-year overall survival stratified by risk, stage at diagnosis, or subtype showed significant difference for most cancer types (Appendix 3.11) Significant differences in survival rates were observed on stratification by stage at diagnosis for children with non-Hodgkin lymphoma (NHL), neuroblastoma, retinoblastoma, Wilms tumours, hepatoblastoma, osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, and germ cell tumours (GCT) ($p<0.0001$, for each cancer type).

Similarly, significant differences in survival were noted on stratification by disease risk for children with ALL, AML, Hodgkin lymphoma, neuroblastoma, rhabdomyosarcoma, other soft tissue tumours, GCT, and Langerhans cell histiocytosis (LCH) ($p\leq0.001$). Children who have undergone bone marrow transplant (BMT) showed significantly better survival that those without BMT in Myelodysplastic Syndrome (MDS) (77.4% versus 29.6%, $p=0.039$) and high-risk neuroblastoma (53.8% versus 25.0%, $p<0.0001$), and near significance in Juvenile myelomonocytic leukaemia (JMML) (51.6% versus 29.3%, $p=0.056$). The distribution of stage at diagnosis, risk, and subtype was almost steadily uniform over the years (Appendix 3.12).

3.6.5 Comparing age-standardised survival with international benchmarks

The age-standardized 5-year survival rate for all childhood cancers combined at CCHE was lower than survival in England by 9.0% (72.0% vs. 81%, $p<0.001$), and lower than that in the US by 11.2% (72.0% vs. 83.2%, $p<0.001$) (Table 3.4). Survival at CCHE was inferior (than both benchmarks) for children with ALL ($p<0.001$), AML ($p<0.001$), MDS ($p<0.001$) and JMML ($p=0.001$), NHL ($p<0.001$), CNS tumours ($p<0.001$), neuroblastoma ($p<0.001$), retinoblastoma ($p<0.001$), renal tumours ($p<0.001$), hepatoblastoma ($p<0.001$), osteosarcoma ($p<0.001$) and rhabdomyosarcoma ($p=0.003$) (Table 3.4, Figure 3.5).

Table 3.4. Comparing 5-year age-standardized survival rates for children with cancer (aged, 0–14 years) at CCHE/Egypt [2007–2017] with survival in England [2001–2015] and the US [2008–2014], by ICCC-3 diagnostic groups

ICCC–3 Diagnostic Groups	**No. of patients at CCHE**	**Survival at CCH/Egypt % (95% CI)**	**Survival in England (%) (95% CI) ****	**Survival in the US (%) *****	**Diff. in survival *P***
All cancer combined*	13,835	72.0 (71.3–72.8)	81 (81-82)	83.2	<0.001˜
Acute Lymphoid Leukaemia^	2,746	77.6 (76.1–79.2)	92 (91-93)	90.3	<0.001˜
Acute Myeloid Leukaemia	907	51.6 (48.3–54.8)	67 (64-70)	66.8	<0.001˜
Chronic Myeloid Leukaemia	95	90.5 (84.6–96.5)	88 (79-94)	*NA*	0.66
Myelodysplastic Syndrome	46	39. (25.1–53.3)	73 (62-80)	-- [X]	<0.001˜
Juvenile myelomonocytic leukaemia	70	38.1 (26.7–49.4)	65 (54-75)	-- [X]	0.001˜
Hodgkin's Lymphoma	1,039	95.8 (94.6–97.0)	95 (94-97)	97.1	0.45
Non-Hodgkin Lymphoma	1,078	80.9 (78.6–83.3)	87 (84-88)	90.0	<0.001˜
CNS tumours	2,456	64.6 (62.7–66.5)	73 (72-74)	73.1	<0.001˜
Neuroblastoma	1,539	52.4 (49.9–54.9)	67 (64-70)	78.1	<0.001˜
Retinoblastoma	785	91.9 (90.0–93.8)	99 (98-100)	94.6	<0.001˜
Renal tumours	896	78.4 (75.7–81.1)	87 (85-89)	89.1	<0.001˜
Hepatoblastoma	206	45.7 (38.9 – 52.5)	78 (72-83)	83.5	<0.001˜
Osteosarcoma	360	41.5 (36.3–46.6)	60 (56-65)	69.1	<0.001˜
Ewing Sarcoma	431	67.6 (63.2–72.0)	66 (61-71)	83.3	0.67
Rhabdomyosarcoma	499	58.7 (54.4–63.0)	67 (64-71)	69.5	0.003˜
Germ cell tumours	232	88.7 (84.7–92.8)	93 (90-94)	93.7	0.05
Other soft tissue tumours	143	77.3 (87.3-69.6)	-- [X]	*NA*	--
Other Tumours (LCH)	307	90.8 (94.3-87.3)	-- [X]	*NA*	--

* For all cancers combined, only the primary tumours were included based on ICCC-3 diagnostic groups at CCHE and for England results; At CCHE ICCC-3 groups excluded Ia.1, I.e, VII.b, XI, XII; ** Survival rates in England were reported from National Cancer Registration and Analysis Service (NCRAS), for children up to 14 years old. Survival estimates were reported without decimal points. *** Survival rates in the US were reported based on SEER database by ICCC-3, for children up to 14 years old; excluding benign brain and MDS; no 95% CI were reported for survival from the US. ^ Acute lymphoid leukaemia at CCHE, England and in the US are aged 1 – 14 years in survival analysis. ˜ indicates significant difference at $P<0.05$. [X] indicates survival for this cancer group is not reported. *NA* Survival for these cancers is not included in US SEER report.

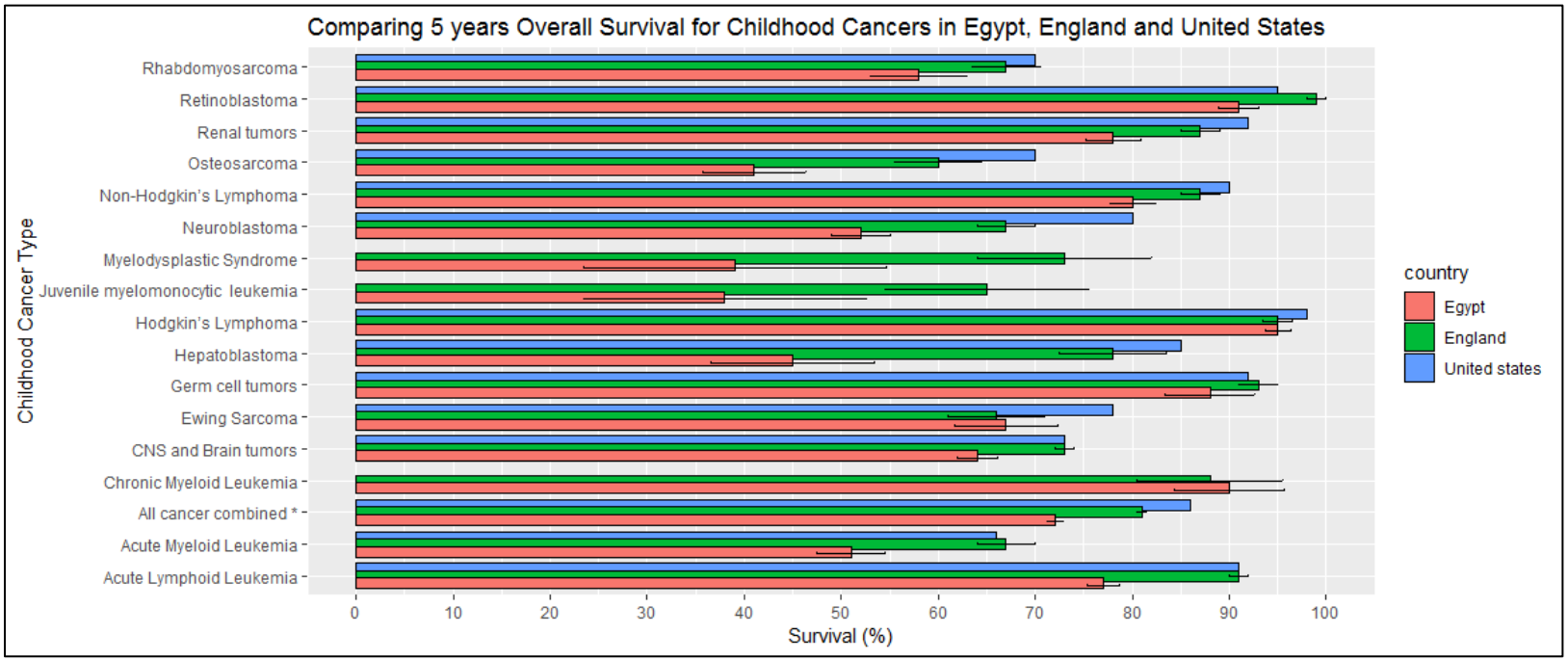


Figure 3.5. Comparing 5-year childhood cancer age-standardised survival (aged 0–14 years) at CCHE/Egypt with international benchmarks from England and the US (n= 13,835)

The only childhood cancer types at CCHE/Egypt that showed statistically comparable survival (<10% difference in survival) with international benchmarks were chronic myeloid leukaemia (CML), Hodgkin lymphoma, Ewing sarcoma, and germ cell tumours.

For the cancers with inferior survival identified in Table 3.4, the main cause of death (cause-specific mortality) was presented in Table 3.5. It was found that treatment-related mortality (TRM) (also known as toxic deaths) was higher than cancer-related mortality in children with NHL (10.8% versus 7.3%, respectively), and almost the same percentages in AML (23.3% versus 23.8%, respectively) and ALL (9.1% versus 9.2%, respectively) (Table 3.5). Nevertheless, the proportion of TRMs decreased in recent diagnosis periods for the majority of cancers, except for children with renal tumours which showed higher percent of toxic deaths in the most recent diagnosis period.

Furthermore, the adverse events for cancers with inferior survival were determined in Table 3.6. The highest percentages of adverse events included treatment-related mortality (described in Table 3.5) and disease relapse in majority of cancers. In haematological malignancies, patients with AML and ALL showed the highest percentages of disease relapse (20.4% and 10.3%, respectively). In solid tumours, children with rhabdomyosarcoma and osteosarcoma had the highest percentages of disease relapse (40.1% and 33.0%, respectively).

Table 3.5. Cause-specific mortality for childhood cancers with inferior survival at CCHE/Egypt

Cancer Type	**Total no. of Deaths (% from total patients) [2007 – 2017]**	****Cancer-related deaths, n (% from total patients) [2007 – 2017]**	*****Treatment-related mortality (TRM), (% from total patients) [2007 – 2017]**	**TRM / Toxic deaths (by diagnosis period)**		
				Toxic deaths (%) [2007 – 2009]	**Toxic deaths (%) [2010 – 2013]**	**Toxic deaths (%) [2014 – 2017]**
Acute Lymphoid Leukaemia	537/2914 (18.4%)	269/2914 (9.2%)	268/2914 (9.1%)	62/506 (12.2%)	107/1008 (10.6%)	99/1400 (7.0%)
Acute Myeloid Leukaemia	465/987 (47.1%)	235/987 (23.8%)	230/987 (23.3%)	51/176 (28.9%)	90/321 (28.0%)	89/490 (18.1%)
Myelodysplastic Syndrome	29/50 (58.0%)	22/50 (44.0%)	7/50 (14.0%)	3/14 (21.4%)	2/16 (12.5%)	2/20 (10.0%)
Juvenile myelomonocytic leukaemia	38/70 (54.2%)	37/70 (52.8%)	1/70 (1.4%)	--	--	1/40 (2.5%)
Non-Hodgkin Lymphoma	213/1173 (18.1%)	86/1173 (7.3%)	127/1173 (10.8%)	27/217 (12.4%)	55/434 (12.6%)	45/522 (8.6%)
CNS tumours	822/2588 (31.7%)	469/2588 (18.1%)	353/2588 (13.6%)	49/327 (14.9%)	154/802 (19.2%)	150/1459 (10.2%)
Neuroblastoma	575/1547 (37.1%)	380/1547 (24.5%)	195/1547 (12.6%)	33/222 (14.8%)	64/508 (12.5%)	98/817 (11.9%)
Retinoblastoma	49/786 (6.2%)	34/786 (4.3%)	15/786 (1.9%)	3/98 (3.0%)	5/241 (2.0%)	7/441 (1.5%)
Renal tumours	144/900 (16.0%)	114/900 (12.6%)	30/900 (3.3%)	2/124 (1.6%)	9/331 (2.7%)	19/445 (4.2%)
Hepatoblastoma	85/208 (40.8%)	72/208 (34.6%)	13/208 (6.2%)	4/26 (15.3%)	4/73 (5.4%)	5/109 (4.5%)
Osteosarcoma	215/502 (42.8%)	191/502 (38.0%)	24/502 (4.7%)	4/79 (5.0%)	8/169 (4.7%)	12/254 (4.7%)
Rhabdomyosarcoma	177/523 (33.8%)	149/523 (28.4%)	28/523 (5.3%)	12/89 (13.4%)	6/162 (3.7%)	10/272 (3.6%)

* AML deaths were counted after 14 days from diagnosis, based on study eligibility criteria. ** Cancer-related deaths included deaths before starting treatment, deaths early on treatment, deaths after disease relapse, refractory disease, progressive disease or 2ry malignancy. **Treatment-related death was defined as death occurring in the absence of progressive cancer, including deaths in complete remission (CR), during induction chemotherapy, deaths with no evidence of disease (NED), or deaths due to toxicity-related effects.

Table 3.6. Adverse events for childhood cancers with inferior survival at CCHE/Egypt

Cancer Type	***No. of patients with adverse events (% from total patients)***	***No. of Events (Percent from total patients)***				
		Treatment-related Deaths*	***Disease Relapse***	***Refractory Disease***	***Disease Progression***	***2ry Malignancy***
Acute Lymphoid Leukaemia	602/2914 (20.6%)	268/2914 (9.1%)	300/2914 (10.3%)	20/2914 (0.7%)	*NA*	14/2914 (0.5%)
Acute Myeloid Leukaemia	438/987 (44.3%)	230/987 (23.3%)	202/987 (20.4%)	6/987 (0.6%)	*NA*	--
Myelodysplastic Syndrome	32/50 (64.0.%)	7/50 (14.0%)	6/50 (12.0%)	14/50 (28.0%)	*NA*	5/50 (10.0%)
Juvenile myelomonocytic Leukaemia (JMML)*	18/70 (25.7%)	1/70 (1.4%)	13/70 (18.6%)	*NA*	4/70 (5.7%) *	--
Non-Hodgkin Lymphoma	250/1173 (21.3%)	127/1173 (10.8%)	67/1173 (5.7%)	--	56/1173 (4.7%)	--
CNS tumours	1031/2588 (39.8%)	353/2588 (13.6%)	234/2588 (9.0%)	*NA*	444/2588 (17.1%)	--
Neuroblastoma	744/1547 (48.1%)	195/1547 (12.6%)	252/1547 (16.2%)	*NA*	289/1547 (18.6%)	8/1547 (0.5%)
Retinoblastoma	51/786 (6.4%)	15/786 (1.9%)	20/786 (2.5%)	*NA*	13/786 (1.6%)	3/786 (0.3%)
Renal tumours	208/900 (23.1%)	30/900 (3.3%)	122/900 (13.5%)	*NA*	56/900 (6.2%)	*NA*
Hepatoblastoma	103/208 (49.5%)	13/208 (6.2%)	34/208 (16.4%)	*NA*	56/208 (26.9%)	--
Osteosarcoma	276/502 (54.9%)	24/502 (4.7%)	166/502 (33.0%)	*NA*	83/502 (16.5%)	3/502 (0.6%)
Rhabdomyosarcoma	244/523 (46.6%)	28/523 (5.3%)	210/523 (40.1%)	*NA*	5/523 (0.9%)	1/523 (0.1%)

NA: event is not applicable for this cancer type. * In JMML, 4 patients progressed to AML. * AML deaths were counted after 14 days from diagnosis, based on study eligibility criteria. ** Cancer-related deaths included deaths before starting treatment, deaths early on treatment, deaths after disease relapse, refractory disease, progressive disease or 2ry malignancy. **Treatment-related death was defined as death occurring in the absence of progressive cancer, including deaths in complete remission (CR), during induction chemotherapy, deaths with no evidence of disease (NED), or deaths due to toxicity-related effects.

3.7 Discussion

3.7.1 Summary and interpretation of findings

I have analysed survival rates and trends in survival for 14,808 children with cancer who were diagnosed and treated at CCHE between 2007 and 2017. The 5-year overall survival of all childhood cancers combined is 72.1%. Previous estimate of childhood cancer survival in Egypt reported in 2008 was postulated to be 40% based on modelled data from field surveys.[19] This variation could be explained by recent advances in paediatric oncology care, and/or the difference between modelled and observed survival estimates.

Temporal trends in 5-year overall survival for all childhood cancers combined improved significantly by single year of diagnosis, and by diagnosis periods from 69.6% in 2007–2012 to 74.2% in 2013–2017. Survival trends improved over time for children for ALL, AML, NHL, CNS tumours, neuroblastoma, hepatoblastoma, Ewing sarcoma, and retinoblastoma. These improvements in survival suggest for improved quality of care at CCHE; providing more intensified chemotherapy protocols; and providing better supportive care and infection control leading to decrease in toxic deaths. Since improved temporal trends in cancer survival could also be attributable to change in diagnosis patterns,[38] I studied the distribution of patient demographics, cancer types, stage at diagnosis, and risk groups over the years (Appendix 3.8; Appendix 3.12) and found that these trends were steadily uniform over time. This suggests that improvements in survival were likely not related to changes in patient demographics or disease severity (stage/risk), thus reducing the possibility of a chronological bias.

Furthermore, the increasing trend of newly diagnosed children with cancer over the years is likely due to increase in numbers of patients treated at CCHE. This is likely attributed to more

referrals to tertiary care,[39] rather than an increase in childhood cancer incidence rates in Egypt. However, there are no national-level incidence data over this duration to support this.[21,40]

The age-standardised 5-year survival at CCHE was lower than international benchmarks from England (by 9%) and the US (by 11.2%), where inferior survival was observed in 12 out of the 18 childhood cancer types. Inferior survival for acute leukaemia (ALL/AML) was likely due to high-risk of infections and toxic deaths, limited capacity for bone marrow transplant (BMT) for indicated patients, and less treatment options for relapsing patients. Whereas, inferior survival for solid tumours was likely due to delayed diagnosis, advanced stage at diagnosis; around 42% of patients presented with metastatic disease, compared to around 28% in a HIC context.[41] More information about the potential reasons for inferior survival based on discussions with lead paediatric oncologists at CCHE/Egypt are listed in Appendix 3.13.

3.7.2 Comparison with other published literature

No previous research studies were published about childhood cancer survival in Egypt on a national or a population-based level, due to absence of survival data in the population-based cancer registry.[21,40] A narrative review by Basbous *et al.* (2021) summarised the published research on childhood cancer outcomes in Egypt, and found that prior research only focused on estimating survival for a few types of childhood cancer in a small sample size, and no studies stratified survival by cancer type/stage/risk.[22]

Even though childhood cancer observed survival and survival trends were reported in many studies from HICs, little is known about these in LMIC contexts (including Egypt), making it unfeasible for comparisons.[5,42] To account for this, I compared findings from this study to the results reported by Ward *et al*. (2019) about global childhood cancer survival, based on

simulation-based analysis (modelled data).[43] The 5-year survival rates at CCHE/Egypt were greatly higher than those reported for Africa (mostly includes LMICs) for all childhood cancers by ICCC-3 groups.[43] Survival rates at CCHE/Egypt were comparable (<10% difference in survival) with 5-year survival estimates for Europe and North America for ALL, Hodgkin's lymphoma, NHL, CML, retinoblastoma, Wilms tumour and Ewing sarcoma, while the rest of the cancer types showed more inferior outcomes.[43]

Improvements in 5-year overall survival for some childhood cancer types at CCHE/Egypt are comparable to improvements in survival in the more developed countries.[14,33,44–46] Survival for children with ALL, Brain/CNS tumours and lymphoma is comparable to results from the CONCORD-3 study.[47] However, survival estimates at CCHE/Egypt for children with AML, hepatoblastoma and neuroblastoma are >10% lower than survival in England, the US, and Australia.[33,44,45] Although survival of Hodgkin lymphoma and germ cell tumours showed no improvement over time, it is comparable to recent results from HICs.[33,35,45] Unlike other HIC, survival of osteosarcoma, MDS and JMML showed no improvement and is significantly lower than international benchmark.[33,35]

3.7.3 Strengths and limitations

To the best of my knowledge, this study presents the first results of childhood cancer survival rates and temporal trends in survival for the largest cohort of children with cancer in Egypt, categorised by ICCC-3 groups, and compared to international benchmarks. This is also the first study to present survival rates for all childhood cancers combined, and stratified by patients' demographics, cancer type/subtype, disease risk, and stage at diagnosis. These findings can help

address the gap in evidence about limited published literature regarding childhood cancer survival based on real-world data from Egypt.

Another strength of this study is the availability and use of high-quality survival data from the hospital-based registry at CCHE; data quality checks were routinely done every six months over ten years [2007–2017], and at the time of study initiation, ensuring the validity of study findings.

Despite the valuable findings obtained from this study, some limitations exist. First, a potential limitation in this study is selection bias, which could be attributed to selecting/including patients from CCHE who are not representative of the whole childhood cancer population in Egypt, or in case some patients could have died before being referred to CCHE. This potential bias could be reduced by matching patient demographics and the main childhood cancer types at CCHE with population-based statistics.[40] Besides, children with cancer (in this study cohort) were diagnosed and treated at CCHE regardless of age, gender, socio-economic status, geographical distribution, type of cancer, stage/risk of disease preferences. potentially resulting in an unbiased selection of patients. Therefore, given the large proportion of children with cancer treated at CCHE (around 40% of all childhood cancers across Egypt), matching patient statistics, and treating all patients without discrimination, this would potentially result in an unbiased selection of patients. It is likely appropriate to propose that the study cohort can well represent children with cancer in the Egyptian population. Although I cannot be sure that this is a representative sample of the population due to the unavailability of national-level statistics in Egypt with cancer type/risk/stage stratification, I have no reasons to believe otherwise.

Second, children with rare cancers (n=513, 3.2% of initial study cohort) were not included in survival analysis (shown in Figure 3.1) as their disease-specific and survival outcomes data were not readily-available in the hospital-based registry. The data collection forms for these cancer

groups were still under revision, and their data were not yet collected at time of study initiation. Nevertheless, since these patients represent a very small percent of the initial study cohort and are rare types of cancer, it is therefore assumed that excluding them will have no/minimal effect on survival rates.

Third, this study is limited by the short follow-up duration of patients diagnosed in the recent years (2016 and 2017). This is because some of ALL patients were still active on treatment, and were at risk of dying from TRMs, disease, or late relapses, which would have been reflected on declined survival with longer follow-up duration.[48] However, patients with shorter follow-up duration (less than five years) are censored observations in survival calculation using the Kaplan-Meier method. Period analysis could have been used to tackle this issue by predicting long-term survival estimates for patients diagnosed in recent years.[49] However, I used the cohort method to determine observed survival rather than predicted estimates, to compare with international benchmarks and other published studies. Nevertheless, I also estimated survival trends over time by single year of diagnosis as modelled estimates rather than direct estimate that would require five years of follow-up. The estimate comes from a Cox regression model across the whole cohort with the 'year of diagnosis' as a covariate in the model. In effect, the Cox model extrapolates survival for these patients based on the survival patterns from previous years.

Fourth, survival estimates are prone to lead-time bias where diagnosing cancer early can improve survival.[50] Nevertheless, this is more common in adults where cancer screening can lead to early diagnosis. I accounted for this potential bias through stratifying survival by risk and stage at diagnosis. Fifth, this study was conducted at a single centre, limiting the generalisability of the survival outcomes to other centres in Egypt due to differences in treatment protocols and

standards of care. To help address this issue, I transparently disclosed the treatment protocols adopted at CCHE for each childhood cancer type.

3.7.4 Implications

3.7.4.1 Implications for policymakers

As part of the WHO Global Initiative for Childhood Cancer, policy-makers should find effective solutions to prevent delays in childhood cancer diagnosis in LMIC contexts (including Egypt), which lead to late presentation with advanced disease and consequently more inferior survival. Furthermore, policy-makers at CCHE should find ways to better target and allocate the available resources to improve care and outcomes effectively for the cancers with inferior survival rates.

3.7.4.1 Implications for clinicians

Clinicians at CCHE should focus their efforts to improve survival of the childhood cancer types with inferior survival compared to international benchmarks, especially those with the largest volumes of patients and those with the largest gaps in survival (>10% difference in survival from international benchmarks). This can be done through (a) revising and/or modifying the clinical practice guidelines and treatment protocols for cancers with inferior survival, (b) improving the supportive care for cancers with high rates of treatment-related mortalities (toxic deaths), and (c) providing evidence-based novel treatments for cancers with advanced stage/high-risk groups. These efforts can help improve 5-year survival from 72.1% to over 80% similar to HICs.[14,33,35,45]

3.7.4.3 Implications for researchers

Future research should focus on determining the resources used, costs and cost-effectiveness estimates during childhood cancer treatment at CCHE. I addressed these in chapters 4, 5, and 6.

Further research should focus on conducting in-depth analysis to study factors contributing to inferior outcomes, and adopting tailored strategies to optimally improve survival outcomes.

3.7.4.3 Implications for patients

Determining which cancers had inferior survival compared to international benchmarks would help clinicians focus their efforts to improve their health outcomes. This could, in turn, lead to improved survival rates, and reduced preventable treatment-related toxicities (TRMs) by adapting treatment protocols to local supportive care capabilities and patients' tolerability.

3.7.5 Evidence-based recommendations for improvement

Accordingly, I suggest the following key recommendations (Panel 3.1) in policy-making (points 1, 2 and 3), current practice (points 4, 5, and 6), and future research (points 7 and 8) to overcome current barriers to optimal care and improve survival of children with cancer in Egypt/CCHE.

Panel 3.1 Recommendations to improve survival of children with cancer at CCHE/Egypt

1. Determine reasons for late presentation; and promote national awareness for early diagnosis of childhood cancer in Egypt.
2. Perform hospital-wide resource planning to accommodate need and demand for services, and avoid delays in treatment which lead to inferior patients' outcomes.
3. Collaborate efforts to enable access to novel therapies in Egypt at an affordable cost.
4. Tailor treatment protocols and clinical practice guidelines at CCHE/Egypt to the local context, based on evidence generated from real-world data.
5. Modify treatment protocols and/or enhance supportive care measures for patients with ALL, AML and NHL to reduce the risk of treatment-related mortality (preventable toxic deaths).
6. Provide BMT for indicated patients to improve their survival rates.
7. Estimate childhood cancer hospital resource use, costs, and cost-effectiveness of treatment.
8. Study the factors associated with high-risk of relapse in cancers with inferior survival.

3.8 Conclusions

Survival of childhood cancers combined and some individual cancers is improving over the years at CCHE in Egypt, however, some types still show inferior survival compared to results from HICs. Generating evidence from local context in Egypt will reflect on practice and policy.

3.9 Chapter How this study fits with my overall thesis

My thesis aims to generate evidence to improve childhood cancer health outcomes and resource use in Egypt. Chapter 3 generates real-world evidence from local context (CCHE/Egypt) about childhood cancer survival rates and temporal trends in survival. This chapter identifies the childhood cancer types with inferior survival outcomes and provides evidence-based recommendations to improve survival rates. Survival outcomes derived in this chapter will then be used to estimate the cost-effectiveness of childhood cancer treatment in Chapter 5.

3.10 Chapter summary

- This chapter determines the survival rates and temporal trends in survival for 14,808 children with cancer treated at CCHE/Egypt between 2007 and 2017.
- For all childhood cancers combined, the 5-year overall survival was 72.1%.
- Survival trends improved significantly over time for children with leukaemia, lymphoma, Brain/CNS tumours, neuroblastoma, hepatoblastoma, and Ewing Sarcoma.
- The 5-year age-standardised survival rate at CCHE/Egypt was significantly lower by 9% and 11.2% than survival rates in England and the US, respectively.
- Inferior survival was observed for the majority of childhood cancers.

Chapter Three References

1. GBD 2017 Childhood Cancer Collaborators. The global burden of childhood and adolescent cancer in 2017: an analysis of the Global Burden of Disease Study 2017. *Lancet Oncol* 2019; 20: 1211–25.
2. Bhakta N, Force LM, Allemani C, Atun R, Bray F, Coleman MP, Steliarova-Foucher E, Frazier AL, Robison LL, Rodriguez-Galindo C, and Fitzmaurice C. Childhood cancer burden: a review of global estimates. *Lancet Oncol* 2019; 20: e42–53.
3. Quilty R. Mind the Gap: Improving paediatric cancer care in developing countries. Commentary. *UOJM. Global Health*. 2016:6(2).
4. Magrath I, Steliarova-Foucher E, Epelman S, Ribeiro RC, Harif M, Li C, *et al*. Paediatric cancer in low-income and middle-income countries. *Lancet Oncol*. 2013;14(3):e104-e116.
5. Rodriguez-Galindo C, Friedrich P, Alcasabas P, Antillon F, Banavali S, Castillo L, *et al*. Toward the cure of all children with cancer through collaborative efforts: pediatric oncology as a global challenge. *J Clin Oncol* 2015, 33:3065-3073.
6. International Agency for Research on Cancer (IARC). Much remains to be done to fight childhood cancer. *IARC ireport*, 2016.
7. Israels T, Challinor J, Howard S, and Arora RH. Treating children with cancer worldwide: challenges and interventions. *Pediatrics* 2015;136;607.
8. Ribeiro RC, and Pui C. Saving the children: improving childhood cancer treatment in developing countries. *N Engl J Med/* 2005;352;21.
9. Gupta S, Rivera-Luna R, Ribeiro R, and Howard S. Paediatric oncology as the next global child health priority: the need for national childhood cancer strategies in low- and middle-income countries, *PLoS Med.* 2014;11(6):e1001656.

10. Childhood Cancer International (CCI). 8 Reasons Why Childhood Cancer Should be a Global Child Health Priority. *CCI*. 2017.
11. Atun R, Bhakta N, Denburg A, Frazier AL, Friedrich P, Gupta S, *et al*. Sustainable care for children with cancer: a Lancet Oncology Commission. *Lancet Oncol*. 2020;21(4):e185-e224.
12. Ward ZJ, Yeh JM, Bhakta N, Frazier AL, Girardi F, Atun R. Global childhood cancer survival estimates and priority-setting: a simulation-based analysis. *Lancet Oncol*. 2019;20(7):972-83.
13. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Niksic M, *et al*. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet*. 2018;391(10125):1023-75.
14. Gatta G, Botta L, Rossi S, Aareleid T, Bielska-Lasota M, Clavel J, *et al*. Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5--a population-based study. *Lancet Oncol*. 2014;15(1):35-47.
15. The World Bank Group. Arab Republic of Egypt [Internet]. World Bank Group. 2023 [cited 2023 Feb]. Available from: https://data.worldbank.org/country/EG
16. Worldometer. Egypt population. Population of Egypt (2020 and historical) [Internet]. Worldometer. 2023 [cited 2023 Jan]. Available from: https://www.worldometers.info/world-population/egypt-population/#:~:text=Egypt%202020%20population%20is%20estimated,year%20according%20to%20UN%20data

17. Statista. Egypt: Age structure from 2011 to 2021 [Internet]. Statista. 2022 [cited 2023 Feb]. Available from: https://www.statista.com/statistics/377306/age-structure-in-egypt/#statisticContainer

18. Fadhil I, **Soliman R**, Jaffar S, Al Madhi S, Saab R, Belgaumi A, *et al*. Estimated incidence, prevalence, mortality, and registration of childhood cancer (ages 0-14 years) in the WHO Eastern Mediterranean region: an analysis of GLOBOCAN 2020 data. *Lancet Child Adolesc Health*. 2022;6(7):466-73.

19. Ribeiro RC, Steliarova-Foucher E, Magrath I, Lemerle J, Eden T, Forget C, *et al*. Baseline status of paediatric oncology care in ten LMICs receiving My Child Matters support: a descriptive study. *Lancet Oncol.* 2008;9(8):721-9.

20. World Health Organization (WHO). The Global Initiative for Childhood Cancer (GICC). Increasing access, advancing quality, saving lives [Internet]. 2023 [cited 2023 Jan]. Available from: https://www.who.int/initiatives/the-global-initiative-for-childhood-cancer

21. Ibrahim AS, Khaled HM, Mikhail N, Baraka H, and Kamel H. Cancer incidence in Egypt: results of the national population-based cancer registry program. *J Cancer Epidemiol*. 2014;2014:437971.

22. Basbous M, Al-Jadiry M, Belgaumi A, Sultan I, Al-Haddad A, Jeha S, *et al*. Childhood cancer care in the Middle East, North Africa, and West/Central Asia: A snapshot across five countries from the POEM network. *Cancer Epidemiol*. 2021;71(Pt B):101727.

23. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61(4):344-349.

24. Children's Cancer Hospital 57357–Egypt (CCHE). CCHE Homepage [Internet]. 2023 [cited 2023 Jan]. Available from: https://www.57357.org/

25. Steliarova-Foucher E, Stiller C, Lacour B, and Kaatsch P. International Classification of Childhood Cancer, third edition. *Cancer*. 2005;103:1457-1467.

26. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, *et al*. International classification of diseases for oncology, third edition (ICD-O-3). Geneva: World Health Organization, 2013.

27. Gupta SK. Intention-to-treat concept: A review. *Perspect Clin Res*. 2011;2(3):109-12.

28. Becker C, Graf N, Grabow D, Creutzig U, Reinhardt D, Weyer-Elberich V, Spix C, and Kaatsch P. Early deaths from childhood cancer in Germany 1980-2016. *Cancer Epidemiol*. 2020;65:101669.

29. Oxford Centre for Evidence-Based Medicine (CEBM). Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence. [Internet]. CEBM. 2011 [cited 2020 Mar]. Available from: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence

30. Berger ML, Sox H, Willke RJ, Brixner DL, Eichler H, Goettsch W, *et al*. Good practices for real-world data studies of treatment and/or comparative effectiveness. *Pharmacoepidemiol Drug Saf*. 2017 Sep; 26(9): 1033–1039.

31. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, and Conde JG. Research electronic data capture (REDCap), *J Biomed Inform*. 2009 Apr;42(2):377-81.

32. Makkar N, Ostrom Q, Kruchko C and Barnholtz-Sloan J. A comparison of relative survival and cause-specific survival methods to measure net survival in cancer populations. *Eur J Cancer*. 2017 Feb;72:78-83.

33. National Cancer Registration and Analysis Service (NCRAS). Childhood Cancer Statistics, England Annual report 2018. Appendix B cancer survival tabulation [Internet]. NCRAS. 2018 [cited 2020]. Available from: http://www.ncin.org.uk/publications/reports/

34. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing 2013. Vienna, Austria. URL: http://www.R-project.org/

35. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2016, National Cancer Institute. Bethesda, MD, based on November 2018 SEER data submission, posted to the SEER web site, April 2019. Available from: https://seer.cancer.gov/csr/1975_2016

36. Alexander S, Pole JD, Gibson P, Lee M, Hesser T, Chi SN, *et al*, and International Paediatric Oncology Mortality Classification Group. Classification of treatment-related mortality in children with cancer: a systematic assessment. *Lancet Oncol* 2015; 16: e604–10.

37. National Cancer Institute (NCI). NCI dictionary of cancer terms. Adverse event [Internet]. 2019 [cited 2019 Nov]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/adverse-event

38. Welch HG, Schwartz LM, and Woloshin S. Are increasing 5-year survival rates evidence of success against cancer? *JAMA*. 2000;14;283(22):2975-8.

39. Catalogue of Bias Collaboration. Bankhead C, Nunan D, Aronson JK. Referral filter bias**.** In: Catalogue of Biases 2019 [Internet]. 2023 [cited 2020 Mar]. Available from: https://catalogofbias.org/biases/referral-filter-bias/

40. International Agency for Research on Cancer (IARC). Gharbiah Cancer Registry to the IARC project International Incidence of Childhood Cancer, Volume III. 2020.

41. Youlden DR, Frazier AL, Gupta S, Pritchard-Jones K, Kirby ML, Baade PD, *et al*. Stage at diagnosis for childhood solid cancers in Australia: A population-based study. *Cancer Epidemiol*. 2019;59:208–214.

42. Rodriguez-Galindo C, Friedrich P, Morrissey L, and Frazier L. Global Challenges in Paediatric Oncology. *Curr Opin Pediatr* 2013;25:3–15.

43. Ward ZJ, Yeh JM, Bhakta N, Frazier AL, Girardi F, and Atun R. Global childhood cancer survival estimates and priority-setting: a simulation-based analysis. *Lancet Oncol*. 2019; 20(7): 972-983.

44. Noone A Howlader N, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD, based on November 2017 SEER data submission, posted to the SEER web site, April 2018. Available from: https://seer.cancer.gov/csr/1975_2015/

45. Cancer Council Queensland. Childhood cancer in Australia 1983-2015. A report from the Australian Childhood Cancer Registry. 2019.

46. Nakata K, Ito Y, Magadi W, Bonaventure A, Stiller C, Katanoda K, *et al*. Childhood cancer incidence and survival in Japan and England: A population-based study (1993-2010). *Cancer Sci*. 2018;109(2):422-434.

47. Ogunbiyi OJ, Silva GA, Chen W, Eser S, Engholm G, Stiller CA, *et al*, and CONCORD Working Group. Global surveillance of trends in cancer survival: analysis of individual

records for 37,513,025 patients diagnosed with one of 18 cancers during 2000–2014 from 322 population-based registries (CONCORD-3). *Lancet*. 2018;17;391(10125):1023–1075.

48. Wasilewski-Masker K, Liu Q, Yasui Y, Leisenring W, Meacham LR, Hammond S, *et al*. Late recurrence in paediatric cancer: a report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2009;101(24):1709–1720.

49. Jansen L, Hakulinen T, Brenner H. Study populations for period analyses of cancer survival. *Br J Cancer*. 2013;108(3):699–707.

50. Oke J, Fanshawe T. Cancer Statistics: A Survival Guide. *Significance*. 2020;17(1):26-9.

Chapter Four: Childhood cancer hospital resoucre use and costs in Egypt

It takes a village to treat a child with cancer.

Childhood cancer treatment is complex, resource-intensive, and costly. Generating real-world evidence from the local context about the resources used and their associated costs can provide helpful insights to better target the available resources and manage costs effectively.

4.1. Publication statement

Features of this chapter are published in the following peer-reviewed journal:

Soliman R, Elhaddad A, Oke J, Eweida W, Tarek N, Hamza M, *et al.* Childhood cancer hospital resource utilization and costs in Egypt, 2013-2017; patterns, trends, and associated factors for 8886 patients from Children's Cancer Hospital, Egypt. *Pediatr Blood Cancer*. 2021;68(11):e29347. DOI: 10.1002/pbc.29347.

4.2 Introduction

Treatment of children with cancer is complex, resource-intensive, and incurs high costs, imposing great economic and financial burdens on healthcare systems.[1–5] Estimating the resources used and the costs of care can help with better resource management to improve survival outcomes efficienly.[4,5,6] This is particularly important in low- and middle-income countries (LMICs), where nearly 90% of children with cancer reside in areas with limited access to resources and great demand for services.[7–10] Although childhood cancer treatment in LMICs was found to be cost-effective yielding rewarding outcomes, yet the most important barrier to improved survival is the limited resources.[11]

Egypt has the second highest estimated number of incident childhood cancer cases in the WHO Eastern Mediterranean Region.[12] Yet, limited resources exist to accommodate the great need and demand for paediatric oncology services in Egypt. Therefore, there is a need to maximise the use of the available resources and funds to improve care and outcomes efficiently, as described in the Background Chapter 2 (section 2.5.3). However, childhood cancer resource use and costs data are lacking from the local context in Egypt, creating a gap in knowledge based on a systematic literature review of costs and cost-effectiveness of childhood cancer treatment in LMICs.[11]

In Chapter 3, I determined survival rates and trends in survival for children with cancer treated in a resource-limited setting in Egypt using real-world data and identified which cancers had inferior survival. In this chapter, I set out to estimate the hospital resources used and associated costs incurred during childhood cancer treatment in the local context of Egypt.

4.3 Aim of work

To determine childhood cancer hospital resource use and costs of care for children with cancer treated at the Children's cancer Hospital Egypt (CCHE) between 2013 and 2017.

4.4 Study Objectives

1. To determine patterns and trends of childhood cancer hospital resource use and costs.
2. To identify childhood cancer types with the highest resource use and costs (over time).
3. To study the factors associated with high resource use and high costs (cost drivers).
4. To provide evidence-based recommendations to better target the available resources and manage costs effectively.

4.5 Methods

This chapter was conducted following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist[13] (Appendix 4.1), and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist[14] (Appendix 4.2).

4.5.1 Population and setting

I included a retrospective cohort of 8,886 children with cancer (aged 0–18 years) who were newly diagnosed and received protocol treatment at CCHE between January 1st, 2013 and December 31st, 2017. Children with cancer were diagnosed and categorised according to the *International Classification of Childhood Cancer, 3rd edition* (ICCC-3)[15] (previously listed in Appendix 3.2) using ICD-O-3 data codes.[16] Patients diagnosed before the year 2013 were not included because CCHE had not yet implemented an electronic medical record (EMR) before that date, so the resource use and cost data were not easily accessible.

CCHE is a non-governmental organization (NGO) that was established and operates based solely on philanthropic donations and treats children with cancer free of charge.[17] The hospital diagnoses and treats an average of 2,000 new patients per year. It has 320 inpatient beds, day-care/single-day treatment unit serving around 300 patients daily, and outpatient clinics which serve 124,000 outpatient visits annually. CCHE provides up-to-date diagnostic services (clinical laboratory, surgical and molecular pathology, diagnostic imaging, and nuclear medicine), and comprehensive treatment services (chemotherapy, surgical oncology, neuro-surgery, orthopaedic surgery, bone marrow transplant (BMT), external beam radiation therapy, and radio-surgery using the Cyberknife).[17] Full scope of services at CCHE with latest technologies are available at (https://www.57357.org/en/departments-services/).

Children with cancer are treated based on CCHE standard treatment protocols adopted from international protocols (listed in Appendix 3.3) including: the Children's Oncology Group (COG) protocol for the majority of cancers, and the St. Jude Total XV protocol for Acute Lymphoblastic Leukaemia (ALL). All patients receive treatment with curative intent, except for osteosarcoma patients with initial bone metastasis, and diffuse intrinsic pontine glioma who only receive palliative care. Management of fever neutropenia follows the National Comprehensive Cancer Network (NCCN) guidelines; providing empirical combination of antibiotics, then de-escalation (rather than monotherapy and escalation) due to high rates of multi-drug resistance.

4.5.2 Data collection and validation

Patients' demographic and disease-related data were retrieved from the hospital-based cancer registry on *Research Electronic Data Capture* online platform.[18] Patients' resource use data were extracted from the electronic medical record '*Cerner*',[19] by retrieving all hospital encounters (resource use measures) determined by the episodes of care.[20] Resource use measures quantify the frequency by which specific resources are utilised in a healthcare setting (CCHE),[21] which included: numbers of inpatient days, hospital admissions, outpatient visits, laboratory tests, imaging tests, medications/drugs, surgery, radiotherapy, and supplies (as described in Table 4.1).

Patients' costs data were electronically captured from the readily available costing costing/billing database at *Oracle* system.[22] Cost categories/sub-categories included: investigation costs (laboratory tests and imaging tests); treatment costs (medications/drugs, surgeries, radiotherapy, supplies); personnel costs (medical and non-medical personnel); and overhead costs from central administrative departments and operations of inpatient/outpatient units. Definitions of cost categories/sub-categories are described in Table 4.1.

Patients' resource use and cost data were extracted for patients diagnosed between January 1st, 2013 and December 31st, 2017, until December 30th, 2019 in order to be able to calculate patients' costs during the first one- and three-years post-diagnosis (explained in section 4.5.3).

Data validation and quality checks were done by the clinical informatics team, and the finance department who extracted and validated the data at the time of study initiation. Resource use and cost data were validated at the time of data extraction by matching medication chart audits with the costing/billing data, with a 96.5% concordance between records.

Approval for data release was granted by the Scientific Medical Advisory Committee (SMAC) at CCHE. Ethics approval was not required by the institutional review board (IRB), as this study involves secondary use of routinely collected data with de-identified patients' records.

Table 4.1. Description of resource use measures and cost categories/sub-categories, definitions and methods of measurement/allocation

Variable/sub-variable	Definition	How it is measured/allocated?
Resource use measures		
Inpatient days	Total duration of inpatient hospital stays (in days) during the first 1- and 3 years post-diagnosis.	Duration of total in-hospital stay (in days), as retrieved from the EMR.
Inpatient admissions	Total number of inpatient hospital admissions to the inpatient units (wards, paediatric ICU, BMT, surgical unit).	Number of admission encounters to inpatient department, as retrieved from the EMR.
Outpatient visits	Total number of visits to outpatient department including: day-care visits (single-day treatment unit), paediatric oncology clinics, multi-specialty clinics, and ED visits.	Number of encounter visits to outpatient department, as retrieved from the EMR.
Total encounters	Total number of encounters including inpatient admissions and outpatient visits.	Sum of inpatient and outpatient encounters, as retrieved from the EMR.
Investigations - Laboratory tests	-Total number of tests done in the medical laboratory and pathology units.	Number of laboratory/pathology tests per patient, as retrieved from the EMR.
- Imaging tests	-Total number of imaging tests done in radiology (x-ray, CT, MRI, ultrasound) and nuclear medicine (PET-CT).	Number of imaging tests (in radiology and nuclear medicine units), as retrieved from EMR.
Treatment interventions - Medications (Drugs)	Total number of drug doses combined and categorized as: - Chemotherapy; or - Supportive care drugs (IV/oral) ^	Number of drug doses combined, and separated as either chemotherapy or supportive drugs, as retrieved from the EMR, per patient.
- Surgery	Total number of surgeries and surgical procedures.	Number of surgeries/surgical procedures, as retrieved from the EMR.
- Radiotherapy	Total number of radiotherapy sessions.	Number of radiotherapy sessions (per patient), as retrieved from the EMR.
- Supplies	Total number of medical supplies (syringes, cannulas, needles, etc.) consumed by the patient during treatment in the inpatient units and the day-care 'single-day treatment unit' in the outpatient department.	Number of medical supplies consumed per patient, as retrieved from the EMR.
Cost Categories		
Personnel costs - Medical [a] - Non-medical [b]	Include costs (salaries) of all medical personnel directly related to patient care, and non-medical personnel providing administrative and managerial functions. Full salaries are included in personnel costs, as all medical and non-medical personnel are 100% full-time dedicated to paediatric oncology care at CCHE.	Personnel costs are allocated to patients by dividing total personnel costs for each unit by these allocation keys (per month): number of patients (inpatient units); number of visits (outpatient units); number of surgeries (surgery unit); number of radiotherapy sessions (radiotherapy unit); number of lab tests (lab unit); number of imaging tests (imaging unit).
Investigation costs: Laboratory costs	Costs of all laboratory and pathology tests including costs of materials (kits, reagents, others), facilities (electricity, water, gas),	Cost data of all laboratory/pathology tests per patient, as captured from the costing database/Oracle.

	and maintenance/depreciation of equipment in the lab unit.	
Investigation costs: Imaging costs	Costs of all imaging tests including costs of materials (contrast, FDG, anaesthesia), facilities (mentioned above), and maintenance/depreciation of equipment in the radiology/nuclear medicine units.	Cost data of all imaging tests per patient, as captured from the costing database/Oracle.
Treatment cost: Medications/drugs costs	Costs of all medications/drugs including both chemotherapy and supportive care drugs. ^	Cost data of all medications/drugs, per patient, as captured from the costing database/Oracle.
Treatment cost: Surgery costs	Costs of surgery incurred in the operating room (OR) including materials, drugs/anaesthesia, facilities (mentioned above), and maintenance/depreciation of equipment in the surgery unit.	Cost data of surgery and/or radiotherapy, per patient as captured from the costing database/Oracle. Costs of drugs, materials, anaesthesia are directly allocated to the patient, and other costs are estimated for the whole department/unit, then a proportion is allocated to patient based on: - Type of surgery (major/minor) - Number of radiotherapy sessions/month
Treatment cost: Radiotherapy costs	Costs of radiotherapy sessions including materials, drugs/anaesthesia, facilities (mentioned above), and maintenance/depreciation of equipment in the unit.	
Treatment cost: Supplies costs	Costs of medical supplies consumed by the patient during treatment in the inpatient or outpatient units.	Costs of supplies directly consumed by patient, as captured from costing database/Oracle.
Overhead costs	Costs that are not directly related to patient care and costs of operations of the inpatient and outpatient departments (that are not incurred in any of the above-mentioned cost categories): 1. Total costs of central administrative departments [c] 2. Operational costs in the inpatient and outpatient units including: facilities (electricity, water, gas), space cost, and maintenance/depreciation costs for the inpatient and outpatient departments. [Treatment costs in the inpatient/outpatient units are included under the various treatment categories headings].	1. Total costs of central administrative departments are allocated to inpatient and outpatient units, based on flat rate (distributed equally among each unit), then allocated to the patient based on number of patients (inpatient units) and number of visits (outpatient units). 2. Total overhead costs (assigned to inpatient and outpatient units from administrative departments and those estimated from operations of inpatient/outpatient) are then allocated to the patient based on number of patients (inpatient units) and the number of visits (outpatient units).

^ Supportive care drugs include: antibiotics, antifungals, anti-emetics, nutritional products, and all drugs other than chemotherapy. [a] Medical personnel costs include: paediatric oncologists, radiation oncologists, clinical pharmacists, nurses, oncology surgeons, neuro-surgeons, orthopaedic surgeons, physicians in multi-specialty outpatient clinics, intensivists, anaesthesiologists, pathologists, laboratory and imaging consultants and technicians. [b] Non-medical personnel include departmental secretaries, data entry specialists, and administrative managers for the inpatient, outpatient, pharmacy, laboratory, pathology, imaging, surgery, and radiotherapy departments. [c] Includes total costs (salaries, non-medical materials, facilities) for the central administrative departments which serve the whole hospital and are not directly related to patient care, including finance, Information Technology (IT), Human Resources (HR), purchasing, biomedical engineering, quality, research, catering, security, housekeeping, laundry, learning & development departments. Abbreviations: EMR: Electronic Medical Record; BMT: Bone Marrow Transplant; ED: Emergency Department; OR: Operating Room.

4.5.3 Costing approach

I estimated childhood cancer costs from the healthcare provider perspective, based on the available hospital costs data. The costing system at CCHE depends on dividing the hospital into cost centres (departments/units), where costs were captured and/or allocated (as outlined in Table 4.1) as follows: personnel costs (medical and non-medical) for the unit/department were divided by pre-defined allocation keys, and a proportion was allocated to the patient; costs of drugs and supplies were directly allocated to the patient on the EMR/costing systems; costs of laboratory, imaging, surgery and radiotherapy services were calculated by the finance/costing team, updated on the EMR/costing systems, then assigned to the patient; overhead costs include total costs of administrative departments (allocated to inpatient/outpatient units based on a flat rate, then a proportion was assigned to the patient) and the operational costs of inpatient/outpatient units. Overhead costs were then allocated to the patient based on number of patients (inpatient units) and number of visits (outpatient units). At CCHE costs are exactly equal to hospital charges as it is a not-for-profit organization that does not earn a surplus by charging patients at higher prices.[23] Therefore, the extracted data from the costing/billing database provided actual costs.

I estimated incidence costs to provide the costs of care (treatment costs) of newly diagnosed childhood cancers.[24] Resource use measures and costs were estimated at one- and three-years post diagnosis (i.e., during the first one year, and the first three years from the date of diagnosis) to cover the whole treatment duration. This is because all children with cancer complete their protocol treatment within the first-year post-diagnosis, except for children with ALL whose treatment protocol extends up to three years. Costs (and resource use) data were only extracted until December 31st, 2019. Therefore, on estimating the 3-year costs (and resource use measures)

for patients diagnosed in 2017, I accounted for the rather incomplete 3-year costs/resource use measures by adding adjusted weights from previous years for each childhood cancer type.

Cost adjustments were done as per Turner *et al.* (2019) to adjust for costs obtained at different time periods (between 2013 and 2017).[25] First, I converted costs from local currency in Egyptian Pounds (EGP) to US dollars (USD) using the World Bank official exchange rate,[26] and then inflated using US inflation rates to the reference year (2019) based on the World Bank GDP deflator.[27,28] Cost outcomes were expressed in USD.

4.5.4 Statistical analysis

I analysed and reported median (Interquartile Range, IQR) values of resource use and costs (at 1- and 3- years post-diagnosis) as the main descriptive statistics due to non-normality of data, stratified by cancer type. Mean (± Standard Deviation, SD) costs were reported as a secondary measure. Trends in resource use and costs were examined using linear regression, with 'year of diagnosis' as the independent variable. I log-transformed costs and resource use variables, to adjust for the positively skewed nature of the data. Trends were considered significant if $p<0.05$.

I determined what contributes to long duration of inpatient-stays and high total costs using univariate and multivariate OLS (Ordinary Least Squares) linear regression, adjusting for age, gender, cancer type, survival and relapse status, and paediatric intensive care unit (PICU) admission during first year post-diagnosis. I also estimated how resource use measures contribute to total costs for the main cancer types using multivariate analysis. I standardized the regression coefficients by scaling the independent variables (dividing by their standard deviation). All statistical analyses were performed in *R* statistical package version 4.0.2.[29]

4.6 Results

4.6.1 Patient characteristics

I analysed resource use and cost data for 8,886 children with cancer who presented at CCHE between 2013–2017. Table 4.2 shows the patient- and disease-related characteristics, where the mean age at diagnosis was 6.4 years (SD ±4.7), and the male to female ratio was 1.4:1. The main childhood cancer types were distributed as follows: 26.5% had leukaemia, 15.2% had lymphomas, 18.6% had CNS/brain tumours, and 39.7% had other solid tumours.

At the end of the first-year post-diagnosis, 7,668 patients (86.3%) were alive, 934 patients (10.5%) relapsed, and 36 patients (0.4%) lost follow-up and abandoned treatment. Age-group distribution by cancer types is presented in Appendix 4.3, showing that 45% of leukaemia patients were within the 0–5 years age-group.

Table 4.2. Patient-related and disease-related characteristics at CCHE/Egypt, (N=8,886)

	No. of patients	**Percent (%)**
Age (y) at diagnosis		
Mean ± SD Median (IQR)	6.4 (± 4.7) years 5.1 (2.5–9.7) years	
Age-groups		
0–4 years	4,319	48.2%
5–9 years	2,444	27.5%
10–14 years	1,518	17.5%
15–18 years	605	6.8%
Gender		
Male	5,151	58%
Female	3,735	42%
Malignancy type		
Haematology	3,701	41.6%
Solid tumours	5,185	58.4%
Main diagnosis subtypes		
Leukaemia	2,357	26.5%
Lymphoma	1,344	15.2%
CNS tumours	1,659	18.6%
Other solid tumours	3,526	39.7%
Number of patients, by year of diagnosis		
Year 2013	1,395	15.7%
Year 2014	1,678	18.9%
Year 2015	1,822	20.5%
Year 2016	1,872	21.1%
Year 2017	2,119	23.8%
Survival status*		
Alive	7,668	86.3%
Died	1,182	13.3%
Lost follow-up**	36	0.4%
Relapse status*		
Yes	934	10.5%
No	7,732	89.5%

***** Survival and relapse status were determined at the end of first year post-diagnosis. ****** Patients who lost follow-up are those who did not show for treatment for at least 3 months, and were not reachable through contact by phone.

4.6.2 Hospital resource use

4.6.2.1 Resource use patterns

Table 4.3 shows the main resource use measures at 1-year post-diagnosis categorised by ICCC-3 groups. The longest median inpatient-days (length of inpatient-stays) were noted in patients with acute myeloid leukaemia (AML) at 110 days (IQR: 90–130), myelodysplastic syndrome (MDS) at 93 days (IQR: 59–110), and osteosarcoma at 65 days (IQR: 50–78) days. These cancers also had the longest inpatient-days at 3-years post-diagnosis (Appendix 4.4). Patients with osteosarcoma, neuroblastoma and hepatoblastoma had the highest number of inpatient admissions at 1-year post-diagnosis with a median of 16 (IQR: 12–18), 10 (IQR: 4–14), and 10 (IQR: 7–13), respectively (Table 4.3).

During the first-year post-diagnosis, patients with leukaemia had the highest in-patient hospitalization rate (98%), while patients with lymphoma were least admitted to the hospital. Highest PICU admission rates were observed for patients with brain/CNS tumours (61.8%) (Table 4.4).

Table 4.3. Main resource use measures at 1-year post diagnosis, by ICCC-3 groups (N=8 886)

ICCC-3 groups	Median (IQR)					
	Inpatient days	**No. of All encounters [a]**	**No. of Inpatient admissions**	**No. of Outpatient visits**	**No. of Investigations [b]**	**No. of Treatment Interventions [c]**
All cancers combined *	38 (17–	51 (32–70)	6 (3–9)	45 (29–62)	517 (177–879)	1941 (743–3045)
I. Leukaemia and related cancers	51 (37–75)	88 (69–111)	6 (4–8)	84 (61–105)	942 (784–1,242)	2,899 (2,262–3,925)
Ia. Acute Lymphoblastic Leukaemia	46 (36–58)	70 (58–79)	6 (4–8)	63 (53–72)	890 (781–1069)	2707 (2228–3460)
Ib. Acute Myeloid Leukaemia	110 (90–	33 (25–41)	7 (5–9)	25 (18–33)	1360 (1101–	4186 (3029–5708)
Ic. Chronic Myeloid Leukaemia	25 (11–39)	28 (20–36)	2 (1–2)	28 (20–35)	173 (142–546)	176 (107–1411)
Id. Myelodysplastic Syndrome	93 (59–110)	44 (34–55)	6 (4–8)	37 (31–49)	1373 (1077–	3594 (2699–4345)
Ie. JMML	46 (28–72)	45 (36–52)	4 (3–8)	39 (33–48)	1068 (539–1442)	2793 (1194–4819)
II. Lymphomas	44 (25–62)	36 (30–47)	7 (4–9)	34 (27–43)	234 (137–755)	704 (297–2444)
IIa. Hodgkin's lymphoma	5 (3–14)	35 (30–42)	2 (1–3)	35 (30–41)	141 (120–171)	311 (241–446)
IIb. Non-Hodgkin lymphoma	48 (37–66)	41 (31–64)	7 (6–10)	33 (24–51)	763 (564–1067)	2447 (1746–3500)
IIIa-e CNS and Brain Tumours	19 (9–34)	40 (21–69)	3 (2–6)	36 (19–63)	208 (83–415)	1193 (623–2140)
IV-XII. Other solid tumours	30 (11-57)	54 (37- 70)	6 (2-12)	47 (34-61)	400 (183-707)	1,583 (696 –
IVa. Neuroblastoma**	49 (23–69)	60 (43–72)	10 (4–14)	50 (37–59)	751 (410–1023)	2706 (1546–3766)
V. Retinoblastoma	7 (3–25)	36 (29–43)	2 (1–6)	35 (29–43)	118 (80–182)	516(368–760)
VI. Renal Tumours	13 (8–28)	45 (36–56)	2 (1–5)	43 (34–52)	238 (158–449)	1060 (702–1942)
VIIa. Hepatoblastoma	34 (24–50)	61 (51–70)	10 (7–13)	51 (41–60)	518 (427–714)	1798 (1431–2609)
VIII. Malignant Bone Tumours	45 (17-67)	70 (60-84)	10 (4-16)	62 (48- 3)	553 (408 -714)	2,373 (1,643 -
VIIIa. Osteosarcoma	65 (50-78)	67 (57-82)	16 (12-18)	52 (44-65)	631 (497-755)	2927 (2307–3581)
VIIIb. Ewing Sarcoma	19 (9-41)	73 (64-85)	5 (2-9)	69 (59-79)	481 (366-649)	1894 (1431–2448)
IX. Soft tissue/extra-osseous sarcoma	30 (11–54)	42 (24- 53)	6 (2-10)	35 (22-45)	324 (114-542)	1,315 (596-2,457)
IXa. Rhabdomyosarcoma	15 (7–26)	71 (62–80)	3 (2–6)	68 (59–76)	381 (276–533)	1551 (912–2222)
IXb-d. Other soft tissue tumours	30 (11–54)	43 (24–53)	6 (2–10)	35 (22–45)	324 (114–542)	1315 (596–2457)
XI. Germ Cell Tumours	34 (13–51)	31 (18–40)	6 (3–8)	25 (16–33)	338 (141–606)	1285 (497–2180)
XII. Langerhans's cell	6 (2–8)	47 (30–57)	1 (1–3)	46 (26–57)	181 (129–233)	459 (287–651)

[a] All encounters include sum of the total number of inpatient admissions and outpatient visits. [b] Investigations include laboratory tests and radiology tests. [c] Treatment interventions include total number of drug doses, radiotherapy sessions, surgeries, and medical supplies. * For all cancers combined, only the primary tumours were included based on ICCC-3 diagnostic groups excluding (Ia.1.) Precursor cell leukaemia – aged <1); (I.e.) Unspecified and other specified leukaemia; (VII.b.) Hepatic carcinomas; (XI.) Other malignant epithelial neoplasms and malignant melanomas. ** IVa. Neuroblastoma includes Neuroblastoma and ganglioneuroblastoma. *** XII includes Langerhans's cell histiocytosis (LCH) only.

Table 4.4. In-patient hospital admission, PICU admission, and BMT rates, by 4 main childhood cancer types, during the first-year post-diagnosis (N=8,886)

	Number of patients (%)
Inpatient admission (hospitalization rate) *	
All cancers combined	
Leukaemia	2310/2357 (98%)
Lymphoma	736/1344 (54.7%)
Brain tumours	1421/1652 (86%)
Other solid tumours	2857/3533 (80.8%)
PICU admission rate**	
All cancers combined	3,564/5322 (40.1%)
Leukaemia	928/2357 (39.3%)
Lymphoma	368/1344 (27.3%)
Brain tumours	1022/1652 (61.8%)
Other solid tumours	1252/3533 (35.3%)
BMT***	
All cancers combined	103/8,886 (1.2%)
Leukaemia	74/2357 (3.1%)
Lymphoma	5/1344 (0.37%)
Brain tumours	*NA*
Other solid tumours	24/3533 (0.67%)

*Patients who have been admitted to inpatient department at least once during first year post-diagnosis, from total patients per caner type.**Patients who used the PICU at least once during first year post-diagnosis, from total patients per caner type. *** Patients who have undergone BMT by diagnosis; Leukaemia patients include ALL (n=8), AML (n=32), CML (n=10), MDS (n=8), and JMML (n=16); Lymphoma patients include Hodgkin lymphoma (n=3) and non-Hodgkin lymphoma (n=2); Other solid tumours patients include high-risk neuroblastoma (n=21), retinoblastoma (n=2), germ cell tumours (n=1). Abbreviations: PICU: Paediatric Intensive Care Unit; BMT: Bone Marrow Transplantation; *NA*: not applicable.

Resource use measures for all investigations and treatment interventions at 1-year post-diagnosis are outlined in Table 4.5. Patients with AML had the highest number of laboratory tests (median: 1,356; IQR: 1,071–1,675) and intravenous (IV) supportive drugs (median: 1,719; IQR: 1,116–2,433). While, patients with osteosarcoma had the largest numbers of imaging tests (median: 40; IQR: 32–48).

At 3-years post-diagnosis, patients with ALL received the highest number of chemotherapy doses (median: 282; IQR: 237–331), while patients with MDS had the highest number of laboratory tests (median: 1,912; IQR: 1,309–2,327) and IV supportive drugs (median: 1,134; IQR: 942–1,567). Resource use measures for all investigations and treatment interventions at 3-years post-diagnosis are presented in Appendix 4.5.

Table 4.5. Resource use measures of investigations and treatment interventions at 1-year post diagnosis, (N=8,886)

	Median (IQR)						
	Investigations		Treatment (interventions)				
	No. of Lab tests	No. of Imaging tests	No. of total Drug doses	No. of Chemotherapy doses	No. of Supportive IV drugs doses	No. of Surgeries	No. of Supplies^
All childhood cancers combined*	506 (172 – 869)	17 (12-25)	789 (278 – 1357)	124 (50 – 176)	414 (129–756)	2 (1 – 3)	10782–1678)
I. Leukaemia and related cancers	935 (780–1227)	18 (13-28)	1317 (989–1824)	165 (138–190)	645 (452 – 945)	--	1544 (1186–2112)
Ia. Acute Lymphoblastic Leukaemia	883 (775-1058)	16 (12-21)	1252 (984-1627)	162 (140 – 185)	1092 (834 – 1445)	1 (1-2)	1440 (1164-1818)
Ib. Acute Myeloid Leukaemia	1356 (1071-1675)	34 (28-43)	1900 (1279-2622)	178 (136 – 206)	1719 (1116 – 2433)	2 (1-2)	2294 (1590-3062)
Ic. Chronic Myeloid Leukaemia	173 (138-546)	3 (3-6)	106 (67-608)	81 (56 – 115)	808 (416 – 1156)	1 (1-2)	87 (34-894)
Id. Myelodysplastic Syndrome	1365 (1070-1613)	29 (24-35)	1493 (1152-1777)	158 (94 – 194)	1461 (1042 – 1634)	2 (2-3)	2184 (1596-2737)
Ie. JMML	1046 (538-1442)	22 (12-30)	1045 (451-1588)	120 (74 – 196)	902 (386 – 1501)	2 (2-3)	1796 (879-3034)
III. Lymphomas	232 (132–745)	14 (10–19)	345 (143–1142)	67 (45–150)	112 (19–618)	--	362 (151–1264)
IIa. Hodgkin's lymphoma	135 (116-166)	11 (9-14)	150 (112-220)	50 (40 – 60)	100 (65 – 170)	1 (1-1)	162 (114-226)
IIb. Non-Hodgkin lymphoma	745 (408-1004)	19 (14-24)	1149 (775-1633)	151 (120 – 192)	1006 (655 – 1452)	1 (1-2)	1260 (851-1864)
IIIa-e CNS and Brain Tumours	204 (76-407)	15 (11-21)	424 (218-803)	56 (7 – 89)	492 (252 – 912)	2 (1-3)	778 (382-1340)
IV-XII. Other solid tumours	391 (181-696)	1 (1-1)	612 (249-1,191)	112 (42-182)	296 (95-690)	2 (1-3)	914 (435 – 1,568)
IVa. Neuroblastoma**	745 (408-1004)	23 (18-29)	1116 (592-1568)	170 (124 – 228)	981 (566 – 1406)	1 (1-2)	1488 (862-2140)
V. Retinoblastoma	116 (79-182)	4 (3-5)	157 (108-245)	40 (35 – 46)	132 (83 – 222)	1 (1-2)	349 (222-530)
VI. Renal Tumours	230 (153-446)	17 (13-21)	394 (226-741)	35 (30 – 145)	344 (202 – 631)	1 (1-1)	642 (441-1203)
VIIa. Hepatoblastoma	502 (412-682)	31 (27-36)	633 (458-920)	81 (64 – 96)	542 (369 – 836)	1 (1-2)	1254 (914-1678)
VIII. Malignant Bone Tumours	535 (397-697)	33 (25 – 41)	980 (639 – 1,434)	179 (106 – 215)	514 (278 – 927)	2 (1-3)	1,302 (939–1,733)
VIIIa. Osteosarcoma	619 (479 – 726)	40 (32–48)	1340 (960 – 1739)	108 (69 – 153)	1220 (877 – 1632)	2 (2 -4)	1513 (1133-1909)
VIIIb. Ewing Sarcoma	459 (353 – 628)	29 (24 – 35)	704 (560 – 996)	212 (188 – 235)	495 (342 – 755)	2 (1-2)	1131 (816-1452)
IX. Soft tissue/extra-osseous sarcoma	314 (107 – 540)	17 (13–21)	490 (214 – 802)	116 (61 – 166)	275 (140 – 448)	2 (1-2)	848 (402 – 1,572)
IXa. Rhabdomyosarcoma	374 (266-528)	19 (16-23)	702 (355-1118)	108 (89 – 125)	579 (251 – 1001)	1 (1-2)	747 (487-1153)
IXb-d. Other soft tissue tumours	314 (107-540)	17 (13-21)	490 (214-802)	116 (62 – 166)	508 (291 – 786)	2 (1-2)	848 (402-1572)
XI. Germ Cell Tumours	325 (131-586)	17 (12-24)	538 (177-900)	148 (70 – 208)	516 (269 – 812)	1 (1-2)	750 (320-1292)
XII. Langerhans cell histiocytosis***	174 (120-218)	16 (11-20)	198 (122-312)	22 (18 – 32)	212 (143 – 318)	1 (1-1)	231 (152-369)

***** For all cancers combined, only the primary tumours were included based on ICCC-3 diagnostic groups excluding (Ia.1.) Precursor cell leukaemia – aged <1); (I.e.) Unspecified and other specified leukaemia; (VII.b.) Hepatic carcinomas; (XI.) Other malignant epithelial neoplasms and malignant melanomas. ** IVa. Neuroblastoma includes Neuroblastoma and ganglioneuroblastoma. *** XII includes Langerhans's cell histiocytosis (LCH) only. ^Supplies include total number of medical supplies (syringes, cannulas, needles, etc.) consumed per patient during treatment.

4.6.2.2 Trends in resource use over time

Trends in 1-year resource use over time for each childhood cancer type are presented in Figure 4.1, and described in details in Appendix 4.6. Trends in 1-year resource use showed that the use of IV supportive drugs increased significantly over time for the majority of solid tumours by 24.3% ($p<0.001$), and this increase was greatest (>30%) for patients with retinoblastoma, renal tumours and hepatoblastoma ($p<0.001$). Whereas, trends in oral supportive care use significantly decreased over time for children with ALL (by 21%), brain/CNS tumours (by 28%), and rhabdomyosarcoma (by 23%). Patients with Hodgkin lymphoma showed significantly decreasing trend in inpatient days (length of hospital stay) by 23% ($p=0.001$), whereas, inpatient days (length of hospital stay) significantly increased for patients with Hepatoblastoma (by 12%) and Ewing sarcoma (by 10%).

Childhood cancer type (No. of patients)	Inpatient days	Inpatient admissions	Outpatient visits	ED visits	Laboratory tests	Chemotherapy doses	IV supportive	Oral supportive	Supplies	Surgery
Acute Lymphoid Leukemia (n=1660)	- 4%*	- 5%*	+ 14%*	+ 5%*	- 0.1%	-0.3%	+ 9%*	- 21%*	- 11%*	X
Acute Myeloid Leukemia (n=544)	+ 7%*	- 2%*	- 15%*	- 7%*	+ 3%*	+ 2%	+ 3%	- 12%*	- 13%*	X
Chronic Myeloid Leukemia (n=77)	- 16%	+ 12%	- 6%	-6 %	- 9%	- 6%	+ 16%	+ 19%	- 28%*	X
Myelodysplastic Syndrome (n=28)	+ 9%	+ 10%	+ 17%*	+ 22%	+ 10%	- 3%	+ 17%	- 3%	- 0.1%	X
Juvenile myelomonocytic Leukemia (n=48)	+ 5%	+ 3%	+ 12%	+ 8%	+ 11%	+ 8%	+ 10%	- 3%	- 8%	X
Hodgkin lymphoma (n=709)	- 23%*	- 8%*	- 18%	+ 0.1%	- 1%	+ 12%*	+ 6%	-39%	- 3%	X
Non-Hodgkin lymphoma (n=635)	- 1%	+ 2%	+ 17%	+ 5%*	+ 5%	+ 1%	+ 10%*	- 13%*	- 12%*	X
Brain and CNS tumors (n=1659)	- 2%	- 0.4%	- 17%*	+ 3%*	- 4%*	- 15%	+ 10%*	- 28%*	- 12%*	- 1.7%
Neuroblastoma (n=967)	+ 4%	+ 4%	-25%	+ 3%*	+ 0.8%	- 6%*	+ 21%*	- 12%*	- 7%*	- 0.5%
Retinoblastoma (n=523)	- 7%	- 6%	- 15%*	+ 3%	- 4%	- 2%	+ 31%*	- 19%	- 18%*	+ 3%*
Renal tumours (n=521)	+ 5%*	+ 6%*	+ 13%	+ 6%*	+ 7%*	- 2%	+ 30%*	- 13%*	- 4%*	+ 2%
Hepatoblastoma (n=122)	+ 12%*	+ 13%*	+ 23%*	+17%*	+ 8%*	+ 2%	+ 32%*	- 4%	+ 3%	+ 3%
Osteosarcoma (n=305)	- 4%	- 3%	- 26%*	+ 8%*	- 1%	- 16%*	+ 8%*	+ 6%	- 9%*	+ 5%*
Ewing sarcoma (n=297)	+ 10%*	+ 11%*	+ 17%	+ 7%*	+ 6%*	- 3%*	+ 27%*	- 3%	- 5%*	+ 8%*
Rhabdomyosarcoma (n=317)	+ 1%	+ 2%	- 25%	+ 7%*	+ 4%	+ 9%*	+ 27%*	- 23%*	- 7%*	+ 2%
Other soft tissue tumors (n= 127)	- 10%	- 14%*	- 16%*	- 1%	- 19%*	- 13%	+ 11%	- 7%	- 23%*	+ 0.7%
Germ cell tumors (n=150)	- 5%	- 8%	+ 21%	+ 3%	- 7%	- 17%*	+ 15%*	- 13%	- 11%*	+ 0.1%
Langerhans cell histocytosis (n=197)	- 11%	- 4%	- 10%	+ 5%	- 4%	- 8%*	+ 27%*	- 46%*	- 10%*	- 0.2%

Decreasing trend (statistically significant)

Greatly decreasing trend, >20% decrease (statistically significant)

*** Statistically significant at $p<0.05$**

Increasing trend (statistically significant)

Greatly increasing trend, >20% increase (statistically significant)

Increasing or decreasing trend, not statistically significant

Figure 4.1. Trends in resource use over time at one-year post-diagnosis, per ICCC-3 groups

4.6.2.3 Factors associated with resource use

Table 4.6 shows the factors associated with resource use by univariate and multivariate regression analysis. On univariate analysis, longer duration of inpatient-days (length of hospital stay) was associated with older age at diagnosis (p=0.002), male gender (p=0.009), and PICU admission during first year post-diagnosis (p<0.001). Whereas, on multivariate analysis, independent predictors of inpatient-days included older age at diagnosis, leukaemia type, patients who survive/relapse, or had PICU admissions (p<0.001).

Table 4.6. Factors associated with length of inpatient stay (in weeks) during first year post-diagnosis, using univariate and multi-variate analysis (N=8,886)

	Univariate analysis			**Multi-variate analysis**		
	Coefficient (95% CI)	***p*-value***	**Overall *p*-value***	**Coefficient (95% CI)**	***p*-value***	**Overall *p*-value***
Age at diagnosis						Overall *p*-value of the multivariate model is <0.0001*
0–4 years	Ref. group	Ref. group		Ref. group	Ref. group	
5–9 years	2.6% (-3.1–8.2%)	0.367	0.002*	4.1% (-0.9–9.1%)	0.108	
10–14 years	9.8% (3.1–16.5%)	0.004*		8.7% (2.9–14.5%)	0.003*	
15–18 years	14.3% (4.6–24.1%)	0.003*		12.5% (4.2–20.9%)	0.003*	
Gender						
Female	Ref. group	Ref. group	0.009*	Ref. group	Ref. group	
Male	6.3% (1.5–11.1%)	0.009*		1.3% (-2.7–5.5%)	0.511	
Main childhood cancer types						
Brain Tumours	Ref. group	Ref. group	<0.0001*	Ref. group	Ref. group	
Leukaemia	116% (110–225%)	<0.0001*		142% (135–148%)	<0.0001*	
Lymphoma	62% (53.8–70.5%)	<0.0001*		80.5% (72.4–88.6%)	<0.0001*	
Solid Tumours	36% (30.7–42.7%)	<0.0001*		60.6% (54.5–66.6%)	<0.0001*	
Survival status						
Alive	Ref. group	Ref. group	0.939	Ref. group	Ref. group	
Died	0.7% (-0.5–7.1%)	0.819		-6.1% (-12.0– -0.2%)	0.041*	
Lost FU	-5.7% (-48–36.7%)	0.792		-10.5% (-46.9–25.8%)	0.568	
Relapse status						
No	Ref. group	Ref. group	0.859	Ref. group	Ref. group	
Yes	-0.6% (-0.8–6.7%)	0.86		27.6% (20.7–34.5%)	<0.0001*	
PICU admission						
No	Ref. group	Ref. group	<0.0001*	Ref. group	Ref. group	
Yes	44% (39.5–48.8%)	<0.0001*		63.4% (59.1–67.6%)	<0.0001*	

**p*-value obtained from OLS linear regression model using univariate and multi-variate analysis. Statistically significance at p<0.05.
Abbreviations: FU: Follow-up; PICU: Paediatric Intensive Care Unit.

4.6.3 Costs of childhood cancer care

4.5.3.1 Cost patterns

Median total costs for all childhood cancers combined [2013–2017] were $14,774 (IQR: $6,559–$23,738) at 1 year and $19,799 (IQR: $8,921–$34,204) at 3 years post-diagnosis. Highest median total costs were noted for children with AML, MDS, osteosarcoma and ALL (Table 4.7). These cancers also showed the highest mean (±SD) costs as shown in Appendix 4.7. Lowest costs were estimated for children with Hodgkin lymphoma, and retinoblastoma at 1- and 3-years post-diagnosis.

Total cost of all children with cancer (n=8,886) incurred during first year post-diagnosis [2013–2017] was $152,453,412; where personnel costs represented 36.3%; costs of treatment interventions (drugs, surgery/radiotherapy, supplies) represented 27.8%; investigation costs (laboratory and imaging tests) represented 8.8%, while overhead costs represented 27.4% (Appendix 4.8).

Table 4.7. Median total costs (in USD) for childhood cancers at 1 -and 3- years post-diagnosis, by ICCC-3 diagnostic groups (N=8,886)

ICCC-3 diagnostic groups	No. of patients (%)	Median Cost (IQR) in USD	
		1-year post-diagnosis	3 years post-diagnosis
All cancers combined *	N=8,886	$14,774 (6,559–23,738)	$19,799 (8,921–34,204)
I. Leukaemia and related cancers	2,357 (26.5%)	$23,736 (17,872 – 32,855)	$35,185 (25,604 – 47,445)
Ia. Acute Lymphoblastic Leukaemia	1,660 (18.7%)	$22,209 (17,635 – 28,080)	$33,043 (25,270 – 43,201)
Ib. Acute Myeloid Leukaemia	544 (6.1%)	$36,761 (26,511 – 48,567)	$43,309 (31,201 – 59,997)
Ic. Chronic Myeloid Leukaemia	77 (0.9%)	$10,863 (6,291 – 16,615)	$27,790 (14,149 – 47,499)
Id. Myelodysplastic Syndrome	28 (0.3%)	$31,503 (23,427 – 41,416)	$45,618 (29,012 – 55,227)
Ie. Juvenile myelomonocytic leukaemia	48 (0.5%)	$20,295 (13,305 – 28,084)	$31,055 (21,404 – 43,632)
II. Lymphomas	1,344 (15.1%)	$7,542 (4,365 – 18,513)	$10,803 (5,698 – 23,595)
IIa. Hodgkin's lymphoma	709 (8.0%)	$4,474 (3,712 – 5,617)	$5,960 (4,925 – 7,513)
IIb. Non-Hodgkin’s lymphoma	635 (7.1%)	$18,516 (13,211 – 26,209)	$21,509 (15,037 – 34,167)
III. Brain Tumours	1,659 (18.7%)	$8,534 (4,504 – 14,286)	$12,607 (6,469 – 19,726)
IV-X. Other solid tumours	3,526 (39.6%	$12,601 (6,403 – 20,907)	$16,882 (8,555 – 30,385)
IVa. Neuroblastoma**	967 (10.9%)	$19,994 (11,456 – 27,337)	$25,459 (14,479 – 38,746)
V. Retinoblastoma	523 (5.9%)	$5,221 (3,839 – 6,951)	$7,433 (5,476 – 9,647)
VI. Renal Tumours	521 (5.9%)	$8,224 (5,622 – 13,084)	$10,357 (7,599 – 19,177)
VIIa. Hepatoblastoma	122 (1.4%)	$13,024 (9,915 – 17,715)	$17,477 (13,106 – 21,760)
VIII. Malignant bone tumours	602 (6.7%)	$22,272 (16,995 – 27,816)	$30,277 (23,061 – 39,745)
VIIIa. Osteosarcoma	305 (3.4%)	$24,279 (17,155 – 30,969)	$34,519 (22,761 – 42,897)
VIIIb. Ewing sarcoma	297 (3.3%)	$20,327 (16,874 – 24,717)	$28,398 (23,203 – 35,881)
IX. Soft tissue/extra osseous sarcoma	444 (4.9%)	$11,989 (8,569 – 16,599)	$16,401 (11,320 – 24,012)
IXa. Rhabdomyosarcoma	317 (3.6%)	$11,913 (8,974 – 15,597)	$16,607 (12,137 – 23,946)
IXb-d. Other soft tissue tumours	127 (1.4%)	$12,366 (5,405 – 17,952)	$14,829 (6,646 – 25,538)
Xa-c. Germ Cell Tumours	150 (1.7%)	$9,768 (3,820 – 15,695)	$11,984 (5,136 – 18,348)
XII. LCH***	197 (1.2%)	$5,804 (3,788 – 7,389)	$7,821 (4,711 – 11,304)

***** For all cancers combined, only the primary tumours were included based on ICCC-3 diagnostic groups excluding (Ia.1.) Precursor cell leukaemia – aged <1); (I.e.) Unspecified and other specified leukaemia; (VII.b.) Hepatic carcinomas; (XI.) Other malignant epithelial neoplasms and malignant melanomas. ** IVa. Neuroblastoma includes ganglioneuroblastoma. *** XII includes LCH (Langerhans cell histiocytosis) only.

Figure 4.2 shows that cumulative costs for all 544 children with AML represent 26.5% of total childhood cancer costs, followed by ALL patients (n= 1,660) representing 13.7%, and neuroblastoma patients (n =967) representing 12.9% of total cumulative costs. Combined total costs for patients with acute leukaemia (ALL and AML) and neuroblastoma altogether represent 53.1% of all childhood cancer costs Highest drug costs were noted for patients with AML (median: $10,029; IQR: 5,607–17,202) and MDS (median: $8,333; IQR: 4,607–13,505) (Table 4.8). Median cost of leukaemia patients who underwent BMT was $46,032 compared to $23,558 for those without BMT.

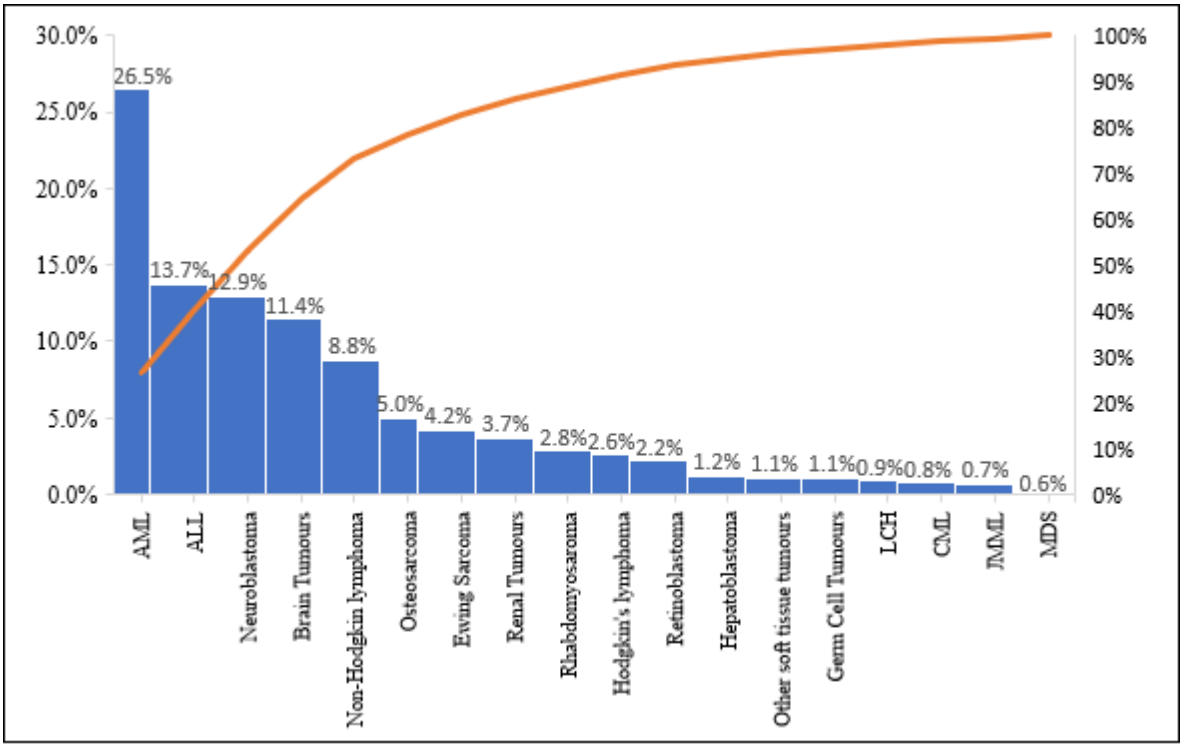


Figure 4.2. Proportion (%) of total cost (USD) by childhood cancer type from the total cumulative costs of all cancers combined, at 1-year post-diagnosis (n=8,886)

Abbreviations: AML: Acute Myeloid Leukaemia; ALL: Acute Myeloid Leukaemia; JMML: Juvenile myelomonocytic leukaemia; LCH: Langerhans cell histiocytosis; CML: Chronic Myeloid Leukaemia; MDS: Myelodysplastic Syndrome

Table 4.8. Main cost categories and sub-categories (USD) at 1-year post-diagnosis, per ICCC-3 groups (N=8,886)

ICCC-3 groups	Median (IQR) USD						
	Personnel Costs	Investigation costs		Treatment costs			Overhead costs (USD)
		Laboratory costs (USD)	Imaging costs (USD)	Drugs costs (USD)	Supplies costs (USD)	Surgery and/or RTH costs (USD	
All cancers combined *	5,740 (2,552 – 8,900)	1,018 (467–1,932)	138 (57–246)	1,825 (637–4,376)	612 (228–1,227)	182 (68–376)	4,330 (1,925–6,714)
I. Leukaemia/related cancers	8,850 (6,898 – 11,296)	2,304 (1,541–3,08)	122 (54–203)	4,138 (2,298–8,694)	1,059 (606-1,648)	71 (34–153)	6,676 (5,204 – 8,521)
Ia. Acute Lymphoblastic Leukaemia	8,581 (7,033 – 10,366)	2,195 (1,427–2,811)	144 (60–222)	3,225 (2,058–5,805)	925 (535–1,282)	55 (23–138)	6,474 (5,306 – 7,820)
Ib. Acute Myeloid Leukaemia	11,469 (8,491 – 14,147)	3,351 (2,128–4,489)	105 (50–158)	10,029 (5,607–17,202)	1,990 (1,331–2,785)	120 (53–184)	8,652 (6,405 – 10,672)
Ic. Chronic Myeloid Leukaemia	1,060 (828 – 2,166)	1,645 (1,160–2,439)	23 (5 – 42)	5,976 (3,007–11,252)	74 (36–189)	42 (42–42)	799 (624 – 1,634)
Id. Myelodysplastic Syndrome	9,288 (5,650 – 12,640)	3,601 (2696–4,354)	116 (64 – 163)	8,333 (4,607–13,505)	2,170 (1,662–2,726)	154 (116–192)	7,007 (4,262 – 9,536)
Ie. JMML	6,000 (4,524 – 8,453)	2,263 (1,6171–3,747)	61 (35 – 123)	4,032 (2,176 – 6,879)	1,109 (486–1,659)	23 (13–31)	4,526 (3,413 – 6,377)
II. Lymphomas	2,594 (1,492 – 6,678)	691 (428–1,589)	273 (186–383)	1,287 (644–3,521)	167 (60–662)	59 (37–87)	1,957 (1,126 – 5,038)
IIa. Hodgkin's lymphoma	1,541 (1,233 – 2,043)	450 (311–575)	296 (202 – 390)	735 (496 – 1,200)	64 (41–100)	57 (36–82)	1,163 (930 – 1,541)
IIb. Non-Hodgkin lymphoma	6,805 (4,996 – 9,457)	1,599 (1,107–2,238)	257 (167 – 373)	3,238 (1,632 – 6,371)	660 (353–1,148)	113 (65–197)	5,134 (3,769 – 7,134)
IIIa-e CNS and Brain Tumours	3,420 (1769 – 5,787)	408 (161–797)	63 (38 – 104)	833 (385 – 1,541)	555 (259–1,011)	355 (202–530)	2,580 (1,335 – 4,366)
IV-XII. Other solid tumours	5,081 (2,732 – 8,222)	842 (454–1405)	156 (65–278)	1,341 (448–3,870)	508 (191–1,158)	152 (62–306)	3,833 (2,061 – 6,203)
IVa. Neuroblastoma**	7,719 (4,692 – 10,359)	1,339 (921 – 2,182)	233 (160 – 347)	3,064 (923 – 5,123)	994 (445–1,580)	41 (20–82)	5,823 (3,540 – 7,815)
V. Retinoblastoma	2,203 (1,599 – 2,959)	233 (160 – 347)	16 (8.5 – 49)	429 (268 – 720)	146 (91–270)	302 (220–416)	1,662 (1,206 – 2,232)
VI. Renal Tumours	3,628 (2,353 – 5,715)	600 (431 – 9797)	73 (35 – 132)	73 (35 – 132)	425 (205–805)	64 (40–105)	2,737 (1,775 – 4,311)
VIIa. Hepatoblastoma	5,634 (4,295 -8,139)	1,038 (728 – 1,427)	153 (97 – 279)	973 (604 – 1,421)	623 (391–1,138)	99 (51–184)	4,250 (3,240 – 6,140)
VIII. Malignant Bone Tumours	5,740 (2,552 - 8,900)	1,112 (775 – 1,501)	168 (110-250)	4,362 (3,078–6,300)	1,027 (529–2,264)	232 (105 – 487)	4,330 (1,925–6,714)
VIIIa. Osteosarcoma	8,775 (6,227 – 10,860)	1,254 (850 – 1,612)	207 (136 – 338)	3,804 (2,490 – 5,489)	1,643 (764–4,825)	349 (188–653)	6,619 (4,698 – 8,193)
VIIIb. Ewing Sarcoma	7,022 (5,525 – 8,944)	1,032 (726 – 1,3480	134 (90 – 209)	5,036 (3,714 – 6,849)	687 (446–1,349)	152 (76–302)	5,297 (4,168 – 6,747)
IX. Soft tissue/extra-osseous sarcoma	5,660 (2,512–8,868)	899 (591–1,230)	251 (136–397)	1,241 (744–2,294)	406 (19–775)	110 (62–228)	4,270 (1,895–6,690)
IXa. Rhabdomyosarcoma	4,825 (3,692 – 6,528)	931 (677 – 1,188)	311 (213 – 418)	1,256 (815 – 2,056)	378 (192–727)	110 (62–221)	3,640 (2,785 – 4,925)
IXb-d. Other soft tissue tumours	4,762 (2,102 – 7,311)	819 (385 – 1,390)	102 (64 – 178)	1,150 (242 – 3,490)	455 (193–910)	139 (56–263)	3,592 (1,585 – 5,515)
XI. Germ Cell Tumours	4,045 (1,689 – 6,342)	758 (395 – 1,293)	103 (48 – 202)	725 (169 – 1,874)	309 (125–609)	96 (76–173)	3,052 (1,271 – 4,784)
XII. Langerhans cell histiocytosis***	2,419 (1,631 – 3,320)	476 (234 – 658)	323 (182–517)	255 (127 – 455)	82 (46–130)	142 (92–184)	1,825 (1,231 – 2,504)

***** For all cancers combined, only the primary tumours were included based on ICCC-3 diagnostic groups excluding (Ia.1.) Precursor cell leukaemia – aged <1); (I.e.) Unspecified and other specified leukaemia; (VII.b.) Hepatic carcinomas; (XI.) Other malignant epithelial neoplasms and malignant melanomas. ** IVa. Neuroblastoma includes ganglioneuroblastoma. *** XII includes LCH (Langerhans cell histiocytosis) only. Abbreviations**:** RTH: Radiotherapy.

4.6.3.2 Trends in costs over time

Cost trends decreased by 2.9% over time ($p<0.001$) for all childhood cancers combined, where greatest decline was noted between 2015 (median $15,335) and 2017 (median: $12,473) (Table 4.9) Patients with ALL, AML, CML, lymphomas, retinoblastoma, and osteosarcoma showed significantly decreasing cost trends, while patients with renal tumours and Hepatoblastoma had increasing costs trends over time (Table 4.9) For all cancers combined, investigation and treatment costs decreased over time by 18.2% and 12.3%, respectively, whereas, personnel and overhead costs increased by 2.4% and 2.1%, respectively ($p<0.001$) (Appendix 4.9).

Table 4.9. Trends in total costs (USD) at 1-year post diagnosis, for the ICCC-3 groups, by year of diagnosis (N=8,886)

	Median cost (IQR) in USD			% change in coefficient ^	*p*-value*
	Year 2013	Year 2015	Year 2017		
All cancers combined	15,762 (6,870-24,773)	15,335 (6,707-26,021)	12,473 (5,616-19,029)	-2.9% (-4.4 – -1.9%)	<0.001*
I. Leukaemia/related cancers	24,268 (18,506 – 36,157)	26,543 (20,982 – 38,524)	18,970 (15,340 – 24878)	-5.6% (-7.04 – -4.30%)	<0.001*
Ia. Acute Lymphoblastic Leukaemia	22,230 (18,355 – 27,942)	24,435 (20,799 – 30,729)	17,857 (15,192 – 21687)	-4.8% (-6.01 – -3.54%)	<0.001*
Ib. Acute Myeloid Leukaemia	42,814 (32,078 – 53,810)	39,116 (29,778 – 51,651)	27,552 (22,909 – 33,474)	-6.9% (-10.42 – -3.63%)	<0.001*
Ic. Chronic Myeloid Leukaemia	17,717 (14,993 – 27,609)	14,562 (8,418 – 28,454)	4,423 (3,875 – 6,361)	-24.3% (-31.61 – -15.63%)	<0.001*
Id. Myelodysplastic Syndrome	34,330 (23,536 – 49,297)	42,105 (29,895 – 48,769)	26,594 (23,117 – 30,891)	2.5% (-13.06 – 20.93 %)	0.762
Ie. JMML	12,499 (9,707 – 28,531)	21,126 (18,977 – 29,782)	12,336 (10,835 – 23,096)	1.5% (-8.52 – 12.75%)	0.766
II. Lymphomas	8,289 (4,477 – 19,652)	10,875 (4,752 – 19,635)	5,137 (3,461 – 13,549)	-5.5% (-8.97 – -2.95%)	<0.001*
IIa. Hodgkin's lymphoma	4,474 (3,857 – 5,406)	4,785 (3,964 – 5,881)	3,659 (3,079 – 4,424)	-3.1% (-5.64 – -0.82%)	0.009*
IIb. Non-Hodgkin lymphoma	18,798 (12,346 – 27,190)	19,107 (13,886 – 28,268)	14,449 (10,437 – 20,586)	-3.2% (-6.39 – -0.01%)	0.049*
IIIa-e CNS and Brain Tumours	9,162 (3,978 – 16,214)	8,139 (4,095 – 14,387)	6,968 (4,119 – 11,311)	-0.7% (-4.3 – 1.71%)	0.653
IV-XII. Other solid tumours	12,014 (5,946 – 22,128)	13,323 (6,669 – 23,953)	11,045 (5,588 – 17,881)	-1.3% (-3.44 – 0.54 %)	0.193
IVa. Neuroblastoma**	20,836 (10,689 - 27,779)	21,568 (11,823 – 30,411)	17,707 (11,337 – 22,639)	-2.1% *-5.45 – 1.41 %)	0.232
V. Retinoblastoma	4,693 (3,735 – 5,929)	6,247 (4,541 – 8,402)	4,053 (3,242 – 5,725)	-4.3% (-8.06 – -0.54 %)	0.025*
VI. Renal Tumours	6,680 (4,909 – 12,424)	7,111 (4,904 – 12,165)	7,857 (5,601 – 12,926)	4.9% (0.88 –9.31 %)	0.016*
VIIa. Hepatoblastoma	9,921 (8,030 – 12,476)	13,346 (11,579 – 17,068)	12,150 (10,814 – 16,294)	9.5% (3.25 – 16.18%)	0.002*
VIII. Malignant Bone Tumours	21,015 (15,327–26,552)	26,621 (21,431– 31,786)	15,979 (13,196–20,517)	2.6% (-5.1 – -0.06%)	0.045*
VIIIa. Osteosarcoma	24,969 (20,298 – 32,259)	27,837 (22,825 – 36,387)	16,198 (12,994 – 20,423)	-6.7% (-10.42 – -2.57%)	0.001*
VIIIb. Ewing Sarcoma	16,322 (12,574 – 20,035)	23,101 (18,006 – 27,640)	18,079 (15,381 – 22,039	1.9% (-0.56 – 5.60 %)	0.126
IX. Soft tissue sarcoma	11,497 (8,625 – 15,144)	12,372 (8,647 – 17,935)	9,329 (7,057 – 12,547)	-2.8% (-7 – 1.6%)	0.21
IXa. Rhabdomyosarcoma	11,352 (8,499 – 14,248)	13,034 (9,459 – 18,357)	9.528 (7,623 – 12,484)	0.3% (-3.25 – 3.98 %)	0.864
IXb-d. Other soft tissue tumours	17,581 (11,485 – 22,010)	10,654 (6,307 – 17,212)	6,574 (4,334 – 13,169)	-11.7% (-22.89 – 1.51 %)	0.079
XI. Germ Cell Tumours	12,465 (8,463 – 15,330)	11,953 (5,356 – 16,876)	7,708 (2,781 – 12,035)	-7.5% (-16.47 – 2.53 %)	0.138
XII. Langerhans cell histiocytosis***	5,818 (4,439 – 6,637)	6,211 (4,256 – 7,701)	4,898 (3,343 – 6,328)	-4.2% (-12.19 – 4.71 %)	0.341

^ Coefficient of trend obtained from linear regression model with 'Year of diagnosis" as independent variable and log-transformed total costs as outcome variable. % change in coefficient obtained by multiplying anti-log of coefficient by 100. * Statistically significant at *p*-value <0.005.

4.7.5.1 Factors contributing to total costs

On univariate analysis, higher costs were associated with older age at diagnosis (p=<0.001), male gender (p=0.009), leukaemia and solid tumours (p<0.001), relapse status (p=0.004) and PICU admission during first year post-diagnosis (p<0.001) (Table 4.10). On multivariate analysis, independent predictors of total cost included older age at diagnosis, leukaemia and solid tumours, or patients who survive/relapse or had PICU admissions during the first-year post-diagnosis (p<0.001) (Table 4.10).

Furthermore, resource use measures also contributed differently to total costs for the different cancer types, as shown in multivariate analysis in Appendix 4.10. In leukaemia, inpatient-days contributed mainly to total cost, followed by outpatient visits and IV supportive drugs (p<0.001) Whereas number of outpatient visits was the main contributor to total costs in lymphoma. For patients with brain and solid tumours, both inpatient-days and outpatient visits contributed to total cost.

Table 4.10. Factors associated with total costs (USD) during first year post-diagnosis, using univariate and multivariate analysis (N=8,886)

	Median costs	Univariate analysis			Multi-variate analysis		
		Coefficient (95% CI)	***p*-value^**	**Overall *p*-value^**	**Coefficient (95% CI)**	***p*-value^**	**Overall *p*-value^**
Age at diagnosis							Overall *p*-value of the multivariate model is <0.0001*
0–4 years	$14,023	Ref. group	Ref. group	<0.001*	Ref. group	Ref. group	
5–9 years	$14,341	0.01% (-4.3–4.3%)	0.995		8.1% (4.5–11.7%)	<0.001*	
10–14 years	$16,894	15.9% (10.8–21.1%)	<0.001*		21.7% (17.5–29.5%)	<0.001*	
15–18 years	$17,875	24.2% (16.8–31.7%)	<0.001*		28.6% (22.5–34.6%)	<0.001*	
Gender							
Female	$14,417	Ref. group	Ref. group	0.609	Ref. group	Ref. group	
Male	$14,927	0.96% (-2.7–4.6%)	0.609		0.5 (-2.4–3.5%)	0.715	
Main cancers							
Brain Tumours	$8,534	Ref. group	Ref. group	<0.001*	Ref. group	Ref. group	
Leukaemia	$23,736	114% (109–119%)	<0.001*		133% (129–138%)	<0.001*	
Lymphoma	$7,557	16.2% (10.7–21.8%)	<0.001*		39.0% (33.6–44.4%)	<0.001*	
Solid Tumours	$10,934	39.2% (34.7–43.7%)	<0.001*		63.4% (59–67.8%)	<0.001*	
Survival status							
Alive	$14,943	Ref. group	Ref. group	0.143	Ref. group	Ref. group	
Died	$13,987	-5.1% (-10.2–0.04%)	0.051		-17.8% (-22– -0.13%)	<0.001*	
Lost FU	$9,439	-6.4% (-40.2–27.3%)	0.707		-23.1% (-50– -3.8%)	0.092	
Relapse status							
No	$14,767	Ref. group	Ref. group	0.004*	Ref. group	Ref. group	
Yes	$14,850	8.6% (2.7–14.6%)	0.004*		34.2% (29.1–39.4%)	<0.001*	
PICU admission							
No	$10,923	Ref. group	Ref. group	<0.001*	Ref. group	Ref. group	
Yes	$18,497	52.2% (48.7–55.8%)	<0.001*		61.9% (58.9–65%)	<0.001*	

^ *p*-value obtained from OLS linear regression model using univariate and multi-variate analysis. * Statistically significance at $p<0.05$.
Abbreviations: FU: Follow-up; PICU: Paediatric Intensive Care Unit.

4.7 Discussion

4.7.1 Summary and interpretaton of findings

In this study, I analysed hospital resource use and costs data for 8,886 children with cancer newly diagnosed at CCHE between 2013–2017. Hospital resource use measures and costs varied considerably among the different childhood cancer types. This variation can be largely explained by differences in treatment protocols[4] and severity of the disease, where resource use and costs increase with treatment complexity.[11]

At CCHE, children with leukaemia had the highest median total costs of $23,736 at 1 year, increasing to $35,185 at 3 years post-diagnosis. Patients with leukaemia imposed the greatest economic and financial burden on CCHE due to the large volume of patients and high cost per patient. High costs were mainly attributed to intensive chemotherapy treatment, high hospitalization rate (98%) (Table 4.4), and long inpatient-days.[20,30,31] Specifically, patients with AML incurred the highest costs, due to intensive supportive care to manage infections and treatment-related complications, and the long hospital stays.[30] Moreover, leukaemia patients who underwent BMT had almost double the costs ($46,032) compared to those who did not receive BMT ($23,558).

Patients with lymphoma had median total cost of $7,542 at 1 year and $10,803 at 3 years post-diagnosis. Low costs for patients with lymphoma were attributed to their less complex treatment, which was mainly received in an outpatient setting.[11] Hodgkin's lymphoma costs (median: $4,474) were much lower than those for non-Hodgkin's lymphoma (median: $18,516) due to shorter inpatient-days and less intensive therapy. Patients with brain tumours had the highest PICU admission rate (61.8%) (Table 4.4), as their treatment involves high-risk neurosurgeries

with post-operative PICU admission.[20,31] Nevertheless, brain tumours costs were relatively low at CCHE (median: $8,534) as treatment mainly depends on surgery and/or radiotherapy (with/without outpatient chemotherapy).[31] Patients with osteosarcoma, Ewing sarcoma and neuroblastoma had the highest costs among all solid tumours; osteosarcoma costs were exacerbated by expensive orthopaedic surgeries;[32] patients with Ewing sarcoma received expensive Granulocyte colony-stimulating factor (G-CSF) drugs;[33,34] and patients with high-risk neuroblastoma received costly intensive chemotherapy and supportive care.[11]

Cost trends (USD) for all cancers combined significantly decreased by 2.9%, due to the economic instability in Egypt between 2013–2017, and devaluation of the EGP in 2016 which led to increase in local prices in 2017.[35] Only patients with Hepatoblastoma and renal tumours showed significantly increasing costs trends over time. This can be explained by shifting treatment for high-risk hepatoblastoma patients to a more resource-intensive one. Besides, the use of IV supportive drugs significantly increased over time for patients with solid tumours, likely due to shifting to more intensive treatments in patients with high-risk neuroblastoma, Hepatoblastoma, and relapsed patients which requires more intensive supportive care. However, further research is required to determine any potential overuse in resources in this area.

4.7.2 Comparison with other published literature

At CCHE, the number of hospital admissions and inpatient-days at 3 years post-diagnosis were similar to those reported by Rosenman *et al.* (2005).[5] Patients with leukaemia and brain tumours were most commonly hospitalized, as reported by Hendrickson *et al.* (2009).[20] Findings from this study were comparable to data reported from the Healthcare Cost and Utilization Project (HCUP), where patients with leukaemia had the longest inpatient-days.[36] Whereas, contrary to

the results reported in this study, HCUP data reported longer inpatient-days for patients with brain and renal tumours, and shorter inpatient-days for osteosarcoma.[36] This is likely due to differences in treatment protocols.

Cost estimates varied markedly among studies due to differences in the adopted treatment protocols, variation in costing methodologies and perspectives, and varying contexts among countries.[4,11] The childhood cancer costs estimated in this study were much lower than those reported from high-income countries[3,5,20,30,37] even after correction for currency exchange and purchasing power.[4] This is likely attributed to the relatively lower personnel and overhead costs in Egypt (due to lower country income level), which represented 36.3% and 27.4%, respectively.

Similar to other published literature, inpatient hospitalisation was a main cost driver,[5] and the highest cost categories in other LMIC settings included personnel, medications, and overhead costs, which is in line with the findings of the systematic review by Fung *et al.* (2019).[11] Childhood cancer costs varied by cancer type, where patients with leukaemia (mainly AML), osteosarcoma, and neuroblastoma incurred the highest costs, while lower costs were reported for patients with brain tumours and lymphomas.[3,4,5, 30,37,38] Only data from the HCUP and the Cancer Council NSW reports showed higher costs for brain tumours.[36,39] The main cost drivers identified in this study (inpatient-days, inpatient admissions, and outpatient visits) were similar to those reported by the European Expert Paediatric Oncology Reference Network guide (2017) based on systematic review of data.[4]

In this study cohort, adolescents (15–18 years) had higher costs compared to younger children (0–14 years), unlike what is reported by other studies in the literature.[3,37] This is likely because adolescents are treated at CCHE based on the same paediatric protocols but receive higher drug

doses, incurring higher costs. Also, contrary to the published literature, patients who died during the first-year post-diagnosis at CCHE had lower costs than those who survived.[1,3,5,20,38] This is likely due to the higher percentages of early deaths at CCHE (within 30 days of diagnosis) as a result of late presentation with advanced disease, treatment-related complications, and infections. Furthermore, this study reported higher medication costs than those reported by Renner *et al.* (2018) from Ghana.[11] This is likely due to the fact that the treatment protocols implemented by CCHE are more intensive and costly than those adopted in Ghana, which are less intensive and less expensive.[11]

4.7.3 Strengths and limitations

To the best of my knowledge, this study presents the first results of childhood cancer resource use and costs using real-world data from a local setting in Egypt. Besides, findings from this study report the most comprehensive and detailed childhood cancer cost estimates from a LMIC context, compared to results from the systematic review by Fung *et al.* (2019).[11] The resource use measures and associated costs estimated from this study reflect the total burden of childhood cancer care from a health system perspective, as patients received all the necessary paediatric oncology services at the same centre (CCHE). Therefore, full costs of care were included, unlike other studies in the literature that did not include all cost elements.[11] Furthermore, this study provides costing methodological improvements compared to other published studies from LMICs based on cost analysis best practice;[4,11] clearly stated costing perspective; complete cost inputs; actual costs presented (not extra charges);[30] and median (IQR) and mean (±SD) values reported.[4] Finally, it is the only study from a LMIC context that analysed resource use and costs for all childhood cancer types by ICCC–3 groups, and examined potential cost drivers.

Despite the valuable significance of these findings, several limitations exist. First, owing to the retrospective study design, the estimated cost categories were limited by the structure of the cost items at CCHE costing/billing database,[5] where it was not possible to calculate unit costs for inpatient hospitalization and outpatient visits as separate cost categories. Second, analysis of costs/resource use outcomes was not time-based, but was calculated at 1- and 3- years post-diagnosis, where patients who died early would incur less costs. However, this was accounted for in univariate/multivariate analysis where survival status was analysed as an independent variable contributing to total costs. Third, costs were estimated up to three years post diagnosis only, where long-term costs (beyond three years) were not included.[5] This could be more of a problem for patients with ALL whose treatment lasts up to three years. Nevertheless, since 70% of disease relapse occurs within the first three years post-diagnosis, therefore, most relapses and their associated costs were already accounted for.

Fourth, findings from this study are not necessarily representative of childhood cancer resource use and costs all over Egypt, as data was obtained from a single centre (CCHE). The resources utilised and associated costs may vary from one centre to another in Egypt based on treatment protocols and quality of care. To address this issue, I transparently disclosed the adopted standard treatment protocols at CCHE for better transferability of findings. Furthermore, such data do not exist at the national level; therefore, this study provides valuable insights from a local context in Egypt that are comparable to other published literature.

.

4.7.4 Implications

4.7.4.1 Implications for policymakers

Findings from this study would help policy-makers develop tailored strategies and policies for optimal resource use and cost containment in priority areas where unjustified high resource use/costs exist (over time). Determining the costs of each childhood cancer type can form the basis to estimate future budgets and make hospital-wide financial planning accordingly.

3.7.4.2 Implications for clinicians

Based on these findings, clinicians would be more conscious of the economic impact of their clinical decisions on hospital resource utilisation and associated costs, allowing them to make better informed clinical decisions.[5,40] Some examples for implications for clinical practice include: avoiding unnecessary use of resources that represent the main cost drivers (such as unnecessary hospital admissions); and evaluating clinical practice guidelines for interventions with increasing trends over time (such as IV supportive care drugs for solid tumours). This can ideally lead to maximising value in the delivery of childhood cancer care at CCHE/Egypt and other similar resource-limited contexts.

4.7.4.3 Implications for researchers

This study identifies key future research areas in cancers with unjustified overuse of resources and high associated costs (hepatoblastoma and renal tumour). Cost of care could be related to survival outcomes of the disease, which requires conducting formal health economic analysis. Therefore, costing studies serve as the foundation for future cost-effectiveness research that examines survival outcomes relative to the costs.

3.7.4.4 Implications for patients

Findings from this study could help reduce any unwarranted overuse of resources (such as: unnecessary admissions, tests, or drugs) that does not add benefits to patients, but could have potential harms. This could lead to improved patients' experiences with health service delivery.

4.5.1 Evidence-based recommendations for improvement

Accordingly, I suggest the following key recommendations (Panel 4.1) in policy-making (points 1, 2, and 3), current practice (points 4 and 5), and future research (points 6 and 7) to better utilise the available childhood cancer resources and manage costs effectively.

Panel 4.1. Recommendations to optimise resource use and manage costs effectively at CCHE

1. Facilitate hospital-wide resource planning based on real-world data, to make informed decisions regarding optimal resource use and allocation.
2. Predict childhood cancers costs based on identified predictors, and validate model accuracy.
3. Estimate future budgets for childhood cancers, based on the estimated cost per patient and the expected patients' volume.
4. Avoid unwarranted overuse of resources (e.g., unnecessary hospitalisations, investigations, interventions) that contribute to high costs of care.
5. Revise and modify the current practice guidelines for IV supportive drugs for solid tumours.
6. Study reasons behind increasing cost trends for Hepatoblastoma and renal tumour patients.
7. Evaluate cost-effectiveness of treatment to determine the health benefits gained relative to the money spent during childhood cancer care.

4.8 Conclusion

Patients with ALL, AML and neuroblastoma impose the greatest economic and financial burden on CCHE. Trends in childhood cancer costs over time were affected by the instability of the economic situation in Egypt between 2013–2017. The estimated resource use and costs will inform hospital resource planning and future budgeting, based on real-world evidence, to promote value in care delivery, with implications for paediatric oncology policy, practice and research in Egypt/CCHE.

4.9 How this chapter relates to the overall thesis

My thesis aims to generate evidence to improve childhood cancer health outcomes and resource use in Egypt. Chapter 4 generates real-world evidence from local context (CCHE/Egypt) about childhood cancer hospital resource use and associated costs. This chapter identifies the childhood cancer types with the highest patterns and trends in resource use and costs, and identifies the main cost drivers. Accordingly, I provide evidence-based recommendations to optimise resource use and manage costs effectively. Cost outcomes derived in this chapter will then be used to estimate the cost-effectiveness of childhood cancer treatment in Chapter 5.

4.10 Chapter summary

- This chapter estimates patterns and trends in hospital resource use and costs for 8,886 children with cancer who were treated CCHE/Egypt between 2013 and 2017.
- For all childhood cancers combined, median costs were $14,774 at 1 year, and $19,799 at 3 years post-diagnosis.
- Patients with AML patients had the highest costs/resource use of all childhood cancers.

- Patients with acute leukaemia (ALL/AML) and neuroblastoma imposed the greatest financial burden on CCHE, representing 53.1% of total costs.
- Children with solid tumours showed a significantly increasing trend (by 24.3%) in the use of IV supportive drugs over time.

Chapter Four References

1. Lansky SB, BlackJ L,Cairns NU. Childhood cancer: medical costs. *Cancer*.1983;52:762-6.
2. Barr, R. D., Feeny, D., & Furlong, W. Economic evaluation of treatments for cancer in childhood. *Eur. J. cancer*. 2004;40(9),1335-1345.
3. de Oliveira C, Bremner KE, Liu N, Greenberg ML, Nathan PC, McBride ML, *et al*. Costs for Childhood and Adolescent Cancer, 90 Days Prediagnosis and 1 Year Postdiagnosis: A Population-Based Study in Ontario, Canada. *Value Health*. 2017;20(3):345-356.
4. European Expert Paediatric Oncology Reference Network (ExPO-r-Net). Deliverable 4: An analysis of economic impact of childhood cancers based on systematic review of data to inform national and regional policymakers across the EU. Final Report ICP (ECRMF) and Birmingham University. June 2017.
5. Rosenman MB, Vik T, Hui SL, Breitfeld PP. Hospital resource utilization in childhood cancer. *J Pediatr Hematol Oncol*. 2005;27(6):295-300.
6. IARC and WHO. Providing better cancer data will help reduce the burden of childhood cancer. *IARC/WHO report*. Press release no. 265. February 2019.
7. GBD 2017 Childhood Cancer Collaborators. The global burden of childhood and adolescent cancer in 2017: an analysis of the Global Burden of Disease Study 2017. *Lancet Oncol.* 2019;20: 1211–25.
8. Bhakta N, Force LM, Allemani C, Atun R, Bray F, Coleman MP, *et al*. Childhood cancer burden: a review of global estimates. *Lancet Oncol.* 2019;20: e42–53.
9. Magrath I, Steliarova-Foucher E, Epelman S, Ribeiro RC, Harif M, Li C, *et al*. Paediatric cancer in low-income and middle-income countries. *Lancet Oncol*. 2013;14(3):e104-e116.

10. Quilty R. Mind the Gap: Improving paediatric cancer care in developing countries. Commentary. *UOJM. Global Health*. 2016:6(2).
11. Fung A, Horton S, Zabih V, Denburg A, and Gupta S. Cost and cost-effectiveness of childhood cancer treatment in low-income and middle-income countries: a systematic review. *BMJ Glob. Health*. 2019;4:e001825.
12. Fadhil I, **Soliman R**, Jaffar S, Al Madhi S, Saab R, Belgaumi A, *et al*. Estimated incidence, prevalence, mortality, and registration of childhood cancer (ages 0-14 years) in the WHO Eastern Mediterranean region: an analysis of GLOBOCAN 2020 data. *Lancet Child Adolesc Health*. 2022;6(7):466-73.
13. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61(4):344-349.
14. Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs A H, Carswell C *et al*. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. *BMJ*. 2022;376:e067975.
15. Steliarova-Foucher E, Stiller C, Lacour B, and Kaatsch P. International Classification of Childhood Cancer, third edition. *Cancer*. 2005;103:1457-1467.
16. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, and Whelan S. International classification of diseases for oncology, third edition (ICD-O-3). Geneva: World Health Organization, 2013.

17. Children' Cancer Hospital 57357–Egypt (CCHE). CCHE Homepage [Internet]. 2023 [cited 2023 Jan]. Available from: https://www.57357.org/

18. Harris P, Taylor R, Thielke R, Payne J, Gonzalez N and Jose G. Conde, Research electronic data capture (REDCap), *J Biomed Inform*. 2009;42(2):377-81.

19. Oracle Cerner. Cener [Internet]. *Kansas City*, USA. 2023 [cited 2023 Mar]. Available from: https://www.cerner.com/about

20. Hendrickson K and Rimar J. Patterns of Hospital Resource Utilization of Children with Leukemia and CNS Tumors: A Comparison of Children Who Survive and Those Who Die within 3 Years of Diagnosis. *Nurs Econ*. 2009.27(1): 35-44.

21. Centers for Medicare & Medicaid Services (CMS). Cost and Resource Use Measures. Measures Management System Hub [Internet]. CMS. 2023 [cited 2023 Jan]. Available from: https://mmshub.cms.gov/sites/default/files/Cost-and-Resource-Use-Measures.pdf

22. Oracle Corporation. Enterprise resource planning (ERP) [Internet]. Oracle. 2023 [cited 2023 Jan]. Available from: https://www.oracle.com/applications/erp/What-is-erp.html

23. Williams T and Saine T. Understanding Hospital Charges, Costs and Payments [Internet]. Strategic Dynamics Firm. 2023 [cited 2023 Jan]. Available from: https://strategicdynamicsfirm.com/understanding-hospital-charges-costs-and-payments/

24. Barlow E. Overview of Methods to Estimate the Medical Costs of Cancer. *Med Care*. 2009; 47(7 Suppl 1):S33–S36.

25. Turner H, Lauer J, Tran B, Teerawattananon Y, and Jit M. Adjusting for inflation and currency changes within health economic studies. *Value Health*. 2019;22(9):1026–1032.

26. The World Bank Indicators. Official exchange rate (LCU per US$, period average) [Internet]. World Bank Group. 2023 [cited 2023 Jan]. Available from: https://data.worldbank.org/indicator/PA.NUS.FCRF?view=chart

27. The World Bank Indicators. GDP deflator (base year varies by country) [Internet]. World Bank Group. 2023 [cited 2023 Jan]. Available from: https://data.worldbank.org/indicator/NY.GDP.DEFL.ZS

28. Kumaranayake L. The real and the nominal? Making inflationary adjustments to cost and other economic data. *Health Policy Plan*. 2000;15:230–234.

29. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing 2013. Vienna, Austria. Available from: http://www.R-project.org/

30. Kaul S, Barbeau B, Wright J, Fluchel M, Kirchhoff AC, Nelson RE. Statewide Longitudinal Hospital Use and Charges for Pediatric and Adolescent Patients with Cancer. *J Oncol Pract*. 2015;11(4):e468-e475.

31. Pizzo, P.A., & Poplack, D.G. (Eds.). Principles and practice of pediatric Oncology (6th ed.). Philadelphia: Lippincott, Williams, and Wilkins. 2006.

32. Ward W. and Watkins-Castillo S. Economic cost of malignant bone tumours. Bone and Joint Burden [Internet]. United States Bone and Joint Initiative. 2014 [updated 2023; cited 2023 Feb]. Available from: https://www.boneandjointburden.org/2014-report/viiiab14/economic-cost-malignant-bone-tumors

33. Womer RB, Daller RT, Fenton JG, Miser JS. Granulocyte colony stimulating factor permits dose intensification by interval compression in the treatment of Ewing's sarcomas and soft tissue sarcomas in children. *Eur J Cancer*. 2000;36(1):87-94.

34. Hadji P, Kostev K, Schröder-Bernhardi D, Ziller V. Cost comparison of outpatient treatment with granulocyte colony-stimulating factors (GCSF) in Germany. *Int J Clin Pharmacol Ther*. 2012;50(4):281-9.

35. PwC. Middle East. The EGP Devaluation; a new beginning [Internet]. PwC. Middle East. 2017 [cited 2023 Feb]. Available from: https://www.pwc.com/m1/en/publications/the-egp-devaluation-a-new-beginning.html

36. Anhang Price, R. (RAND), Stranges, E. (Thomson Reuters) and Elixhauser, A. (Agency for Healthcare Research and Quality). Pediatric Cancer Hospitalizations, *2009*. HCUP Statistical Brief #132. May 2012. Agency for Healthcare Research and Quality. Rockville, MD. Available from: http://www.hcup-us.ahrq.gov/reports/statbriefs/sb132.pdf

37. de Oliveira C, Bremner KE, Liu N, Greenberg ML, Nathan PC, McBride ML, *et al*. Costs of cancer care in children and adolescents in Ontario, Canada. *Pediatr Blood Cancer*. 2017;64(11).

38. Luo W, Lane R, Stobart K, Morrison H, Schanzer D, Barr R, *et al*. The medical care cost of childhood and adolescent cancer in Manitoba,1990–1995. *Chronic Dis Can.* 2002;23:83–90.

39. Cancer Council NSW. Cost of Cancer in New South Wales. A report by Access Economics Pty Limited for The Cancer Council NSW. 2007.

40. Russell HV, Panchal J, Vonville H, Franzini L, Swint JM. Economic evaluation of pediatric cancer treatment: a systematic literature review. *Pediatrics*. 2013;131(1):e273-87.

Chapter Five: Cost-effectiveenss of childhood cancer treatment in Egypt

"*Maximising value for a specific population can be achieved by optimising outcomes given the resources available*." — Professor Sir Muir Gray

Providing cost-effective treatment strategies is an effective solution to maximise health benefits gained relative to money/resources spent. Generating real-world evidence from the local context about the cost-effectiveness of childhood cancer treatment (survival relative to costs) provides valuable information about current practice and identifies key priority areas for improvement.

5.1. Publication statement

Features of this chapter are published in the following peer-reviewed journal:

Soliman R, Oke J, Sidhom I, Bhakta N, Bolous NS, Tarek N, *et al.* Cost-effectiveness of childhood cancer treatment in Egypt: Lessons to promote high-value care in a resource-limited setting based on real-world evidence. *EClinicalMedicine*. 2023;55:101729. DOI: 10.1016/j.eclinm.2022.101729.

5.2 Introduction

Diagnosed childhood cancers were predicted to contribute to 11.5 million disability-adjusted life years (DALY) globally based on modelled data, with 82% of this burden occurring in low- and middle-income countries (LMICs).[1,2] Estimating DALYs from observed data is essential to determining real-world burden of childhood cancers to better inform local policy and practice.[1,2]

Despite the perception that childhood cancer treatment is too costly for LMIC health systems, recent evidence shows that treating children with cancer is (very) cost-effective in LMICs contexts.[2,3] However, it was only evaluated for a few cancers (not all cancers combined), and without stratifying by cancer type/subtype, risk, stage at diagnosis, or disease status.[2] Childhood cancer is a health priority in Egypt owing to the large numbers of children with cancer, great need and demand for services, limited resources, and inferior survival.[4,5] Therefore, there is a need to provide cost-effective childhood cancer treatment in Egypt and find ways to optimise value in care delivery, as described in the Background in Chapter 2 (section 2.6.3). Yet, limited data exist about the costs and effects of childhood cancer treatment from Egypt, creating a gap in existing literature.[2]

In Chapter 3, I determined the childhood cancer survival in a local paediatric oncology setting in Egypt. In Chapter 4, I estimated the resources used (and associated costs) during their treatment. In this chapter, I set out to estimate the cost-effectiveness of childhood cancer treatment using survival and costs outcomes reported in the previous chapters.

5.3 Aim of work

To estimate cost-effectiveness of treatment for children with cancer treated at the Children's Cancer Hospital Egypt (CCHE) between 2013 and 2017.

5.4 Objectives

1. To determine the cost-effectiveness of treatment for children with cancer, stratified by cancer type/sub-type, risk, stage at diagnosis, and disease status.
2. To identify childhood cancer groups whose treatment is not cost-effective; poor survival outcomes and high costs.

3. To determine the association between costs and survival, accounting for potential confounders
4. To provide evidence-based recommendations to increase treatment cost-effectiveness and promote high-value care

5.5 Methods

This chapter was conducted following the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist,[6] (Appendix 5.1).

5.5.1 Patients and setting

I included the same retrospective cohort (included in chapter 4) of 8,886 children with cancer newly diagnosed between January 1st, 2013 and December 31st, 2017 at CCHE, following the International Classification of Childhood Cancer, 3rd edition (ICCC-3).[7] Eligible patients for cost-effectiveness/survival analysis met the following criteria: received treatment at CCHE; were not lost to follow-up or referred outside CCHE early on treatment (during first 14 days from diagnosis); and had complete disease-specific data [disease characteristics (stage/risk/subtype), disease status (relapse/refractory/progressive), and updated survival data].

Figure 5.1 shows the flowchart of inclusion/exclusion criteria. Some ICCC-3 subgroups (n=330) were excluded from survival/cost-effectiveness analyses because their clinical/survival data were incomplete and data were not readily available. Eligible patients were monitored with active follow-up, and their survival data was updated until 31st December 2020. Patients were treated based on CCHE standard treatment protocols (Appendix 3.3). Patients with relapsed/refractory disease were treated based on second- and/or third-line therapies as outlined in CCHE guidelines, or as discussed in combined clinics to manage the atypically complicated cases.

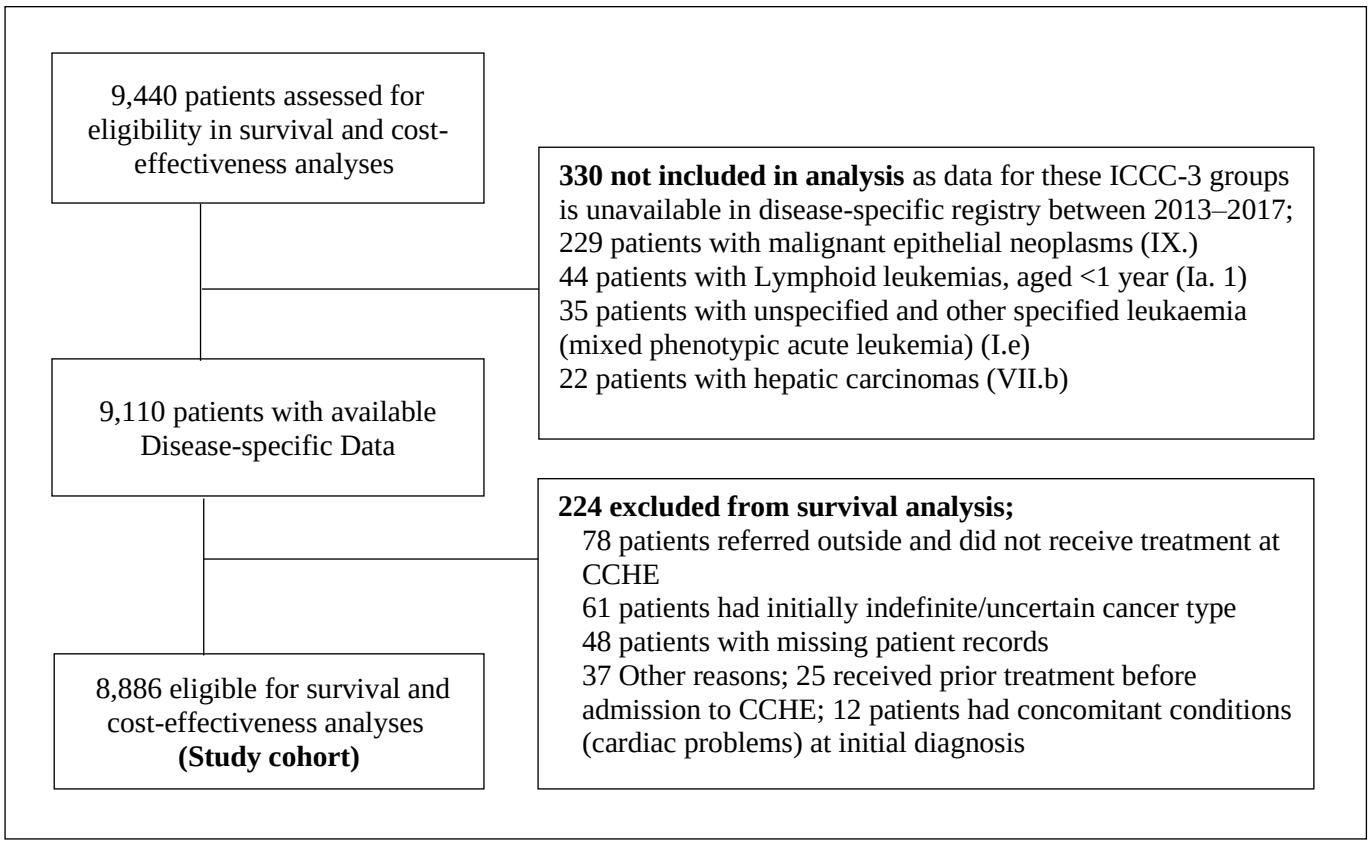


Figure 5.1. Flowchart of included/excluded patients in survival/cost-effectiveness analyses

5.5.2 Data collection and validation

Patients' demographics, disease characteristics, and survival data were retrieved from CCHE hospital-based registries (on the Research Electronic Data Capture online platform)[8] for patients diagnosed between January 1st, 2013 and December 31st, 2017, and followed up until 31st December 2020. Data variables included childhood cancer types by ICCC-3 groups, initial stage at diagnosis, disease risk, survival status, date of last contact, and disease status (relapse, refractory, or progressive disease – PD). Relapse was defined as cancer recurring after complete remission (no evidence of disease),[9] whereas, refractory disease was defined as not responding to treatment or as treatment failure.[10] PD was defined as at least a 20% growth in the size of the tumour or spread of the tumour since the beginning of treatment.[11]

The costs data captured for the same cohort of patients in Chapter 4 were also used in this chapter. Total costs and cost categories were extracted from the readily available costing/billing database at CCHE. The definitions of cost categories and methods of measurement/allocation were previously described in Chapter 4 in Table 4.1.

Costs data were analysed following the same costing methodology reported in Chapter 4. I estimated incident costs (from health system perspective) of newly diagnosed children with starting from the date of diagnosis until the end of the first three years post-diagnosis (3-year costs).[12] Incident costs were calculated to cover the costs of first-line treatment and subsequent treatment of relapse/refractory or PD within the first three years post-diagnosis. I made cost adjustment as per Turner *et al*. (2019) methodology, which adjusts for inflation and currency exchange.[13] First, I converted costs from local currency (Egyptian Pounds, EGP) to US dollars (USD) using the World Bank average exchange rates for each year between 2013 and 2017.[14]

Then, I adjusted for inflation using the US inflation rates based on the World Bank GDP deflator[15] to the reference year '2019' as this is the year in which patients diagnosed in 2017 completed 3-years costs post-diagnosis. Cost outcomes were reported in USD only, whereas, the change in costs over time (described in section 5.5.3.4) was calculated in both currencies (EGP and USD) to account for the devaluation of the EGP in November 2016.[16] Costs in EGP were adjusted for domestic inflation using Egypt's inflation rates to the same reference year (2019) based on World Bank GDP deflator, to present changes in costs in real terms.

Data quality checks were done every six months over the five years by the research department and lead paediatric oncologists at CCHE through continual monitoring and validation of the cancer registry and disease-specific registries. Disease-related and survival data were reviewed upon study initiation and validated for integrity, completeness, and accuracy. Cost data were validated at time of data extraction by comparing medication chart audits with the costing/billing data, with 96.5% concordance between records. Approval for data release was granted by the Scientific Medical Advisory Committee (SMAC) at CCHE. Ethics approval was not required by the institutional review board (IRB), as this study involves secondary use of routinely collected data with de-identified patients' records.

5.5.3 Cost-effectiveness analysis

I estimated the cost-effectiveness of childhood cancer treatment compared to that of no treatment, following the assumption that children with cancer would not survive if left untreated.[17,18] Cost-effectiveness was calculated using the disability-adjusted life-year (DALY) methodology reported by *Bhakta et al*. (2013)[17] and *Fuentes-Alabi et al*. (2018),[18] based on the standard methods from the WHO Global Burden of Disease (GBD) working group.[19,20] In

accordance with the expected course of the disease based on several clinicians' opinions at CCHE, it was assumed that patients with acute leukaemia will survive for one month, lymphomas and other leukaemia types for three months, and solid tumours for six months if left untreated.

5.5.3.1 DALY estimation

DALY estimates were calculated based on years of life lost (YLL) and years lived with disability (YLD),[17] calculated from mean age at diagnosis (for each cancer at CCHE), life expectancy in Egypt (72.06 years in 2020),[21] and 5-year OS at CCHE. I made utility adjustments for late-effect morbidity and for excess late morbidity and mortality to avoid over-estimation of cost-effectiveness.[17] Cost-effectiveness calculations were completed using a modified version of the Excel sheet for DALY Calculation Model provided in supplementary files of the study published by Bhakta *et al.* (2013).[17] Detailed DALY calculation is described in (Appendix 5.2).

I calculated actual 5-year overall survival and cost/DALY averted for all cancers combined in the study cohort (n=8,886), and stratified by cancer type (ICCC-3 groups), risk, stage at diagnosis, sub-type, and disease status (relapse/refractory/PD) at 3 years post–diagnosis. I did not intend to evaluate cost-effectiveness of treatment of relapse separately, rather, it was evaluated as part of the overall treatment (first- and second-line) with disease status stratification. Definitions of risk and stage stratification were previously outlined in Chapter 3 in (Appendix 3.4).

5.5.3.2 Sensitivity analysis

At the base-case scenario, I discounted costs and effects (future years of life saved) at 3% discount rate to obtain cost per DALY (cost/DALY) averted. On sensitivity analysis, I discounted costs and effects at 6% discount rate, to allow for comparability with previously

published studies, taking a similar conservative approach.[17,18] Discounting at 6% was made for all cost per DALY averted calculations, stratified by cancer type (ICCC-3 groups), stage/risk, and disease severity (relapse/progressive disease).

For all cancers combined, I also conducted two-way sensitivity analyses by varying discount rates (at 0%, 3%, 6%), potential utility-adjustment for excess late-effect morbidity, and potential early mortality due to childhood cancer treatment (reduction in life expectancy at 15% and 30%), following the methodology by Fuentes-Alabi *et al.* (2018).[18]

5.5.3.3 Cost-effectiveness threshold

I used the WHO-CHOICE (CHOosing Interventions that are Cost-Effective) threshold to determine cost-effectiveness of health interventions, in terms of cost/DALY averted relative to the country's GDP per capita.[22] The WHO threshold suggests that interventions costing less than one time (<1×) the GDP per capita are 'very cost-effective', and those less than three times (<3×) GDP per capita are 'cost-effective'.[22] In Egypt, GDP per capita was $3,019 in 2019.[23] I used the GDP-based DALY threshold as it is a consistent methodology allowing for fair comparisons across disease areas,[24] and it is the most commonly used threshold to judge cost-effectiveness of interventions in LMICs lacking locally developed thresholds.[25] This method enables comparison with findings from similar previously published studies,[2,17,18] and provides an indication of whether, in a given context/country, an intervention would represent good or poor value for the money spent (i.e. cost-effective or not).[26]

5.5.3.4 Change in cost and survival over time

Since cost-effectiveness of interventions may change over time, I determined the change in costs relative to the change in effects (outcomes) of treatment by year of diagnosis (2013 versus 2017).

This was calculated using the incremental cost-effectiveness ratio (ICER) following *Lin et al.* (2016) methodology as change in cost (incremental cost) per change in survival (incremental survival) for patients diagnosed in 2013 versus 2017.[27] In ICER calculation, costs were estimated in EGP to account for change in the currency exchange rate and economic instability in Egypt between 2013 and 2017. I used 3-year survival in ICER calculation because patients diagnosed in 2017 only completed 3 years follow-up and 5-year survival could not be estimated.

5.5.4 Statistical analysis

I analysed and reported median values and 95% CI of the cost estimates as the main descriptive statistics due to non-normality of data. I used Wilcoxon and Kruskall-Wallis tests to compare costs between the following patient groups, as appropriate: risk/stage/subtype groups, relapse/PD status, patients who underwent bone marrow transplant (BMT) versus those who did not, and between patients diagnosed in 2013 versus 2017. The 5-year overall survival (95% CI) was calculated using the Kaplan–Meier method, and I used log-rank tests to compare the difference in survival between groups. Statistical significance was determined at $p<0.05$. The calculated 5-year overall survival rates and the 3-year costs were then used as input variables to perform cost-effectiveness analysis.

Cox proportional hazards (PH) models were used to evaluate the association between treatment costs (USD) and 5-year OS, adjusting for 'year of diagnosis', 'sex', 'age at diagnosis', and 'diagnostic group' variables. I used stratified cox model using the *strata*() function for the 'age at diagnosis' and 'diagnostic group' variables, as appropriate. I also conducted the Cox PH model for each of the four main cancer groups (leukaemia, lymphoma, brain tumours, other solid tumours), adding the 'disease status' as a confounding factor. I derived hazard ratios (HRs), 95%

confidence intervals (CIs), and coefficients from Cox models. I tested the Cox PH model assumptions statistically and graphically using the scaled Schoenfeld residuals, and the model's goodness-of-fit using the partial log-likelihood.

For survival analysis, patients were followed-up from the date of diagnosis, until either last date-of-follow-up (December 30th, 2020) or date of death; patients who did not complete 5 years of follow-up were censored observations. All statistical analyses were performed in *R* statistical package version 4.0.2. by using *dplyr*, *survival*, *survminer*, and *scales* packages.

5.6 Results

5.6.1 Patient characteristics

I extracted data of 9,440 children with cancer who were treated at CCHE between 2013–2017, of which 8,886 were eligible for inclusion in this study. Table 5.1 shows patient and disease-related characteristics; mean age at diagnosis was 6.4 years (SD ± 4.7), and male to female ratio was 1.4:1. Cancer types were distributed as follows: 26.5% had leukaemia, 15.2% had lymphomas, 18.6% had CNS/brain tumours, 37.5% had solid tumours, and 2.2% had other tumours. At 3-years post-diagnosis, 2,024 patients (22.7%) died; 120 patients (1.5%) were lost follow-up, and 1,258 (14.2%) experienced relapse/refractory or PD.

Table 5.1. Patient and disease characteristics at initial diagnosis, and survival/disease status at 3 years post-diagnosis, (N=8,886)

	No. of	**Percent (%)**
Age (y) at diagnosis		
Mean ± SD Median (IQR)	6.4 (± 4.7) years	
Age-groups		
0–1 year	732	8.2%
1–4 years	3,587	40.4%
5–9 years	2,444	27.5%
10–14 years	1,518	17.1%
15–18 years	605	6.8%
Gender		
Male	5,151	58%
Female	3,735	42%
Childhood cancer types, ICCC-3 groups		
I. leukaemia	2,357	26.5%
Ia. Acute Lymphoblastic Leukaemia	1,660	18.7%
Ib. Acute Myeloid Leukaemia	544	6.1%
Ic. Chronic Myeloid Leukaemia	77	0.9%
Id. Myelodysplastic Syndrome	28	0.3%
Ie. Juvenile myelomonocytic leukaemia	48	0.5%
II. Lymphomas	1,344	15.1%
IIa. Hodgkin Lymphoma	709	8.0%
IIb. Non-Hodgkin Lymphoma	635	7.1%
III. Brain Tumours	1,659	18.7%
IV–X. Other Solid tumours	3,329	37.5%
IV.a Neuroblastoma	967	10.9%
V. Retinoblastoma	523	5.9%
VI. Renal Tumours	521	5.9%
VII.a Hepatoblastoma	122	1.4%
VIIIa Osteosarcoma	305	3.4%
VIIIc Ewing sarcomas	297	3.3%
IXa. Rhabdomyosarcoma	317	3.6%
IXb-d Other soft tissue tumours	127	1.4%
X. a-c Germ Cell Tumours	150	1.7%
XII. Other Tumours (LCH)	197	2.2%
Survival status*		
Alive	6,742	75.8%
Died	2,024	22.7%
Lost follow-up (during/after treatment)	120	1.5%
Relapse/refractory or PD status*		
Yes	1,258	14.1%
No	7,628	85.9%

***** Survival and relapse/refractory/PD status were determined at the end of 3 years post-diagnosis. ****** Patients who lost follow-up are those who did not show for treatment or lost contact (after completing treatment) for at least 3 months, and were not reachable through contact by phone. Abbreviations: ICCC-3: International Classification of Childhood Cancer, 3rd edition; LCH: Langerhans cell histiocytosis. PD: Progressive Disease. PD was defined as cancer that is growing, spreading or getting worse (at least a 20 percent growth in the size of the tumour or spread of the tumour since the beginning of treatment).

5.6.2 Cost-effectiveness analysis

5.7.5.1 Cost-effectiveness for all cancers combined, and stratified by cancer type

For all childhood cancers combined, median total 3-year costs were $19,799, and 5-year overall survival was 73.1% (Table 5.2). Cost/DALY averted for all cancers combined was $1,384, which is 0.5 times the GDP per capita, thus treatment was considered ‘very cost-effective’ as per WHO–CHOICE criteria (Table 5.2). The highest cost/DALY averted (*i.e. least cost-effective*) was noted for patients with leukaemia, while it was lowest (*i.e. most cost-effective*) for patients with lymphoma, and retinoblastoma (range: 0.1–1.3 times GDP per capita). On sensitivity analysis at 6% discount rate, cost/DALY averted was either <1× or <3× GDP per capita. In the two-way sensitivity analyses at varying discount rates (at 0%, 3%, and 6%), the resultant cost/DALY averted remained below 1× GDP per capita (i.e.: very cost-effective) (Table 5.3).

Table 5.2. Cost per DALY averted for childhood cancers, by ICCC-3 groups, diagnosed between 2013–2017

Childhood Cancer type (No. of patients)	**5-year Overall survival (%) (95% CI)**	**Median Costs* (95% CI)**	**Cost/DALY averted (3% discount rate) ****	**Ratio of cost/DALY averted to GDP/Capita (3% discount) ***	**Cost/DALY averted (6% discount) ****	**Ratio of cost/DALY averted to GDP per Capita (6% discount) ***
All cancers combined (n=8,886)	73.1 (72.1–0.74.0)	$19,799 (8,921–34,204)	$1,384	0.5	$2,347	0.8
I. Leukaemia (n=2,357)	74.6 (72.7–76.4)	$35,193 (34,240 – 35,817)	$1,762	0.6	$2,904	1.0
Ia. Acute Lymphoblastic Leukaemia (n=1660)	81.6 (79.7–83.5)	$33,043 (25,270–43,201)	$1,512	0.5	$2,505	0.8
Ib. Acute Myeloid Leukaemia (n=544)	54.5 (50.2–59.2)	$43,309 (31,201–59,997)	$3,033	1.0	$5,077	1.7
Ic. Chronic Myeloid Leukaemia (n=77)	94.8 (89.9–99.8)	$27,790 (14,149–47,499)	$1,205	0.4	$1,808	0.6
Id. Myelodysplastic Syndrome (n=28)	38.8 (23.8–63.3)	$45,618 (29,012–55,227)	$3,898	1.3	$6,521	2.2
Ie. Juvenile myelomonocytic leukaemia (n=48)	35.3 (23.0–54.0)	$31,055 (21,404–43,632)	$4,010	1.3	$7,727	2.6
II. Lymphomas (n=1,344)	89.7 (88.0–91.4)	$10,799 (9,333 – 12,106)	$644	0.2	$1,037	0.3
IIa. Hodgkin Lymphoma (n=709)	95.2 (93.4–97.0)	$5,960 (4,925–7,513)	$297	0.1	$464	0.2
IIb. Non-Hodgkin Lymphoma (n=635)	83.6 (80.6–86.5)	$21,509 (15,037–34,167)	$1,105	0.4	$1,831	0.6
III. Brain Tumours (n=1,659)	60.8 (57.9–63.7)	$12,607 (6,469–19,726)	$848	0.3	$1,416	0.5
IV–X. Other Solid tumours (n=3,329)	70.4 (67.5–70.8)	$17,607 (17,156 – 18,494)	$1,132	0.4	$2,005	0.7
IV.a Neuroblastoma^ (n=967)	55.4 (52.2–58.8)	$25,459 (14,479 38,746)	$1,973	0.7	$3,693	1.2
V. Retinoblastoma (n=523)	95.1 (93.0–96.9)	$7,433 (5,476–9,647)	$377	0.1	$725	0.2
VI. Renal Tumours (n=521)	83.1 (79.9–86.4)	$10,357 (7,599–19,177)	$708	0.2	$1,298	0.4
VII.a Hepatoblastoma (n=122)	63.4 (55.1–72.7)	$17,477 (13,106–21,760)	$1,176	0.4	$2,232	0.7
VIIIa Osteosarcoma (n=305)	46.2 (40.7–52.5)	$34,519 (22,761–42,897)	$2,137	0.7	$3,043	1.0
VIIIc Ewing sarcomas (n=297)	67.6 (62.0–73.7)	$28,398 (23,203–35,881)	$1,433	0.5	$2,197	0.7
IXa. Rhabdomyosarcoma (n=317)	58.4 (52.9–64.3)	$16,607 (12,137–23,946)	$1,248	0.4	$2,154	0.7
IXb-d Other soft tissue tumours (n=127)	80.5 (73.7–87.8)	$14,829 (6,646–25,538)	$721	0.2	$1,157	0.4
X. a-c Germ Cell Tumours (n=150)	88.3 (83.1–93.6)	$11,984 (5,136–18,348)	$560	0.2	$986	0.3
XII. Other tumours (LCH) (n=197)	90.2 (86.1–94.4)	$7,821 (4,711 – 11,304)	$395	0.1	$708	0.2

* Median costs are estimated in US dollars. ** Costs and effects (survival) were discounted at 3% (base-case scenario), and 6% on sensitivity analysis. *** Ratio <1 (very cost-effective); ratio between 1 and 3 (cost-effective); Ratio >3 (not cost-effective). ^ Includes Neuroblastoma and ganglioneuroblastoma.

Table 5.3. Base-case and sensitivity analysis for Cost per DALY averted, (N=8,886)

Scenarios of Life Expectancy (LE)* and Late Effect Morbidity	**Cost/ DALY averted (Ratio of cost/DALY averted to GDP/capita)**		
	0% discount	**3% discount**	**6% discount**
Optimal Case (Normal LE, No Utility Adjustment for Late Effect Morbidity	$478 (0.1)	$1,245 (0.4)	$2,289 (0.7)
Base Case (Normal LE + Utility Adjustment for Late Effect Morbidity)	$535 (0.1)	$1,384 (0.4)	$2,347 (0.7)
15% Reduction in LE + Utility Adjustment for Late Effect Morbidity	$683 (0.2)	$1,507 (0.5)	$2,482 (0.8)
30% Reduction in LE + Utility Adjustment for Late Effect Morbidity	$819 (0.2)	$1,662 (0.5)	$2,579 (0.8)

5.6.2.2 Cost-effectiveness stratified by cancer risk, stage, and subtype

On stratifying patients by stage/risk/subtype at diagnosis, it was observed that cost/DALY averted varied by disease severity, with higher cost/DALY averted noted for the high-risk and advanced stage (defined as: metastatic disease, stage IV) groups. Figure 5.2 shows that the ratio of cost/DALY averted to GDP per capita exceeded 1 (i.e., cost-effective but not very cost-effective) for high-risk ALL, high-risk acute myeloid leukaemia (AML), advanced myelodysplastic syndrome (MDS), high-risk neuroblastoma, metastatic osteosarcoma, and metastatic rhabdomyosarcoma (detailed in Appendix 5.3).

Whereas, this ratio was less than 1 (i.e., very cost-effective) for patients with all lymphoma subtypes, intra-ocular retinoblastoma, low-risk rhabdomyosarcoma, and germ cell tumour subtypes. Additionally, patients with MDS and high-risk neuroblastoma who underwent BMT had lower cost/DALY averted (more cost-effective) than those who did not undergo BMT (Figure 5.2; detailed in Appendix 5.3).

Cancer Type	Risk groups or Subtypes	5-year survival	3-year median costs (USD)	Cost/DALY Averted (3% discount) ^	Ratio of Cost/DALY averted to GDP/ Capita (3%)
ALL[NA~]	Low	0.925	$38,114	$1,041	0.3
	Standard	0.762	$26,820	$1,766	0.6
	High	0.545	$57,272	$3,785	1.3
AML	Low	0.731	$42,598	$2,268	0.8
	Intermediate	0.467	$42,216	$3,178	1.1
	High	0.373	$52,909	$4,544	1.5
MDS	Low	0.333	$29,168	$4,258	1.4
	Intermediate	0.667	$26,684	$1,563	0.5
	High	0.324	$49,364	$4,936	1.6
	Very high	0.286	$52,103	$6,319	2.1
Hodgkin Lymphoma	Low	0.988	$5,123	$191	0.1
	Intermediate	0.943	$6,467	$301	0.1
	High	0.917	$7,310	$487	0.2
CNS and brain tumours	Astrocytoma	0.699	$12,357	$709	0.2
	Ependymoma	0.661	$11,009	$716	0.2
	Medulloblastoma /Embryonal	0.573	$23,082	$1,524	0.5
	Neuronal & Mixed Neuronal	0.867	$10,963	$514	0.2
	Optic Gliomas	0.858	$11,912	$486	0.2
	Brain stem lesions	0.116	$3,481	$1,273	0.4
	Others**	0.832	$11,217	$607	0.2
Neuroblastoma	Low	1	$5,613	$303	0.1
	Intermediate	0.893	$14,599	$697	0.2
	High	0.328	$34,852	$4,232	1.4

Cancer Type	Stages or Subtypes		5-year survival	3-year median costs (USD)	Cost/DALY Averted (3% discount) ^	Ratio of Cost/DALY averted to GDP/ Capita (3%)
CML	Chronic phase		0.944	$27,336	$1,125	0.4
	Blast crisis		1	$67,950	$2,371	0.8
	Accelerated		1	$64,354	$1,983	0.7
AML	AML		0.515	$45,165	$3,316	1.1
	APL		0.768	$33,555	$1,701	0.6
	AML Down Syndrome		0.691	$39,611	$1,738	0.6
MDS	MDR-AML		0.521	$49,364	$3,469	1.1
	RAEB		0.381	$52,103	$3,961	1.3
	RC		0.333	$28,545	$3,523	1.2
	BMT	Yes	0.686	53,296	$2,361	0.8
		No	0.238	42,311	$6,106	2.0
JMML	BMT	Yes	0.464	36,700	$3,303	1.1
		No	0.254	22,642	$4,393	1.5
Non-Hodgkin Lymphoma	Stage I		1	$13,865	$500	0.2
	Stage II		0.942	$15,400	$643	0.2
	Stage III		0.847	$20,436	$1,053	0.3
	Stage IV		0.728	$33,281	$1,691	0.6
Retinoblastoma	Intra-ocular		0.984	$7,149	$304	0.1
	Extra-ocular		0.539	$20,340	$1,624	0.5
	Unilateral		0.984	$6,401	$270	0.1
	Bilateral		0.988	$8,314	$349	0.1
Neuroblastoma	Stage 1		0.954	$5,503	$320	0.1
	Stage 2		0.972	$5,933	$275	0.1
	Stage 3		0.755	$19,655	$1,282	0.4
	Stage 4		0.378	$31,281	$3,354	1.1
	Stage 4S		0.765	$10,576	$792	0.3

Renal Tumours	Wilms tumour	0.859	$10,076	$659	0.2	***Wilms Tumours***	Stage I	0.978	$7,955	$383	0.1
	Rhabdoid tumour	*X*	$17,639	*X*	*X*		Stage II	0.968	$7,705	$384	0.1
	CCSK	0.779	$24,498	$1,291	0.4		Stage III	0.875	$9,800	$592	0.2
	RCC	0.716	$4,576	$266	0.1		Stage IV	0.785	$16,970	$986	0.3
	Others	0.941	$8,993	$225	0.1		Stage V	0.742	$13,295	$882	0.3
Hepatoblastoma	Very Low	*X*	$5,111	*X*	*X*	***Hepatoblastoma***	Stage I	1	$7,126	$245	0.1
	Low	1	$9,918	$429	0.1		Stage II	*X*	*X*	*X*	*X*
	High	0.614	$17,617	$1,187	0.4		Stage III	0.711	$17,627	$1,043	0.3
							Stage IV	0.359	$17,967	$1,986	0.7
Ewing Sarcoma	Localized	0.777	$28,638	$1,253	0.4	***Osteosarcoma***	Localized	0.589	$36,863	$1,798	0.6
	Metastatic	0.444	$27,780	$2,158	0.7		Metastatic	0.222	$27,992	$3,753	1.2
RMS	Low	0.858	$12,215	$643	0.2	***RMS***	Stage I	0.792	$14,599	$784	0.3
	Intermediate	0.688	$17,112	$1,073	0.4		Stage II	0.784	$17,066	$1,036	0.3
	High	0.263	$17,056	$2,612	0.9		Stage III	0.646	$17,153	$1,019	0.3
							Stage IV	0.212	$17,056	$3,421	1.1
Germ Cell tumours	Low	1	$3,109	$123	<0.1	***Germ Cell Tumours***	Stage I	1	$3,145	$784	0.3
	Intermediate	0.921	$7,991	$436	0.1		Stage II	0.891	$7,599	$1,036	0.3
	High	0.811	$17,104	$886	0.3		Stage III	0.887	$16,793	$1,019	0.3
							Stage IV	0.638	$17,595	$3,421	1.1
Other soft tissue tumours	Low	0.929	$6,432	$337	0.1	**Langerhans cell histiocytosis**	Multisystem RO-LR	0.984	$8,924	$385	0.1
	Intermediate	0.849	$18,612	$804	0.3		Multisystem RO+ HR	0.523	$7,863	$1,339	0.4
	High	0.307	$24,491	$2,729	0.9		Uni-system Multifocal	0.969	$7,863	$349	0.1
							Uni-system Unifocal	0.984	$3,609	$186	0.1

^ Costs and effects were discounted at 3% (base-case scenario) and 6% (sensitivity analysis). * Not cost-effective treatment (>3 times GDP per Capita). ~ ALL risk was undetermined for 27 patients who died before risk stratification. 'X' refers to sub-groups of patients who did not complete 5 years of follow-up, or had no deaths or survivors within this group, and for which 5-year survival could not be calculated. ** Other CNS/brain tumours include: Other specified and unspecified intracranial and intraspinal neoplasms. Abbreviations: ALL: Acute Lymphoid Leukaemia; AML: Acute Myeloid Leukaemia; APL: Acute Promyelocytic Leukaemia; MDS: Myelodysplastic Syndrome; JMML: Juvenile myelomonocytic Leukaemia; CML: Chronic Myeloid Leukaemia; BMT: Bone Marrow Transplant; RMS: Rhabdomyosarcoma; CCSK: Clear Cell Sarcoma of the Kidney; RCC: Renal Cell Carcinoma. RAEB: Refractory anaemia with excess blasts; RC: refractory cytopenia.

5-year Overall Survival		3-Year Median Cost		Cost/DALY Averted		Ratio of Cost/DALY to GDP/Capita	
	Survival below 30%		More than 30,000 USD		More than 9,000 USD		Not cost-effective (ratio > 3)
	Survival 30%-60%		10,000 to 30,000 USD		3,000 to 9,000 USD		Cost-effective (ratio >1 up to 3)
	Survival above 60%		Up to 10,000 USD		Up to 3,000 USD		Very cost-effective (ratio <1)

Figure 5.2. Cost per DALY averted for childhood cancers, stratified by stage/risk, subtype, BMT status

5.6.2.3 Cost-effectiveness stratified by disease status

Patients with acute leukaemia (ALL and AML) who had relapsed/refractory disease within the first 3 years post-diagnosis (early relapse) had cost/DALY averted >3× GDP per capita (i.e., not cost-effective) (Figure 5.3, Appendix 5.4). In relapsed/refractory acute leukaemia, cost/DALY averted was not cost-effective for patients with either ALL that was initially standard or high-risk, high-risk at time of relapse, T-cell ALL, or high-risk AML (Appendix 5.5).

Patients with high-risk ALL at the time of relapse and those with relapsed/refractory AML who underwent BMT had more cost-effective treatment than those who did not undergo BMT (Figure 5.3, Appendix 5.4). Furthermore, the ratio of cost/DALY averted to the GDP/capita also exceeded 3 (i.e.: not cost-effective) for the patient groups with relapsed/progressive brain tumours, hepatoblastoma, Ewing sarcoma, neuroblastoma, and MDS (Figure 5.3, Appendix 5.4).

Cancer Type	Relapse/refractory or Progressive disease (PD) status			5-year overall Survival	3-Year Median Costs (USD)	Costs/DALY averted (3% discount) ^	Ratio of Costs/ DALY to GDP/Capita (3%) *
Acute Lymphoblastic Leukaemia	Relapse/refractory			0.164	$50,261	$11,014	3.6
	No			0.886	$31,905	$1,321	0.4
	Relapsed/ refractory ALL	Initial Risk	Low	0.404	$40,157	$3,749	1.2
			Standard	0.094	$52,385	$18,751	6.2
			High	0.136	$57,853	$16,404	5.4
		Subtype	T-cell	0.109	$56,486	$18,068	6.0
			B-cell	0.191	$49,191	$8,947	3.0
	Relapsed ALL	Site of relapse	Haematological or combined	0.058	$49,634	$30,717	10.2
			Isolated extra medullary	0.326	$54,467	$5,696	1.9
		Risk of relapse**	Low-risk	0.462	$50,170	$4,489	1.5
			High-risk	0.089	$47,593	$20,146	6.7
		BMT for high-risk relapse ALL	Yes	0.312	$91,359	$7,053	2.3
			No	0.077	$49,535	$22,865	7.6
Acute Myeloid Leukaemia	Relapse/refractory			0.099	$59,519	$20,075	6.6
	No			0.699	$39,540	$2,150	0.7
	Relapsed/ refractory AML	Initial Risk ***	Low	0.427	$65,546	$5,809	1.9
			Intermediate	0.286	$53,087	$6,419	2.1
			High	0.108	$64,860	$21,183	7.0
		BMT	Yes	0.394	$93,388	$8,061	2.7
			No	0.038	$57,148	$59,265	19.6
Brain and CNS tumours	Relapse/PD			0.081	$20,904	$9,710	3.2
	No			0.665	$11,789	$729	0.2
Chronic Myeloid Leukaemia	PD			1	$34,260	$1,246	0.4
	No			0.944	$27,790	$1,191	0.4
Ewing Sarcoma	Relapse/PD			0.122	$34,056	$9,530	3.2
	No			0.888	$27,224	$994	0.3
Germ cell tumours	Relapse/PD			0.615	$16,836	$1,041	0.3
	No			0.909	$11,503	$524	0.2

Hepatoblastoma	Relapse/PD	0.076	$17,362	$10,199	3.4
	No	0.899	$17,617	$808	0.3
Hodgkin Lymphoma	Relapse/PD	0.754	$24,204	$1,090	0.4
	No	0.967	$5,821	$253	0.1
JMML	Relapse/PD	1	$32,014	$1,711	0.6
	No	0.449	$31,055	$2,980	1.0
LCH	Relapse/PD	0.812	$13,586	$851	0.3
	No	0.931	$6,845	$261	0.1
Myelodysplastic Syndrome	PD	0.147	$39,552	$10,284	3.4
	No	0.875	$54,488	$1,876	0.6
Neuroblastoma	Relapse/PD	0.156	$37,984	$9,662	3.2
	No	0.623	$23,161	$1,635	0.5
Non-Hodgkin Lymphoma	Relapse/PD	0.416	$48,700	$4,542	1.5
	No	0.867	$20,436	$982	0.3
Osteosarcoma	Relapse/PD	0.222	$38,076	$4,939	1.6
	No	0.574	$32,149	$1,615	0.5
Other soft tissue tumours	Relapse/PD	0.392	$21,181	$1,940	0.6
	No	0.934	$12,881	$547	0.2
Renal Tumours	Relapse/PD	0.303	$29,419	$3,889	1.2
	No	0.961	$9,876	$569	0.2
Retinoblastoma	Relapse/PD	--	$22,626	--	-
	No	0.969	$7,282	$353	0.1
Rhabdomyosarcoma	Relapse/PD	0.146	$23,801	$6,657	2.2
	No	0.917	$13,485	$591	0.2

^ Costs were discounted at 3% and 6%. * Not cost-effective treatment (>3 times GDP per Capita). ** Low-risk of relapse includes B-cell with isolated extra-medullary relapse, who relapse within 18 months from date of diagnosis. All patients not meeting these criteria are high-risk relapsing patients. *** For relapsed/refractory AML by risk groups, only 3-year OS was calculated as the high-risk group did not complete 5 years follow-up.

5-year Overall Survival		3-Year Median Cost		Cost/DALY Averted		Ratio of Cost/DALY to GDP/Capita	
	Survival below 30%		More than 30,000 USD		More than 9,000 USD		Not cost-effective (ratio > 3)
	Survival 30%-60%		10,000 to 30,000 USD		3,000 to 9,000 USD		Cost-effective (ratio >1 up to 3)
	Survival above 60%		Up to 10,000 USD		Up to 3,000 USD		Very cost-effective (ratio <1)

Figure 5.3. Cost per DALY averted, stratified by relapse/refractory or progressive disease (PD) status at 3 years post-diagnosis

5.6.2.4 Change in cost relative to change in survival

Change in cost per change in 3-year overall survival (ICER) is shown in Appendix 5.6. Between 2013 and 2017, median costs increased by 25.0% for all cancers combined, from EGP 316,228 ($22,117) to EGP 395,302 ($16,409) (p<0.001), with varying rise in costs among the different cancer types. However, costs (USD) decreased by 25.8% due to EGP devaluation. The 3-year overall survival rates improved from 74.1% to 78.7% for all cancers combined (p <0.001), ALL (by 6.9%, p=0.007), Ewing sarcoma (by 19.5%, p=0.012), non-Hodgkin lymphoma (NHL) (by 12.7%, p=0.040), and hepatoblastoma by (27.4%, p=0.018) (Appendix 5.6). Whereas, the 3-year survival decreased for neuroblastoma by 11.3% (p=0.045), and the remaining cancers showed no significant change in survival over time. The disease characteristics of the two cohorts (diagnosed in 2013 versus 2017) were almost uniform for majority of cancers (Appendix 5.7).

5.6.3 Association between costs and survival

On multivariate Cox regression analysis, higher costs (each 1,000 USD) were associated with inferior survival [HR (95% CI): 1.025 (1. 023 – 1.028); p<0.001] for all cancers combined, after adjusting for potential confounders (Table 5.4). Similarly, higher costs were associated with significantly worse survival outcomes within each of the four cancer groups; leukaemia, lymphoma, brain tumours, and other solid tumours**,** as follows: leukaemia [HR (95% CI): 1.012 (1.006–1.02); p<0.001], lymphoma [HR (95% CI): 1.035 (1.024–1.045); p<0.001], brain tumours [HR: 1.017 (1.003 – 1.03); p<0.001], and other solid tumours (HR: 1.026 (1.023- 1.03); p<0.001) (Table 5.4). The Cox PH assumptions were met indicating goodness-of-fit.

Table 5.4. Hazard ratio (95% CI) estimated in Cox regression model for the association between costs and risk of mortality controlling for confounders, for all cancers combined and four main cancer types (who survived >1 year)

Variable	HR (95% CI)	Coefficient	*p*-value
All cancers combined (n=7,667)			
Costs of treatment** (1,000 USD)	1.025 (1. 023 – 1.028)	0.025	<0.001*
Sex			
Female	Ref. group	Ref. group	Ref. group
Male	0.931 (0.832 – 1.043)	-0.071	0.219
Year of diagnosis	0.947 (0.908 – 1.989)	-0.053	0.014*
Leukaemia (n= 2,067)			
Costs of treatment** (1,000 USD)	1.012 (1.006 – 1.02)	0.011	<0.001*
Sex			
Female	Ref. group	Ref. group	Ref. group
Male	0.862 (0.684 – 1.09)	-0.148	0.213
Year of diagnosis	0.937 (0.859 – 1.02)	-0.065	0.142
Age at diagnosis			
0-4 years	Ref. group	Ref. group	Ref. group
5-9 years	0.839 (0.636 – 1.11)	-0.175	0.221
10-14 years	0.849 (0.608 – 1.19)	-0.164	0.344
15-18 years	1.161 (0.758 – 1.78)	0.148	0.493
Relapse/refractory status			
No	Ref. group	Ref. group	Ref. group
Yes	20.865 (16.287 – 26.73)	3.038	<0.001*
Lymphomas (n= 1,344)			
Costs of treatment** (1,000 USD)	1.035 (1.024 – 1.045)	0.033	<0.001*
Sex			
Female	Ref. group	Ref. group	Ref. group
Male	0.565 (0.336 – 0.958)	-0.571	0.033*
Year of diagnosis	0.810 (0.660 – 0.994)	-0.211	0.044*
Age at diagnosis			
0-4 years	Ref. group	Ref. group	Ref. group
5-9 years	1.088 (0.526 – 2.248)	0.084	0.717
10-14 years	0.898 (0.430 – 1.873)	-0.107	0.856
15-18 years	1.138 (0.473 – 2.741)	0.129	0.588
Relapse/refractory status			
No	Ref. group	Ref. group	Ref. group

Yes	12.928 (7.718 – 21.654)	2.559	<0.001*
Brain Tumours (n= 1,659)			
Costs of treatment** (1,000 USD)	1.017 (1.003 – 1.03)	0.016	0.019*
Sex			
Female	Ref. group	Ref. group	Ref. group
Male	0.912 (0.714 – 1.16)	-0.092	0.459
Year of diagnosis	1.029 (0.934 – 1.13)	0.028	0.566
Age at diagnosis			
0-4 years	Ref. group	Ref. group	Ref. group
5-9 years	0.873 (0.659 – 1.16)	-0.135	0.345
10-14 years	0.972 (0.698 – 1.35)	-0.028	0.866
15-18 years	0.897 (0.512 – 1.57)	-0.108	0.704
Relapse/progressive status			
No	Ref. group	Ref. group	Ref. group
Yes	7.079 (5.306 – 9.44)	1.957	<0.001*
Other Solid Tumours (n= 2,908)			
Costs of treatment** (1,000 USD)	1.026 (1.023- 1.03)	0.025	<0.001*
Sex			
Female	Ref. group	Ref. group	Ref. group
Male	0.917 (0.780 – 1.080)	-0.085	0.301
Year of diagnosis	0.956 (0.898 – 1.021)	-0.044	0.170

* Significant at *p*-value <0.05. In Cox PH models for all cancers combined and for the solid tumours group, the 'age at diagnosis' and 'diagnostic group' variables were stratified in the Cox model using the *strata*() argument for which there are no hazards ratios for the stratification variables.

5.7 Discussion

5.7.1 Summary and interpretation of findings

Childhood cancer treatment was very cost-effective at CCHE, as the ratio of cost/DALY averted to GDP per capita (0.5) was far below the WHO–CHOICE threshold. Cost-effectiveness of treatment varied substantially by cancer type, as differences in costs depend on treatment complexity and duration, and differences in survival vary with disease nature.[2]

Patients with AML had the highest cost/DALY averted (i.e., least cost-effective) due to intensive chemotherapy and supportive care with long hospital stays incurring high costs, despite their inferior survival outcomes. The cost/DALY averted was also high for ALL patients due to longer chemotherapy duration, for osteosarcoma due to expensive orthopaedic surgeries, and for neuroblastoma due to highly intensive chemotherapy.[2] On the other hand, patients with lymphoma had low cost/DALY averted due receiving less-intensive chemotherapy in the outpatient units of short duration.[2]

Notably, the treatment of patients with relapsed/refractory acute leukaemia (ALL/AML) was not cost-effective, owing to high treatment costs (first-line and second-line/third-line therapy) and inferior survival. Furthermore, indicated patient groups who received BMT (high-risk relapsing ALL, relapsed/refractory AML, and high-risk neuroblastoma) showed more cost-effective treatment than those who were ineligible or unable to receive BMT. However, only a small number of patients who have human leukocyte antigen (HLA)–matched donor underwent BMT, due to limited BMT bed capacity at CCHE.

Between 2013–2017, costs of treatment (EGP) increased for all cancers combined by 25.0% in real terms after adjusting for increasing local prices due to inflation. Neuroblastoma survival decreased significantly over time due to shifting to a more intensive treatment protocol for high-risk patients with more treatment-related mortalities. It is unlikely that changes in costs or survival over time were due to changes in patient-related or disease-related characteristics as they were nearly uniform for most cancers (Appendix 5.7). After controlling for confounding factors, the multivariate Cox model showed that patients with higher treatment costs had worse survival. This is likely because the high-risk/advanced-stage or relapsed/PD groups have higher costs and much inferior survival.

5.7.2 Comparison with other published literature

Overall, findings form this study confirm prior results of the systematic review by Fung *et al.* (2019) that childhood cancer treatment is very cost-effective in LMICs.[2] In this study, the ratio of cost/DALY averted to GDP per capita was 0.5, similar to results by *Githang'a et al.* (2021) in Tanzania and Zimbabwe.[3] A few published studies reported treatment cost-effectiveness of individual childhood cancers from LMICs, limiting comparison. The ratio of cost/DALY averted to GDP per capita for ALL patients treated at CCHE was 0.5; higher than that reported in other studies (range: <0.1–0.25), likely due to varying protocols in the different countries.[2] At CCHE, this ratio was higher for Hodgkin lymphoma (0.1 versus 0.05 in South Africa), and lower for retinoblastoma (0.1 versus 0.2 in Uganda).[28,29] There is a lack of published literature about cost-effectiveness of childhood cancer treatment in the Eastern Mediterranean countries.[30]
Although abandonment of treatment is a major cause of treatment failure in LMICs, particularly where parents are required to pay out-of-pocket,[3,18,31] this was not a problem at CCHE as the

abandonment rate is 1.5% which would not likely affect the results. Low abandonment rate is attributed to regular patients' follow-up and offering treatment for free.

Financing childhood cancer treatment at CCHE based on philanthropic donations was found to be a successful funding scheme, similar to other centres in LMICs.[18,32] Although treatment at CCHE is very cost-effective, affordability is a distinct issue as reported by *Renner* and colleagues (2018).[31] At CCHE, median 3-year treatment cost is $19,799 which is six times the GDP per capita, which would not have been affordable for families if they had to pay out-of-pocket, as reported in other studies.[33,31]

5.7.3 Strengths and limitations

To the best of my knowledge, this is the first study from Egypt and from a LMIC to report the cost-effectiveness of all childhood cancer types by ICCC-3 groups, stratified by stage/risk and relapse/progressive disease status.[2] A main advantage of this study compared to the other 12 studies included in the systematic review by Fung *et al.* (2019) is that it includes sub-group analysis by cancer type/subtype, risk, stage, and disease status. This provides important new insights that can help decision-makers plan therapy and prioritise treatment interventions.

This study evaluates the cost-effectiveness of treatment for 8,886 children with cancer, representing around 40% of all childhood cancers in Egypt,[33] thus, the findings have implications for a significant number of children with cancer in Egypt. Another strength of the study is the availability and use of high-quality data, where quality checks were routinely done every six months over the five years, and at the time of study initiation ensuring validity of study outcomes. CCHE is the only paediatric oncology centre in Egypt with a reliable costs/survival database enabling cost-effectiveness analysis, therefore, it provides unique

insights addressing the gap in knowledge in Egypt. Finally, this chapter follows the recommendations made by Fung *et al.* (2019) for conducting reliable economic evaluations in LMICs using the CHEERS checklist in study design and reporting of results.[2]

Despite the validity of the study methods, some limitations exist. First, although WHO-CHOICE thresholds are informative in assessing cost-effectiveness of interventions, they are debatable as using GDP-based thresholds seems to lack country specificity. That, in addition to the uncertainty in the modelled cost-effectiveness ratios, can lead to wrong decisions about how to spend healthcare resources.[26] Therefore, these findings should be interpreted with caution, rather than using the threshold values separately.[26] The marginal productivity-based threshold provides a good option for informing decisions around healthcare resource allocation. [34] Yet, this threshold should be country-specific to reflect national health opportunity costs,[34] and is lacking in most LMICs, including Egypt, limiting applicability to local context. Although some health economists consider the 3× GDP/capita threshold too high for LMICs, treatment would still be 'cost-effective' at CCHE based on stricter thresholds.[35] Another threshold exist at 0.5× GDP per capita as opportunity cost threhsolds.[25] Yet, the WHO-CHOICE thresholds remain the standard generic method for CEA for countries that lack local thresholds, and until a more appropriate replacement is found, researchers will continue to use this GDP-based DALY threshold. Furthermore, I conducted sensitivity (uncertainty) analysis to account for the potential uncertainty in the modelled cost-effectiveness ratios.

Second, I included 3-year costs post-diagnosis, covering costs of all first-line treatment and early relapse or treatment failure, whereas late relapses (beyond 3 years) were not accounted for. Nevertheless, since 70% of disease relapse occurs within the first three years post-diagnosis,

therefore, most relapses and their associated costs were already accounted for. This will not likely affect the findings, as the ratio of cost/DALY averted to GDP/capita is far below 1, so, treatment would still be cost-effective.

Third, I excluded some cancer subtypes that lacked complete clinical/survival data at the time of study initiation (Figure 5.1). Nevertheless, these patients represent 3.4% of the initial study cohort and excluding them would not likely impact the results. Additionally, the exclusion criteria were determined upfront before study initiation, and no patient groups with high/low costs, good/poor survival, or advanced disease were intentionally removed that would potentially affect outcomes. Fourth, patients were followed-up until December 2020 (during the COVID-19 pandemic), so, it is possible that COVID-19 could have affected patients' outcomes. Nevertheless, it is unlikely to have affected survival outcomes since all patients in the study cohort have already completed their first-line treatment before 2020. A study conducted by Hammad *et al.* (2021) at CCHE reported that out of 76 children with cancer with confirmed COVID–19, sixty were on first-line treatment, seven were on relapsing protocols, and nine patients were under follow-up.[36] Besides, there were no drug shortages or major delays in treatment during this time at CCHE.

Fifth, this study was conducted at a single centre, so, the generalisability of the results to other centres in Egypt and other LMICs is unknown due to differences in treatment protocols and standards of care. However, to address this issue I transparently disclosed the treatment protocols adopted by CCHE for each cancer type. Finally, since cost-effectiveness is based on survival rates calculated at CCHE, therefore, this study is also prone to same limitations in Chapter 3.

5.7.4 Implications

5.7.4.1. *Implications for policymakers*

At the institution level, knowledge about the cost-effectiveness of treatment at CCHE can help make evidence-informed policy decisions regarding future investments in key priority areas, such as: advocating the adoption of cost-effective novel treatment strategies; and scaling-up of BMT capacity as a cost-effective intervention. At the national level, these findings can help policymakers prioritise childhood cancer national plans by incorporating cost-effective treatment strategies into Egypt's universal health insurance program. Besides, these can also encourage the development of local cost-effectiveness thresholds that consider budget impact and affordability. At the level of LMICs, policy-makers can learn to focus efforts on improving survival for cancers with the most cost-effective treatment strategies. This shall contribute to the WHO Global Initiative of Childhood Cancer (Pillar 3); improve survival with optimal resource use.[37]

5.7.4.2. *Implications for clinicians*

Determining the cost-effectiveness of treatment by ICCC-3 groups, stratified by risk/stage and disease status would help clinicians in making evidence-informed clinical decisions about the most cost-effective treatment options. Additionally, this study presents novel insights into how cancer type/risk/stage/disease status contribute to treatment cost-effectiveness, with potentially generalizable findings; patients with relapsed/progressive cancers, and advanced-stage/high-risk cancers show less cost-effective treatment (despite varying costs and survival from one setting to another); offering BMT for the indicated patients leads to more cost-effective therapy. These interesting findings would trigger similar resource-limited settings in Egypt or other LMICs to assess treatment cost-effectiveness in order to drive improvements in their clinical practice.

5.7.4.3. *Implications for researchers*

These findings pave the way for future research in key priority areas identified in the local context to find solutions to promote the cost-effectiveness of childhood cancer treatment. Moreover, the rigorous methodological approach described in this study serves as a template for future childhood cancer cost-effectiveness studies in other resource-limited contexts.

5.7.4.3 Implications for patients

Providing cost-effective treatment would potentially lead to improved patients' survival outcomes while avoiding unnecessary treatment interventions that do not add value to the patients, in terms of improved health outcomes. This would also reduce potential harms to the patients due unwarranted use of cost-(in)effective treatment interventions.

5.7.5 Evidence-based recommendations for improvement

Accordingly, I suggest the following key recommendations (Panel 5.1) in policy-making (points 1 and 2), current practice (points 3 and 4), and future research (points 5 and 6) to promote cost-effectiveness of childhood cancer treatment and promote high-value care.

Panel 5.1. Recommendations to increase cost-effectiveness and promote high-value care at CCHE/Egypt:

1. Focus on the realistic goal of improving curative outcomes for the cancers with the most cost-effective treatments (relatively low-cost and high survival outcomes).
2. Advocate adopting the most cost-effective treatment strategies for childhood cancers by making price negotiations and establishing collaborations with international institutions.
3. Maximise cost-effectiveness of treatment by providing BMT services for indicated patients.
4. Revise the clinical practice guidelines for cancers with cost-(in)effective treatment and/or low cost-effectiveness estimates; relapsed/progressive and high-risk/advanced-stage cancers.
5. Modify treatment protocol for high-risk neuroblastoma to lower treatment-related mortality.
6. Systematically review the evidence to determine the cost-effective treatment strategies for children with relapsed/refractory acute leukaemia.
7. Understand the clinicians' perception of barriers and facilitators to implementing cost-effective evidence-based treatment interventions.

5.8 Conclusion

Childhood cancer treatment is cost-effective in a resource-limited setting in Egypt, except for relapsed/refractory acute leukaemia and other relapsed/PD cancer groups. Evaluating treatment cost-effectiveness for all childhood cancers and stratifying by stage/risk and disease status helps

identify priority areas for improvement. Cost-effectiveness of treatment varied by disease severity, where patients with higher costs were associated with inferior survival. This is likely attributed to the high cost of treating high-risk/advanced-stage and relapsed/PD cancers, which have inferior survival. The provided evidence-based recommendations and lessons learnt will have practice, policy, and research implications to promote high-value paediatric oncology care in local context, and in other resource-limited settings in LMICs which would learn from the potentially generalizable insights obtained from these study findings.

5.9 How this chapter relates to the overall thesis

My thesis aims to generate evidence to improve childhood cancer health outcomes and resource use in Egypt. Chapter 5 generates real-world evidence from local context (CCHE/Egypt) about the cost-effectiveness of childhood cancer treatment, using updated survival outcomes (derived from Chapter 3) and cost outcomes (derived from Chapter 4). This chapter identifies the childhood cancer types/groups whose treatment was not cost-effective and provides evidence-based recommendations to improve cost-effectiveness. Findings from Chapter 5 highlight a key priority area for improvement (i.e., treatment of relapsed/refractory acute leukemia is not cost-effective), which informs conducting a systematic literature review in Chapter 6.

5.10 Chapter summary

- This chapter estimates the cost-effectiveness of childhood cancer treatment in terms of cost/DALY averted following the WHO–CHOICE criteria.
- Treatment of all childhood cancer types/groups was either ‘very cost-effective’ or ‘cost-effective’, except for relapsed/refractory acute leukaemia and other cancers with relapsed/progressive disease.

- Higher treatment costs were associated with inferior survival outcomes, likely due to the high costs of treating advanced-stage/high-risk and relapsed/progressive cancers, which have poor survival outcomes.

Chapter Five References

1. GBD 2017 Childhood Cancer Collaborators. The global burden of childhood and adolescent cancer in 2017: an analysis of the Global Burden of Disease Study 2017. *Lancet Oncol*. 2019;20(9):1211-1225.
2. Fung A, Horton S, Zabih V, *et al*. Cost and cost-effectiveness of childhood cancer treatment in low income and middle-income countries: a systematic review. *BMJ Global Health* 2019;4:e001825.
3. Githang'a J, Brown B, Chitsike I, Schroeder K, Chekwenda-Makore N, Majahasi F, Ogundoyin O, Renner L, Petricca K, Denburg AE, Horton SE, Gupta S. The cost-effectiveness of treating childhood cancer in 4 centres across sub-Saharan Africa. *Cancer*. 2021;1;127(5):787-793.
4. Fadhil I, **Soliman R**, Jaffar S, Al Madhi S, Saab R, Belgaumi A, *et al*. Estimated incidence, prevalence, mortality, and registration of childhood cancer (ages 0-14 years) in the WHO Eastern Mediterranean region: an analysis of GLOBOCAN 2020 data. *Lancet Child Adolesc Health*. 2022;6(7):466-73.
5. Basbous M, Al-Jadiry M, Belgaumi A, Sultan I, Al-Haddad A, Jeha S, *et al.* Childhood cancer care in the Middle East, North Africa, and West/Central Asia: A snapshot across five countries from the POEM network. *Cancer Epidemiol*. 2021;71(Pt B):101727.
6. Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs A H, Carswell C *et al*. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations *BMJ*. 2022;376:e067975.

7. Steliarova-Foucher E, Stiller C, Lacour B, and Kaatsch P. International Classification of Childhood Cancer, third edition (ICCC-3). *Cancer*. 2005;1;103(7):1457-1467.
8. Harris P, Taylor R, Thielke R, Payne J, Gonzalez N and Jose G. Conde, Research electronic data capture (REDCap), *J Biomed Inform*. 2009 Apr;42(2):377-81.
9. National Cancer Institute (NCI). NCI Dictionary of Cancer Terms: Relapse [Internet]. NCI. 2023 [cited 2023 Mar 16]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/relapse
10. National Cancer Institute (NCI). NCI Dictionary of Cancer Terms: Refractory [Internet]. NCI. 2023 [cited 2023 Mar 16]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/refractory-cancer
11. Verywell Health. Progressive Disease and Cancer [Internet]. Verywell Health. 2022 [updated 2022 Nov; cited 2023 Mar 19]. Available from: https://www.verywellhealth.com/definition-of-progressive-disease-2249171
12. Barlow E. Overview of Methods to Estimate the Medical Costs of Cancer. *Med Care*. 2009;47(7 Suppl 1):S33–S36.
13. Turner H, Lauer J, Tran B, Teerawattananon Y, and Jit M. Adjusting for inflation and currency changes within health economic studies. *Value Health*. 2019;22(9):1026–1032.
14. The World Bank. Official exchange rate (LCU per US$, period average) [Internet]. World Bank Group. 2023 [cited 2020 Aug]. Available from: https://data.worldbank.org/indicator/PA.NUS.FCRF?view=chart
15. The World Bank. GDP deflator (base year varies by country) [Internet]. World Bank Group. 2023. [cited 2020 Aug]. Available from: https://data.worldbank.org/indicator/NY.GDP.DEFL.ZS

16. PwC Middle East. The EGP Devaluation: a new beginning [Internet]. PwC Middle East. 2023 [cited 2020 Aug]. Available from: https://www.pwc.com/m1/en/publications/the-egp-devaluation-a-new-beginning.html

17. Bhakta N, Martiniuk AL, Gupta S, Howard SC. The cost effectiveness of treating paediatric cancer in low-income and middle-income countries: a case-study approach using acute lymphocytic leukaemia in Brazil and Burkitt lymphoma in Malawi. *Arch Dis Child*. 2013;98:155-160.

18. Fuentes-Alabi S, Bhakta N, Vasquez RF, Gupta S, Horton SE. The cost and cost-effectiveness of childhood cancer treatment in El Salvador, Central America: A report from the Childhood Cancer 2030 Network. *Cancer*. 2018;15;124(2):391-397.

19. Murray CJ, Lopez AD, World Health Organization. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Global Burden of Disease and Injury Series, Vol II. Cambridge, MA: Harvard School of Public Health; 1996.

20. World Health Organization (WHO). The Global Burden of Disease: 2004 Update [Internet]. World Health Organization. 2008 [cited 2021 Nov]. Available from: https://apps.who.int/iris/handle/10665/43942

21. Macrotrends LLC. Egypt Life Expectancy 1950-2021 [Internet]. Macrotrends LLC. 2021 [cited on 2021 Nov] Available from: https://www.macrotrends.net/countries/EGY/egypt/life-expectancy#:~:text=The%20life%20expectancy%20for%20Egypt,a%200.22%25%20increase%20from%202018.

22. World Health Organization (WHO). WHO guide to cost-effectiveness analysis. WHO. 2003 (cited 2021 Dec). Available from: https://apps.who.int/iris/bitstream/handle/10665/42699/9241546018.pdf?sequence=1

23. World Bank Group. GDP per capita (current US$) - Egypt, Arab Rep [Internet]. World Bank Group. 2021 [cited 2021 May]. Available from: https://data.worldbank.org/indicator/NY.GDP.PCAP.CD?locations=EG

24. World Health Organization (WHO). New cost-effectiveness updates from WHO-CHOICE. WHO. 2021 (updated 2021 Oct; cited 2021 Dec). WHO. Available from: https://www.who.int/choice/cost-effectiveness/en/

25. Kazibwe J, Gheorghe A, Wilson D, Ruiz F, Chalkidou K, Chi YL. The Use of Cost-Effectiveness Thresholds for Evaluating Health Interventions in Low- and Middle-Income Countries From 2015 to 2020: A Review. *Value Health*. 2022;;25(3):385-389.

26. Bertram MY, Lauer JA, De Joncheere K, Edejer T, Hutubessy R, Kieny MP, *et al*. Cost-effectiveness thresholds: pros and cons. Bull World Health Organ. 2016;1;94(12):925-930.

27. Lin PJ, Winn AN, Parsons SK, Neumann PJ, Weiss ES, Cohen JT. Linking Costs and Survival in the Treatment of Older Adults with Chronic Myeloid Leukaemia. *Med Care*. 2016;54(4):380-5.

28. Stefan DC, Stones D. How much does it cost to treat children with Hodgkin lymphoma in Africa? *Leuk Lymphoma*. 2009;50:196–9.

29. Waddell KM, Kagame K, Ndamira A, *et al*. Improving survival of retinoblastoma in Uganda. *Br J Ophthalmol*. 2015;99:937–42.

30. Gheorghe A, Chalkidou K, Shamieh O, Kutluk T, Fouad F, Sultan I, *et al*. Economics of Pediatric Cancer in Four Eastern Mediterranean Countries: A Comparative Assessment. *JCO Global Oncol.* 2020:6,1155-1170.

31. Renner L, Shah S, Bhakta N, Denburg A, Horton S, Gupta S. Evidence from Ghana Indicates That Childhood Cancer Treatment in Sub-Saharan Africa Is Very Cost Effective: A Report from the Childhood Cancer 2030 Network. *J Glob Oncol*. 2018;4:1-9.

32. Ribeiro RC, Antillon F, Pedrosa F, Pui CH. Global Pediatric Oncology: Lessons from Partnerships Between High-Income Countries and Low- to Mid-Income Countries. *Journal of clinical oncology*: official journal of the American Society of Clinical Oncology. 2016; **34(**1):53–61.

33. Children' Cancer Hospital Egypt (CCHE). Our vision [Internet]. 2022 [cited 2022 Feb]. Available from: https://www.57357.org/en/home-page/

34. Ochalek J, Claxton K, Lomas J, Thompson KM. Valuing health outcomes: developing better defaults based on health opportunity costs. *Expert Rev Pharmacoecon Outcomes Res*. 2021;21(4):729-736.

35. Leech AA, Kim DD, Cohen JT, Neumann PJ. Use and Misuse of Cost-Effectiveness Analysis Thresholds in Low- and Middle-Income Countries: Trends in Cost-per-DALY Studies. *Value Health*. 2018;21(7):759-761.

36. Hammad M, Shalaby L, Sidhom I, Sherief N, Abdo I, Soliman S, *et al.* Management and Outcome of Coronavirus Disease 2019 (COVID-19) in Pediatric Cancer Patients: A Single Centre Experience from a Developing Country. *Clin Lymphoma Myeloma Leuk*. 2021;21(11):e853-e64.

37. World Health Organization (WHO). The Global Initiative for Childhood Cancer (GICC): Increasing access, advancing quality, saving lives [Internet]. 2022 [cited on 2022 Jan]. Available from: https://www.who.int/initiatives/the-global-initiative-for-childhood-cancer

Chapter Six: Systematic review of costs and cost-effectiveness of treatment for relapsed/refractory acute leukaemia in children

"Doing more of what doesn't work won't make it work any better." — Charles J. Givens.

Providing more of the same cost-(in)effective treatment will not make it any more cost-effective. To improve outcomes for children with relapsed/refractory acute leukaemia, it is essential to generate systematic evidence from the literature about other alternative cost-effective treatment options.

6.1. Publication statement

Features of this chapter are published in the following peer-reviewed journal:

Soliman R, Heneghan C, Bolous NS, Sidhom I, Ahmed S, Roberts N, *et al.* Systematic review of costs and cost-effectiveness of treatment for relapsed/refractory acute leukemia in children and young adults. *Expert Rev Hematol*. 2022;15(4):345-57. DOI: 10.1080/17474086.2022.2069096.

6.2 Introduction

Leukaemia is the most common cancer in children and adolescents, accounting for around 35% of all childhood cancers, of which 75% are acute lymphoblastic leukaemia (ALL) and the remaining cases are mostly acute myeloid leukaemia (AML).[1] Approximately 15–20% of childhood ALL patients relapse, and 2% of patients do not respond to treatment (i.e., refractory disease),[2,3,4] whereas around 30% of children with AML relapse.[5]

The survival outcomes of children with relapsed/refractory (r/r) acute leukaemia (ALL and AML) remain poor (around 40%), requiring intensive salvage chemotherapy, bone marrow transplant (BMT) or stem cell transplant (SCT), and/or other novel drugs.[4,6,7] Novel treatments have been developed to improve their survival rates (such as targeted or immunotherapy),[8,9,10] where current treatment incurs high costs due to greater hospital admissions, longer inpatient stays, and expensive novel drugs.[11,12] Therefore, there is a need to determine which treatment strategies are the most cost-effective (i.e., providing greatest health benefit relative to money/resources spent),[13,14] as described in the Background Chapter 2 (section 2.6.3). This is particularly important in resource-limited settings in LMICs, which suffer from much lower survival rates and limited (precious) resources. Yet, limited evidence exists on the cost-effectiveness of treatment for relapsed/refractory paediatric acute leukaemia.[14]

In Chapter 5, I estimated the cost-effectiveness of childhood cancer treatment in a resource-limited setting in Egypt (CCHE), and notably, the treatment of children with relapsed/refractory acute leukaemia was found to be not cost-effective. To address this local problem, I set out to summarise systematic evidence from the literature about the costs and cost-effectiveness of treatment for relapsed/refractory acute leukaemia in children.

6.3 Aim of work

To establish the health economic evidence-base to determine the costs and cost-effectiveness of treatment for relapsed/refractory acute leukaemia in children.

6.4 Objectives

1. To summarise the economic systematic evidence about the costs/cost-effectiveness of the different treatment strategies for relapsed/refractory acute leukaemia in children.

2. To compare the costs, benefits, and cost-effectiveness estimates of the alternative treatment options.
3. To assess the quality of the included studies.
4. To determine the cost-effectiveness of treating relapsed/refractory paediatric acute leukaemia in resource-limited contexts in LMICs.
5. To provide evidence-based recommendations for improvement.

6.5 Methods

This systematic review was conducted and is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist (Appendix 6.1),[15] and the Consolidated Health Economics Evaluation Reporting Standards (CHEERS) checklist (Appendix 6.2).[16] I followed the guidelines by the Centre for Reviews and Dissemination (CRD) for conducting systematic reviews of economic evaluation,[17] and the Campbell and Cochrane Economic Methods Group (CCEMG) guidance for incorporating economic evidence.[13]

6.5.1 Protocol

The protocol of this systematic review is not registered, but is available online (open access) on the institutional website (CCHE) and is available here: https://www.57357.org/app/uploads/2023/02/Systematic-review-of-cost-effectiveness-studies_-Protocol_-SolimanR.pdf

6.5.2 Search strategy

A comprehensive search was conducted by a medical librarian (Nia Roberts) from inception to August 12th, 2021 in the following databases: Medline (OvidSP) [1946-present] Embase

(OvidSP) [1974-present], Cochrane Database Reviews & Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley) [Issue 8 of 12, August 2021], Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS–EED) & Health Technology Assessment Database (HTA) (Centre for Reviews & Dissemination https://www.crd.york.ac.uk/CRDWeb/) [inception to 31/03/2015], Science Citation Index & Social Science Citation Index (Web of Science Core Collection) [1900-present] and Cost Effectiveness Analysis Registry (http://healtheconomics.tuftsmedicalcenter.org/cear2n/search/search.aspx).

Detailed search strategy is presented in Appendix 6.3. The search strategy was developed by a medical librarian (Nia Roberts), and consisted of title/abstract keywords and subject headings to describe the key concepts of 'children', 'leukaemia' and 'relapse'. The search was restricted to English language; no publication limits were applied. I also screened reference list of included articles (snowball search), and duplicate articles were removed in Endnote 20. Full electronic searches are shown in Appendix 6.4.

6.5.3 Eligibility criteria

I included studies with the following inclusion criteria: (1) relapsed acute leukaemia in children and young adults (up to 25 years old) (2) analysis of the cost, cost-effectiveness analysis (CEA), cost-utility (CUA), or cost-benefit of any interventions to treat relapsed/refractory acute leukaemia, including acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML); (3) measurement of economic costs, cost per life year gained (LYG) or quality-adjusted life year (QALY) gained, cost per life saved, cost per Disability-Adjusted Life Year (DALY) averted, incremental cost-effectiveness ratio (ICER), or any other measures of economic

evaluations without restrictions. I excluded studies that only reported clinical effectiveness in terms of survival outcomes, quality of life (QOL), patient-reported outcomes and utilities without cost analysis. The following study types were also excluded: qualitative studies, conference abstracts, reviews, editorials, commentaries or methodological articles. Bibliographies of review articles were searched for including relevant studies.

6.5.4 Study selection and data extraction

Two reviewers (myself and Nancy Bolous) independently screened the titles and abstracts of the initial search results for potential inclusion. Then, the same reviewers conducted full-text review of the selected articles (from titles/abstract screening), and decided on their eligibility based on the above-mentioned inclusion/exclusion criteria. Disagreements between authors were resolved by discussion and consensus in the presence of another senior reviewer (Carl Heneghan).

Data extraction was performed by the same two reviewers on a pilot-tested standardised form on Microsoft Excel. The data extraction form (shown in Appendix 6.5) was structured based on the format and guidelines for summarising the findings of economic evaluation studies, including the NHS Economic Evaluation Database (NHS–EED),[18] the CCEMG,[13] the CHEERS statement,[16] and data items included in published studies.[14,19] The extracted data items from the studies included: main intervention, comparator, costing perspective, study design/setting, economic model used, model specification and assumptions, time horizon, measures of clinical effectiveness and cost-effectiveness, cost categories and main cost drivers, discount rate, willingness-to-pay (cost-effectiveness threshold), and sensitivity analysis.

I extracted costs/cost-effectiveness data from the healthcare and/or payer perspectives only to allow for consistency and comparability across the different health care or payer systems in

different countries and contexts. Whereas costs from the societal perspective were not included in this review (and not extracted) as they provided a greater source of variation based on community preferences, and varying definitions of cost of the lost productivity across different countries and contexts.

6.5.5 Quality assessment of included studies

The same two reviewers (myself and Nancy Bolous) assessed the methodological quality of the included studies and risk of bias, using the CHEERS checklist.[16] The CHEERS checklist evaluates 24 key items recommended by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)[20] to be reported in economic evaluations. To validate the quality assessment, the process was independently checked for completeness and accuracy by another reviewer (Jason Oke). Discordance in quality assessment was resolved by discussion with a senior reviewer (Carl Heneghan).

6.5.6 Data synthesis and analysis

I summarized the main characteristics and results of the included studies by tabulating the characteristics and key findings of the included studies. This was supported by a narrative summary that compared the main results among the included studies. I reported the original costs and reference year of the treatment interventions as presented in the included articles. Then, I converted all cost outcomes to USD (2019) using the World Bank exchange rates (for currencies in different countries),[21] and inflated using the US inflation rates to the reference year (2019) based on the World Bank GDP deflator.[22] I reported median (IQR), mean (±SD) values, and ranges of costs, LYs gained, and QALYs gained. I calculated the incremental costs and ICERs between the different treatment strategies in a standardised currency and reference year (USD

2019), to allow for comparability of results among the included studies. I also calculated the median values and ranges of the CHEERS checklist scores of the included studies.

6.6 Results

6.6.1 Search results and characteristics of included studies

I included 12 studies from the 1,219 references identified.[23–34] Figure 6.1 shows PRISMA flow diagram of included/excluded studies. The characteristics of the 12 included articles are summarized in Table 6.1. All studies were conducted in high-income countries (HICs), and none were reported from resource-limited settings in low- and middle-income countries (LMICs). Ten studies [25–34] (83.3%) addressed r/r paediatric ALL, and only two studies, evaluated the costs/cost-effectiveness of treating r/r ALL and AML altogether. [23,24] All studies reported CEA or CUA except for the study by Yang *et al.* (2020)[31] which only analysed cost outcomes, and Schulthess *et al.* (2021)[32] which reported cost and clinical outcomes separately (Table 6.1). Only two studies addressed societal costs (data not extracted),[27,29] in addition to the healthcare/payer costs.

The majority of studies (10 out of 12)[24–31,33,34] used decision-analytic models, while only two studies[23,32] analysed real-world data using cohort/observational study designs. For r/r ALL/AML, Lin *et al.* (2010)[23] compared allogeneic peripheral blood stem cell transplant (PBSCT) versus BMT, and Maser *et al.* (2020)[24] compared levofloxacin prophylaxis versus no prophylaxis.

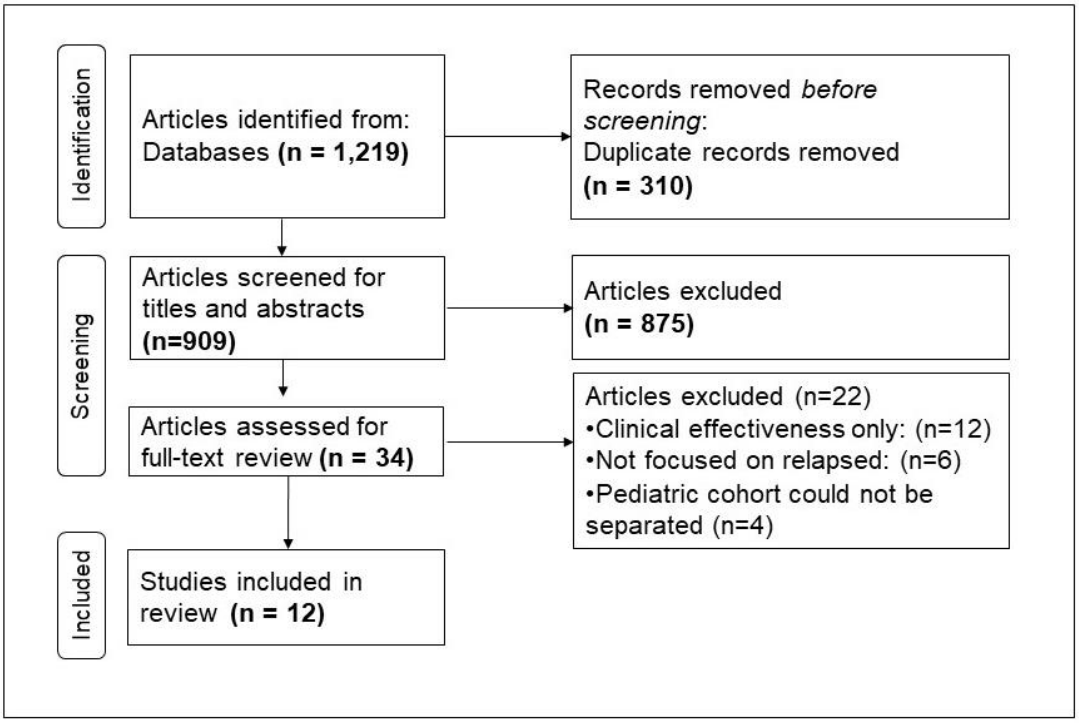


Figure 6.1. PRISMA flow diagram

Ten studies[25–34] evaluated CAR–T cell therapy (a novel immunotherapy for r/r ALL, generic name: tisagenlecleucel, tisa-cel) as the main intervention, compared to any of these alternative treatments: Blinatumomab (Blina); Clofarabine therapy [Clofarabine monotherapy (Clo–M) or Clofarabine combination therapy (Clo–C; Clofarabine/cyclophosphamide/etoposide); FLA–IDA salvage chemotherapy (Fludarabine/cytarabine/idarubicin) to achieve complete remission (CR), followed by BMT or haematopoietic stem-cell transplantation (HSCT) as a general approach (Table 6.1). Six studies evaluated cost-effectiveness of CAR–T cell therapy (tisagenlecleucel) in paediatrics and young adults (up to 25 years), as it was approved by the Food and Drug Adminstartion (FDA) and indicated for this age-group.[26,28,29,32,33,34]

Table 6.1. Characteristics of included studies

Author (Year)	Country	Study perspective (setting)	Economic evaluation type	Study design/model structure	Population	Treatment intervention	Comparator(s)	CHEERS score (Out of 24)
Relapsed/refractory acute Leukaemia (ALL/AML)								
Lin *et al.* (2010)[23]	USA	Healthcare system (SCT Unit at Texas Children's Hospital)	Cost analysis and CEA	Retrospective cohort study	Patients aged 0-18 years with R/R acute leukemia in 1st or subsequent relapses; 2 cohorts: 30 received allogenic PBSCT; 110 received BMT	Allogeneic PBSCT	BMT	19.5
Maser *et al.* (2020)[24]	Canada	Single-payer healthcare system	CEA	Decision-tree and state-transition model	Paediatric patients with R/R ALL/AML; assumed cohort 12-year-old	Levofloxacin prophylaxis	No prophylaxis	19.5
Relapsed/refractory ALL								
Lin *et al.* (2018)[25]	USA	US health payer perspective	CEA	Markov model	R/R B-cell ALL	CAR-T cell therapy	Blinatumomab; Clo-M; and Clo-C*	21
Whittington *et al.* (2018) [26]	USA	Payer perspective	CEA	Decision tree, and semi-Markov partitioned survival model	Patients <25 years with B-cell ALL; refractory or in second or later relapse	CAR-T cell therapy	Blinatumomab; Clo-C*	21
Sarkar *et al.* (2019)[27]	USA	Payer perspective	CEA	State-transition microsimulation model	Paediatric patients with R/R B-cell ALL	CAR-T cell therapy	Standard of care (Clo-C* followed by HSCT)	19.5
Santasusana *et al.* (2020)[28]	Spain	Spanish NHS perspective	CEA	Partitioned survival model	Patients <25 years with R/R B-cell ALL post-transplant or in second or later relapse	CAR-T cell therapy	FLA-IDA salvage chemotherapy**	21.5
Thielen *et al.* (2020)[29]	Netherlands	Healthcare perspective	CEA	Three-state partitioned survival model	Patients <25 years with R/R ALL	CAR-T cell therapy	Blinatumomab; Clo-M; and Clo-C*	19
Furzer *et al.* (2020)[30]	Canada	Public insurer perspective	CEA	Multistate & individual-level model, using patient cohorts	Paediatric patients with R/R ALL at second relapse; 192 patients in	CAR-T cell therapy	Standard care for Tisa-cel-eligible patients (salvage chemotherapy and HSCT).	21

				from population-based registry	treatment arm, 118 in control arm			
Yang *et al.* (2020)[31]	USA	U.S. hospital's perspective	Cost analysis	Economic model using a fee-for-service approach	Paediatric patients with R/R ALL	CAR-T cell therapy with subgroup analysis	No comparator	15.5
Schulthess *et al.* (2021)[32]	USA	Healthcare perspective (VUMC University medical center)	Cost analysis and clinical effectiveness	Longitudinal observational cohort study, using RWD from EHR	Patients<25 years with R/R ALL; 2 cohorts: 29 received HSCT; 14 received CAR-T cell therapy	CAR-T cell therapy	BMT/HSCT (next-best treatment option)	17.5
Wakase *et al.* (2021)[33]	Japan	Japanese public healthcare payer's perspective	CEA	Partitioned survival model (decision tree)	Patients<25 years with R/R ALL	CAR-T cell therapy	Blinatumomab; and Clo-C*	19.5
Moradi-Lakeh *et al.* (2021)[34]	Switzerland	Switzerland healthcare system	CEA	Partitioned survival model	Patients <25 years with R/R B-cell ALL in second or later relapse	CAR-T cell therapy	FLA-IDA salvage chemotherapy**, Blinatumomab; and Clo-C*	19.5

*****Clofarabine combination therapy includes clofarabine, cyclophosphamide, and etoposide. ** FLA-IDA salvage chemotherapy includes combination of fludarabine, cytarabine and idarubicin. Abbreviations (ordered alphabetically): BMT: Bone Marrow Transplant; CEA: cost-effectiveness analysis; Clo-C: Clofarabine combination therapy; Clo-M: Clofarabine monotherapy; DI: Double intensification; DDI: double delayed intensification; EHR: Electronic Health Record; PBSCT: Peripheral blood stem cell transplantation; R/R: Relapsed/refractory; RWD: Real-world data; SCT: Stem Cell Transplant; VUMC: Vanderbilt University Medical Center.

6.6.2 Quality of included studies

Table 6.1 shows the CHEERS checklist scores for each included study, with a median score of 19.5 (range: 15.5–21.5) out of 24. The overall quality of the included studies is moderate to high based on the CHEERS scores (detailed in Appendix 6.6). Three studies were of moderate quality (CHEERS score below the median) as follows: 15.5 for Yang *et al.* (2020)[31] 17.5 for Schulthess *et al.* (2021)[32] and 19 for Thielen *et al.* (2020).[29] Whereas the remaining studies were of high-quality (CHEERS score above the median). The most common methodological errors included: not describing population subgroups or characterising heterogenicity to explain variations in costs and outcomes; not reporting method of adjusting unit costs; and not explaining the reasons for choosing a specific decision-analytic model. Besides, in some studies, the authors did not report potential conflict of interest (despite the study being funded), nor the role of the funder. Detailed CHEERS checklist scoring for each study is shown in Appendix 6.6

6.6.3 Approach to cost-effectiveness analyses

For studies that used decision-analytic models, economic analyses were based on a lifetime horizon, while observational studies reported follow-up periods (Table 6.2). Discounting of costs and benefits was done at 3% discount rate in five studies at the base-case scenario, [25–28,32] other five studies[2429,30,33,34] used different discount rates, while two studies did not report costs discounts.[23,31] I summarised the key model input parameters in Appendix 6.7, including sources of clinical evidence, utilities (quality of life), and listed drug(s) prices. Evidence for clinical effectiveness and utility data were sourced from a combination of clinical trials and published literature as outlined in Appendix 6.7. Listed drugs' prices of the main and comparator treatment interventions varied among studies conducted in different countries. Cost categories for each

treatment intervention were also summarised for each study, which contributed to different cost outputs. The majority of studies (n=11, 91.6%) conducted sensitivity (uncertainty) analysis as either deterministic and/or probabilistic analyses, or scenario analysis (Appendix 6.8).

Table 6.2. Costs, clinical outcomes, and cost-effectiveness estimates to treat relapsed/refractory acute leukaemia

Author (Year)	Country, Currency (Ref. Year)	Discount rate	Time horizon	Costs of alternative treatment strategies	Clinical effects/outcomes	Cost-effectiveness (ICER/ICUR) *	WTP threshold	Conclusion/ comments
Acute Leukaemia (ALL/AML)								
Lin *et al.* (2010)[23]	USA, USD (2008)	Not reported.	Follow-up period	• BMT: $438,473 (success), BMT: $462,803 (failure); • PBSCT: $263,392 (success), PBSCT: $403,606 (failure)	Probability of treatment success (disease-free survival at 1-year post-transplant): Standard risk: 80.3% in BMT group, and 57.1% in PBSCT group; High risk: 23.5% in BMT group, and 18.8% in PBSCT group.	ICER for the high-risk subgroup was $1.69 million per additional treatment success in BMT group compared with the PBSC group.	N/A	The comparative economic evaluation supports BMT in standard-risk patients, but much uncertainty in advantage in high-risk patients***
Maser *et al.* (2020)[24]	Canada, CaD (2018)	1.5% (costs, effects).	Lifetime horizon	• Levofloxacin prophylaxis: $1,416 • No prophylaxis: $1,997.	Levofloxacin prophylaxis showed LYG of 0.13; and 0.11 QALYs gained.	Levofloxacin prophylaxis showed cost savings of $542 and increased survival of 0.13 QALY, with cost savings of $5,059 per QALY gained.	$50,000	Levofloxacin prophylaxis is cost saving in children receiving intensive chemotherapy for AML or relapsed ALL.
ALL								
Lin *et al.* (2018)[25]	USA, USD (2018)	3% (costs, effects).	Lifetime horizon	• Tisa-cel: at 5-year RFS of 40%: $599,000; Bridge to transplant: 713,000 • Blinatumomab: $282,000 • Clo-C: $374,000 • Clo-M: $314,000	• Tisa-cel: 12.1 LYG; 5.5 QALYs gained. • Blinatumomab: 8.55 LYG: 3.57 QALYs gained. • Clo-C: 8.55 LYG; 3.52 QALYs gained. • Clo-M: 6.7 LYG; 3.12 QALYs gained.	Tisa-cel increased cost $61,000/QALY gained.	$50,000, $100,000, $150,000 per QALY gained	Long-term effectiveness of tisa-cel is a critical but uncertain determinant of its cost-effectiveness.

Whittington *et al.* (2018)[26]	USA, USD (2017)	3% (costs, effects).	Lifetime horizon	• Tisa-cel: $667,000 • Clo-M: $337,000	• Tisa-cel: LYG: 10.34; QALYs gained: 9.28. • Clo-M: LYG: 2.43 QALYs gained: 2.10	ICER $37,000–$78,000 per QALY gained, >40% on Tisa-cel becoming long-term survivors.	$100000 per QALY gained	Tisagenlecleucel likely provides gains in survival and seems to be priced in alignment with these benefits.
Sarkar *et al.* (2019)[27]	USA, USD (2017)	3% (costs, effects).	Lifetime horizon	• CAR-T cell therapy: $968,800 • Standard therapy (Clo-C): $440,600	• CAR-T cell therapy: 16.76 QALYs gained • Clo-C: 8.58 QALYs gained.	ICER of $64,600/QALY, compared to Clo-C	$100,000 per QALY gained	CAR-T therapy may represent a cost-effective option for pediatric R/R B-ALL, although longer FU is required to confirm validity of findings.
Santasusana *et al.* (2020)[28]	Spain, EURO (2018)	3% (costs, effects).	Lifetime horizon	• CAR–T cell: 357,425 • Salvage chemotherapy (FLA-IDA): 99,046	• CAR–T cell therapy: 10.97 LYG; 9.43 QALYs gained; EFS: 10.05%. • FLA-IDA: 0.87 LYG and 0.46 QALYs gained; EFS: 0.62.	ICER per LYG: 25,576. ICUR per QALY gained: 28,818.	€30,000 per QALY gained	Tisa-cel would represent a cost-effective intervention for treating children and young adults with R/R ALL.
Thielen *et al.* (2020)[29] ****	Netherlands, EURO	4% (costs) and 1.5% (effects).	Lifetime horizon	• Tisa-cel: 409,563 EURO	• Tisa-cel: 14.01 LYG, 11.26 QALYs gained. • Blinatumomab: 3.17 LYG and 2.25 QALYs gained. • Clo-C: 2.46 LYG and 1.70 QALYs gained. • Clo-M: 0.74 LYG and 0.49 QALYs gained.	ICERs of Tisa-cel ranged between 31,682 EUR/QALY for Blinatumomab and 37,531 EUR/QALY for Clo-C.	80,000 EURO per QALY gained	At the current price and WTP threshold, Tisa-cel is cost-effective.
Furzer *et al.* (2020)[30]	Canada, CaD (2018)	1.5% (costs, effects).	Lifetime horizon	• Tisa-cel: 584,000 CaD • Chemo/HSCT: 114,000 CaD.	• Tisa-cel: 5-year overall survival (OS): 0.22; 9.72 LYG and 6.79 QALYs gained. • Chemo/HSCT:5-year OS: 0.16; LYG: 5.05; 3.46 QALYs gained.	Incremental cost per QALY gain ranging from CaD $71,000 at 40% cure rate, to CaD $281000 at 10% cure rate.	$150,000 per QALY gained	At a WTP $150,000/QALY, Tisa-cel had a 32% likelihood of being cost-effective. Cost-effectiveness would fall below $50,000/QALY with a long-term cure rate of >40% or a price discount of 49%.

Yang *et al.* (2020)[31]	USA, USD (2019)	Not reported.	Costs were estimated from time of leukapheres is to 2 months post-infusion.	• Tisa-cel: $612,779	N/A	N/A	N/A	In addition to the Tisa-cel price, costs of adverse event management, and inpatient and ICU admissions were main cost drivers.
Schulthess *et al.* (2021)[32]	USA (USD, 2019)	3% (costs, effects).	3 years of outcomes	• CAR–T cell therapy: $590,112 • HCT: $303,065	• CAR–T cell therapy: 3-year RFS 46% (95% CI: 08–79%) • HCT: 3-year RFS 68% (95% CI: 46–83%)	N/A	N/A	Lower RFS probability with CAR-T compared to HCT is due to CAR-T cohort had a far higher level of disease burden.
Wakase *et al.* (2021)[33]	Japan (JPY, 2018)	2% (costs, effects).	Lifetime horizon	• Tisa-cel: JPY 40,276,340 • Blinatumomab: JPY 22,976,259 • Clo-C: JPY 14,986,473	• Tisa-cel: 13.3 LYG; 11.6 QALYs gained • Blinatumomab: 4.0 LYG; 3.1 QALYs gained. • Clo-C: 2.7 LYG; 2.1 QALYs gained.	ICERs per QALY gained for Tisa-cel were JPY 2,035,071 vs. Blinatumomab, and JPY 2,644,702 vs. Clo-C.	JPY 7.5 million per QALY gained	Tisa-cel l is a cost-effective treatment for R/R B-ALL from a Japanese public healthcare payer's perspective.
Moradi-Lakeh *et al.* (2021)[34]	Switzerland, CHF (2018)	3.5% (costs, effects).	Lifetime horizon	• Tisa-cel: CHF 511,939 • Clo-C: CHF 282,388 • Blinatumomab: CHF 285,595 • Salvage chemotherapy: CHF 259,565	• Tisa-cel: 9.64 LYG; 8.29 QALYs gained. • Blinatumomab: 2.75 LYG; and 2.07 QALYs gained. • Clo-C: 2.25 LYG; 1.64 QALYs gained. • Salvage chemotherapy: 0.78 LYG; 0.39 QALYs gained.	Incremental cost per QALY gained for Tisa-cel in pALL was CHF 31,961, CHF 34,530 and CHF 36,419 compared to salvage chemotherapy, Clo-C and blinatumomab, respectively.	CHF 100,000–150,000 per QALY gained	Tisa-cel was shown to be dominant (more effective and less costly) over all the comparators.

*Cost-effectiveness was presented as incremental cost per benefit gained, incremental cost per life year gained (ICER), or incremental cost per QALY gained (ICUR). ** EFSV refers to estimated number of event-free survivors (EFSVs) at 5 years (patient); *** In Lin *et al.* (2010), standard risk was defined as ALL or AML in first or second remission, and high risk was defined as ALL or AML in third or subsequent remission or in relapse or in patients with secondary AML. I only included the high-risk group which is the second relapse as costs and outcomes of the first relapse could not be separated from first-line treatment.

**** In Thielen *et al.* (2020), costs of comparators were presented in Appendix 6 (adjusted to USD 2019). Abbreviations (ordered alphabetically): BM: Bone Marrow; CaD: Canadian Dollars; CE: cost-effectiveness; CHF: Swiss franc; Clo-C: Clofarabine combination; Clo-M: Clofarabine monotherapy; DI: delayed intensification; ; EFS: Event-free survival; FU: follow-up; HCT: hematopoietic cell transplant; ICER: Incremental cost-effectiveness ratio; ; ICUR: incremental cost utility ratio; JPY: Japanese Yen; LE: life expectancy; LYs: Life-years; LYG: Life year gained; PBSCT: Peripheral blood stem cell transplant; QALY: quality-adjusted life-year; QOL: Quality of Life; RFS: relapse-free survival; Tisa-cel: Tisagenlecleucel; WTP: Willingness-to-pay.

6.6.4 Costs, benefits, and cost-effectiveness estimates

Table 6.2 summarises key information about costs (in actual currency as reported in each study), clinical effects, and cost-effectiveness estimates for main intervention versus the alternative treatment option (the comparator). Willingness-to-pay (WTP) thresholds varied among studies. Lin *et al.* (2010)[23] reported that in r/r acute leukaemia (ALL/AML), the probability of treatment success was higher (23.5%) in the BMT group compared to 18.8% in the PBSCT group, which was cost-effective in standard-risk patients. Levofloxacin prophylaxis showed cost savings of $5,059 per QALY gained in children receiving intensive chemotherapy, as reported by Maser *et al.* (2020),[24] compared to not administering levofloxacin. In nine studies, CAR–T cell therapy was found to be more cost-effective compared to the other alternative treatments (Table 6.2).[25–31,33,34] Whereas, only Schulthess *et al.* (2021)[32] reported lower 3-year relapse-free survival (RFS) for CAR–T cell therapy (46%, 95% CI: 8–79%) at a higher cost, compared to 68% (95% CI: 46–83%) with hematopoietic cell transplant (HCT), due to higher tumour burden in the CAR–T cell therapy cohort.

Table 6.3 summarises outcomes of the nine studies, reporting standardised costs (adjusted to USD 2019), QALYs gained, incremental costs and QALYs gained, and ICERs for CAR–T cell therapy (tisa-cel) compared to other alternative treatment options. QALYs gained ranged between 5.5–16.76 for CAR-T cell therapy, 2.07–3.57 for Blina, 1.7–8.58 for Clo-C, 0.49–3.12 for Clo-M, 0.39–0.46 for FLA-IDA, and was 3.46 for chemotherapy/HSCT. Blinatumomab achieved higher QALYs gained (better clinical benefit) compared to Clo-M and Clo-C therapies.[25,29,33,34] Whereas, FLA-IDA showed the least favourable clinical outcome (lowest QALYs gained), compared to the other interventions as reported by Santasusana *et al.* (2020)[28] and Moradi-Lakeh *et al.* (2021).[34]

Table 6.3. Costs (USD 2019) and QALYs gained of CAR–T cell therapy and comparator(s) to treat relapsed/refractory ALL

Author (year)	Costs (USD 2019)			QALYs gained			Incremental cost-effectiveness ratio (ICER), $
	CAR-T Cell (Tisa-cel)	Comparator(s)	Incremental	CAR-T Cell (Tisa-cel)	Comparator(s)	Incremental	
Lin *et al.* (2018)[25]	$596,748	• Blina: $293,687 • Clo-C: $389,500 • Clo-M: $327,014	• Blina: $303,061 • Clo-C: $207,248 • Clo-M: $269,734	5.5	• Blina: 3.57 • Clo-C: 3.52 • Clo-M: 3.12	• Blina: 1.93 • Clo-C: 1.98 • Clo-M: 2.38	• Blina: $157,026 • Clo-C: $104,671 • Clo-M: $113,334
Whittington *et al.* (2018)[26]	$694,644	• Clo-M: $350,967	• Clo-M: $343,677	9.28	• Clo-M: 2.10	• Clo-M: 7.18	• Clo-M: $47,866
Sarkar *et al.* (2019)[27*]	$1,008,952	• Clo-C**:** $58,861	• Clo-C: $950,091	16.76	• Clo-C: 8.58	• Clo-C: 8.18	• Clo-C: $116,148
Santasusana *et al.* (2020)[28**]	$428,841	• FLA-IDA: $118,836	• FLA-IDA: $310,005	9.43	• FLA-IDA: 0.46	• FLA-IDA: 8.97	• Chemo: $34,560
Thielen *et al.* (2020)[29]	$482,975	• Blina: $259,897 • Clo-C**:** $160,459 • Clo-M: $110,657	• Blina: $223,078 • Clo-C: $322,516 • Clo-M: $372,318	11.26	• Blina: 2.25 • Clo-C: 1.70 • Clo-M: 0.49	• Blina: 9.01 • Clo-C: 9.56 • Clo-M: 10.77	• Blina: $24,759 • Clo-C: $33,736 • Clo-M: $34,570
Furzer *et al.* (2020)[30]	$458,121	• Chemo/HSCT: $89,428	• Chemo/HSCT: $368,693	6.79	• Chemo/HSCT: 3.46	• Chemo/HSCT: 3.33	• Chemo/HSCT: $110,719
Schulthess *et al.* (2021)[32]	$590,112	• BMT/HSCT: $308,349	• BMT/HSCT: $281,763	NR	• BMT/HSCT: NR	• BMT/HSCT: NR	• BMT/HSCT: NR
Wakase *et al.* (2021)[33]	$371,102	• Blina: $211,701 • Clo-C**:** $138,084	• Blina: $159,401 • Clo-C: $233,018	11.6	• Blina: 3.1 • Clo-C: 2.1	• Blina: 8.5 • Clo-C: 9.5	• Blina: $18,753 • Clo-C: $24,528
Moradi-Lakeh *et al.* (2021)[34**]	$532,038	• Blina: $296,808 • Clo-C**:** $293,475 • FLA-IDA: $269,756	• Blina: $235,230 • Clo-C: $238,563 • FLA-IDA: $262,282	8.29	• Blina: 2.07 • Clo-C: 1.64 • FLA-IDA: 0.39	• Blina: 6.22 • Clo-C: 6.65 • FLA-IDA: 7.9	• Blina: $37,818 • Clo-C: $35,874 • Chemo: $33,200

*Sarkar *et al*. (2019), Clo-C included Clofarabine combination therapy and HSCT; FLA-IDA salvage chemotherapy includes combination of fludarabine, cytarabine and idarubicin. **In Santasusana *et al.* (2020) and Moradi-Lakeh (2021): salvage chemotherapy included FLA-IDA (Fludarabine, Cytarabine and Idarubicin). Abbreviation**s:** Clo-M: Clofarabine monotherapy; Clo-C: Clofarabine combination therapy (Clofarabine, cyclophosphamide, and etoposide); NR: Not reported.

Figure 6.2 shows the health benefit gained in terms of QALYs gained by the alternative treatment options as reported in each study. ICER for CAR–T cell therapy relative to the other comparators ranged from $18,753 to $157,026 per QALY gained, with varying outcomes on sensitivity analysis (presented in Appendix 6.8). The clinical benefit (LYG and QALYs) gained from CAR–T cell therapy varied among the different studies as shown in Appendix 6.9.

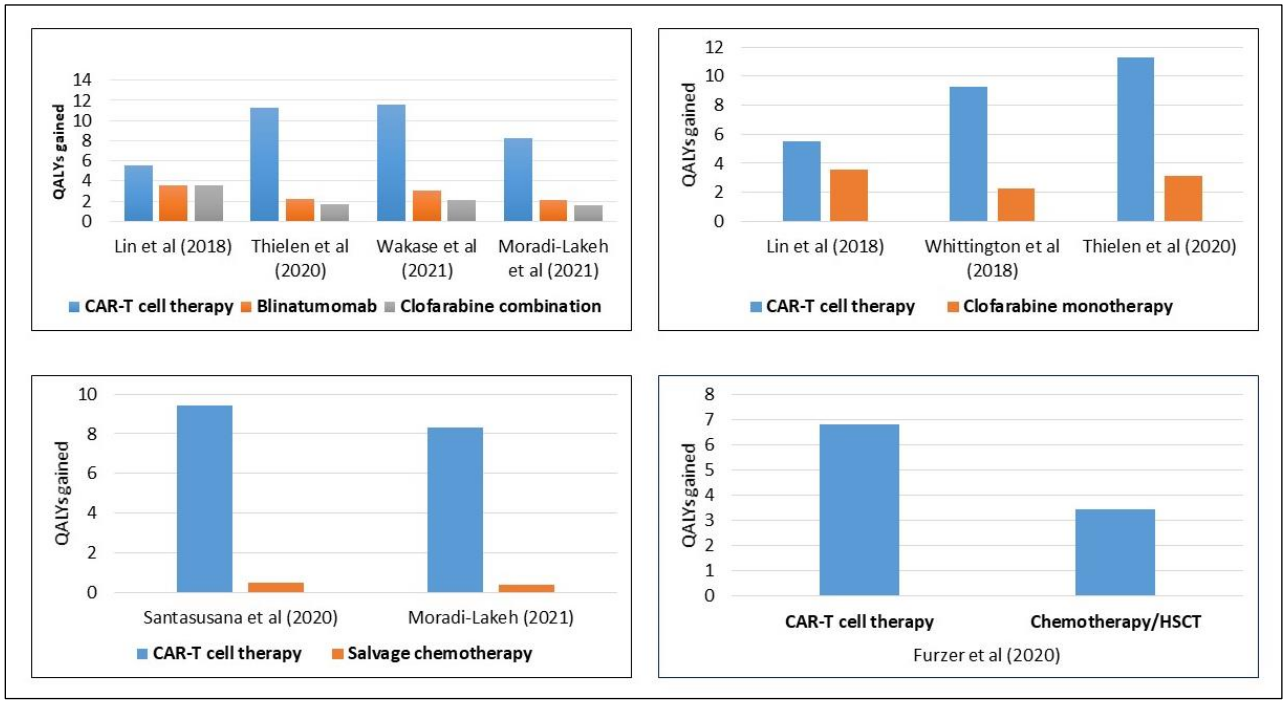


Figure 6.2. QALYs gained for CAR-T cell therapy versus alternative interventions to treat relapsed/refractory paediatric ALL

The estimated costs of CAR–T cell therapy included all cost components of treatment and not just the listing price of tisagenlecleucel, calculated over a life-time horizon. Median cost (USD 2019) of CAR–T cell therapy in the included studies was $561,075 (IQR: $464,335–$612,779), and mean cost was $577,631 (SD: ± $180,000), where highest cost estimates were reported by Sarkar *et al.* (2019).[27]

Figure 6.3(A) shows the variation in costs of CAR–T cell therapy among the different studies, where it was noted that studies conducted in the US had higher CAR–T cell therapy costs compared to studies conducted in the other countries (Canada, Japan, Netherlands, Spain, Switzerland). Median costs of CAR–T cell therapy in the US was $612,779 (IQR: $596,748–$694,644) compared to a median cost of $458,121 (IQR: $428,841–$482,975) in studies conducted in other countries, as illustrated in Figure 6.3(B).

The main cost driver was the drug list price, and the other top three cost drivers of 'additional cost' were adverse events management (51.6%), inpatient and intensive care unit (ICU) admissions not attributed to adverse events (42.1%), and laboratory tests and procedures (3.8%) (Appendix 6.7).

Figure 6.3(B). Costs of CAR-T cell therapy (USD 2019) among different published studies

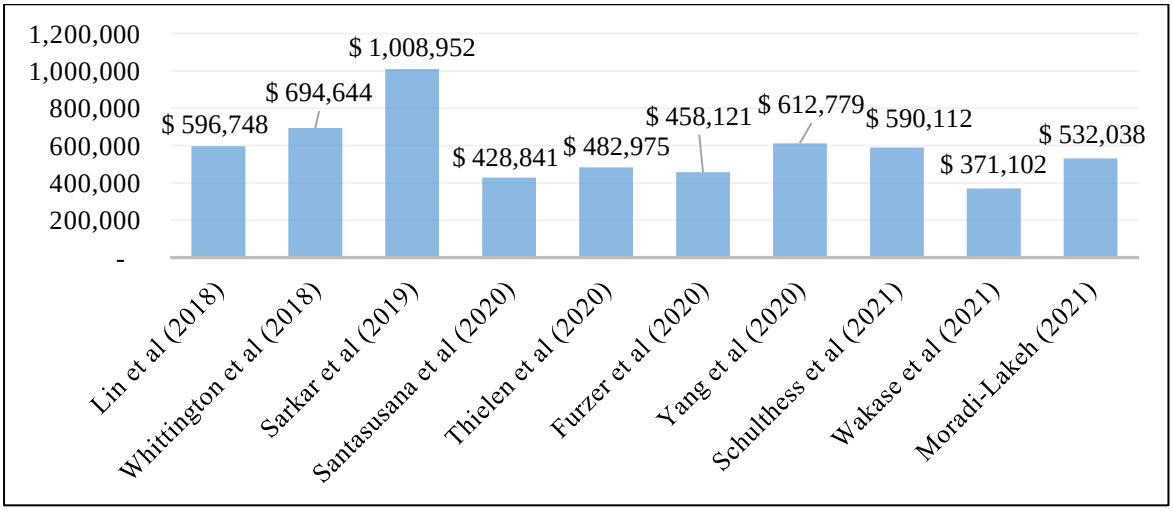
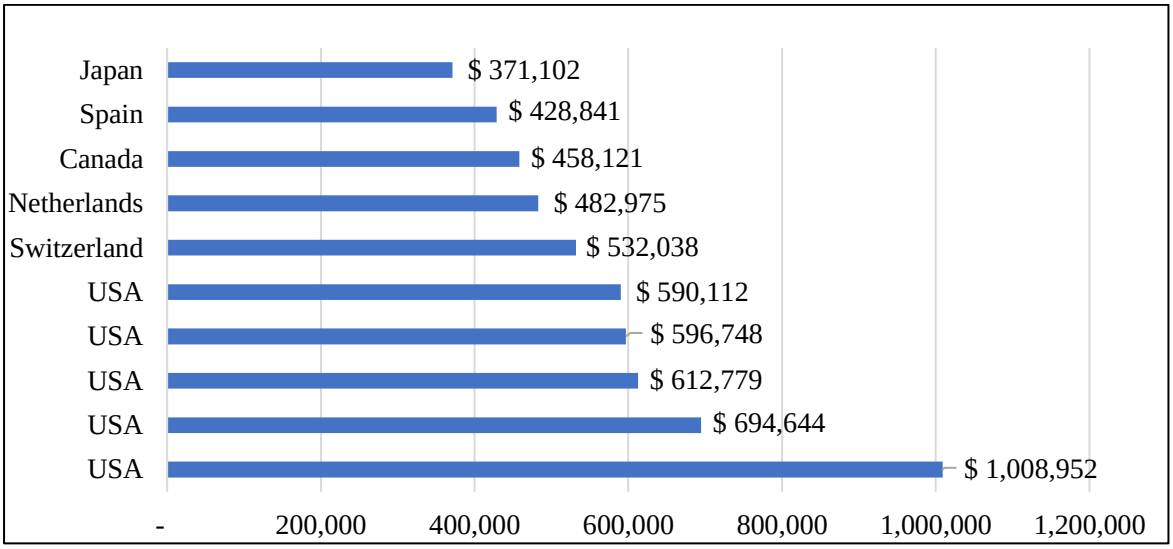


Figure 6.3(B). Costs of CAR-T cell therapy (USD 2019), by country of published study



* Costs were discounted at 3% annually for all studies, except for Thielen *et al.* (2020) at 4%; Furzer *et al.* (2020) at 1.5%; Wakase *et al.* (2021) at 2%; Moradi-Lakeh *et al.* (2021) at 3.5%; and no discounting for Yang *et al.* (2020). All studies estimated lifetime horizon. Study perspectives were as follows: Lin *et al.* (2018): US health payer perspective; Whittington *et al.* (2018) and Sarkar *et al.* (2019): payer perspective; Santasusana *et al.* (2020): Spanish NHS perspective; Thielen *et al.* (2020): Netherlands Healthcare perspective; Furzer *et al.* (2020): Public insurer perspective; Yang *et al.* (2020) and Schulthess *et al.* (2021): U.S. healthcare (hospital) perspective; Wakase *et al.* (2021): Japanese public healthcare payer's perspective; Moradi-Lakeh *et al.* (2021): Switzerland healthcare system.

Figure 6.3. Costs of CAR–T cell therapy (USD 2019) for relapsed/refractory ALL

6.7 Discussion

6.7.1 Summary and interpretation of findings

This systematic review summarises the existing evidence on the costs and cost-effectiveness of treatment for relapsed/refractory acute leukaemia (ALL/AML) in children/young adults. The majority of the studies (10 out of 12) evaluated the costs/cost-effectiveness of CAR–T cell therapy compared to other treatment strategies for r/r ALL. Whereas only two studies addressed r/r acute leukaemia (ALL and AML) considering different approaches.

The high upfront cost of CAR–T cell therapy (drug cost only is 475,000 USD) raises important concerns about its cost-effectiveness and value for money on the longer term. Therefore, there was a greater need to conduct cost-effectiveness analysis for CAR–T cell therapy (compared to other treatment options) to justify its high cost relative to the health benefits gained during the drug approval process. However, although earlier treatments were used to treat r/r ALL, a few studies analysed their costs and cost-effectiveness creating a significant evidence gap.

There is sufficient evidence to suggest that CAR–T cell therapy (tisagenlecleucel) may provide survival gains and is a cost-effective strategy to treat r/r ALL in children compared with other currently available therapies. The best measure of a health economic evaluation is costs per QALY gained. This parameter takes into consideration the costs of treatment in a standardised currency (USD 2019) and QALY gained as a composite outcome measure including both survival and utility scores (quality of life). CAR–T cell therapy showed the greatest cost/QALYs gained compared to the other alternatives. Nevertheless, there remain serious concerns over the uncertainty of its long-term effectiveness.[23]

At the most optimistic scenario (40% 5-year RFS), tisagenlecleucel would result in significant survival gains (12.1 life-years) with good economic value (<$100,000/QALY), however, with lower long-term outcomes (20%–0% 5-year RFS), its economic value is reduced and may not meet the accepted cost-effectiveness thresholds.[23] Other concerns include affordability of the drug price, equity in access for children residing in LMICs,[35,36,37] and the serious side effects which occur in the majority of patients.[38] Outcomes-based pricing could be a good option, where reimbursement depends on achieving and maintaining favourable clinical outcomes (initial remission).[23]

The next best treatment option was Blinatumomab which showed the greatest QALYs gained relative to cost, followed by Clo–C, and Clo–M regimens (at lower/comparable costs to Blinatumomab),[25,29,34] whereas FLA-IDA salvage chemotherapy showed the least favourable clinical outcomes at comparable costs.[34] There is poor evidence about the cost-effectiveness of treating r/r paediatric AML, due to limited published articles. Lin *et al.* (2010)[23] conducted comparative economic evaluation of allogeneic PBSCT versus BMT in r/r ALL/AML in children and found that BMT was more favourable for the standard risk patients. Maser *et al.* (2020)[23] evaluated cost-effectiveness of prophylactic Levofloxacin antibiotic for relapsed ALL/AML, and found that it was cost-saving in children receiving intensive chemotherapy.

Quality appraisal using the CHEERS checklist showed moderate to high quality of the generated evidence, as the included modelling studies followed good economic evaluation practices (good internal validity). Whereas, the external validity is poor, due to limited confidence in generalisability and applicability of the findings in real practice. This is because most studies (10 out of 12) were modelled (simulation-based) depending on clinical trial data from limited sample

numbers. In addition to this, major variations in other input parameters across the studies led to high levels of uncertainty in the studies' outcomes.

6.7.2 Sources of variability and addressing uncertainty

Despite consistency in the main findings that CAR–T cell therapy was more cost-effective than the other comparators to treat r/r ALL in children, there was a large variation among the included studies in the estimated costs, clinical outcomes, and ICERs. Variation in costs is likely common as they vary across countries due to differences in list prices of drugs, hospital costs, and varying contexts and practices.[39] This could explain the higher costs of CAR–T cell therapy in studies conducted from the US health system perspective, compared to studies conducted in other countries, as the list price of tisagenlecleucel in the US ($475,000) is higher than that in the other countries. Other potential reasons for variation in costs among studies include: discount rate of costs, costing perspective and context, time horizon, and the included cost categories.

Heterogeneity of findings among studies can also be contributed to difference in key model inputs and parameters; different types of decision-analytic models used with varying assumptions and inconsistency in the sources of clinical evidence (survival outcomes and utilities). I summarized the key model inputs in Appendix 6.7 to show how the variability in model inputs lead to variation in model outputs. Besides, findings from modelled studies differed from those reported by pragmatic studies using real-world data.[23,32]

Uncertainty of results was addressed by most of the modelled studies by conducting deterministic and/or probabilistic sensitivity analyses or scenario analysis. Model results remained robust to alternative model assumptions and inputs (i.e., CAR–T cell therapy remained more cost-effective than the comparators) in studies reported by Whittington *et al.* (2018)[26]

Santasusana *et al.* (2020)[28] Furzer *et al.* (2020)[30] Wakase *et al.* (2021)[33] and Moradi-Lakeh *et al.* (2021).[34] Whereas, CAR–T cell therapy was no longer cost-effective with sensitivity analysis in the study conducted by Sarkar *et al.* (2019).[27] CAR–T cell therapy was no longer cost-effective when the 1-year survival was assumed to be 57.8% (instead of 76% in the base-case model), when the complete remission rate decreased from 81% to 56.2%, and when the health utility of disease-free survivors decreased from 0.94 to 0.66.[27] Also, Thielen *et al.* (2020) reported that CAR–T cell therapy was less cost-effective with a shorter time-horizon (20 years versus lifetime horizon).[29] The most influential input parameters that most affected the results included: discount rate for costs and benefits (0–5%; 3% base-case); cost of tis-cel, starting age (1–25 years; 12 years base-case); time horizon (20 years; versus lifetime in the base-case); and different overall survival parametric functions.[27,28,29]

6.7.3 Comparison with other studies in the literature

This systematic review summarises the health economic evidence about costs and cost-effectiveness of treatment with a focus on r/r acute leukaemia in children/young adults, contrary to other reviews in the literature which had different scopes and perspectives. Other published systematic reviews addressed economic evaluation of CAR–T cell therapy but were not focused solely on relapsed paediatric acute leukaemia. A systematic review by Gye *et al.* (2022) conducted health technology assessments (HTA) of CAR–T cell therapy in younger compared with older patients, summarising the evidence generated by HTA agencies (not peer-reviewed original studies).[39] It included 14 HTA evaluations; five for paediatric ALL evaluating tisagenlecleucel, and nine for adult diffuse large B-cell lymphoma (DLBCL) evaluating axicabtagene ciloleucel.[39] The sources of variability identified in the systematic review by Gye *et al.* (2022) were similar to those reported in this systematic review.

Another systematic review conducted by Petrou *et al.* (2019) assessed the economic evaluations of tisagenlecleucel and axicabtagene in ALL and large B cell lymphoma.[40] This review only evaluated three peer-reviewed full-text articles and three abstracts about r/r ALL and included expert opinion, suggesting that these products demonstrate a potentially favourable cost-effectiveness ratio, yet their budget impact is very high, and more affirmative clinical data are imperative in order to mitigate uncertainty.[40]

Another review article about the health economic aspects of CAR–T cell therapies for haematological cancers was conducted by Heine *et al.* (2020), which conducted a review of list prices, HTA reports, budget impact analysis dossiers, and published cost-effectiveness analyses.[41] It also forecasted the 10-year health expenditures on CAR–T cell for several haematological cancers in selected European Union (EU) countries.[41] Heine *et al.* (2020) only evaluated cost-effectiveness of tisagenlecleucel in six published studies.[41]

None of the above-mentioned systematic reviews focused on the other alternative treatment options for relapsed r/r paediatric ALL, to allow for comparability of results. One conference abstract by Pechlivanoglou *et al.* (2021) compared two alternative treatments for r/r ALL in children, apart from CAR–T cell therapy.[42] Pechlivanoglou *et al.* (2021) reported that Blinatumomab was more cost-effective compared to standard intensive chemotherapy (followed by SCT) for high-risk relapse ALL (relapsing within 18 months from diagnosis).[42]

There were no identified systematic reviews about the cost-effectiveness of r/r paediatric AML treatments, identifying a substantial gap in knowledge in this area. Only one systematic review of clinical effectiveness exists, conducted by Hoffman *et al.* (2021)[43] that evaluated clinical outcomes of relapsed AML patients, without reflecting on costs/cost-effectiveness of treatment.[43]

Although a novel targeted therapy (Gemtuzumab ozogamicin) was approved in 2017 in the US to treat patients ≥2 years of age with r/r CD33+ AML, its budget impact analysis was mainly evaluated in adults and limited data exist for r/r paediatric CD33+ AML patients.[44]

6.7.4 Strengths and limitations

To the best of my knowledge, this systematic review provides the most comprehensive and updated results about the costs, clinical benefits, and cost-effectiveness of the alternative treatment options for r/r acute leukaemia in children. It used a rigorous methodology to standardise costs (in USD 2019) among the different studies, allowing for comparability of results. Besides, this systematic review objectively assessed the quality of the generated evidence using the CHEERS checklist, reflecting on the sources of variability and how this affects the generalisability and applicability of the findings.

Despite the valuable evidence generated from this systematic review, some limitations exist. First, the systematic review was limited by the small number of published original studies comparing costs/cost-effectiveness of the alternative treatment options for r/r paediatric ALL, and the substantial lack of published literature for r/r paediatric AML. Second, the majority of studies were modelled with high levels of uncertainty in cost estimates, and the study outcomes were greatly affected by model input parameters and assumptions. As previously outlined by Gye *et al*. (2022),[39] although there was consistency in the clinical evidence from clinical trials and the literature, variability in ICERs (mainly QALYs) was attributed to the different methods used to extrapolate overall survival data beyond the trial period.[39] Thus, variability in costs and outcomes result in weak external validity due to limited confidence in generalisability of results.

Third, there were no studies conducted in LMICs, therefore, the cost-effectiveness and affordability of CAR–T cell therapy and alternative treatments remain unknown, limiting the applicability and equity in access to resource-limited contexts. Although data from developing countries could not be included as the novel treatments for r/r paediatric acute leukaemia are hardly available, yet, salvage chemotherapy and HSCT are reasonably available across these countries and sibling donor/matched unrelated donor/haploidentical donors are extensively used. Even though the mean cost of allogenic HSCT for ALL in a developing country can be estimated at $11,053 (SD: ±2,817),[45] however, no data exist about cost-effectiveness of HSCT in these LMIC contexts. Fourth, there were no sub-group analyses for r/r ALL patients by age-group, risk, site, time, number of relapses, or tumour burden in any of the included studies, limiting the ability to target treatment to specific groups where it would be most cost-effective.

6.7.5 Implications

6.7.5.1 Implications for policymakers

Findings from this systematic review would encourage policy-makers to find innovate ways for value-based payment systems, through making deals with pharmaceutical industry (manufacturer) to lower drug prices of CAR–T cell therapy and other advanced treatment options. Policy-makers in LMICs should advocate promoting equity and access to novel treatments for r/r paediatric ALL at an affordable price, and include the cost-effective treatment strategies within national health insurance plans.

6.7.5.2 Implications for clinicians

Clinicians can use findings from this review to make better informed clinical decisions regarding the treatment of relapsed/refractory paediatric ALL in a more cost-effective approach, based on the available and affordable treatment options in their contexts.

6.7.4.1 Implications for researchers

This systematic review has identified gaps in existing knowledge that would pave the way for future research in key areas including: limited cost-effectiveness studies for r/r paediatric AML; limited pragmatic studies for r/r paediatric ALL using real-world data with long-term follow-up; and lack of sub-group analyses by age-group, risk/site/time/number of relapse, or tumour burden.

6.7.4.2 Implications for Patients

Children with relapsed/refractory acute lymphoblastic leukaemia (ALL) can benefit from receiving advanced novel therapies such as CAR–T cell therapy, which showed to be a cost-effective treatment option based on current literature, yet its long-term effectiveness is unknown. However, CAR–T cell therapy and other novel therapies are not currently available to patients living in LMICs due to limited access to novel therapies and unaffordability to pay.

6.7.6 Evidence-based recommendations for improvement

Accordingly, I suggest the following key recommendations (Panel 6.1) in policy-making (points 1 and 2), current practice (point 3), and future research (points 4, 5, 6, and 7) to deliver cost-effective treatment for relapsed/refractory acute leukaemia in children.

Panel 6.1. Key recommendations to deliver cost-effective treatment for r/r paediatric acute leukaemia in children.

1. Evaluate the applicability of adopting novel treatment interventions for r/r ALL in Egypt, and negotiate prices with pharmaceutical industry to allow affordability.
2. Engage policymakers to set cost-effectiveness (WTP) thresholds for introducing novel treatment interventions for r/r ALL in resource-limited settings in LMICs.
3. Guide clinicians to make better informed decisions regarding r/r ALL and adopt more cost-effective treatment strategies, based on real-world evidence.
4. Determine cost-effectiveness of different treatment strategies for r/r AML in children.
5. Study long-term cost-effectiveness of treating r/r ALL from longitudinal cohorts to provide more robust results and reduce the uncertainty in outcomes observed in modelling studies.
6. Identify the most cost-effective treatment option(s) for each sub-group of r/r ALL patients, stratified by risk, site, time of relapse, and disease burden.
7. Use health and economic outcome data outputs from this systematic review to develop new model-based economic evaluations in the local setting (CCHE/Egypt).

6.8 Conclusion

CAR–T cell therapy is the primary candidate in treating r/r ALL and based on the generated evidence it seems like a cost-effective treatment strategy for r/r ALL in children and young adults compared to other treatment strategies. The next best treatment option was Blinatumomab, followed by Clofarabine therapy (Clo–C and Clo–M), whereas FLA–IDA salvage chemotherapy (with/without HSCT) provides the least value for money. The overall quality of the generated evidence is moderate to high, with limited confidence in generalizability and applicability of findings due to the high variability in outcomes among the included studies. Further research is needed to determine the long-term cost-effectiveness of r/r ALL in real-world contexts, stratified by risk, site, time of relapse and disease burden, and to evaluate cost-effectiveness of r/r AML treatments to address the gap in current knowledge. Policymakers should find innovative approaches to allow affordability and applicability in clinical practice and promote equity of access to novel treatments for patients residing in resource-limited settings in LMICs.

6.9 How this chapter relates to the overall thesis

My thesis aims to generate evidence to improve childhood cancer health outcomes and resource use in Egypt. Chapter 6 generates systematic economic evidence from the literature to address a local problem (i.e., treatment of relapsed/refractory acute leukaemia is not cost-effective) that was identified as a key priority area for improvement based on findings from Chapter 5. This chapter identifies alternative cost-effective treatment strategies and provides evidence-based recommendations to improve cost-effectiveness of treatment for children with relapsed/refractory acute leukaemia.

6.10 Chapter summary

- This chapter summarises the health-economic evidence base about the costs and cost-effectiveness of treatment for relapsed/refractory acute leukemia in children.
- The majority of the included studies focused on CAR-T cell therapy, as a cost-effective novel treatment option for r/r ALL. Yet, there remain concerns over its long-term effectiveness, affordability, and equity in access.
- The next best (cost-effective) treatment option is Blinatumomab, followed by Clofarabine therapy, whereas FLA-IDA salvage chemotherapy provides least value for money.
- The quality of evidence is moderate to high, with limited generalisability of findings due to high variability in outcomes obtained from modelling studies.
- Limited studies evaluated cost-effective treatment options for r/r AML.

Chapter Six References

1. American Cancer Society (ACS). Key Statistics for Childhood Leukemia [Internet]. ACS. 2023 [updated 2023 Jan; cited 2023 Mar]. Available from: https://www.cancer.org/cancer/leukemia-in-children/about/key-statistics.html
2. Sun, W., Malvar, J., Sposto, R. Verma A, Wilkes JJ, Dennis R, *et al*. Outcome of children with multiply relapsed B-cell acute lymphoblastic leukemia: therapeutic advances in childhood leukemia & lymphoma study. *Leukemia.* 2018;32(11):2316-2325.
3. Martin A, Morgan E, Hijiya N. Relapsed or refractory pediatric acute lymphoblastic leukemia: current and emerging treatments. *Paediatr Drugs*. 2012;1;14(6):377-87.
4. Locatelli F, Schrappe M, Bernardo M, *et al*. How I treat relapsed childhood acute lymphoblastic leukemia. *Blood*. 2012;4;120(14):2807-16.
5. Rasche M, Steidel E, Zimmermann M, *et al.* Second Relapse of Pediatric Patients with Acute Myeloid Leukemia: A Report on Current Treatment Strategies and Outcome of the AML-BFM Study Group. *Cancers* (Basel). 2012;13(4):789.
6. Scalo F, and Rascati K. L. Trends and issues in oncology costs. Expert Rev. *Pharmacoecon. Outcomes Res*. 2014;14(1):35-44.
7. Chhatwal, J, Mathisen M, and Kantarjian H. Are high drug prices for hematologic malignancies justified? A critical analysis. *Cancer.* 2015;121(19):3372–9.
8. Pui, H, and Evans E. A 50-year journey to cure childhood acute lymphoblastic leukemia. *Semin. Hematol*. 2013;50(3):185–196.
9. Stephen P. Hunger,Elizabeth A. Raetz, How I treat relapsed acute lymphoblastic leukemia in the pediatric population, *Blood.* 2020;136(16):1803–1812.

10. Anne E Hoffman, Linda J Schoonmade, Gertjan JL Kaspers. Pediatric relapsed acute myeloid leukemia: a systematic review, *Expert Rev. Anticancer Ther*. 2021;21(1):45-52.

11. Kaul S, Korgenski EK, Ying J, *et al*. A retrospective analysis of treatment-related hospitalization costs of pediatric, adolescent, and young adult acute lymphoblastic leukemia. *Cancer Med*. 2016;5(2):221-29.

12. Forsythe A, Sandman KE. What Does the Economic Burden of Acute Myeloid Leukemia Treatment Look Like for the Next Decade? An Analysis of Key Findings, Challenges and Recommendations. *J Blood Med*. 2021;12:245-55.

13. Shemilt I, Mugford M, Byford S, *et al*. Chapter 15: Incorporating economics evidence. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0. p. 449-80. [Internet]. The Cochrane Collaboration. 2011 [updated: 2011 Mar; cited: 2021 Jul]. Available from: www.handbook.cochrane.org

14. Russell HV, Panchal J, Vonville H, *et al*. Economic evaluation of pediatric cancer treatment: a systematic literature review. *Pediatrics*. 2013;131(1):e273-87.

15. Moher D, Liberati A, Tetzlaff J, *et al*. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;51:264-269.

16. Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs A H, Carswell C *et al*. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations *BMJ*. 2022;376:e067975.

17. Centre for Reviews and Dissemination (CRD). Systematic Reviews: CRD's guidance for undertaking reviews in healthcare. CRD. University of York. 2009. [cited 2021 Aug]. Available from https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf
18. Craig D, Rice S. NHS economic evaluation database handbook: Centre for Reviews and Dissemination [Internet]. University of York. 2007 [cited 2021 Mar].
19. Fung A, Horton S, Zabih V, *et al*. Cost and cost-effectiveness of childhood cancer treatment in low-income and middle-income countries: a systematic review. *BMJ Glob. Health.* 2019;4:e001825.
20. The Professional Society for Health Economics and Outcomes Research (ISPOR). ISPOR 2023 [cited 2021 Nov]. Available from: https://www.ispor.org/home
21. The World Bank Indicators. Official exchange rate (LCU per US$, period average) [Internet]. World Bank Group. 2023 [cited 2020 Aug 28]. Available from: https://data.worldbank.org/indicator/PA.NUS.FCRF?view=chart
22. The World Bank Indicators. GDP deflator (base year varies by country). World Bank Group. 2023 [cited 2020 Aug 28]. Available from: https://data.worldbank.org/indicator/NY.GDP.DEFL.ZS
23. Lin YF, Lairson DR, Chan W, *et al*. The costs and cost-effectiveness of allogeneic peripheral blood stem cell transplantation versus bone marrow transplantation in pediatric patients with acute leukemia. *Biol Blood Marrow Transplant*. 2010;16(9):1272-81.
24. Maser B, Pelland-Marcotte M-C, Alexander S, *et al*. Levofloxacin prophylaxis in hospitalized children with leukemia: A cost-utility analysis. *Pediatr Blood Cancer*. 2020;67:e28643.

25. Lin JK, Lerman BJ, Barnes JI, *et al*. Cost Effectiveness of Chimeric Antigen Receptor T-Cell Therapy in Relapsed or Refractory Pediatric B-Cell Acute Lymphoblastic Leukemia. *J Clin Oncol*. 2018;10;36(32):3192-202.

26. Whittington MD, McQueen RB, Ollendorf DA, *et al*. Long-term Survival and Value of Chimeric Antigen Receptor T-Cell Therapy for Pediatric Patients with Relapsed or Refractory Leukemia. *JAMA Pediatr*. 2018;172(12):1161-68.

27. Sarkar RR, Gloude NJ, Schiff D, *et al*. Cost-Effectiveness of Chimeric Antigen Receptor T-Cell Therapy in Pediatric Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia. *J Natl Cancer Inst*. 2019;1;111(7):719-726.

28. Santasusana R, Saldaña A, García-Muñoz N, *et al*. Cost-Effectiveness Analysis of Tisagenlecleucel in the Treatment of Relapsed or Refractory B-Cell Acute Lymphoblastic Leukaemia in Children and Young Adults in Spain. *Clinicoecon Outcomes Res*. 2020;12:253-264.

29. Thielen FW, van Dongen-Leunis A, Arons AMM, *et al*. Cost-effectiveness of Anti-CD19 chimeric antigen receptor T-Cell therapy in pediatric relapsed/refractory B-cell acute lymphoblastic leukemia. A societal view. *Eur J Haematol*. 2020;105(2):203-215.

30. Furzer J, Sumit G, Paul C, *et al*. Cost-effectiveness of Tisagenlecleucel vs Standard Care in High-risk Relapsed Pediatric Acute Lymphoblastic Leukemia in Canada. *JAMA Oncol*. 2020;6(3):393-401.

31. Yang H, Hao Y, Qi CZ, *et al*. Estimation of Total Costs in Pediatric and Young Adult Patients with Relapsed or Refractory Acute Lymphoblastic Leukemia Receiving Tisagenlecleucel from a U.S. Hospital's Perspective. *J Manag Care Spec Pharm*. 2020;26(8):971-980.

32. Schulthess D, Gassull D, Makady A, *et al*. Are CAR-T therapies living up to their hype? A study using real-world data in two cohorts to determine how well they are actually working in practice compared with bone marrow transplants. *BMJ Evid Based Med*. 2021;26(3):98-102.

33. Wakase S, Teshima T, Zhang J, *et al*. Cost-Effectiveness Analysis of Tisagenlecleucel for the Treatment of Pediatric and Young Adult Patients with Relapsed or Refractory B Cell Acute Lymphoblastic Leukemia in Japan. *Transplant Cell Ther*. 2021;27(3):241.e1-241.e11.

34. Moradi-Lakeh M, Yaghoubi M, Seitz P, *et al*. Cost-Effectiveness of Tisagenlecleucel in Paediatric Acute Lymphoblastic Leukaemia (pALL) and Adult Diffuse Large B-Cell Lymphoma (DLBCL) in Switzerland. *Adv Ther*. 2021;38(6):3427-43.

35. Fiorenza, S., Ritchie, D.S., Ramsey, S.D. *et al*. Value and affordability of CAR T-cell therapy in the United States. *Bone Marrow Transplant.* 2020; 55(9):1706-1715.

36. Pepper MS, Alessandrini M, Pope A, *et al*. Cell and gene therapies at the forefront of innovative medical care: Implications for South Africa. *S Afr Med J*. 2018;13;109(1):20-22.

37. Cornetta K, Patel K, Wanjiku CM, *et al*. Equitable Access to Gene Therapy: A Call to Action for the American Society of Gene and Cell Therapy. *Mol Ther*. 2018;5;26(12):2715-16.

38. European Medicines Agency (EMA). Kymriah (*tisagenlecleucel).* What are the risks associated with Kymriah? [Internet]. 2023 [cited: 2022 Jan]. Available from : https://www.ema.europa.eu/en/medicines/human/EPAR/kymriah

39. Gye A, Goodall S, and De Abreu L. A Systematic Review of Health Technology Assessments of Chimeric Antigen Receptor T-Cell Therapies in Young Compared with Older Patients, *Value Health.* 2022;25(1):47-58.

40. Petrou P. Is it a Chimera? A systematic review of the economic evaluations of CAR-T cell therapy. *Expert Rev Pharmacoecon Outcomes Res*. 2019;19:5:529-36.

41. Heine R, Thielen FW, Koopmanschap M, *et al*. Health Economic Aspects of Chimeric Antigen Receptor T-cell Therapies for Hematological Cancers: Present and Future. *Hemasphere*. 2021;5(2):e524.

42. Pechlivanoglou P, Luu L, Li Q, *et al*. Blinatumomab Is Cost-Effective Compared to Standard Chemotherapy for Children with high-risk Relapses of Acute Lymphoblastic Leukemia: A Cost-Effectiveness Analysis Using Population-Based Healthcare Data. *Blood*. 2021;138(Supplement 1):565.

43. Hoffman A, Schoonmade L, and Kaspers G. Pediatric relapsed acute myeloid leukemia: a systematic review. *Expert Rev of Anticancer Ther.* 2021;21(1):45-52.

44. Mamolo C, Welch V, Walter RB, *et al*. Budget Impact Analysis of Gemtuzumab Ozogamicin for the Treatment of CD33-Positive Acute Myeloid Leukemia. *Pharmacoeconomics*. 2021;39(1):121-131.

45. Jaime-Pérez JC, Heredia-Salazar AC, Cantú-Rodríguez OG, *et al*. Cost structure and clinical outcome of a stem cell transplantation program in a developing country: the experience in northeast Mexico. *Oncologist*. 2015;20(4):386-92.

Chapter Seven: Barriers and facilitators to implementing cost-effective evidence-based childhood cancer treatment in Egypt

"*It is not the answer that enlightens, but the question.*" — Eugene Ionesco

Interviewing clinicians and asking about their perceptions of barriers and facilitators to implementing cost-effective evidence-based treatment generates qualitative evidence from experts' opinions in the local context. This helps address the implementation gaps and translate the generated evidence into practice.

7.1. Publication statement

Features of this chapter are accepted for publication in the following peer-reviewed journal:

Soliman R, Heneghan C, Boylan AM, Oke J, Eweida W, and ElHaddad A. Barriers and facilitators to implementing cost-effective evidence-based childhood cancer treatment in a resource-limited setting in Egypt: A qualitative interview study. *JCO Glob Oncol*. 2023. DOI: 10.1200/GO.22.00424

7.2 Introduction

Evidence-based practice (EBP) in paediatric oncology is crucial for delivering optimal childhood cancer care and improving health outcomes effectively by making informed decisions in practice using the best available evidence.[1] A key step in implementing EBP is identifying the implementation gaps between evidence and current practice that may exist for many reasons, ranging from systems-related issues to individual factors.[2] Providing childhood cancer treatment in low- and middle-income countries (LMICs) should be informed by the best evidence relevant

to local contexts and based on cost-effective strategies to optimise the use of the limited resources. Nevertheless, LMIC contexts (including Egypt) face many barriers to translating evidence into practice due to limited resources, social and cultural contexts, and resistance to change.[3]

Effective implementation of cost-effective evidence-based childhood cancer treatment requires knowledge about the barriers and facilitators influencing its use.[4] That is why there is a need to determine the barriers and facilitators to effectively implement evidence-based childhood cancer treatment in these resource-limited settings to address the implementation gap, as described in the Background Chapter 2 (section 2.7.3).

In chapters 3–5, I generated relevant evidence from the local context in Egypt about potential ways to improve childhood cancer survival outcomes (Chapter 3), optimise resource use and costs (Chapter 4), and increase the cost-effectiveness of treatment (Chapter 5). In Chapter 6, I generated systematic evidence from the literature about potential strategies to promote the cost-effectiveness of treatment for relapsed/refractory acute leukaemia in children. In this chapter, I set out to determine the barriers and facilitators that affect implementing cost-effective evidence-based treatment for children with cancer in a resource-limited setting in Egypt, to help translate the generated evidence (from Chapters 3–6) into practice.

7.3 Aim of work

To determine the clinicians' perceptions of barriers and facilitators to implementing cost-effective evidence-based childhood cancer treatment in a local setting in Egypt (CCHE).

7.4 Objectives

1. To understand the clinicians' perceptions of the barriers and facilitators.
2. To determine the clinicians' suggestions to tackle the existing barriers to implementation.
3. To provide evidence-based recommendations to implement cost-effective evidence-based treatment at CCHE/Egypt.

7.5 Methods

The study was designed and reported in line with the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist.[5] The completed checklist is included in Appendix 7.1.

7.7.6 Design, setting, and scope

I conducted a descriptive qualitative study at CCHE based on semi-structured interviews guided by some predefined topics and open-ended questions. At CCHE, childhood cancer care is delivered through shared decision-making in multidisciplinary teams for each childhood cancer type known as "study teams".[6] The study team is responsible for making high-level decisions regarding childhood cancer treatment, such as the selection or modification of the standard treatment protocols. Each study team is led by a senior paediatric oncologist/haematologist (study team leader), and includes surgeons, radiation oncologists, pathologists, radiologists, pharmacist(s), and clinical researcher(s).[6]

Patients are treated at CCHE according to standard protocols adopted from international protocols from high-income countries (HICs); the Children's Oncology Group (COG)[7] for the majority of cancers, and the St. Jude Total XV protocol for acute lymphoblastic leukaemia.[8] The treatment protocols were selected by the study teams based on evidence of clinical effectiveness

and feasibility of their adoption at CCHE, depending on resource availability. Some atypically complicated patients (whose management is not indicated in the treatment protocols) are discussed by senior clinicians in weekly multidisciplinary combined clinics, where tailored decisions are made about disease relapse/progression, treatment failure, or palliative care for non-curative intent.

The main scope of this study focused on implementing cost-effective treatment (i.e., providing greatest health benefit/outcome relative to the money/resources spent) on these two decision-making levels; (1) high-level decisions to select/modify treatment protocols, and (2) tailored decisions to manage atypically complicated cases. Whereas, day-to-day individual decisions were outside the scope of this study.

7.5.2 Ethical considerations

Ethics approval for this study was granted by the institutional review board (IRB) at CCHE on September 9, 2021 (Ref. number: CCHE-35) (Appendix 7.2) and by the Oxford Tropical Research Ethics Committee (OxTREC) for minimal risk studies at the University of Oxford on January 7, 2022 (OxTREC ref. 569-21) (Appendix 7.3). All participants gave written informed consent using the forms approved by the ethics committees of both institutions, to ensure all ethical considerations in qualitative research studies were met.[9] The two informed consent forms are available in Appendix 7.4 and Appendix 7.5.

7.5.3 Participants and recruitment

Purposive sampling was used to recruit senior clinicians who provide treatment for children with cancer at CCHE.[10] The inclusion criteria included: (1) senior clinicians involved in the high-stake/tailored decisions regarding the treatment of children with cancer (senior paediatric

oncologists, radiation oncologists, and surgeons); (2) willingness and availability to participate in the study; and (3) providing written informed consent. Whereas, exclusion criteria included less experienced young clinicians and other study team members who are not the main key players in the high-level decision-making process.

The study aimed to conduct 12–15 interviews, with the final number of participants determined by data saturation.[10] Announcement about the interview study was done through internal communication of Recruitment Material (Appendix 7.6) with potentially eligible clinicians through posters and emails. Recruitment of the participants was done through direct communication with the potentially eligible participants and sharing the *Participant Information Sheet* including full details about the study (Appendix 7.7)

7.5.4 Data collection

I developed a semi-structured interview guide in consultation with a senior qualitative researcher (Anne-Marie Boylan). The interview guide includes the main interview topics and example questions under each topic and is available in Appendix 7.8. Participants were asked about their perceptions of barriers and facilitators on the two decision-making levels, where the interviewed senior clinicians were part of both committees; Study Teams and Combined Clinics.

Qualitative data was collected during in-depth face-to-face interviews that took place between July 1st and September 5th, 2022, at CCHE on a one-to-one basis. I received training in qualitative research methods qualifying me to conduct qualitative interview studies. Therefore, I conducted all the audio-recorded interviews, translated them from the Arabic to the English language, and transcribed them verbatim.

7.5.5 Thematic data analysis

Thematic analysis was conducted, where qualitative data were analysed semantically and inductive analysis was performed with full presentation of themes.[11] I began by familiarising myself with the data by reading and listening again to the interviews I conducted. I then coded the data, assigning labels to chunks of text of various lengths. Data coding was done without trying to fit into a pre-existing coding frame or the researchers' analytic preconceptions, and thematic analysis was data-driven.[11] I used NVivo (version 1.6.1) software to facilitate coding.[12] I categorised codes of similar concepts/perceptions into related domains and discussed them with other two senior researchers (Anne-Marie Boylan and Carl Heneghan) to develop the final themes. Supporting quotes were chosen to demonstrate and evidence the developed themes. I performed sub-group analyses by level of decision-making (high-level versus tailored decisions), and health profession of included clinicians (paediatric oncologists, surgeons, radiation oncologists). Data analysis was conducted concurrently with data collection, refined throughout the interview process, then finalised upon completion of all interviews in an iterative process.

7.6 Results

7.6.1 Participant characteristics

I interviewed fourteen participants out of the fifteen invited senior clinicians; one declined to participate due to unavailability of time. Interviews lasted between 30–75 minutes, and none were repeated. Based on the iterative process of concurrent data collection and analysis, saturation was reached after conducting twelve interviews, both in terms of the interview content and the categorisation in the analysis. This was confirmed by conducting further two interviews.

Table 7.1 shows the characteristics of the interviewed senior clinicians; nine paediatric oncologists/haematologists (study team leaders), three surgeons, and two radiation oncologists. Most participants (9/14; 64.3%) were males, and the mean age of all participants was 45 years (range: 42–55 years). Years of clinical experience ranged between 15 and 25 years in the different specialities. To maintain data confidentiality, further details were not included as all participants work in the same hospital setting and could be easily identifiable.

Table 7.1. Characteristics of interview participants (N=14)

Characteristic	**Number of Participants (%)**
Gender	
Male	9 (64.2%)
Female	5 (35.8%)
Age	
Mean (median)	45 (47)
Age-groups	
42–49 years	8 (57.1%)
50–55 years	6 (42.9%)
Healthcare professionals	
Paediatric oncologists	9 (64.2%)
Surgeons	3 (21.5%)
Radiation oncologists	2 (14.3%)
Years of experience in field	
15–20 years	9 (64.2%)
>20–25 years	5 (35.8%)

7.6.2 Themes of barriers and facilitators

The following four themes captured the clinicians' perceptions of barriers and facilitators to implementing cost-effective evidence-based treatment for children with cancer at CCHE/Egypt: (1) awareness and orientation; (2) knowledge, skills and attitudes; (3) system, resources and context; and (4) current practice. Figure 7.1 illustrates a thematic framework of inter-related themes of barriers and facilitators that uses themes to conceptualise a belief or an understanding.

Table 7.2 presents an overview of the themes and domains of barriers and facilitators reported by all study participants across the two decision-making levels of interest. Most of the barriers and facilitators were stated by paediatric oncologists addressing the four developed themes, as they represent the majority of participants.

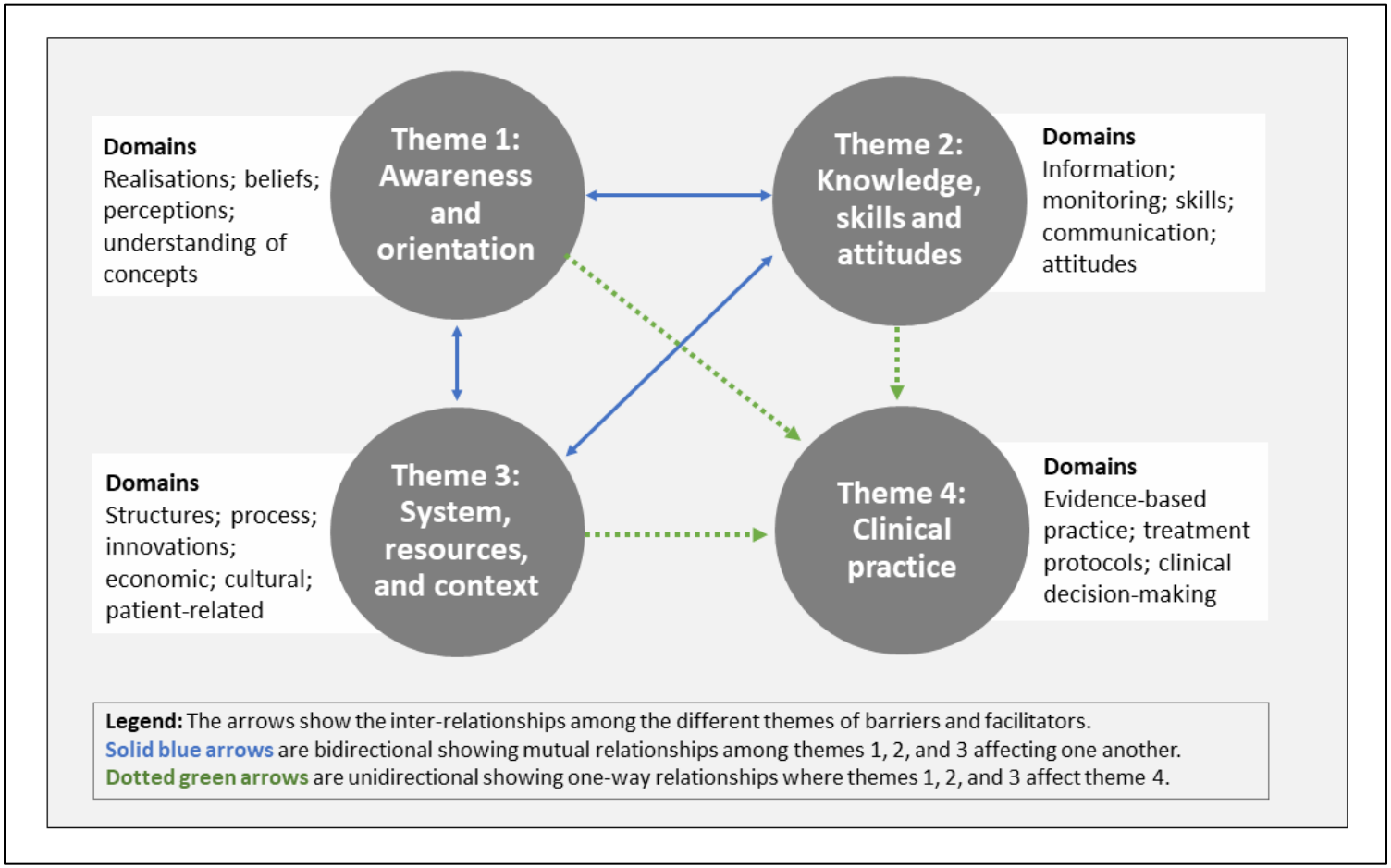


Figure 7.1. Thematic framework of interrelated themes of barriers and facilitators

Table 7.2. Themes and domains of Barriers and facilitators to implement cost-effective evidence-based treatment for children with cancer at CCHE/Egypt

Theme	Domains	Facilitators	Barriers
1. Awareness and orientation	Realisations and beliefs; understanding of core concepts	• Familiarity with the basic concepts of evidence-based practice (EBP). • Basic understanding of adopting cost-effective treatment.	• Limited awareness about exact role of clinicians to provide cost-effective treatment. • Beliefs that clinicians are only concerned with clinical effectiveness, ignoring the costs aspect.
2. Knowledge, skills, and attitudes	Information; monitoring; skills; communication; attitude towards change	• Knowledge about clinical outcomes of treatment from the literature and the local setting at CCHE. • Skilled clinical researchers and health economists (not clinicians) • Willingness to adopt cost-effective treatment and eagerness to learn.	• Gap in knowledge about cost-effectiveness of treatment • Limited clinicians' skills in applying EBP and making cost-effectiveness evaluation for treatment. • Limited published evidence about clinical and/or cost-effectiveness of surgical procedures in paediatric cancers. • Limited clinicians' skills to acquire and assess quality of evidence • Gap in communication among health professionals. • Resistance to change practice in making surgical decisions. • Gap in patient education about disease progression, and treatment options and potential outcomes of treatment
3. System, resources, and context	Structures; processes, policies, mechanisms, infrastructure; innovations (treatment protocols); economics (finances, costs, resources); cultural, social and patient-related factors	• Good governance and supportive leadership. • A policy in place to regularly evaluate patients' clinical outcomes (survival). • Study teams for each cancer type. • Standard treatment protocols (first-line) • Data infrastructure including clinical, administrative and cost data. • Clinical research and health economics units • Culture of research, continuous education, and quality improvement.	• Economic instability and devaluation of local currency • Limited resources, time constraints, and unaffordability to pay for expensive novel therapies (that are cost-effective). • Absence of a mechanism and policies/procedures to evaluate cost-effectiveness of treatment. • Absence of easily-accessible costs data from local context • Limited standard protocols for relapsing patients • Cultural, social, and humanitarian factors impact tailored decisions at the end of life.

4. Clinical Practice	Evidence-based practice; treatment protocols; clinical decision-making	• Implementing clinically effective evidence-based (first-line) treatment • Shared decision-making process in multi-disciplinary study teams/combined clinics • Adapting treatment protocols to local contexts, based on resource availability.	• Gap between research evidence and practice. • Lack of standard practice for treating relapsed patients. • Absence of guidelines/criteria to stop salvage therapy and start palliative non-curative care • Not making bone marrow transplant for all indicated patients • Unavailability of novel therapies, e.g.: targeted and immunotherapies that are cost-effective • Clinical decisions not judged based on cost-effectiveness.

Theme 1: Awareness and orientation

Familiarity with basic EBP concepts and awareness about the importance of implementing cost-effective treatment were important facilitators highlighted by the clinicians. Participants often reported that they follow standard treatment protocols based on evidence, quoting, "*We treat our children with cancer based on standard protocols adapted from international protocols based on best available evidence of clinical effectiveness.*" (PO–01). However, their lack of awareness about the active role they play in selecting cost-effective treatment strategies was a common barrier among clinicians.

Many of them believed that clinicians should only focus on the clinical benefit of treatment, whereas, the costs and financial aspects are not their responsibility, but are the decisions of the hospital management. As one participant said, "*clinicians should only be concerned with the clinical outcomes of treatment, while decisions about the costs of care should be taken by the hospital's upper management*." (PO–04). Only four paediatric oncologists recognised their roles in judging the cost-effectiveness of treatment interventions in the clinical decision-making process: "*we should also make tailored decisions in the combined clinics based on cost-effectiveness of treatment*." (PO–9).

Theme 2: Knowledge, skills, and attitudes

Some participants indicated that adequate knowledge of the clinical outcomes of treatment based on evidence from the literature and the local setting were key facilitators: "*we have an advantage at CCHE because we can generate local knowledge about patients' outcomes from real-world data.*" (PO–5). On the other hand, the absence of easily accessible costs data and the lack of knowledge about cost-effectiveness of treatment from local context were commonly reported

barriers, "*Our biggest problem is that clinicians do not have access to data about how much the treatment costs at CCHE, so we can't make decide whether treatment would be cost-effectiveness or not."* (PO–3).

One surgeon reported that there is limited published literature about the cost-effectiveness of surgical interventions: "*there is limited published literature about clinical and/or cost-effectiveness of surgical procedures in paediatric cancers that is relevant to the patients we see in practice."* (PS–01). While many clinicians mentioned that they lack the necessary skills to understand cost-effectiveness analyses, they were eager to learn how to interpret the findings and willing to change practice, accordingly. As RO–1 said, "*we don't know how to make cost-effectiveness analyses or understand their results*".

Theme 3: System, resources, and context

The main facilitators under this theme included supportive leadership, existing study team groups, standard treatment protocols, clinical/cost data infrastructure, a policy in-place to regularly evaluate patients' clinical outcomes, and an established research department and health economics unit. One clinician commented, "*we have the necessary structures and tools to provide evidence-based treatment, and we should use the existing resources to make it cost-effective as well."* (PO–06).

On the other hand, most participants mentioned that a main barrier was the absence of a mechanism/system to regularly monitor cost-effectiveness of treatment at CCHE, quoting, "*we don't have any written policies to evaluate cost-effectiveness of treatment, and no mechanisms exist about how, when or who should be involved in the process."* (PO–04).

Other significant barriers included limited resources, time constraints, and unaffordability to pay for the expensive (but cost-effective) novel therapies. One of the surgeons commented that, "*we do not have adequate time or resources to evaluate and compare the cost-effectiveness of different surgical interventions*." (PS–2).

Furthermore, patient-related socio-cultural, and humanitarian factors were perceived as barriers to providing cost-effective care while making tailored decisions for relapsing/progressive disease: "*sometimes patients put pressure on doctors to provide additional salvage therapy for terminally-ill relapsed patients, believing that it will save their lives, when they should only receive palliative end-of-life care*." (PO–2).

Theme 4: Clinical practice

Participants reported that adopting evidence-based standard protocols for first-line therapy and shared decision-making in multidisciplinary teams were key facilitators. Whereas, existing implementation gap between evidence from real-world data and current practice was considered a major problem, "*we conduct research studies using real-world data at CCHE, but we do not use research findings to improve clinical practice."* (PO–8).

Additionally, current practice for managing relapsing/progressive patients does not follow (cost-effective) evidence-based protocols for the majority of cancers, and no well-documented guidelines exist regarding criteria for discontinuing salvage therapy for non-responding patients and initiating palliative care for non-curative intent. For example, one participant explained that "*in case of relapsing AML patients who could not undergo bone marrow transplant, recent evidence suggests that it is not cost-effective to provide many cycles of intensive salvage chemotherapy. Yet, this happens while making tailored decisions*." (PO–2).

Sub-group analysis by health profession showed that surgeons and radiation oncologists addressed barriers under only two themes; knowledge-skills-attitudes and systems-resources-context, as shown in Table 7.3. Whereas, sub-group analysis by decision-making level identified distinct barriers and facilitators under each theme, as presented in Table 7.4. There were no differences in participants' perceptions based on gender, age, or years of experience.

Table 7.3. Sub-group analysis of themes of barriers and facilitators to implement cost-effective evidence-based childhood cancer treatment at CCHE/Egypt, by health professions

Health Profession	Theme	Barriers
Surgeons	Knowledge, skills, and attitudes	• Gap in knowledge about cost-effectiveness of surgical procedures in paediatric cancers, due to poor quality of published evidence. • Limited skills in applying EBP and cost-effective treatment interventions. • Absence of cost/cost-effectiveness data about different surgical interventions from the local context. • Resistance (of some surgeons) to change current practice regarding making surgical decisions based on best evidence or cost-effectiveness estimates.
	System, resources, and context	• Limited resources and time constraints making it difficult to evaluate and compare the cost-effectiveness of different surgical interventions. • Unaffordability to pay for expensive surgical expandable prosthesis used in orthopaedic surgeries for children with bone cancers
Radiation oncologists	Knowledge, skills, and attitudes	• Gap in knowledge about the cost-effectiveness of radiotherapy compared to other interventions to treat childhood cancers • Limited clinicians' skills to evaluate or interpret findings from cost-effectiveness analysis of treatment interventions.
	System, resources, and context	• Absence of cost/cost-effectiveness data from the local context to compare outcomes of radiotherapy versus surgery in some cancers such as sarcomas. • Lack of a system in the hospital to evaluate cost-effectiveness of treatment

Table 7.4. Sub-group analysis of themes of barriers and facilitators to implement cost-effective evidence-based childhood cancer treatment at CCHE/Egypt, by level of decision-making

Level of decision-making	Theme	Facilitators	Barriers
High-level decisions (i.e.: choosing treatment protocols for each childhood cancer type, within the Study Teams groups)	Awareness and orientation	• Familiarity with basic evidence-based practice (EBP) concepts.	• Limited awareness about clinicians' role to provide cost-effective treatment. • Beliefs that costs of treatment should not be considered in decisions
	Knowledge, skills and attitudes	• Knowledge about treatment outcomes and skilled researchers in study teams	• Gap in knowledge/skills to estimate cost-effectiveness; no health economists
	System, resources, and context	• Policy to regularly review survival rates • Standard (first-line) treatment protocols • Access to clinical/disease-related data • Culture of research to improve outcomes	• Lack of system and polices to monitor cost-effectiveness of treatment • Limited protocols for disease relapse • Absence of treatment costs data
	Clinical Practice	• Shared decision-making in Study Teams • Following clinically effective treatment protocols; adapted to local context	• Gap between evidence and practice • Not following standard guidelines/ protocols for relapsing patients
Tailored decisions (i.e.: making decisions to manage the atypical complicated group of patients, within Combined Clinics)	Awareness and orientation	• Basic understanding of clinicians' role to adopting cost-effective treatment.	• Limited awareness about how to make clinical decisions considering the costs of treatment
	Knowledge, skills and attitudes	• Knowledge about clinical evidence from literature • Willingness to adopt cost-effective treatment	• Gap in knowledge/skills to judge cost-effectiveness of treatment options based on evidence. • Absence of treatment costs data. • Gap in communication among health professionals.
	System, resources, and context	• Governance; all atypical cases are discussed in Combined Clinics.	• Limited standard protocols for relapsed patients • Limited resources and unaffordability. • Cultural, social, humanitarian factors impacting decisions on palliation. • Gap in patient education about treatment options.
	Clinical Practice	• Shared decision-making across multi-disciplinary teams	• Absence of guidelines/criteria to stop salvage therapy and start palliative care. • Unavailability of novel drugs to treat relapse

			• Clinical decisions not judged based on cost-effectiveness of treatment options.

7.6.3 Participants' suggestions

The participants provided suggestions to address the existing barriers (presented in Table 7.5) classified under the same developed themes. A key recommendation was to achieve good governance by developing mechanisms and processes to ensure the evaluation and implementation of evidence-based cost-effective treatment, specifically that, *"cost-effectiveness of treatment should be regularly evaluated in study teams, and a committee should be formed to oversee the implementation."* (PO–7). Others suggested making cost/cost-effectiveness data available to clinicians, "*we need easy access to cost/cost-effectiveness data for the different treatment interventions to help us make informed clinical decisions*." (RO–2)

Table 7.5. Participants' Suggestions to implement cost-effective evidence-based treatment for children with cancer at CCHE/Egypt

Theme	Domains	Suggestion/recommendation
Awareness and orientation	Orientation	• Orientation to clinicians about core concepts of health economic evaluation, and the importance of making clinical decisions based on the cost-effectiveness of treatment.
	Communication	• Dissemination of research findings with key stakeholders in a systemic approach. • Communication of treatment cost-effectiveness results with hospital management and healthcare professionals. • Ensuring transparency in communicating benefits and harms of treatment to patients based on evidence.
Knowledge, skills, and attitudes	Capacity building	• Developing clinicians' skills to search for recent evidence from literature, and critically appraise evidence. • Expanding the size of health economics team to conduct cost-effectiveness analysis regularly for all cancers. • Training an enthusiastic study team member in health economic evaluation and cost-effectiveness analysis. • Capacity building of clinical research team to make in-depth statistical analysis of clinical outcomes.
	Monitoring and evaluation	• Within the study teams, regularly evaluating and compare cost-effectiveness of treatment interventions • Evaluating the cost-effectiveness of salvage chemotherapy for relapsing/progressive patients, for all cancers
	Collaboration	• Collaborate with international groups and organization to participate in clinical trials involving novel drugs. • Conduct collaborative research studies with international centers and groups. • Partner with other centers in Egypt in different geographical areas (as referral partners) to refer patients for coordinated care regarding simple interventions.
System, resources, and context	Governance; structures, processes, and mechanisms	• Put a hospital-wide mechanism/system to evaluate treatment cost-effectiveness based on local data at CCHE, make high-stake clinical decisions accordingly. • Establishing a committee to monitor evidence-based economic evaluation of treatment interventions; including: hospital administration, doctors, health economists, pharmacists and supply chain specialists. • Set high-stake decisions regarding when to stop salvage therapy for relapsed/progressive patients who do not respond to treatment, and should receive palliative care with a non-curative intent.
	policies and procedures	• Setting policies and procedures in the following areas: o evaluating cost-effectiveness of treatment as a main protocol outcome, with health economics team. o monitoring the implementation of recommendations from research findings into practice o no-further-treatment (NFT) with clear criteria for initiating palliative care at the end-of-life o introducing new drugs for curative intent should be judged based on their cost-effectiveness estimates • Updating the policy of in-depth evaluation of protocol outcomes to be conducted every 2–3 years.
	Innovations; tools, drugs, guidelines	• Providing advanced search engine tools with free access to the recently published research articles. • Developing standard guidelines for relapsed/progressive patients in all cancer types. • Making cost and cost-effectiveness data easily available to clinicians through innovative tools. • Considering the adoption of less expensive targeted therapies of similar efficacy such as biosimilar.

Clinical Practice	protocols; practice guidelines; clinical decision-making processes	• Providing effective evidence-based first-line treatment to reduce relapse rate and improve survival rate. • Adopting cost-effective evidence-based treatment strategies for first-line and consecutive lines of therapy • Making tailored decisions in combined clinics based on evidence of clinical and cost-effectiveness • Modifying clinical practice guidelines and treatment protocols based on cost-effectiveness estimates from the literature and local data at CCHE • Providing bone marrow transplant for all indicated patients being a cost-effective intervention

7.7 Discussion

7.7.1 Summary and interpretation of findings

In this study, I developed four themes of barriers and facilitators to implementing cost-effective evidence-based childhood cancer treatment in Egypt/CCHE; (1) awareness and orientation; (2) knowledge, skills and attitudes; (3) system, resources and context; and (4) current practice.

The main facilitators included the adoption of standard treatment protocols, shared decision-making, availability of clinical and cost data infrastructures, supportive leadership, the presence of trained health economists, and favourable clinician attitudes towards change. Whereas, a gap in knowledge about the cost/cost-effectiveness of treatment, limited resources, unaffordability to pay for novel expensive (cost-effective) therapies, and the absence of standard practice guidelines for relapsed patients were significant barriers.

The participants suggested key effective solutions to address the existing barriers, such as developing a hospital-wide system/mechanism with written policies for evaluating and implementing cost-effective evidence-based treatment. Paediatric oncologists reflected on barriers and facilitators under the four developed themes, while surgeons and radiation oncologists only addressed two themes of barriers as shown in Table 7.3 and Table 7.4. Gender balance was not disregarded in selection of the participants; it is representative of the pool of senior clinicians available at CCHE, which has fewer females in senior decision-making positions, with all surgeons being male.

7.7.2 Comparison with other published literature

The developed themes of barriers and facilitators determined in this study were similar to those identified in the literature, however, no published studies were relevant to implementing cost-effective evidence-based treatment for childhood cancers. Several articles reported on the barriers and facilitators to implementing EBP, however, none of these focused on childhood cancer care.[13,14,15,16] A systematic review by Bach-Mortensen *et al*. (2018) found that limited resource availability was the main barrier to implementing evidence-based interventions, while, organisational culture, and proper implementation strategies were common facilitators.[17]

According to Sugalski *et al.* (2021), the primary barriers to implementing evidence-based supportive care guidelines in paediatric oncology were gap in knowledge, and administrative hurdles, while the main facilitators were willingness to change and implementation mechanisms.[18] As reported in the sub-group analysis by health profession (Table 7.3), barriers to EBP implementation by surgeons included: a lack of EBP skills, time constraints, and limited published evidence in paediatric oncology surgery.[19] The main barriers to evaluate the health economic benefit (cost-effectiveness) of interventions in the Middle Eastern countries, were the limited access to clinical effectiveness and cost data from local contexts, lack of expertise and awareness, and absence of national governing bodies.[20,21]

7.7.3 Strengths and limitations

To the best of my knowledge, this is the first study to determine the clinicians' perceptions of barriers and facilitators in a resource-limited paediatric oncology setting in Egypt through in-depth interviews and thematic data analysis. This study/chapter generates qualitative evidence from experts' opinions based on local clinical experience which helps translate the evidence

(generated in chapters 3–6) into practice and address the implementation gaps. It highlights valuable insights from the local context and findings from this study can guide developing tailored strategies and practical mechanisms for implementation. Furthermore, it presents a thematic framework of inter-related themes of barriers and facilitators that addresses the gap in knowledge in this area.

Despite the strengths of this study, some limitations exist. First, this study was conducted in a single paediatric oncology setting in Egypt where transferability to other settings could be limited by the predominance of the hospital's context and culture. Nevertheless, some of these barriers and facilitators may also exist in similar resource paediatric oncology settings in Egypt or other LIMICs, and transferability of findings to other contexts should be judged by clinical expertise in the local setting. Second, since the majority of participants were paediatric oncologists, the study sample (and findings) could be weighted towards their views. However, at CCHE, childhood cancer care is predominantly administered by paediatric oncologists, with fewer surgeons and radiation oncologists involved, therefore, the study cohort (participants) are representative of the pool of clinicians in practice. Nevertheless, this could be different in other settings, and study findings should be interpreted with caution based on local context.

Third, there remains a potential risk for participants to be identifiable as they work in the same hospital. However, participation was voluntary and all signed informed consent demonstrating they understood the low risk to them. Fourth, although direct translation from Arabic to the English language was conducted during transcription, other semantic meanings may not have been captured. However, this was mediated by the fact that the same person conducted the interviews and analysis.

7.7.4 Implications

7.7.4.2 Implications for policymakers

At CCHE, capitalising on the current facilitators and tackling the existing barriers at the hospital level and the committee level would help develop organization-wide mechanisms and set effective high-level policies to implement cost-effective evidence-based treatment as an inherent process that is part of the system. This can be achieved by prioritising and implementing the participants' recommendations presented in Table 7.5 under the theme 'System, resources, and context'. Furthermore, findings from this study are context-specific and can be extrapolated to other resource-limited paediatric oncology settings in Egypt or other LMICs.

7.7.4.2 Implications for clinicians

The study findings would help clinicians make better informed clinical decisions to implement cost-effective childhood cancer treatment in practice in these two areas: (a) selection and modification of standard treatment protocols; and (b) making informed clinical decisions in combined clinics to manage the atypically complicated cases. This can be achieved through prioritising and implementing the suggestions of the participants (clinicians) presented in Table 7.5 (section 7.6.3 of this chapter) under the theme of 'clinical practice'.

7.7.4.3 *Implications for researchers*

This study paves the way for implementation research using knowledge translation (KT) frameworks; it can serve as the first element of the Ottawa Model of Research Use (OMRU), which focuses on assessing implementation barriers and facilitators within the practice environment and suggests tailoring KT strategies to the local context accordingly.[22] This calls for

future research to determine the perceptions of other key stakeholders (other than clinicians) in future research work, such as consumers (patients/families) and payers (decision-makers in the fundraising foundation responsible for funding childhood cancer treatment at CCHE).

7.7.5 Evidence-based recommendations for improvement

Accordingly, I suggest the following key recommendations (Panel 7.1) in policy-making (points 1 and 2), current practice (points 3 and 4), and future research (points 5, 6, 7 and 8) to implement cost-effective evidence-based treatment for children with cancer.

Panel 7.1. Recommendations to implement cost-effective evidence-based childhood cancer treatment in Egypt, addressing the implementation gaps:

1. Set hospital-wide policies and mechanisms suggested by the participants in Table 7.5 under the theme of 'System, resources, and context'.
2. Prioritise key participants' suggestions and develop an action plan for implementation.
3. Develop an online portal of Evidence database of Cost-effective childhood cancer treatment (EC3T), to serve as a source of knowledge for clinicians and inform clinical practice.
4. Implement key suggestions presented in Table 7.5 under the theme of 'Clinical Practice'.
5. Apply the Ottawa Model of Research Use knowledge translation framework to transfer research-based knowledge into practice.
6. Determine expert opinions of other key stakeholders (patients/families, hospital managers, payers) to implement cost-effective evidence-based treatment.
7. Understand the perceptions of young clinicians about barriers/facilitators to implement cost-effective evidence-based treatment in day-to-day decisions.
8. Study the perceptions of patients' families towards communication about end-of-life care.

7.8 Conclusion

These findings provide an important understanding of barriers and facilitators to implementing cost-effective evidence-based treatment strategies in a resource-limited paediatric oncology setting (CCHE/Egypt). I provide participants' suggestions and specific recommendations to implement cost-effective evidence-based treatment with clinical, policy and research implications, which can be transferable to similar resource-limited centres in Egypt, and other relevant centres in LMICs.

7.9 How this chapter relates to the overall thesis

My thesis aims to generate evidence to improve childhood cancer health outcomes and resource use in Egypt. Chapter 7 generates qualitative economic evidence from experts' opinions in the local setting to understand the clinicians' perceptions of barriers and facilitators to implementing cost-effective evidence-based treatment. This chapters provides tailored strategies and practical recommendations for implementing cost-effective treatment (i.e., providing the greatest health benefit/outcome relative to the money/resources spent). Accordingly, this helps translate the evidence generated in Chapters 3–6 into practice and address the implementation gaps.

7.10 Chapter summary

- This chapter determines the clinicians' perceptions of barriers and facilitators to implement cost-effective evidence-based treatment at CCHE/Egypt.
- The four main themes of barriers and facilitators: 'awareness and orientation'; 'knowledge, skills and attitudes'; 'system, resources and context'; and 'clinical practice'.
- The main barriers included:
    - absence of easily available costs/cost-effectiveness data to clinicians,

- limited resources and unaffordability to pay for expensive novel (cost-effective) drugs,
- gap between evidence/research and practice.

- The main facilitators included:
  - adopting standard treatment protocols based on clinical effectiveness,
  - availability of patients' clinical and costs data from local context, and
  - skilled researchers in clinical research and health economic evaluation.

Chapter Seven References

1. Kremer LCM, Loeffen EAH, Phillips RS. Evidence-Based Paediatric Oncology. In: Caron HN, Biondi A, Boterberg T, Doz F, editors. Oxford Textbook of Cancer in Children: Oxford University Press; 2020.
2. Kitson A, Straus SE. The knowledge-to-action cycle: identifying the gaps. *CMAJ*. 2010;182(2):E73-7.
3. Santesso N, Tugwell P. Knowledge translation in developing countries. *J Contin Educ Health Prof*. 2006;26(1):87-96.
4. Boland L, Graham ID, Legare F, Lewis K, Jull J, Shephard A, *et al*. Barriers and facilitators of pediatric shared decision-making: a systematic review. *Implement Sci*. 2019;14(1):7.
5. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care*. 2007;19(6):349-57.
6. Children' Cancer Hospital Egypt (CCHE). Our Vision [Internet]. CCHE. 2023 [cited 2023 Mar]. Available from: https://www.57357.org/
7. The Children's Oncology Group (COG). Children's Oncology Group [Internet]. COG. 2023 [cited2023 Mar]. Available from: https://childrensoncologygroup.org/
8. Pui CH, Relling MV, Sandlund JT, Downing JR, Campana D, Evans WE. Rationale and design of Total Therapy Study XV for newly diagnosed childhood acute lymphoblastic leukemia. *Ann Hematol*. 2004;83 Suppl 1:S124-6.

9. Sanjari M, Bahramnezhad F, Fomani FK, Shoghi M, Cheraghi MA. Ethical challenges of researchers in qualitative studies: the necessity to develop a specific guideline. *J Med Ethics Hist Med*. 2014;7:14.
10. Palinkas LA, Horwitz SM, Green CA, Wisdom JP, Duan N, Hoagwood K. Purposeful Sampling for Qualitative Data Collection and Analysis in Mixed Method Implementation Research. *Adm Policy Ment Health*. 2015;42(5):533-44.
11. Braun V, Clarke V. Using thematic analysis in psychology. *Qual. Res. Psychol*. 2006;3(2):77-101.
12. Lumivero. NVivo (released in March 2020) [Internet]. Lumivero. 2023 [cited 2023 Mar]. Available from: https://www.qsrinternational.com/nvivo-qualitative-data-analysis-software/home
13. Gifford W, Zhang Q, Chen S, Davies B, Xie R, Wen S-W, *et al.* When east meets west: a qualitative study of barriers and facilitators to evidence-based practice in Hunan China. *BMC Nursing*. 2018;17(1):26.
14. Hisham R, Ng CJ, Liew SM, Hamzah N, Ho GJ. Why is there variation in the practice of evidence-based medicine in primary care? A qualitative study. *BMJ Open*. 2016;6(3):e010565.
15. Shifaza F, Evans D, Bradley H. Nurses' Perceptions of Barriers and Facilitators to Implement EBP in the Maldives. *ANS Adv Nurs Sci*. 2014;2014:698604.
16. Duncombe DC. A multi-institutional study of the perceived barriers and facilitators to implementing evidence-based practice. *J Clin Nurs*. 2018;27(5-6):1216-26.

17. Bach-Mortensen AM, Lange BCL, Montgomery P. Barriers and facilitators to implementing evidence-based interventions among third sector organisations: a systematic review. *Implement. Sci*. 2018;13(1):103.
18. Sugalski AJ, Lo T, Beauchemin M, Grimes AC, Robinson PD, Walsh AM, *et al.* Facilitators and barriers to clinical practice guideline-consistent supportive care at pediatric oncology institutions: a Children's Oncology Group study. *Implement Sci. Commun*. 2021;2(1):106.
19. Sullivan KJ, Wayne C, Patey AM, Nasr A. Barriers and facilitators to the implementation of evidence-based practice by pediatric surgeons. *J Pediatr Surg*. 2017;52(10):1666-73.
20. Almazrou SH, Alaujan SS, Al-Aqeel SA. Barriers and facilitators to conducting economic evaluation studies of Gulf Cooperation Council (GCC) countries: a survey of researchers. *Health Res. Policy Syst*. 2021;19(1):71.
21. Alzarea AI, Khan YH, Alanazi AS, Butt MH, Almalki ZS, AlAhmari AK, *et al*. Barriers and Facilitators of Pharmacoeconomic Studies: A Review of Evidence from the Middle Eastern Countries. *Int J Environ Res Public Health*. 2022;19(13).
22. Graham ID, Logan J. Innovations in knowledge transfer and continuity of care. *Can J Nurs Res*. 2004;36(2):89-103.

Chapter Eight: Discussion

"*The essence of information...is not its content, but its resonance*." — Jose Arguelles

The merit of this thesis lies not in the findings of each study and the information provided, but rather in their relevance and impact on clinical practice, policymaking, and future research, which could in turn lead to saving the lives of children with cancer in Egypt.

8.1. Chapter aim

The aim of this chapter is to summarise the overall work included in my thesis; key findings, strengths and limitations, and implications on practice, policy, patients and future research.

8.2. Introduction

Childhood cancer is a public health priority in low- and middle-income countries (LMICs), where more than 80% of children with cancer reside with limited access to resources and have poor survival rates. In 2018, the WHO Global Initiative for Childhood Cancer was launched to improve global childhood cancer survival to at least 80% by 2030, with a focus on improving the more inferior survival in LMICs, which have limited (precious) resources. Childhood cancer is an urgent priority in Egypt, owing to the large numbers of children with cancer (ranked tenth globally and second regionally), inferior survival, and limited resources. Therefore, there is a need to improve childhood cancer survival outcomes with optimal resource use in Egypt.

8.3. Summary of findings

My DPhil thesis aims to generate evidence to improve childhood cancer health outcomes and resource use in Egypt. In Chapter 1, I introduced my DPhil research work in evidence-based

healthcare, the conceptual framework of evidence synthesis that my thesis work is based on, the thesis structure, and key accomplishments. In Chapter 2, I provided background information and relevant published literature about the burden, treatment, and health outcomes of childhood cancer globally, in LMIC contexts, and nationally in Egypt. I also highlighted the resources used in childhood cancer care, their costs and cost-effectiveness estimates, and the factors affecting paediatric oncology care.

Chapters 3–5 generate real-world evidence using real-world data from a local paediatric oncology setting in Egypt. Real-world data is defined as data relating to patient health status and/or the delivery of health services routinely collected (outside the context of randomised controlled trials).[1,2] In Chapter 3, I determined the survival rates and temporal trends in survival for 14,808 children with cancer treated at the Children's cancer Hospital Egypt (CCHE) between 2007 and 2017, and stratified by cancer type, risk, and stage at diagnosis. I also compared the age-standardised survival rates in Egypt with international benchmarks in England and the US. I estimated that survival for all cancers combined was 72.1%, noting that majority of cancers (12 out of 18) had inferior survival. Survival trends improved significantly for leukaemia, lymphomas, brain/CNS tumours, neuroblastoma, hepatoblastoma, and Ewing Sarcoma.

In Chapter 4, I estimated the patterns and trends in hospital resource use and associated costs for 8,886 children with cancer treated at CCHE between 2013 and 2017. I also studied the factors associated with high resource use and costs. Median costs for all cancers combined were $14,774 at one-year and $19,799 at three-years post-diagnosis. I found that patients with ALL, AML, and neuroblastoma imposed the greatest financial burden on CCHE (53.1% of total costs), where AML had the highest costs/resource use of all childhood cancers. Notably, the use of IV supportive drugs increased by 24.3% ($P < 0.001$) over time for children with solid tumours.

In Chapter 5, I estimated the cost-effectiveness of childhood cancer treatment at CCHE (between 2013 and 2017) in terms of cost per disability-adjusted life years (cost/DALY) averted. I used the WHO–CHOICE threshold. I estimated that cost/DALY averted was $1384 (0.5×GDP/capita) for all cancers combined (i.e., very cost-effective). Cost-effectiveness varied by cancer type/subtype, risk and stage, where it was lowest for Hodgkin lymphoma, and retinoblastoma (highly cost-effective), and highest for high-risk acute leukaemia, and high-risk neuroblastoma (least cost-effective). Notably, I found that treatment was not cost-effective for relapsed/refractory leukaemia and other relapsed/progressive cancer types.

Accordingly, Chapter 6 generates systematic evidence from the literature to address a local problem identified in the local setting. In Chapter 6, I conducted a systematic review to determine the best available evidence regarding the costs and cost-effectiveness of treatment for relapsed/refractory acute leukaemia in children. I found that CAR–T cell therapy was the most cost-effective treatment option, yet, there remain concerns over its long-term effectiveness. The next best treatment option was Blinatumomab, followed by Clofarabine therapy and FLA-IDA salvage chemotherapy. Limited studies evaluated cost-effectiveness of treating relapsed/refractory AML

Chapter 7 generates qualitative evidence based on experts' opinions in the local setting. In Chapter 7, I conducted semi-structured interviews with clinicians to understand their perceptions of barriers and facilitators to implementing cost-effective evidence-based treatment at CCHE. Then, I performed thematic data analysis. I identified four themes of barriers and facilitators and illustrated them in a thematic framework; awareness and orientation; knowledge, skills and attitudes; system, resources and context; and current practice. The clinicians also provided suggestions to overcome the existing barriers and address the implementation gaps.

In this chapter (Chapter 8), I summarised the work included in my thesis; key findings, strengths and limitations, and implications for practice, policy, and for future research. I developed a context-specific conceptual framework of evidence synthesis to improve childhood cancer health outcomes and resource use, using real-world data and addressing the implementation gaps.

8.4. Strengths and limitations

8.4.1 Strengths

Generating the three types of evidence altogether (real-world evidence, systematic evidence from the literature, and qualitative evidence from experts' opinions) in this thesis using hybrid research methods makes for a stronger methodological approach to synthesizing high-quality evidence that can help improve childhood cancer health outcomes and resource use in Egypt. Accordingly, the generated evidence is context-specific and relevant to local clinical practice, which applies to children with cancer in a resource-limited paediatric oncology setting in Egypt (CCHE). I discuss below the methodological strengths of my thesis in comparison to previously published literature.

A narrative review by Basbous *et al.* (2021) summarised the published research and meeting abstracts about childhood cancer outcomes in Egypt, as the outcomes of children with cancer are not available at the national level in Egypt.[3] It reported that survival rates were determined for a few cancers using a small sample size from institution-based data from nine papers and seventeen abstracts.[3] There were no studies that reported survival rates for all childhood cancer combined and categorised patients by cancer type, severity, or stage.

To the best of my knowledge, I have estimated survival rates and trends in survival (in Chapter 3) for the largest cohort of children with cancer (almost 15,000) in Egypt treated at a paediatric oncology setting (CCHE), stratified by ICCC-3 groups (cancer type/subtype), disease risk, and stage at diagnosis. Besides, I compared the age-standardised survival rates of childhood cancer in Egypt with international benchmarks and identified the cancers with inferior survival from local context. Findings from this study can help address the gap in evidence due to limited published studies on childhood cancer survival based on real-world data from Egypt. I followed the STROBE checklist in the design and reporting of results to ensure methodological rigour. Another strength of the study is that I used validated, high-quality survival data from the CCHE hospital-based registry, where data quality checks were routinely done every six months over ten years (2007–2017) and on study initiation, ensuring the validity of the study findings.

Owing to the large numbers of children with cancer in Egypt, limited resources and inferior outcomes, there is a need to optimise resources use and costs to improve care and outcomes in a cost-effective approach. Nevertheless, data about childhood cancer resource use (costs) and treatment cost-effectiveness are lacking in Egypt, creating a gap in knowledge in this area.

A systematic review by Fung *et al.* (2019) reported that no studies were published from Egypt about childhood cancer costs and cost-effectiveness of treatment.[4] To my knowledge, I was the first to estimate childhood cancer hospital resource use and costs of care (in Chapter 4) and cost-effectiveness of treatment (in Chapter 5) based on real-world data from a local setting in Egypt. Findings from Chapter 4 and Chapter 5 report the most comprehensive and detailed childhood cancer resource use/costs and cost-effectiveness estimates from a LMIC (stratified by cancer type, stage/risk and relapse/progressive status), compared to other studies conducted in LMICs.[4]

The two studies conducted in Chapters 4 and 5 provide costing methodological improvements compared to other published studies in LMICs based on cost analysis best practice.[4,5] Moreover, Chapters 4 and 5 follow the recommended criteria to conduct reliable economic evaluations in LMICs using the most recent CHEERS checklist 2022. Since CCHE is the only paediatric oncology centre in Egypt with a reliable costs/survival database enabling cost-effectiveness analysis, it provides unique and valuable insights addressing the gap in knowledge.

In Chapter 5, I identified that the treatment of children with relapsed/refractory acute leukaemia (ALL and AML) was not cost-effective at CCHE. Consequently, I conducted a systematic review (Chapter 6) to provide the most comprehensive and updated results about the costs, clinical benefits, and cost-effectiveness of the alternative treatment options for relapsed/refractory acute leukaemia in children. I objectively assessed the quality of the generated evidence using the CHEERS checklist 2022, reflecting on the sources of uncertainty and variability of findings.

To help translate evidence into practice and address the implantation gaps, in Chapter 7, I determined the clinicians' perceptions of barriers and facilitators to implement cost-effective evidence-based treatment for children with cancer in Egypt/CCHE. This is the first qualitative study to determine experts' opinions from a paediatric oncology setting in Egypt, using semi-structured interviews and thematic data analysis. I followed the COREQ checklist in the study design and report of results to ensure following the standard criteria for reporting qualitative research. Furthermore, Chapter 7 presents a thematic framework of interrelated themes of barriers and facilitators addressing the gap in knowledge in this area.

8.4.2 Limitations

Despite the significance of the research work underpinning my DPhil thesis, some limitations exist. I have extensively addressed the limitations in the Discussion section of each chapter (Chapters 3–7). In this chapter, I will discuss the overarching limitations of my thesis, highlighting the main limitations in each chapter.

In Chapters 3–5, I generate real-world evidence through conducting observational retrospective cohort studies using real-world data from the local setting (CCHE). An overarching limitation of the thesis is using real-world data to conduct observational studies (in Chapters 3–5), which can be limited by potential biases in study design or result interpretation, including heterogeneity in quality of real-world data and limited generalisability of findings.[2,6] Other potential biases may include: selection bias, confounding, chronological bias (temporality), and Hawthorne effect.

Selection bias could be attributed to selecting/including patients from CCHE who are not representative of the whole childhood cancer population in Egypt, or in case some patients have died before referral to CCHE. This could be addressed by matching patient demographics and the main childhood cancer types at CCHE with population-based statistics.[7,8] Besides, children with cancer (in these cohort studies) were diagnosed and treated at CCHE regardless of age, gender, socio-economic status, geographical distribution, cancer type, stage/risk of disease preferences. Therefore, given the large proportion of children with cancer treated at CCHE (around 40% of all childhood cancers across Egypt), matching patient statistics, and treating all patients without discrimination, this would potentially result in an unbiased selection of patients.

Confounding could be attributed to other factors that are independently associated with study outcomes (survival, resource use/costs, or cost-effectiveness outcomes). However, this was

accounted for by stratifying patients based on their demographics, cancer type/subtype, disease risk, and stage at diagnosis, or by multivariate regression analysis. Moreover, chronological bias could be attributed to changing patients' demographics, cancer type distribution, or change in quality of care over the years, that would likely affect survival outcomes. To reduce the possibility of a chronological bias, I studied the distribution of patient demographics, cancer types, stage at diagnosis, and risk groups over the years and found that these trends were steadily uniform over time, (discussed in Chapter 3, presented in Appendix 3.8 and Appendix 3.12). However, changes in quality of care or other practices could not be accounted for. Furthermore, the Hawthorn effect is common in observational studies in which clinicians may have changed their practices and quality of care as a result of being observed.

The main limitations of each chapter are discussed below.

In Chapter 3, on determining survival rates and trends in survival for children with cancer diagnosed between 2007 and 2017, some children with rare cancers (n=513) were not included in survival analysis because their disease-related and survival data were not readily-available in the hospital-based registry. Nevertheless, since these patients have rare types of childhood cancer representing 3.2% of initial study cohort, and were excluded before performing survival analysis (as per pre-defined exclusion criteria shown in Figure 3.1), it is therefore assumed that excluding them will have minimal effect on survival outcomes. Second, this study was limited by the short follow-up duration of patients diagnosed in the recent years (2016 and 2017) who did not complete five years of follow-up post-diagnosis. However, patients with shorter follow-up duration (less than five years) were censored observations in survival calculation using the Kaplan-Meier method. Third, since survival estimates are also prone to lead-time bias where diagnosing cancer early can improve survival,[9] this was not a problem in this study as this type

of bias is more common in adult cancers where cancer screening can lead to early diagnosis. Whereas, there are usually no screening programs for childhood cancers Besides, I stratified survival rates by initial stage at diagnosis to account for any confounders.

In Chapter 4, determining childhood cancer hospital resource use and costs was limited by the cost structure in the costing/billing database at CCHE, where it was not possible to calculate unit costs for inpatient hospitalisation and outpatient visits as separate cost categories. Second, cost estimates were calculated at 1- and 3-years post-diagnosis, and were not time-based (i.e., patients who die early would incur less costs). However, this was accounted for in univariate/multivariate regression analysis where survival status was analysed as an independent variable contributing to total costs. Third, the estimated resource use measures and costs are not necessarily generalizable to other centres in Egypt as data were obtained from a single centre (CCHE), which may differ from one centre to another based on the treatment protocols and quality of care. To help address this issue, I transparently disclosed the adopted standard treatment protocols at CCHE for better transferability of findings.

In Chapter 5, estimating cost-effectiveness of childhood cancer treatment in Egypt was limited by the absence of a national cost-effectiveness threshold. Therefore, I used the WHO–CHOICE threshold as recommended by the WHO for LMICs who lack nationally developed threshold. Nevertheless, some health economists argue that this GDP-based threshold is debatable as it lacks country specificity and may lead to potential uncertainty in the modelled cost-effectiveness ratios. Despite these potential limitations, yet, the WHO-CHOICE thresholds remain the standard generic method for cost-effectiveness for countries that lack local thresholds, and until a more appropriate replacement is found, researchers will continue to use this GDP-based DALY threshold. Moreover, I conducted sensitivity (uncertainty) analysis to account for the potential

uncertainty in the modelled cost-effectiveness ratios. Other potential limitations related to estimating survival and costs outcomes (used in cost-effectiveness analysis) were previously addressed in Chapters 3 and 4.

In Chapter 6, the systematic review was limited by the small number of published studies about the costs/cost-effectiveness of treatment for relapsed/refractory paediatric ALL, and the lack of published studies for AML. Second, the majority of studies were modelled with high levels of uncertainty due to varying cost estimates among studies and varying input parameters and modelling assumptions. To address this issue, I assessed the methodological quality of the included studies, using the CHEERS checklist to ensure internal validity, yet, the external validity was compromised due to limited confidence in generalisability of results. Third, there were no published studies from LMIC contexts, limiting the relevance of the findings to my thesis work in a resource-limited setting in Egypt, where costs vary substantially between high-income countries and LMICs even after cost adjustments.

In Chapter 7, the qualitative interview study was conducted in a single paediatric oncology setting in Egypt where transferability to other settings could be limited by the predominance of the hospital's context and culture. Yet, some of the barriers and facilitators may also exist in similar resource paediatric oncology settings in Egypt or other LIMICs, so, generalisability of findings to other contexts should be judged by clinical expertise in the local setting. Second, since the majority of participants were paediatric oncologists, the study sample could be weighted towards their views. However, at CCHE, childhood cancer care is predominantly administered by paediatric oncologists, with fewer surgeons and radiation oncologists involved, therefore, the cohort of participants is representative of the pool of clinicians in practice.

Nevertheless, this could be different in other settings, and study findings should be interpreted with caution based on relevance to the local context.

8.5. Implications of my DPhil thesis

8.5.1. Implications for policy and practice

8.5.1.1 A context-specific methodological approach of evidence synthesis

In this DPhil thesis, I developed a context-specific methodological approach (conceptual framework) of evidence synthesis to improve childhood cancer health outcomes and resource use in Egypt, using real-world data and addressing the implementation gaps. A conceptual framework is 'a set of interlinked key concepts, factors, or variables that together provide a comprehensive understanding of a phenomenon of interest, where each concept plays an integral role',[10] This conceptual framework builds upon three key concepts to better address this context-specific problem: conducting primary research from local context to address the gap in literature; conducting systematic review as the main gold standard for evidence synthesis; and addressing the implementation gaps in the local context.

In light with the above, the conceptual framework of evidence synthesis (shown in Figure 8.1) proposes to generate three types of evidence using hybrid research methods: (1) real-world evidence from local context; (2) systematic evidence from the literature; and (3) qualitative evidence from experts' opinions in the local context. Table 8.1 presents the implications of each type of evidence.

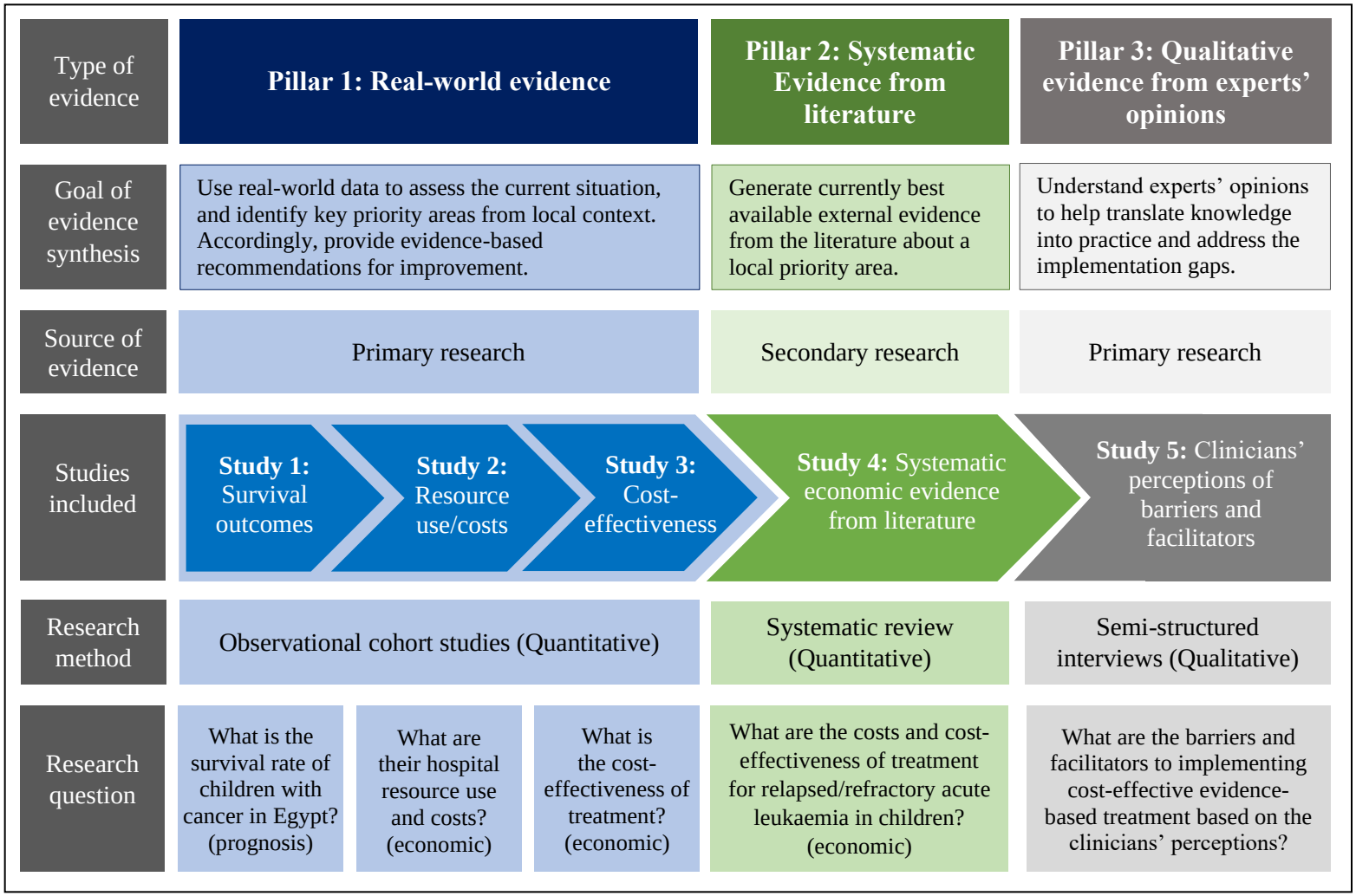


Figure 8.1. Context-specific conceptual framework of evidence synthesis

Table 8.1. Implications of each type of evidence in the conceptual framework

Type of evidence	Implication of this type of evidence
Pillar 1: Real-world evidence	Generating real-world evidence helps assess the current situation at the local context and identify any problems in care and/or outcomes of treatment as key priority areas for improvement. Accordingly, this helps provide evidence-based recommendations to improve outcomes and inform clinical and policy decisions.
Pillar 2: Systematic evidence from the literature	Generating systematic evidence from the literature summarises the currently best available evidence about a significant problem or a key priority area identified in the local context. This can help clinicians and policy-makers make better informed clinical/policy decisions based on the currently based available evidence.
Pillar 3: Qualitative evidence from local context	Generating qualitative evidence based on experts' opinions from the local context about the barriers and facilitators to implementation of cost-effective treatment can help translate the generated evidence into practice, and address the implementation gaps through developing tailored strategies and practical mechanisms for implementation.

Just as different locks need different keys to unlock them, different problems need different solutions to address them. According to the Royal Society, '*evidence synthesis*' refers to the process of bringing together information from a range of sources and disciplines to inform debates and decisions on specific issues.[11] In this context-specific conceptual framework, the term '*evidence synthesis*' refers to generating the above-mentioned three different types of evidence, rather than the commonly used/known term that only refers to *systematic reviews*.

Generating evidence from the three pillars altogether makes for a stronger approach to better research and tackle the local problem in this specific resource-limited context, and address the implementation gaps. This context-specific conceptual framework can serve as a methodological approach (roadmap) to generate relevant evidence in similar resource-limited paediatric oncology settings in Egypt or other LMICs.

Despite the significance of this conceptual framework, some limitations exist, as previously discussed in Chapter 8, section 8.4. Generally, real-world data studies can be limited during study design or result interpretation due to heterogeneity in quality of real-world data, potential biases, and limited generalisability of results.[2,6] To increase transferability of the conceptual

framework to other contexts, I summarised the methodological advantages and disadvantages of each research method in Table 8.2.

In conclusion, the concepts comprising this conceptual framework complement one another, explain their respective phenomena, and build a framework-specific philosophy.[10] For me, creating this conceptual framework contributes to fulfilling the essence of a DPhil, where it is key to "put the philosophy back into the Doctorate of Philosophy." For that, I am grateful to my supervisor, Professor Carl Heneghan, for giving me the space to develop my critical thinking skills and convey my thoughts to develop this conceptual framework, and for encouraging me to become an independent researcher under his guidance and mentorship.

Table 8.2. Advantages and disadvantages of research methods used in the conceptual framework

Research study	Research method	Advantages	Disadvantages
1. Determine survival rates and temporal trends in childhood cancer survival in Egypt/CCHE	Observational retrospective (inception) cohort	• Provides observed survival relevant to the local context using pragmatic study. • Identifies cancers with inferior survival, to drive evidence-informed improvement.	• Short follow-up duration of patients can lead to potential over-estimation of survival rates. • Childhood cancer survival evaluated at a single center in Egypt, limiting generalizability to other contexts.
2. Study hospital resource use and costs of care for children with cancer in Egypt/CCHE	Observational retrospective cohort	• Provides actual resource use and costs data from the local context. • Identifies high resource use patterns and cost drivers for better resource planning.	• Owing to the retrospective study design, there is limitation by the structure of the cost categories/subcategories in the costing database. • Costs and resource use reported from a single center may not represent national estimates.
3. Determine cost-effectiveness of childhood cancer treatment and link costs of care and survival outcomes	Observational retrospective cohort	• Estimates cost-effectiveness of treatment based on actual survival and costs data. • Identifies cancer groups with high costs and inferior survival, as key priority areas for improvement in the local context. • Measures survival trend relative to costs.	• Using the WHO–CHOICE thresholds are debatable and findings should be interpreted with caution. • Calculating 3-year costs covers costs of 1st line treatment and early treatment failure, whereas late relapses (>3 years) are not accounted for. • Estimating cost-effectiveness at a single center can lead to limited generalisability of findings to other centers. due to varying contexts.
4. Conduct a systematic review of cost-effectiveness of treatment for children with relapsed acute leukemia (as a key priority area)	Systematic review	• Generates the currently best available evidence to tackle a local problem. • Provides reproducible results as it follows a systematic methodology. • Critically appraises quality of evidence • Identifies gaps in the literature calling for prioritizing future research work.	• Limited number published articles in the literature, with no studies conducted in LMICs, limiting generalizability to other LMIC contexts. • Majority of cost-effectiveness studies are modelled studies and not pragmatic studies based on real-world data, leading to high level of uncertainty in cost and outcome estimates. • Difficulty to conduct meta-analysis from systematic review as it is not feasible to combine composite cost-effectiveness measures (ICER and ICUR) and compare them across different studies.
5. Determine barriers and facilitators to implement cost-effective evidence-based treatment	Semi-structured interviews	• Understand contextual barriers and facilitators based on the clinicians' perceptions. • Provides context-specific suggestions to overcome exiting barriers of implementation.	• Transferability to other settings could be limited by predominance of the hospital's context and culture, if it is conducted in a single centre. • Study sample could be weighted towards the paediatric oncologists' points of view, as majority of participants were pediatric oncologists. • Potential risk for participants to be identifiable if they work in the same hospital setting

Abbreviations: LMIC: low- and middle-income countries; ICER: Incremental cost-effectiveness ratio; ICUR: Incremental cost-utility ratio.

8.5.1.2. Value-based paediatric oncology care in Egypt/CCHE

Value-based healthcare in the NHS is defined as "the equitable, sustainable and transparent use of the available resources to achieve better outcomes and experiences for every person".[12] Findings from this thesis provide evidence-based recommendations that can help improve survival outcomes (in Chapter 3), optimise resource use and associated costs (in Chapter 4), and increase the cost-effectiveness of treatment (in Chapter 5), thus promoting value in childhood cancer care.

This shall contribute to the 'Triple Value' healthcare model introduced by Professor Muir Gray, which includes 'technical value', 'allocative value', and 'personal value'.[13,14] Improving the survival rates for the childhood cancers with inferior survival (based on recommendations from Chapter 3), as well as maximising the use of the available resources and providing cost-effective treatment (based on recommendations from Chapters 4 and 5) will help promote 'technical value' in care delivery (i.e., achieve best survival outcomes while optimising resource use).

It is also recommended to modify the treatment protocols and/or clinical practice for patient groups whose treatment was not cost-effective in order to achieve better (technical) value in the delivery of services. Besides, policymakers should find innovative solutions to adopt novel cost-effective therapies (such as: CAR–T cell therapy) based on findings from the systematic review in Chapter 6. This can be facilitated through collaboration and participation in international clinical trials, and negotiation with pharmaceutical companies to lower the drug list price to allow affordability in LMIC contexts.

Based on findings from Chapter 5, bone marrow transplant (BMT) was found to be a cost-effective treatment intervention for children with relapsed/refractory acute leukaemia and high-

risk neuroblastoma. However, not all indicated patients received BMT due to limited bed capacity. It is therefore recommended to scale up BMT services and increase BMT bed capacity at CCHE to accommodate the need and demand for all indicated patients. This will help promote 'allocative value' by ensuring the optimal and equitable allocation of resources to all patients in need for which BMT is indicated (i.e., achieving allocative value).

Moreover, findings from Chapter 7 provide clinicians' perceptions on barriers and facilitators to implementing cost-effective evidence-based treatment for the atypically complicated patients who need tailored decisions in 'combined clinics', such as end-of life decisions. Consequently, implementing the clinicians' suggestions and the evidence-based recommendations (provided in Chapter 7) will promote 'personal' value in care delivery by making tailored decisions for each patient based on their clinical condition and personal preferences (i.e., achieving personal value).

8.5.1.3 A mechanism to implement cost-effective evidence-based treatment at CCHE

An important policy implication of my thesis work is achieving good governance through establishing a hospital-wide mechanism and setting policies and procedures to facilitate the implementation of cost-effective evidence-based treatment at CCHE. This was informed by findings from the qualitative study (in Chapter 7) based on the clinicians' suggestions, which are discussed in details in Table 7.5 under the theme of 'System, resources, and context'.

The most important pillars of the governance mechanism include:

1. Forming a committee to regulate the implementation and evaluation of evidence-based cost-effective treatment.
2. Setting high-stake policies and procedures to regularly monitor cost-effectiveness of treatment interventions (including standard protocols).

3. Adopt innovations (tools, guidelines, drugs) to facilitate access to the latest best available evidence on cost-effectiveness of childhood cancer treatment (e.g., The EC3T Tracker, discussed below in Section 8.5.3.1) and novel (cost-effective) targeted therapies.

8.5.1.4 Interventions to improve health outcomes and resource use at CCHE

The evidence-based recommendations provided in the Discussion section of each chapter (Chapter 3–7) provide suggested interventions that can help improve childhood cancer health outcomes and resource use at CCHE. Some of these interventions/recommendations have already been implemented at CCHE after presenting the research findings to senior paediatric oncologists and hospital administrators, including:

1. Modification of treatment protocol for children with AML (de-intensification) to reduce preventable treatment-related mortalities (TRMs) based on recommendation in Chapter 3.
2. Revision and modification of the current supportive care guidelines for IV supportive drugs for patients with solid tumours, based on the recommendations in Chapter 4.
3. Estimation of treatment budgets for each childhood cancer type for the calendar year 2023, based on cost per patient and expected patients' volume, for better cost management, based on the recommendations in Chapter 4.
4. Scaling-up of bone marrow transplant (BMT) bed capacity; currently in the process of raising funds to increase the number of BMT beds from 7 to 27, based on the recommendations in Chapter 5.

Other interventions that would still be implemented include modifying the treatment protocol for children with high-risk neuroblastoma, and training of clinicians (mainly paediatric oncologists) on searching the evidence and interpreting cost-effectiveness estimates

8.5.1.5 National Childhood Cancer Program in Egypt

Findings from Chapter 5 showed that childhood cancer treatment is very cost-effective in a resource-limited setting in Egypt (CCHE). This can encourage policymakers prioritise childhood cancer national plans and incorporate the cost-effective treatment strategies into Egypt's Universal Health Insurance Project (UHIP).[15] Findings from Chapter 6 can also encourage policymakers in Egypt/CCHE to develop local cost-effectiveness thresholds and consider adopting the novel cost-effective therapies for relapsed/refractory paediatric acute leukaemia, based on the budget impact and affordability to pay.

8.5.1.6 Childhood cancer care in other LMIC settings

Given the paucity of evidence from LMIC contexts on childhood cancer health outcomes, resource use and treatment cost-effectiveness, some of the findings presented in this thesis may be relevant and valuable to other LMIC settings. The context-specific conceptual framework of evidence synthesis could be used as a methodological approach (roadmap) to generate relevant evidence in other LMIC settings. Findings from Chapter 5 could help policymakers and clinicians in similar LMICs make better informed decisions to adopt cost-effective treatment interventions (e.g.: BMT for indicated patients). Besides, findings from Chapter 6 provide valuable insights about the cost-effective treatment options for children with relapsed/refractory acute leukaemia. This could help clinicians make better informed clinical decisions based on the available and affordable treatment options in their contexts, and encourage policymakers to advocate access to cost-effective novel therapies. Furthermore, findings from Chapter 7 present barriers and facilitators to implementing cost-effective evidence-based childhood cancer treatment in a resource-limited setting that could be extrapolated to other similar LMIC settings based on their context.

8.5.2. Implications for future research

8.5.2.1. Evidence on Cost-effective Childhood Cancer Treatment (EC3T) Tracker

The research work underpinning this DPhil thesis and its key findings can serve as a reliable source of evidence to help implement cost-effective childhood cancer treatment in resource-limited contexts. This research work (alongside other published evidence about cost-effective interventions for childhood cancers) can be gathered and placed on an online platform that summarises, and appraises the Evidence on Cost-effective Childhood Cancer Treatment (EC3T). The EC3T Tracker will be an online service to provide current best available evidence on cost-effectiveness of childhood cancer treatment to support evidence-based policy and clinical decisions. It shall include: a search engine repository with classified evidence hierarchy, evidence-based resources, and an email alerting system for newly published evidence. The EC3T Tracker will be updated as new evidence emerges.

Establishing the EC3T Tracker will serve as a helpful resource for policymakers and clinicians to make better informed decisions to deliver cost-effective childhood cancer treatment. The EC3T Tracker shall serve a large number of health professionals and policymakers in resource-limited settings since more than 80% of children with cancer live in LMICs.

The EC3T Tracker shall also contribute to the WHO–Global Initiative of Childhood Cancer (WHO–GICC) which focuses on improving the much inferior survival in resource-limited settings in LMICs.[16] Although other platforms provide evidence-based resources for childhood cancer, such as the Cochrane Childhood Cancer[17] and the Global Platform for Access to Childhood Cancer Medicines.[18] Yet, they are not focused on gathering and summarising the evidence on the cost-effective treatment interventions.

8.5.2.2. Implementation research to address the knowledge-to-practice gap

Applying implementation research using knowledge translation frameworks is essential to help translate the evidence-based recommendations into practice; the recommendations to improve survival outcomes and resource use (Chapters 3–7) and the clinicians' suggestions to implement cost-effective evidence-based treatment (Chapter 7). The qualitative study in Chapter 7 paves the way for future implementation research using the Ottawa Model of Research Use (OMRU).[19]

The OMRU is a useful tool to transfer research-based knowledge into practice (see Figure 8.2), as it includes three stages: assessment of barriers and supports; monitoring of interventions and degree of use; and evaluating outcomes. I chose the OMRU model as it begins with assessing the barriers and facilitators to implementation within the practice environment, which corresponds to the qualitative study in Chapter 7 that identifies themes of barriers/facilitators.

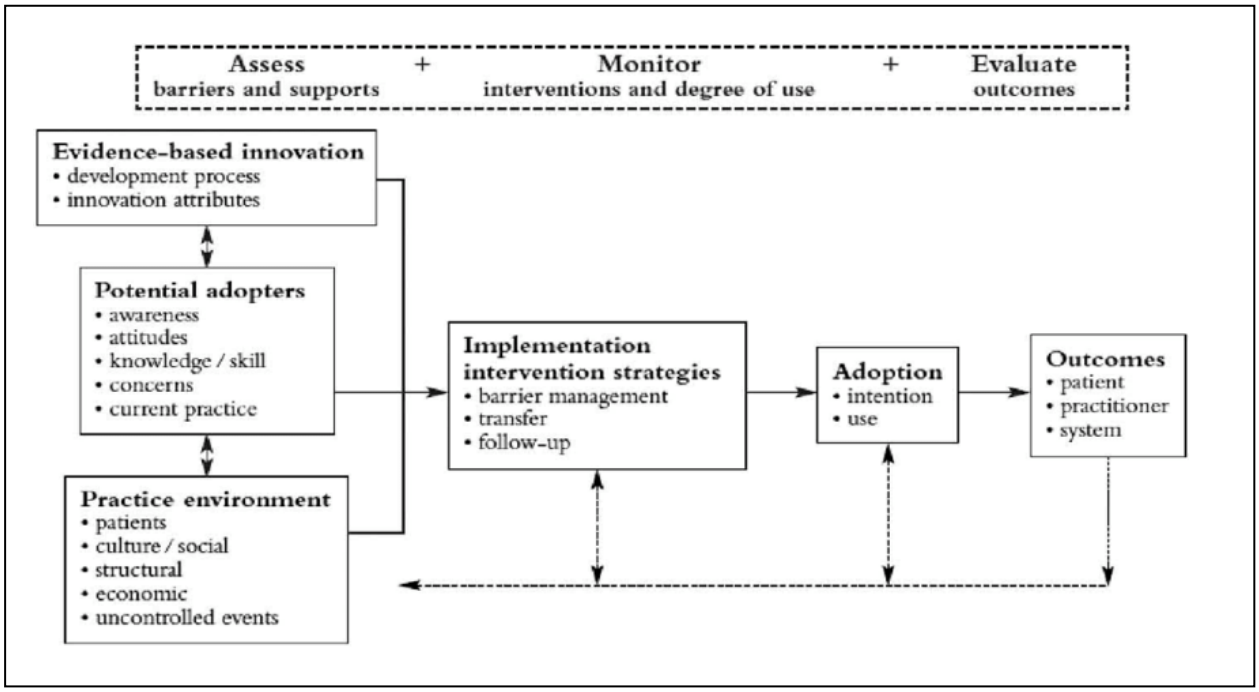


Figure 8.2. The Ottawa Model of Research Use

8.5.2.3. Other future research projects

Other potential future research projects include:

1. Generating economic evidence on the treatment for relapsed/refractory acute leukaemia:
    a. Conduct a living systematic review about the cost-effectiveness of treatment for relapsed/refractory acute leukaemia in children, to continually update the systematic review conducted in Chapter 6. This would be part of the EC3T Tracker.
    b. Apply decision analytic modelling for economic evaluation of treatment for children with relapsed/refractory ALL, using the clinical effects and adjusted costs data outputs from the systematic review conducted in Chapter 6. This shall determine the cost-effectiveness of novel therapies in the local setting at CCHE.
    c. Develop a Markov decision analytic model to determine the cost-effectiveness of the different interventions used to treat children with AML.
2. Study the factors associated with (predictors of) high risk of relapse in relapsed/refractory acute leukaemia whose treatment was not cost-effective, based on findings from Chapter 5.
3. Perform mixed-methods research (using surveys and interviews) to determine the time-to-diagnosis and the referral process from appearance of signs and symptoms to a confirmed diagnosis of childhood cancer at CCHE.
4. Conduct a qualitative interview study to determine the perceptions of parents/families of children with cancer towards communication about end-of-life care in Egypt/CCHE.

8.5.3. Implications for patients

Findings from this thesis would be reflected on improved patient health outcomes in terms of improved survival rates, reduced TRMs and treatment-related toxicities, and better patient

experiences due to higher value in service delivery for children with cancer at CCHE. Providing cost-effective treatment would potentially lead to improved patients' survival outcomes while avoiding unnecessary treatment interventions that do not add value to patients. This would also reduce potential harms to the patients due unwarranted use of cost-(in)effective treatment interventions. This shall contribute to the WHO–GICC by striving to improve the 5-year overall survival of children with cancer at CCHE from 72.1% (current survival) to at least 80% by 2030.

8.6 Personal aspirations after my DPhil

After my DPhil journey in Oxford comes to an end, I am looking forward to continuing to help children with cancer through research in Egypt, the region, and similar LMIC contexts by disseminating the knowledge I gained throughout my DPhil and the knowledge I generated as a contribution to the field. Moreover, I am interested and passionate about promoting evidence-based healthcare research, education, and practice in Egypt and the region.

8.7 Conclusion

In conclusion, my DPhil thesis in evidence-based healthcare generates context-specific high-quality evidence (real-world evidence, systematic evidence from literature, and qualitative evidence) using hybrid research methods to improve childhood cancer health outcomes and resource use in Egypt.

The DPhil research work has addressed the gaps in evidence about childhood cancer survival, resource use/costs and cost-effectiveness estimates, based on data from local contexts in Egypt. Findings from this thesis have identified local problems in care and outcomes (in Chapter 3–7) as key priority areas for improvement, summarised the best available evidence from the literature regarding a local priority area (in Chapter 6), and addressed the implementation gaps (in Chapter

7). Accordingly, each chapter (Chapters 3–7) presents evidence-based recommendations that can help improve childhood cancer health outcomes and resource use in Egypt and translate the generated evidence into practice, with implications for policy, practice and future research.

Chapter Eight references

1. Food and Drug Administration (FDA). Real-world Evidence [Internet]. FDA. 2023 Apr [cited 2023 Apr 2]. Available from: https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence
2. The Professional Society for Health Economics and Outcomes Research (ISPOR). About Real-World Evidence [Internet]. ISPOR. 2023 [cited 2023 Mar 20]. Available from: https://www.ispor.org/strategic-initiatives/real-world-evidence/about-real-world-evidence
3. Basbous M, Al-Jadiry M, Belgaumi A, Sultan I, Al-Haddad A, Jeha S, *et al*. Childhood cancer care in the Middle East, North Africa, and West/Central Asia: A snapshot across five countries from the POEM network. *Cancer Epidemiol*. 2021;71(Pt B):101727.
4. Fung A, Horton S, Zabih V, Denburg A, and Gupta S. Cost and cost-effectiveness of childhood cancer treatment in low-income and middle-income countries: a systematic review. *BMJ Global Health* 2019;4:e001825.
5. European Expert Paediatric Oncology Reference Network (ExPO-r-Net). Deliverable 4: An analysis of economic impact of childhood cancers based on systematic review of data to inform national and regional policymakers across the EU. Birmingham University; 2017.
6. Azoulay L. Rationale, Strengths, and Limitations of Real-World Evidence in Oncology: A Canadian Review and Perspective. *Oncologist*. 2022;27(9):e731-e8.
7. International Agency for Research on Cancer (IARC). Gharbiah Cancer Registry to the IARC project International Incidence of Childhood Cancer, Volume III. 2020.
8. Fadhil I, **Soliman R**, Jaffar S, Al Madhi S, Saab R, Belgaumi A, *et al*. Estimated incidence, prevalence, mortality, and registration of childhood cancer (ages 0-14 years) in the WHO

Eastern Mediterranean region: an analysis of GLOBOCAN 2020 data. *Lancet Child Adolesc Health*. 2022;6(7):466-73.

9. Oke J, Fanshawe T. Cancer Statistics: A Survival Guide. *Significance*. 2020;17(1):26.
10. Jabareen Y. Building a Conceptual Framework: Philosophy, Definitions, and Procedure. *International Journal of Qualitative Methods*. 2009;8(4):49-62.
11. The Royal Society. Evidence synthesis [Internet]. The Royal Society. 2018 Sep [cited 2023 Apr 6]. Available from: https://royalsociety.org/topics-policy/projects/evidence-synthesis/
12. Hurst L, Mahtani K, Pluddemann A, Lewis S, Harvey K, Briggs A, Boylan A-M, Bajwa R, Haire K, Entwistle A, Handa A and Heneghan C. Defining Value-based Healthcare in the NHS: CEBM report May 2019. 2019 Apr [cited 2023 April 7]. Available from: https://www.cebm.ox.ac.uk/resources/reports/defining-value-based-healthcare-in-the-nhs
13. Oxford Value and Stewardship Program (OVSP). Developing Value-based Healthcare and a Culture of Stewardship. OAP LTD. 2023 [cited 2023 April 9]. Available from: https://www.ovsp.net/
14. Jani A, Jungmann S, Gray M. Shifting to triple value healthcare: Reflections from England. *Z Evid Fortbild Qual Gesundhwes*. 2018;130:2-7.
15. The Arab Republic of Egypt Presidency. Universal Health Insurance Project. 2020 [cited 2023 April 4]. Available from: https://www.presidency.eg/en/%D8%A7%D9%84%D9%85%D8%B4%D8%A7%D8%B1%D9%8A%D8%B9-%D8%A7%D9%84%D9%82%D9%88%D9%85%D9%8A%D8%A9/%D8%A7%D9%84%D9%85%D8%B4%D8%B1%D9%88%D8%B9-%D8%A7%D9%84%D9%82%D9%88%D9%85%D9%8A-%D9%84%D9%84%D8%AA%D8%A3%D9%85%D9%8A%D9%86-%D8%A7%D9%84%D8%B5%D8%AD%D9%8A-%D8%A7%D9%84%D8%B4%D8%A7%D9%85%D9%84/

16. World Health Organization (WHO). The Global Initiative for Childhood Cancer (GICC). Increasing access, advancing quality, saving lives [Internet]. 2023 [cited 2023 Jan 23]. Available from: https://www.who.int/initiatives/the-global-initiative-for-childhood-cancer
17. The Cochrane Collaboration. Cochrane Childhood Cancer [Internet]. 2023 [cited 2023 April 4]. Available from: https://childhoodcancer.cochrane.org/
18. St. Jude Children's Research Hospital. The Global Platform for Access to Childhood Cancer Medicines [Internet]. 2023 [cited 2023 April 4]. Available from: https://global.stjude.org/en-us/medicines.html
19. Graham ID, Logan J. Innovations in knowledge transfer and continuity of care. *Can J Nurs Re*s. 2004;36(2):89-103.

Appendix Chapter 1

Appendix 1.1. Non-DPhil blogs, articles, and reviews

1. Centre for Evidence-based Medicine (CEBM). Evidence Resonates: communicating the evidence [Internet]. CEBM. 2023 [cited 2023 April 15]. Available from: https://www.cebm.ox.ac.uk/research/shared-research-from-our-ebhc-dphil-students
2. **Soliman R**. Blog: Is it time for OCEBM Levels of Evidence v.3? [Internet]. Centre for Evidence-based Medicine (CEBM). 2022 Oct [cited 2023 April 15]. Available from: https://www.cebm.ox.ac.uk/news/views/is-it-time-for-ocebm-levels-of-evidence-v-3
3. **Soliman R**. Blog: "And then Evidence Resonates" poem [Internet]. Centre for Evidence-based Medicine (CEBM). 2021 Jul [cited 2023 April 15]. Available from: https://www.cebm.ox.ac.uk/news/views/201cand-then-evidence-resonates201d-poem
4. **Soliman R**. Blog: Evidence resonates with qualitative research [Internet]. Centre for Evidence-based Medicine (CEBM). 2020 Aug [cited 2023 April 15]. Available from: https://www.phc.ox.ac.uk/news/blog/ranin-soliman-evidence-resonates-with-qualitative-research-my-student-experience
5. **Soliman R**. Blog: Cancer and COVID-19: between a rock and a hard place [Internet]. Centre for Evidence-based Medicine (CEBM). 2020 May [cited 2023 April 15]. Available from: https://www.cebm.net/covid-19/cancer-and-covid-19-between-a-rock-and-a-hard-place/
5. **Soliman R**, Brassey J. Pluddemann A and Heneghan C. Does BCG vaccination protect against acute respiratory infections and COVID-19? A rapid review of current evidence [Internet]. Centre for Evidence-based Medicine (CEBM). 2020 Apr [cited 2023 April 15]. Available from: https://www.cebm.net/covid-19/does-bcg-vaccination-protect-against-acute-respiratory-infections-and-covid-19-a-rapid-review-of-current-evidence/

Appendix Chapter 3

Appendix 3.1. The Strengthening Reporting of Observational Studies in Epidemiology (STROBE) checklist

	Item No	Recommendation	Location in thesis where items are reported
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 6, 74
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 6
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 49–51, 74
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 75
Methods			
Study design	4	Present key elements of study design early in the paper	Page 76
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 76, 77
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Page 76
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 79
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 79, 80
Bias	9	Describe any efforts to address potential sources of bias	Page 80

Study size	10	Explain how the study size was arrived at	Page 78
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 79, 80
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 79, 80
		(*b*) Describe any methods used to examine subgroups and interactions	Page 79, 80
		(*c*) Explain how missing data were addressed	Page 79, 80
		(*d*) If applicable, explain how loss to follow-up was addressed	Page 79, 80
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 81, 82
		(b) Give reasons for non-participation at each stage	Page 78
		(c) Consider use of a flow diagram	Page 78
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 82
		(b) Indicate number of participants with missing data for each variable of interest	Page 78
		(c) Summarise follow-up time (eg, average and total amount)	Page 83
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 87, 88
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 84, 85
		(*b*) Report category boundaries when continuous variables were categorized	Page 82
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 93
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 99
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 102
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 99 – 103
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 103
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 5

Appendix 3.2. Childhood cancer types grouped by International Classification of Childhood Cancers, third edition (ICCC-3)

ICCC-3 Diagnostic Groups
I. Leukaemia and related cancers
Ia. Acute Lymphoid Leukaemia
Ib. Acute Myeloid Leukaemia
Ic. Chronic Myeloid Leukaemia
Id. (subset) Myelodysplastic Syndrome
Id. (subset) Juvenile myelomonocytic Leukaemia
Ie. Unspecified and other specified leukemias
II. Lymphomas
IIa. Hodgkin Lymphoma
IIb. Non-Hodgkin Lymphoma
IIIa-e CNS tumours
IIIa. Ependymomas and choroid plexus tumours
IIIb. Astrocytoma
IIIc.1-2 Medulloblastoma/Embryonal CNS tumours
IV.a Neuroblastoma and ganglioneuroblastoma
V. Retinoblastoma
VI. Renal tumours
VIa.1 Wilms tumour
VIa.2 Rhabdoid renal tumours
VIa.3 Kidney sarcomas
VII. Hepatic tumours
VII.a Hepatoblastoma
VII.b Hepatic carcinomas
VIII. Malignant bone tumours
VIIIa Osteosarcoma
VIIIc Ewing sarcomas
IX. Soft tissue and extra osseous sarcoma
IXa. Rhabdomyosarcoma
IXb-d Other soft tissue tumours
X. a-c Germ Cell tumours
XI. Other malignant epithelial neoplasms and malignant melanomas
XII. Other and unspecified malignant neoplasms* includes LCH

* XII includes LCH only. Abbreviations. LCH. Langerhans cell histiocytosis.

Appendix 3.3. Childhood cancer standard treatment protocols adopted at CCHE/Egypt

ICCC-3 Diagnostic Groups	Standard treatment adopted from these protocols
I. Leukaemia and related cancers	
Ia. Acute Lymphoid Leukaemia	St. Jude Total XV protocol
Ib. Acute Myeloid Leukaemia	COG [AAML0531; COG AAML1031; COG AAML1831]
Ic. Chronic Myeloid Leukaemia	European Leukemia Net (ELN) guidelines
Id. Myelodysplastic Syndrome	Bone Marrow Transplant (BMT)
Id. Juvenile myelomonocytic Leukaemia	COG [2x FLA cycle followed by Azacitidine 6 cycles; Maintenance: LDARA-C, 6MP; 13-cis-Retinoic acid; BMT]
II. Lymphomas	
IIa. Hodgkin Lymphoma	ABVD Regimen
IIb. Non-Hodgkin Lymphoma	COG ANHL0131 (ALCL); LMB-96 (Mature B NHL); ALL total XV (LBL)
IIIa-e CNS tumours	
IIIa. Ependymomas and choroid plexus tumours	CCG-9942
IIIb. Astrocytomas	COG A9952 (LGG); CCG-943 (HGG); COG ACNS0126 (HGG)
IIIc.1-2 Medullablastoma/Embryonal CNS tumours	COG-ACNS0331 (SR-MB); ACNS0332 (HR-MB); P9934 (Inf-MB); DFCI 02-294 (ATRT)
IV.a Neuroblastoma	COG A3973 (HR); SFOP VP16-Carbo/CADO (IR)
V. Retinoblastoma	COG ARET0332 (HR); COGARET0231 (Groups C and D); COGARET0331 (Group B); COG ARET0321 (extra-ocular)
VI. Renal tumours	
VIa.1 Wilms tumour	COG AREN0532 and COG AREN0533 (unilateral); COG AREN0534 (bilateral)
VIa.2 Rhabdoid renal tumours	COG AREN0321
VIa.3 Kidney sarcomas	COG AREN0321 (clear cell sarcoma of kidney)
VII. Hepatic tumours	
VII.a Hepatoblastoma	COG AHEP0731
VIII. Malignant bone tumours	
VIIIa Osteosarcoma	EURAMOS-1 (ISRCTN67613327)
VIIIc Ewing sarcomas	POG #9354/CCG #7942; COG AEWS0031; COG
IX. Soft tissue and extra osseous sarcoma	
IXa. Rhabdomyosarcoma	COG ARST0531; COG ARST0331 (LR); COG-D9802
IXb-d Other soft tissue tumours	COG & NRG ONCOLOGY ARST1321
X. a-c Germ Cell tumours	AGCT01P1 (HR) / AGCT0132 (LR/SR)
XI. Other malignant epithelial neoplasms and malignant melanomas	
XII. Langerhans cell histiocytosis	LCH IV protocol from the Histiocyte Society
Management of Fever neutropenia	NCCN guidelines

Abbreviations: COG: Children's Oncology Group; **ELN:** European Leukemia Net; **LBL:** Lymphoblastic Lymphoma; **ALCL:** Anaplastic large cell lymphoma; **CCG:** Children's Cancer Group; **LGG:** Low-grade Glioma; **HGG:** High-grade Glioma; **MB:** Medullablastoma: **ATRT:** Atypical Teratoid Rhabdoid tumor; **HR:** High-Risk; **SR:** Standard Risk; **LR:** Low Risk; **IR:** Intermediate Risk; **POG:** Pediatric Oncology Group; **NCCN:** National Comprehensive Cancer Network.

Appendix 3.4. Definitions of stage at diagnosis, risk stratification and sub-type classifications systems, with references.

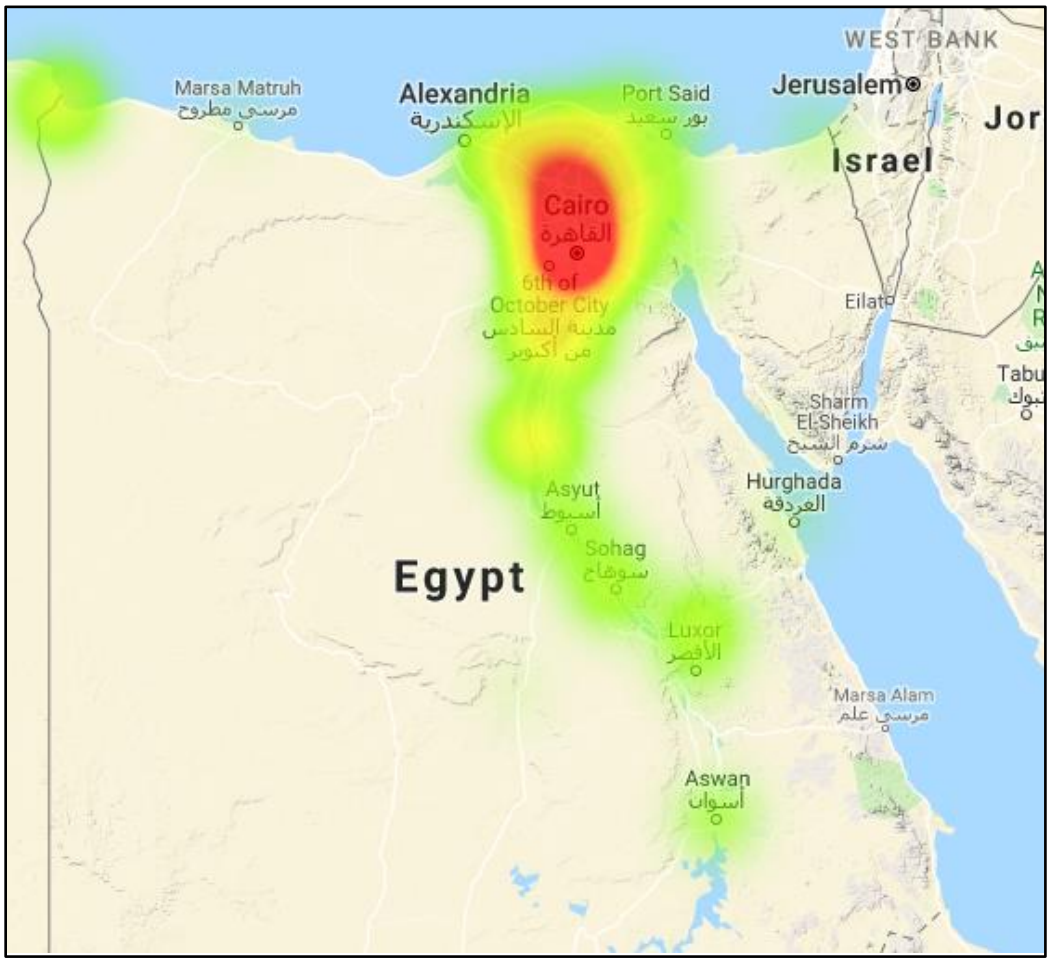
Diagnostic Group	Risk/stage classification	Definition	Reference for definitions
Ia. Acute Lymphoid Leukaemia	Risk	Pui, *et al*. 2009.	a. Pui, C. *et al*. Treating childhood acute lymphoblastic leukemia without cranial irradiation. N Engl J Med. 2009 Jun 25;360(26):2730-41.
Ib. Acute Myeloid leukaemia	Subtype	Creutzig, *et al*. 2012	b. Creutzig, U. *et al*. Diagnosis and management of acute myeloid leukemia in children and adolescents: recommendations from an international expert panel. Blood. 2012 18 October 120;16.
	Risk	COG. AAML1031. 2018.	c. COG. AAML1031: A Phase III Randomized Trial for Patients with de novo AML using Bortezomib and Sorafenib for Patients with High Allelic Ratio FLT3/ITD. Spring 2018 Progress Report.
Id. Myelodysplastic Syndrome	Risk	IPSS. 2012.	d. Greenberg, P., *et al*. Revised International Prognostic Scoring System for Myelodysplastic Syndromes. Blood 2012 120:2454-2465.
	Subtype	ACS. 2018.	e. American Cancer Society. Types of Myelodysplastic Syndromes. ACS. Last Revised: January 22, 2018. Retrieved from: https://www.cancer.org/cancer/myelodysplastic-syndrome/about/mds-types.html
Ic. Chronic Myeloid leukaemia	Subtype	ASCO. 2018.	f. American Society of Clinical Oncology (ASCO). Leukemia - Chronic Myeloid - CML: Phases. Last Revised: March, 2018. Retrieved from: https://www.cancer.net/cancer-types/leukemia-chronic-myeloid-cml/phases
IIa. Hodgkin Lymphoma	Risk	Ferrari, *et al*. 2008	g. Re A, Ferrari S, and Frata P, *et al*. Late Computed Tomography Scan Response Improvement and Gallium Scintigraphy Evaluation as On-Treatment Prognostic Parameters to Tailor Treatment Intensity in Patients with Hodgkin's Lymphoma. *Ann Oncol*, 2008. 19(5), 951-7
IIb. Non-Hodgkin Lymphoma	Staging	Modified Murphy staging	h. Murphy SB. Classification, staging and end results of treatment of childhood non-Hodgkin's lymphomas: dissimilarities from lymphomas in adults. Semin Oncol. 1980;7:332-339.
IIIa-e CNS Tumours	Subtype	WHO. 2016	i. Louis, D. *et al*. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016.
IV.a Neuroblastoma	Risk	Davidoff. 2012	j. Davidoff AM. Neuroblastoma. Semin Pediatr Surg. 2012;21(1):2–14. doi:10.1053/j.sempedsurg.2011.10.009.

	Staging	INSS	k. American cancer society. International Neuroblastoma Staging System (INSS). Last Revised: March 19, 2018. Retrieved from: https://www.cancer.org/cancer/neuroblastoma/detection-diagnosis-staging/staging.html#references
V. Retinoblastoma	Staging	IRSS	l. Chantada, F. Doz, C.B. Antoneli, *et al*., A proposal for an international retinoblastoma staging system, Pediatr. Blood Cancer 47 (2006) 801–805.
VI. Renal Tumours	Subtype	ICCC-3	m. Steliarova-Foucher E, Stiller C, Lacour B, *et al*.: International Classification of Childhood Cancer, third edition. Cancer 103:1457-1467, 2005.
VIa.1 Wilms Tumour	Staging	Metzger, *et al*. 2005	n. M.L. Metzger, J.S. Dome, Current therapy for Wilms' tumor, Oncologist 10 (2005) 815–826.
VII.a Hepatoblastoma	Staging	Meyers, 2017	o. Meyers RL, Maibach R, Hiyama E, *et al*. Risk-stratified staging in paediatric hepatoblastoma: a unified analysis from the Children's Hepatic tumors International Collaboration. *Lancet Oncol*. 2017;18(1):122–131.
	Risk	McCarville, 2012	p. McCarville, M. Diagnosis and Staging of Hepatoblastoma: Imaging Aspects. Pediatr Blood Cancer 2012;59:793–799.
VIIIc Ewing sarcomas	Staging	ASCO, 2018	q. American Society of Clinical Oncology (ASCO). Ewing Sarcoma - Childhood and Adolescence: Stages Approved on January 2018. Retrieved from: https://www.cancer.net/cancer-types/ewing-sarcoma-childhood-and-adolescence/stages
VIIIa Osteosarcoma	Staging	ASCO, 2018	r. American Society of Clinical Oncology (ASCO). Osteosarcoma - Childhood and Adolescence: Stages. Approved on January 2018. Retrieved from: https://www.cancer.net/cancer-types/osteosarcoma-childhood-and-adolescence/stages
IXa. Rhabdomyosarcoma	Risk	COG. 2012	s. Malempati S, Hawkins DS. Rhabdomyosarcoma: review of the Children's Oncology Group (COG) Soft-Tissue Sarcoma Committee experience and rationale for current COG studies. Pediatr Blood Cancer. 2012;59(1):5–10.
	Staging	ASCO, 2018	t. ASCO. Rhabdomyosarcoma - Childhood: Stages and Groups. Approved on October 2018. Retrieved from: https://www.cancer.net/cancer-types/rhabdomyosarcoma-childhood/stages-and-groups
IXb-d Other soft tissue tumours	Risk	COG. 2015	u. Waxweiler, T., *et al*. Non-Rhabdomyosarcoma Soft Tissue Sarcomas in Children: A Surveillance, Epidemiology, and End Results Analysis Validating COG Risk Stratifications. Int J Radiat Oncol Biol Phys. 2015 Jun 1;92(2):339-48.
	Staging	ASCO. 2018	v. ASCO. Germ Cell Tumor - Childhood: Stages. Approved on January 2018. Retrieved from:

			https://www.cancer.net/cancer-types/germ-cell-tumor-childhood/stages
X. a-c Germ Cell Tumours	Risk	Meisel, *et al*. 2015. Gilligan, 2019	w. Meisel, J., *et al*. Development of a risk stratification system to guide treatment for female germ cell tumors. Gynecologic Oncology 138 (2015) 566–572. x. Gilligan, T. and Kantoff, P. Initial risk-stratified treatment for advanced testicular germ cell tumors. Up-To-Date 2019. Retrieved from: https://www.uptodate.com/contents/initial-risk-stratified-treatment-for-advanced-testicular-germ-cell-tumors
XII. Other Tumours (LCH)*	Risk	Krooks, *et al*. 2018	y. Krooks, J. *et al*. Langerhans cell histiocytosis in children. Journal of American academy of dermatology. 78:6. 2018.

* XII includes LCH only. Abbreviations. LCH. Langerhans cell histiocytosis.

Appendix 3.5. Heat map showing geographical distribution of children with cancer from all over Egypt, who were treated at CCHE, (n=15,779)



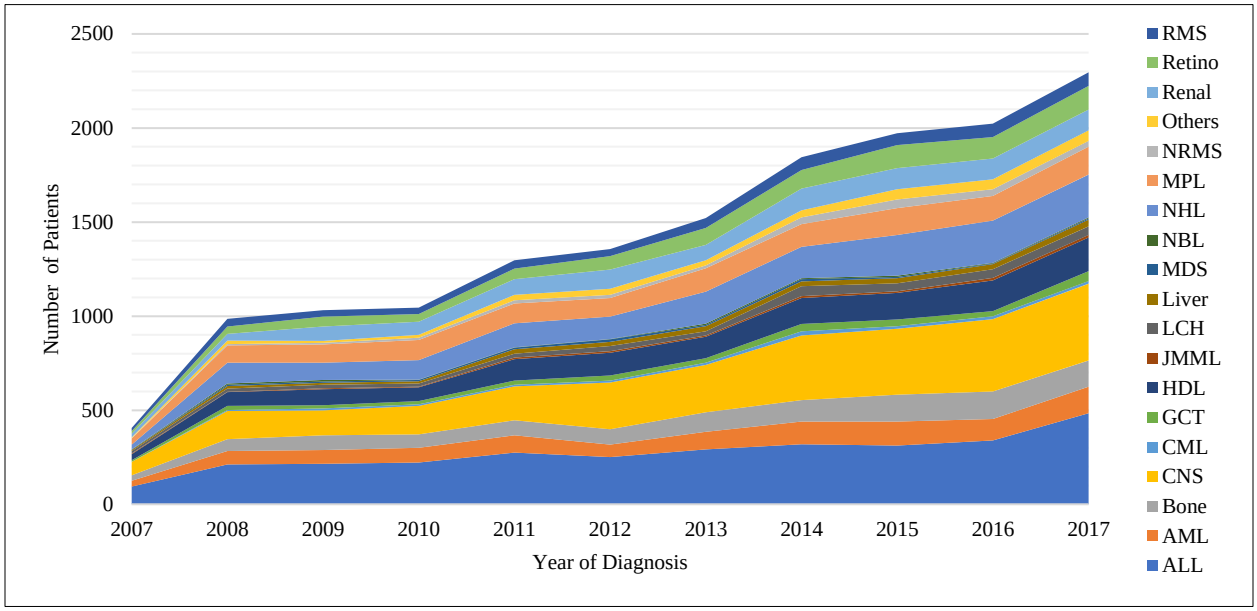
Appendix 3.6. Childhood Cancer groups based on ICCC-3 diagnostic groups, stratified by age-group distribution, (N=15,779).

ICCC-3 Diagnostic Groups	**No. of patients (% from total)**	**0 – 4 years**	**5 – 9 years**	**10 – 14 years**	**15 – 18 years**
All cancers combined	15,779 (100%)	7556 (47.8%)	4213 (26.7%)	2871 (18.2%	1139 (7.2%)
I. Leukemia and related cancers	4364 (27.6%)	2008 (46.0%)	1260 (28.9%)	787 (18.0%)	309 (7.1%)
Ia. Acute Lymphoid Leukaemia	3,013 (19.1%)	1428 (47.4%)	943 (31.3%)	461 (15.3%)	181 (6.0%)
Ib. Acute Myeloid Leukaemia	1,012 (6.4%)	432 (42.7%)	245 (24.2%)	249 (24.6%)	86 (8.5%)
Ic. Chronic Myeloid Leukaemia	121 (0.8%)	13 (10.7%)	31 (25.6%)	49 (40.6%)	28 (23.1%)
Id. Myelodysplastic Syndrome	53 (0.3%)	18 (34.0%)	21 (39.6%)	10 (18.9%)	4 (7.5%)
Id. Juvenile myelomonocytic leukaemia	86 (0.4%)	83 (96.5%)	3 (3.5%)	0	0
Ie. Other specified Leukaemia (Mixed Acute Phenotypic Leukaemia)	79 (0.5%)	34 (43.0%)	17 (21.5%)	18 (22.8%)	10 (12.7%)
II. Lymphomas	2,431 (15.4%)	601 (24.7%)	891 (36.7%)	659 (27.1%)	280 (11.5%)
IIa. Hodgkin Lymphoma	1,230 (7.8%)	185 (15.0%)	466 (37.9%)	401 (32.6%)	178 (14.5%)
IIb. Non-Hodgkin Lymphoma	1,201 (7.6%)	416 (34.6%)	425 (35.4%)	258 (21.5%)	102 (8.5%)
III CNS Tumors	2,671 (16.9%)	949 (35.5%)	1031 (38.6%)	550 (20.6%)	141 (5.3%)
IV.a Neuroblastoma and ganglioneurobalstoma	1,583 (10.0%)	1367 (86.4%)	187 (11.8%)	22 (1.4%)	7 (0.4%)
V. Retinoblastoma	823 (5.2%)	780 (94.7%)	40 (4.9%)	3 (0.4%)	0
VI. Renal tumours	917 (5.8%)	705 (76.9%)	179 (19.5%)	31 (3.4%)	2 (0.2%)

VIa 1 Wilms tumour	763 (4.8%)	575 (75.4%)	154 (20.2%)	31 (4.1%)	3 (0.3%)
VII. Hepatic tumours	228 (1.4%)	198 (86.9%)	8 (3.5%)	20 (8.8%)	2 (0.8%)
VII.a Hepatoblastoma	212 (1.3%)	195 (92.0%)	6 (2.8%)	9 (4.3%)	2 (0.9%)
VII.b Hepatic carcinomas	16 (0.1%)	1 (6.2%)	1 (6.2%)	14 (87.6%)	0
VIII. Malignant bone tumours	1,048 (6.6%)	82 (7.8%)	274 (26.2%)	458 (43.7%)	234 (22.3%)
VIIIa Osteosarcoma	526 (3.3%)	17 (3.3%)	107 (20.4%)	254 (48.2%)	148 (28.1%)
VIIIc Ewing sarcomas	522 (3.3%)	88 (16.9%)	152 (29.1%)	210 (40.2%)	72 (13.8%)
IX. Soft tissue and extra osseous sarcoma	762 (4.8%)	378 (49.6%)	179 (23.5%)	132 (17.3%)	73 (9.6%)
IXa. Rhabdomyosarcoma	537 (3.4%)	304 (56.6%)	140 (26.1%)	67 (12.5%)	26 (4.8%)
IXb-d Other soft tissue tumours	225 (1.4 %)	74 (32.9%)	39 (17.3%)	65 (28.9%)	47 (20.9%)
X.a-c Germ Cell Tumours	294 (1.9%)	185 (62.9%)	38 (12.9%)	49 (16.7%)	22 (7.5%)
XI. Other malignant epithelial neoplasms & malignant melanomas	336 (2.1%)	85 (25.3%)	55 (16.4%)	130 (38.7%)	66 (19.6%)
XII. Other Tumours (LCH)*	322 (2.0%)	218 (67.7%)	71 (22.0%)	30 (9.3%)	3 (0.9%)

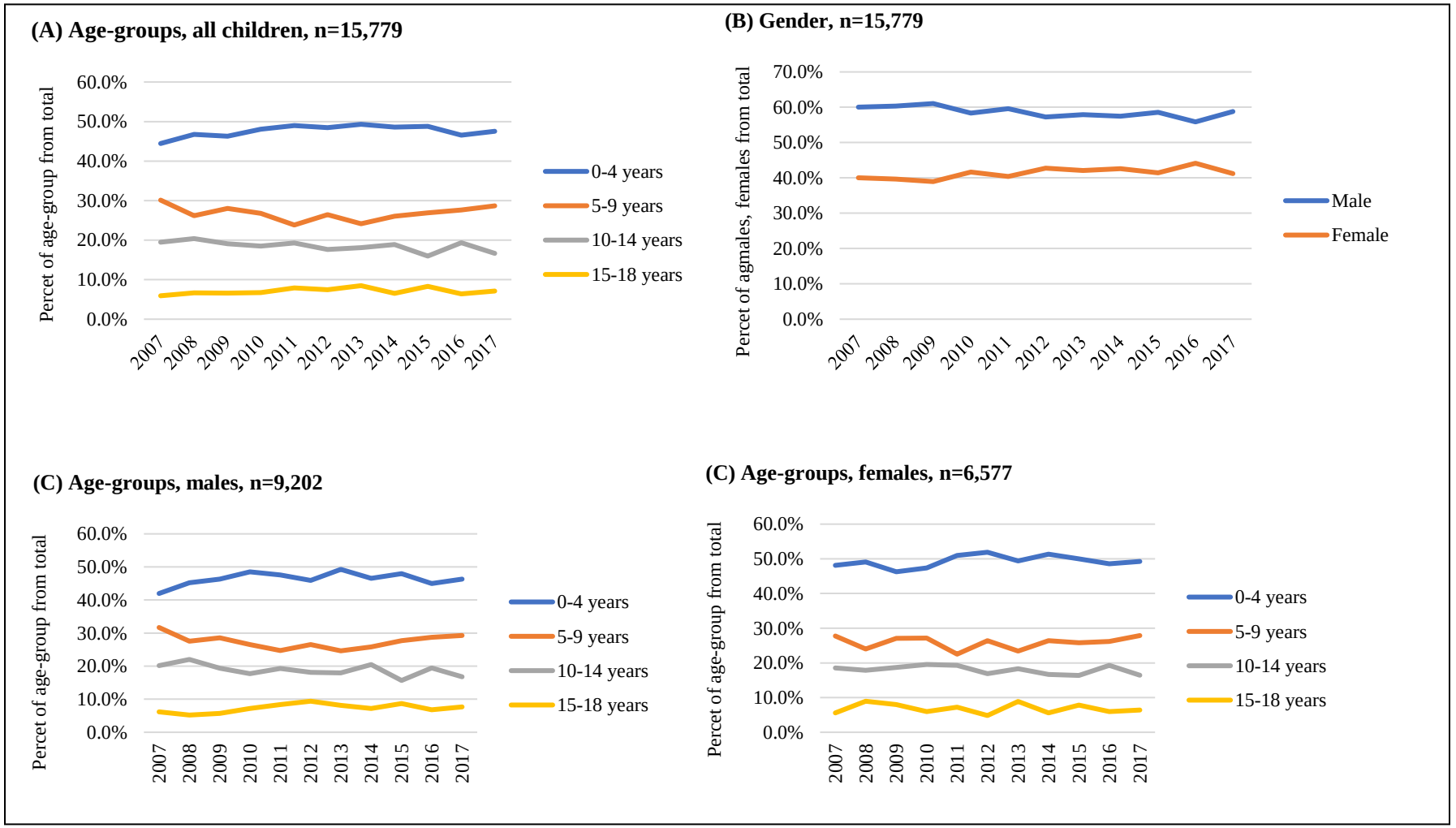
* XII includes LCH only. Abbreviations. 95% CI: 95% Confidence Intervals; LCH. Langerhans cell histocytosis.

Appendix 3.7. Trends of newly diagnosed children with cancer at CCHE, by year of diagnosis



*Year 2007 starting from 7th July until 31st December 2007, as CCHE opened on 7th July 2007.
Abbreviations: ALL: Acute Lymphoblastic Leukemia; AML: Acute Myeloid Leukemia; CML: Chronic Myeloid Leukemia; GCT: Germ Cell Tumors; HL: Hodgkin Lymphoma; JMML: Juvenile myelomonocytic leukemia; LCH Langerhan's Cell histocytosis; MDS: Myelodysplastic Syndrome; NBL: Neuroblastoma; NHL: Non-hodgkin Lymphoma; MPL: Mixed Phenotype Acute Leukemia; NRMS; Non-rhabdomyosarcoma (Other soft tissue Tumors); Others: Other malignant epithelial neoplasms and malignant melanomas; Retino: Retinoblastoma; RMS: Rhabdomyosarcoma.

Appendix 3.8. Trends in gender and age-groups distribution over time, for all children, males and females



Appendix 3.9. Five-year overall survival, by ICCC-3 groups, by gender and age-group distribution, (n= 14,808)

ICCC-3 Diagnostic Group	5-year survival (95% CI)		*P* °	5-year survival (95% CI)				*P* °
	Gender			Age-groups				
	Male	Female		0-4 years	5-9 years	10-14 years	15-18 years	
All cancers combined*	73.0 (71.9-74.1)	70.9 (69.7-72.1)	<0.001˜	72.9 (71.7-74.1)	73.1 (71.5-74.7)	70.2 (68.3-72.1)	67.6 (64.4-71.0)	<0.001˜
Acute Lymphoid Leukemia**	78.5 (76.3-80.7)	79.8 (77.4-82.4)	0.6	83.5 (81.3-85.8)	79.2 (76.3-82.3)	70.4 (65.8-75.4)	66.1 (58.9-74.1)	<0.001˜
Acute Myeloid Leukemia	53.1 (48.6-58.0)	46.3 (41.7-51.5)	0.007˜	48.2 (43.2-53.7)	59.3 (52.6-66.8)	46.8 (40.8-53.7)	44.3 (34.3-57.2)	0.002˜
Chronic Myeloid Leukemia	96.7 (92.3-100)	86.0 (76.8-96.3)	0.08	91.6 (77.2-100)	89.8 (77.0-100)	90.4 (81.8-100)	92.8 (83.7-100)	0.9
Myelodysplastic Syndrome	46.6 (29.7-73.1)	29.4 (14.1-61.4)	0.21	59.1 (38.1-91.5)	28.7 (10.8-76.4)	30.5 (10.4-89.0)	25.0 (4.50-100)	0.29
Juvenile myelomonocytic leukemia	45.8 (30.3-69.1)	21.6 (9.2-50.5)	0.002˜	38.1 (26.1-55.5)	-- ^	X	X	0.57
Hodgkin Lymphoma	96.2 (94.8-97.7)	92.6 (89.6-95.7)	0.04˜	96.6 (93.6-99.7)	94.3 (91.8-96.9)	96.8 (94.9-98.7)	91.2 (86.5-96.1)	0.003˜
Non-Hodgkin Lymphoma	81.7 (78.9-84.6)	77.9 (73.5-82.6)	0.11	79.9 (75.9-84.1)	82.5 (78.8-86.5)	80.4 (75.3-85.9)	74.9 (66.4-84.5)	0.32
CNS tumours	64.9 (62.0-67.8)	63.6 (60.6-66.7)	0.42	64.7 (61.2-68.3)	61.1 (57.7-64.6)	68.3 (64.1-72.8)	68.9 (60.7-78.3)	0.031˜
Neuroblastoma	53.2 (49.2-57.6)	56.3 (52.1-60.8)	0.34	55.5 (52.4-58.8)	48.2 (39.6-58.7)	53.9 (32.6-89.4)	66.7 (30.0-100)	0.81
Retinoblastoma	92.9 (90.2-95.8)	92.2 (89.0-95.5)	0.79	92.6 (90.4-94.8)	91.3 (82.3-100)	-- ^	X	0.78
Renal tumours	80.4 (76.2-84.7)	82.7 (79.1-86.6)	0.44	82.5 (79.5-85.7)	79.6 (73.2-86.7)	73.2 (57.7-92.7)	-- ^	0.18
Hepatoblastoma	50.4 (41.1-61.9)	52.6 (41.6-66.6)	0.78	51.9 (44.3-60.8)	40.0 (13.7-100)	-- ^	-- ^	0.75
Osteosarcoma	49.4 (42.0-58.1)	46.8 (40.2-54.5)	0.28	20.4 (42.4-98.7)	55.9 (46.1-67.9)	47.5 (40.3-56.0)	46.3 (37.6-56.9)	0.21
Ewing sarcomas	63.6 (56.6-71.5)	65.3 (58.1-73.3)	0.95	74.9 (63.4-88.4)	70.6 (62.2-80.2)	57.1 (49.0-66.5)	64.1 (52.6-78.1)	0.21
Rhabdomyosarcoma	62.0 (56.0-68.6)	56.2 (48.7-64.7)	0.21	62.9 (56.6-69.8)	58.7 (50.0-68.9)	54.6 (42.6-70.1)	44.4 (26.7-73.7)	0.15
Other soft tissue tumours	72.8 (60.5-87.5)	84.1 (75.6-93.4)	0.56	85.8 (75.3-97.7)	85.6 (73.4-99.8)	67.1 (50.0-90.1)	76.7 (62.6-93.9)	0.31
Germ Cell tumours	85.1 (77.6-93.3)	87.9 (82.4-93.8)	0.61	85.3 (79.5-91.6)	86.8 (75.5-99.8)	94.2 (86.8-100)	83.6 (64.9-100)	0.77
Other tumour (LCH)	90.4 (85.8-95.2)	91.2 (86.2-96.6)	0.39	87.0 (82.3-92.1)	98.5 (95.6-100)	100 (100)	X	0.012˜

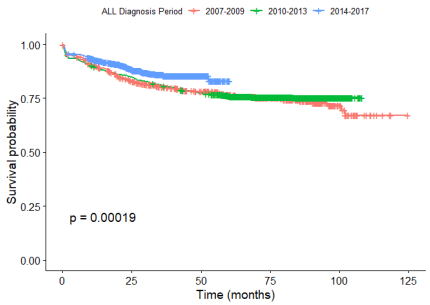
***** For all cancers combined, only the primary tumors were included based on ICCC-3 diagnostic groups excluding (Ia.1.) Precursor cell leukemia – aged <1); (I.e.) Unspecified and other specified leukemia; (VII.b.) Hepatic carcinomas; (XI.) Other malignant epithelial neoplasms and malignant melanomas.

** For ALL, the youngest age group included patients from 1– 4, as patients <1 year were not included in survival.

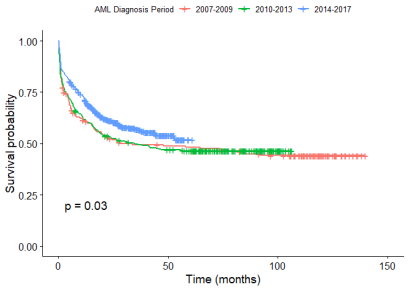
° *P* obtained from log-rank test. ˜ Statistically significant at p<0.005. ^ Patients did not complete 5-year follow-up duration. X No patients in age group.

Appendix 3.10. Change in overall survival over 3 diagnosis periods; 2007-2009, 2010-2013 and 2014-2017.

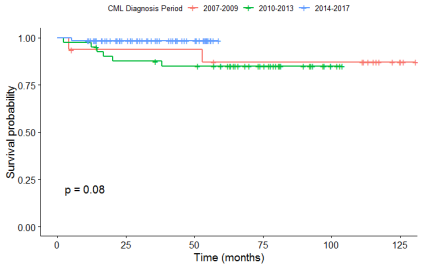
ALL



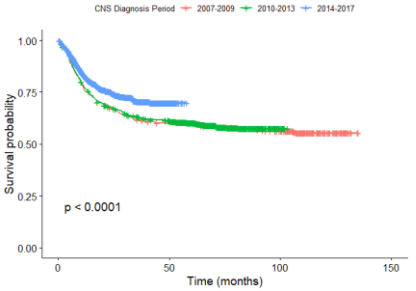
AML



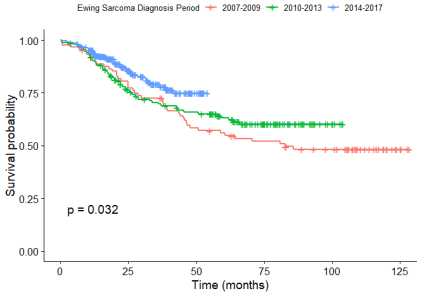
CML



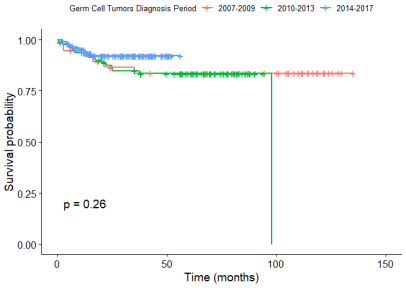
CNS tumours



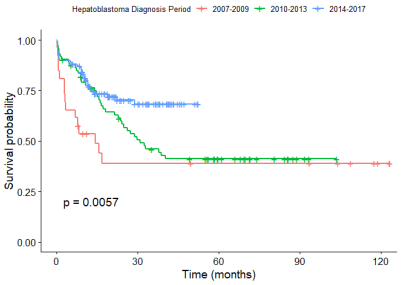
Ewing sarcoma



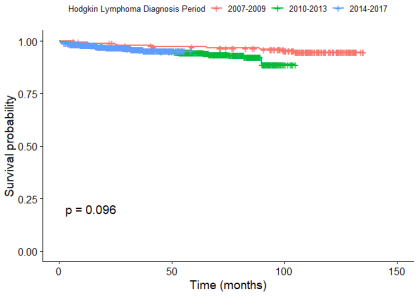
Germ cell tumours



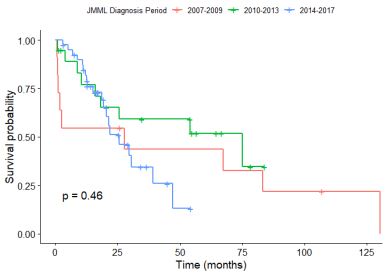
Hepatoblastoma



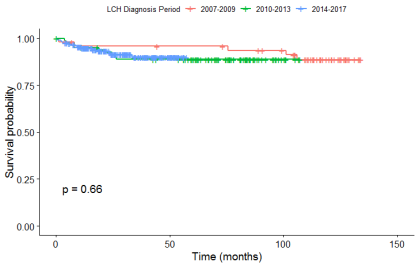
Hodgkin lymphoma



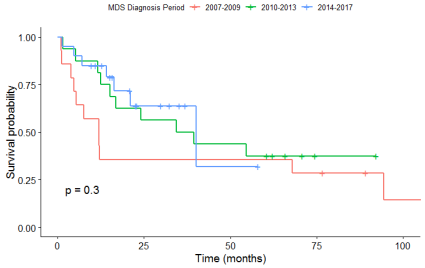
JMML



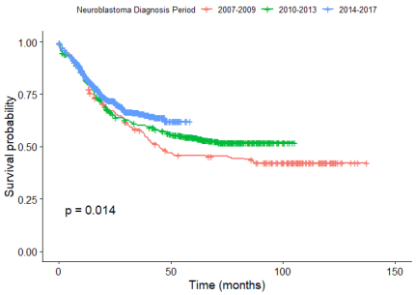
LCH



MDS

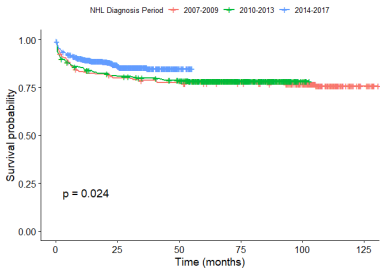


Neuroblastoma

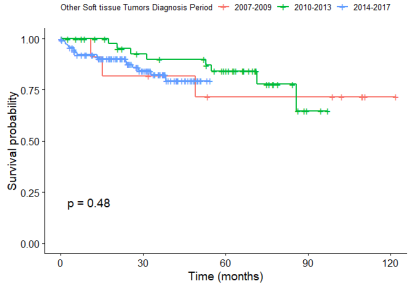


Appendix 3.10. (Continued) Change in 3-year overall survival over 3 diagnosis periods; 2007-2009, 2010-2013 and 2014-2017

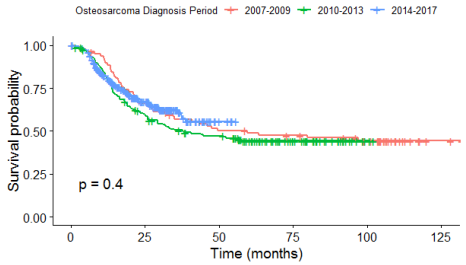
Non-Hodgkin lymphoma



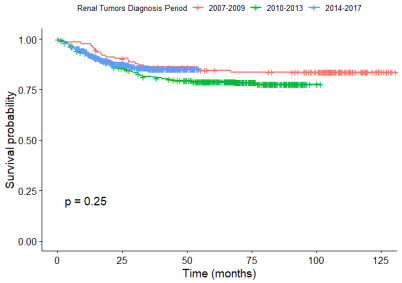
Other soft tissue tumours



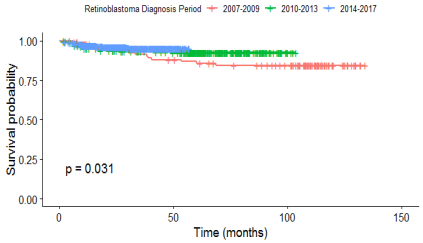
Osteosarcoma



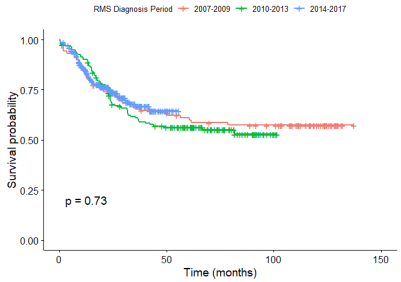
Renal tumours



Retinoblastoma



Rhabdomyosarcoma



Log-rank test *P*. Significant at p<0.05.

Appendix 3.11. Five-year overall survival rates by cancer stage at diagnosis, risk stratification, or sub-type [2007–2017] at CCHE, (n=14,808)

Cancer Type	**Stages/Risk groups/Subtypes**	**No. of patients (%)**	**5-year survival (%) 95% C.I (%)**	***P*** **°**
Acute Lymphoid Leukemia, *n=2,914*				
Risk [a NA]	Low risk	1264 (43.3%)	91.1 (89.3–92.6)	<0.0001*
	Standard risk	1382 (47.4%)	73.8 (71.2 – 76.5)	
	High risk NA	244 (8.4%) 24 (0.8%)	56.7 (50.1 – 64.3) -- [x]	
Acute Myeloid Leukemia, *n=987*				
Sub-type [b]	AML	870 (88.1%)	47.4 (43.9 – 51.2)	0.001*
	APL	65 (6.5%)	74.4 (64.3 – 86.1)	
	AML with Down Syndrome	52 (5.2%)	63.5 (51.2 – 78.6)	
AML risk, *n=870*				
Risk [c NA]	Low	172 (19.7%)	73.5 (66.6 – 81.1)	<0.0001 *
	Intermediate	438 (50.4%)	48.2 (43.3 – 53.7)	
	High NA	198 (22.8%) 62 (7.1%)	39.3 (32.7 – 47.1) -- [x]	
Myelodysplastic Syndrome, *n=50*				
Risk [d NA]	Low	5 (10.0%)	53.3 (21.4 – 100)	0.78
	Intermediate	9 (18.0%)	51.9 (26.7 – 100)	
	High	22 (44.0%)	32.4 (15.8 – 66.7)	
	Very High *NA*	13 (26.0%) 1 (2.0%)	38.9 (17.8 – 85.1) -- [x]	
Sub-type [e]	MDR-AML	9 (18.0%)	40.6 (15.1 – 100)	0.72
	RAEB	25 (50.0%)	41.3 (23.9 – 71.4)	

	RC	16 (32.0%)	37.4 (18.9–73.9)	
Did BMT?	Yes	14 (28.0%)	77.4% (57.8–100)	0.039*
	No	36 (72.0%)	29.6% (17.0–51.5)	
Juvenile myelomonocytic Leukemia, *n=70*				
Did BMT?	Yes	27 (38.6%)	51.6% (33.4–79.7)	0.056
	No	43 (61.4%)	29.3% (16.1–53.1)	
Chronic Myeloid Leukemia, *n=121*				
Sub-type [f]	Chronic phase	114 (94.2%)	91.5 (85.9 – 97.4)	0.4
	Blast crisis	5 (4.1%)	-- [x]	
	Accelerated	2 (1.7%)	-- [x]	
Hodgkin Lymphoma, *n= 1,206*				
Risk [g NA]	Low	567 (47.0%)	99.1 (98.2 – 100)	<0.0001*
	Intermediate	277 (22.9%)	94.4 (91.4 – 97.4)	
	High	353 (29.3%)	91.7 (88.4 – 95.2)	
	NA	9 (0.7%)	-- [x]	
Non-Hodgkin Lymphoma, *n= 1,173*				
Stage [h]	Stage I	51 (4.3%)	94.1 (87.8 – 100)	<0.0001*
	Stage II	222 (18.9%)	88.5 (84.1 – 93.1)	
	Stage III	628 (53.5%)	82.5 (79.3 – 85.7)	
	Stage IV	272 (23.1%)	66.7 (61.0 – 72.9)	
CNS tumours, *n= 2,588*				
Subtype [i NA]	Astrocytoma	749 (28.9%)	76.7 (73.3 – 80.2)	<0.0001*
	Ependymoma	238 (9.1%)	68.4 (54.6 –75.9)	
	Medullablastoma/Embryonal	568 (21.9%)	59.1 (54.6 – 64.0)	
	Neuronal & Mixed Neuronal	127 (5.0%)	92.4 (87.4 – 97.6)	
	Optic Gliomas	106 (4.1%)	97.5 (94.1 – 100)	

	Brain stem lesions	376 (14.5%)	21.0 (16.8 – 26.3)	
	Others**	364 (14.0%)	81.9 (77.5 – 86.6)	
	NA	60 (2.3%)	-- [x]	
Neuroblastoma, n=1,547				
Risk [j] [NA]	Low	103 (6.6%)	93.2 (86.3 – 100)	<0.0001*
	Intermediate	458 (29.6%)	87.7 (84.6 – 90.9)	
	High	971 (62.7%)	33.3 (29.6 – 37.4)	
	NA	15 (0.9%)	-- [x]	
High-risk neuroblastoma, *n=971*				<0.0001*
	Yes		53.8% (46.9 – 61.7)	
Did BMT?	No	246 (25.4%)	25.0% (20.9 – 30.0)	
		725 (74.6%)		
Stage [k] [NA]				
	Stage 1	44 (2.8%)	96.1 (89.0 – 100)	<0.0001*
	Stage 2	54 (3.5%)	94.2 (88.0 – 100)	
	Stage 3	481 (31.0%)	73.7 (69.5 – 78.3)	
	Stage 4	873 (56.4%)	38.0 (34.0 – 42.5)	
	Stage 4S	78 (5.0%)	68.6 (57.4 – 82.0)	
	NA	17 (1.0%)	-- [x]	
Retinoblastoma, *n= 786*				
Stage [l]	Intra-ocular	700 (89.1%)	96.9 (95.3 – 98.6)	<0.0001*
	Extra-ocular	86 (10.9%)	55.5 (45.0 – 68.6)	
Intra-ocular Laterality, n=699	Unilateral	403 (57.7%)	99.2 (98.2 – 100)	<0.0001*
	Bilateral	296 (42.3%)	93.8 (90.2 – 97.6)	
Renal tumours, *n=900*				
Sub-type [m]	Wilms tumour	765 (85.0%)	83.7 (80.8 – 86.7)	<0.0001*

	Rhabdoid tumour	27 (3.0%)	-- [x]	
	Kidney sarcomas	65 (7.2%)	86.3 (77.8 – 95.6)	
	Other renal tumours*	43 (4.8%)	79.9 (63.5 – 100)	
*Wilms t*umour, n=765 [NA]				
Stage [n NA]	Stage I	120 (15.7%)	95.1 (91.0 – 99.4)	<0.0001*
	Stage II	107 (14.0%)	89.7 (83.0 – 97.0)	
	Stage III	291 (38.1%)	85.6 (80.9 – 90.5)	
	Stage IV	149 (19.6%)	75.3 (68.2 – 83.1)	
	Stage V NA	73 (9.6%) 25 (3.0%)	73.4 (63.1 – 85.2) -- [x]	
Hepatoblastoma, *n=208*				
Stage [o NA]	Stage I	6 (2.8%)	100	<0.0001*
	Stage II	1 (0.5%)	-- [x]	
	Stage III	144 (69.3%)	59.4 (50.7 – 69.5)	
	Stage IV NA	52 (25.0%) 5 (2.4%)	27.7 (16.4 – 46.9) -- [x]	
Risk [p NA]	Very Low	1 (0.5%)	-- [x]	0.15
	Low	7 (3.3%)	100	
	High NA	195 (93.8%) 5 (2.4%)	50.8 (43.2 – 59.7) -- [x]	
Ewing Sarcoma, *n=499*				
Stage [q]	Localized	343 (68.7%)	72.6 (66.8 – 78.9)	<0.0001*
	Metastatic	156 (31.3%)	46.4 (37.6 – 57.4)	
Osteosarcoma, *n=502*				
Stage [r]	Localized	321 (63.9%)	62.1 (56.0 – 68.9)	<0.0001*
	Metastatic	181 (36.1 %)	22.0 (15.6 – 31.2)	

Metastases site, n=181	Lung (+/- LN)	131 (72.4%)	30.9 (22.5 – 42.6)	<0.0001*
	Bone + Lung (+/- LN)	31 (17.1%)	-- [x]	
	Bone only	19 (10.5%)	8.51 (1.34 – 54.0)	
Rhabdomyosarcoma, *n=523*				
Risk [s NA]	Low	51 (9.8%)	85.7 (75.7 – 97.1)	<0.0001*
	Intermediate	341 (65.2%)	68.7 (63.0 – 74.9)	
	High NA	123 (23.5%) 8 (0.2%)	26.5 (18.5 – 37.9) -- [x]	
Stage [t NA]	Stage I	106 (20.4%)	88.1 (81.3 – 99.5)	<0.0001*
	Stage II	58 (11.2%)	76.0 (64.3 – 89.8)	
	Stage III	228 (43.6%)	62.1 (54.9 – 70.2)	
	Stage IV NA	123 (23.5%) 8 (0.2%)	26.3 (18.4 – 37.6) -- [x]	
Other soft tissue tumours, *n=178*				
Risk [u NA]	Low	62 (34.9%)	89.7 (77.5 – 100)	<0.0001*
	Intermediate	93 (52.3%)	83.8 (73.8 – 95.2)	
	High NA	22 (12.3%) 1 (0.5%)	-- [x] -- [x]	
Germ Cell tumours, *n=247*				
Site	Gonadal	119 (48.2%)	93.0 (93.0 – 99.9)	0.00065*
	Extra-Gonadal	128 (51.8%)	78.9 (71.4 – 87.1)	
Stage [v]	Stage I	66 (26.7%)	100	<0.0001*
	Stage II	31 (12.6%)	96.7 (90.7 – 100)	
	Stage III	99 (40.1%)	86.3 (79.3 – 93.9)	
	Stage IV	51 (20.6%)	67.1 (54.5 – 82.6)	
Risk [w,x]	Low	63 (25.5%)	100	<0.0001*
	Intermediate High	41 (16.6%)	94.3 (86.8 – 100) 80.3 (73.7 – 87.6)	

		143 (57.9%)		
Langerhans cell histiocytosis, *n=309*				
Risk [y]	Multisystem RO- LR	55 (17.8%)	100	<0.0001*
	Multisystem RO+ HR	62 (20.1%)	62.1 (50.7 – 76.0)	
	Unisystem Multifocal	90 (29.1%)	97.7 (94.7 – 100)	
	Unisystem Unifocal	102 (33.0%)	98.6 (96.0 – 100)	

[NA] Data not available (NA) as patients died before disease risk or stage stratification; ALL risk (NA=24); AML risk (NA=62); MDS risk (NA=1); Hodgkin lymphoma risk (NA=9); CNS subtypes (NA=60); Neuroblastoma risk (NA=15) and stage (NA=17); Wilms tumour stage (NA=25); Hepatoblastoma stage and risk (NA=5); RMS risk and stage (NA=8); other soft tissue tumours risk (NA=1).

[x] Survival and 95% confidence intervals could not be calculated for patients did not complete 5-year follow-up duration, or in case there were no deaths or survivors within this group. Abbreviations: APL: Acute Promyelocytic Leukemia LN: Lymph Nodes; BMT: Bone Marrow Transplant. 95% CI: 95% confidence intervals. ° *P* obtained from log-rank test. * Statistically significant at p<0.005. [a–y] References for definitions of stage at diagnosis, risk stratification and sub-type classifications systems are listed in Appendix 3.3.

Appendix 3.12. Distribution of stage at diagnosis, disease risk and cancer sub-types over the years for children with cancer at CCHE/Egypt, (n=14,808)

Stratification Group (Risk/Stage/subtype)		**Number (%) of patients in each group by year of diagnosis (2007-2017)**										
		2007	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**
Acute Lymphoid Leukemia, n=2,914												
	Low risk	32 (35.1%)	91 (44.6%)	94 (44.7%)	88 (41.1%)	127 (48.7%)	109 (45.6%)	128 (46.2%)	147 (49.0%)	103 (34.8%)	139 (42.3%)	204 (44.1%)
	Standard risk	50 (54.9%)	88 (43.1%)	92 (43.8%)	102 (47.7%)	118 (45.2%)	109 (45.6%)	122 (44.0%)	136 (45.3%)	168 (56.8%)	165 (50.1%)	227 (49.2%)
	High risk	9 (9.8%)	25 (12.2%)	24 (11.4%)	24 (11.2%)	16 (6.1%)	21 (8.8%)	27 (9.8%)	17 (5.7%)	25 (8.4%)	25 (7.6%)	31 (6.7%)
Acute Myeloid Leukemia , n=987												
Subtype	AML	23 (85.2%)	59 (86.8%)	55 (83.3%)	64 (87.7%)	75 (91.5%)	53 (89.8%)	74 (91.4%)	99 (89.2%)	100 (86.2%)	93 (86.1%)	113 (88.2%)
	APL	2 (7.4%)	4 (5.9%)	6 (9.1%)	6 (8.2%)	4 (4.9%)	3 (5.1%)	4 (4.9%)	5 (4.5%)	8 (6.9%)	11 (10.2%)	8 (6.3%)
	AML with Down Syndrome	2 (7.4%)	5 (7.3%)	5 (7.6%)	3 (4.1%)	3 (3.6%)	3 (5.1%)	3 (3.7%)	7 (6.3%)	8 (6.9%)	4 (3.7%)	7 (5.5%)
Sub-type (AML)	Low risk	8 (34.8%)	17 (28.8%)	12 (21.8%)	19 (29.7%)	26 (34.7%)	19 (35.8%)	5 (6.8%)	0	0	31 (33.3%)	35 (31.0%)
	Intermediate risk	11 47.8%)	35 (59.3%)	34 (61.8%)	32 (50.0%)	36 (48.0%)	23 (43.4%)	14 (18.9%)	54 (54.5%)	82 (82.0%)	50 (53.8%)	67 (59.3%)
	High risk	4 (17.4%)	7 (11.9%)	9 (16.4%)	13 (20.3%)	13 (17.3%)	11 (20.8%)	55 (74.3%)	45 (45.5%)	18 (18.0%)	12 (12.9%)	11 (9.7%)
Myelodysplastic Syndrome , n=50												
Risk	Low	*NA*	*NA*	2 (33.3%)	*NA*	*NA*	*NA*	1 (12.5%)	1 (25.0%)	*NA*	*NA*	1 (16.7%)

	Intermediate	*NA*	1 (16.7%)	1 (16.7%)	*NA*	*NA*	1 (33.3%)	2 (25.0%)	1 (25.0%)	1 (16.7%)	1 (25.0%)	1 (16.7%)
	High	*NA*	4 (66.7%)	2 (33.3%)	1 (50.0%)	2 (66.7%)	1 (33.3%)	3 (37.5%)	2 (50.0%)	3 (50.0%)	2 (50.0%)	2 (33.3%)
	Very high	1 (100%)	1 (16.7%)	1 (16.7%)	1 (50.0%)	1 (33.3%)	1 (33.3%)	2 (25.0%)	*NA*	2 (33.3%)	1 (25.0%)	2 (33.3%)
Sub-type	MDR-AML	*NA*	*NA*	*NA*	1 (50.0%)	1 (33.3%)	1 (33.3%)	2 (25.0%)	*NA*	2 (33.3%)	1 (25.0%)	1 (16.7%)
	RAEB	1 (50.0%)	4 (66.7%)	3 (50.0%)	1 (50.0%)	*NA*	1 (33.3%)	4 (50.0%)	2 (50.0%)	3 (50.0%)	3 (75.0%)	3 (50.0%)
	RC	1 (50.0%)	2 (33.3%)	3 (50.0%)	NA	2 (66.7%)	1 (33.3%)	2 (25.0%)	2 (50.0%)	1 (16.7%)	*NA*	2 (33.3)
Chronic Myeloid Leukaemia , n=121												
Sub-type	Chronic phase	1 (100%)	5 (100%)	10 (100%)	8 (88.9%)	7 (87.5%)	11 (100%)	13 (100%)	20 (95.2%)	11 (84.6%)	14 (93.3%)	14 (93.3%)
	Blast crisis	*NA*	*NA*	*NA*	*NA*	1 (12.5%)	*NA*	*NA*	1 (4.8%)	1 (7.7%)	1 (6.7%)	1 (6.7%)
	Accelerated	*NA*	*NA*	*NA*	1 (11.1%)	*NA*	*NA*	*NA*	*NA*	1 (7.7%)	*NA*	*NA*
Hodgkin's Lymphoma , n=1,206 *												
Risk	Low	11 (34.4%)	26 (36.6%)	43 (53.1%)	42 (59.1%)	51 (44.3%)	46 (38.6%)	53 (48.6%)	62 (46.6%)	61 (44.5%)	79 (50.9%)	93 (53.1%)
	Intermediate	11 (34.4%)	23 (32.4%)	18 (22.2%)	10 (14.1%)	32 (27.8%)	30 (25.2%)	20 (18.3%)	35 (26.3%)	28 (20.4%)	36 (23.2%)	34 (19.4%)
	High	10 (31.2%)	22 (30.9%)	20 (24.7%)	19 (26.8%)	32 (27.8%)	43 (36.1%)	36 (33.0%)	36 (27.1%)	48 (35.0%)	40 (25.8%)	48 (27.4%)
Non-Hodgkin's Lymphoma , n=1,173												
Stage	Stage I	2 (6.0%)	2 (2.2%)	4 (4.3%)	5 (4.7%)	2 (1.9%)	10 (10.3%)	7 (5.8%)	7 (6.1%)	2 (1.4%)	3 (2.4%)	6 (4.4%)
	Stage II	11 (33.3%)	24 (27.0%)	16 (17.0%)	15 (14.0%)	48 (45.7%)	20 (20.7%)	17 (13.9%)	12 (10.4%)	24 (16.9%)	17 (13.3%)	18 (13.1%)
	Stage III	14 (42.4%)	43 (48.3%)	55 (58.5%)	63 (58.9%)	34 (32.4%)	50 (51.5%)	61 (50.0%)	70 (60.9%)	90 (63.4%)	73 (57.0%)	74 (54.0%)

	Stage IV	6 (18.2%)	20 (22.5%)	19 (20.2%)	24 (22.4%)	21 (20.0%)	17 (17.5%)	37 (30.3%)	26 (22.6%)	26 (18.3%)	35 (27.3%)	39 (28.5%)
CNS tumours , n=2,588 *												
Sub-type	Astrocytoma	28 (50.9%)	31 (25.4%)	60 (43.1%)	43 (30.6%)	44 (25.7%)	54 (23.1%)	66 (28.3%)	80 (24.8%)	111 (32.7%)	126 (34.2%)	99 (24.9%)
	Ependymoma	4 (7.2%)	13 (10.6%)	14 (10.0%)	12 (8.7%)	25 (14.6%)	21 (9.0%)	24 (10.3%)	26 (8.0%)	24 (7.0%)	30 (8.1%)	45 (11.3%)
	Medulloblastoma/Embryonal	7 (12.7%)	36 (29.5%)	22 (15.8%)	41(29.9%)	40 (23.3%)	60 (25.7%	50 (21.4%)	73 (22.6%)	76 (22.4%)	78 (21.1%)	82 (20.6%)
	Neuronal & Mixed Neuronal	*NA*	6 (4.9%)	2 (1.4%)	1 (0.7%)	7 (4.0%)	13 (5.5%)	15 (6.4%)	23 (7.1%)	21 (6.1%)	15 (4.0%)	23 (5.7%)
	Optic Gliomas	*NA*	2 (1.6%)	3 (2.1%)	1 (0.7%)	3 (1.7%)	5 (2.1%)	3 (1.2%)	18 (5.5%)	25 (7.3%)	23 (6.2%)	23 (5.7%)
	Brain stem lesions	8 (14.5%)	15 (12.3%)	16 (11.5%)	23 (16.7%)	25 (14.6%)	50 (21.4%)	42 (18.0%)	51 (15.8%)	37 (10.9%)	51 (13.8%)	58 (14.6%)
	Others	8 (14.5%)	19 (15.5%)	22 (15.8%)	17 (12.4%)	27 (15.7%)	30 (12.8%)	33 (14.1%)	51 (15.8%)	45 (13.2%)	45 (12.2%)	67 (16.8%)
Neuroblastoma , n=1,547 *												
Risk	Low	3 (13.6%)	7 (6.5%)	6 (6.8%)	4 (3.8%)	7 (5.9%)	3 (2.7%)	3 (1.8%)	13 (7.9%)	17 (8.1%)	26 (12.0%)	14 (6.5%)
	Intermediate	2 (9.0%)	15 (14.0%)	29 (33.0%)	35 (33.7%)	45 (38.2%)	37 (33.0%)	61 (37.0%)	44 (26.7%)	67 (31.9%)	68 (31.5%)	52 (24.2%)
	High	17 (77.2%)	85 (79.5%)	53 (60.2%)	65 (62.5%)	66 (55.9%)	72 (64.3%)	101 (61.2%)	108 (65.4%)	126 (60.0%)	122 (56.5%)	149 (69.3%)
Stage	Stage 1	NA	4 (3.7%)	3 (3.4%)	1 (0.9%)	NA	1 (0.9%)	3 (1.8%)	6 (3.6%)	9 (4.3%)	11 (5.0%)	6 (2.7%)
	Stage 2	3 (13.0%)	3 (2.7%)	1 (1.1%)	2 (1.9%)	6 (5.0%)	2 (1.7%)	*NA*	5 (3.0%)	9 (4.3%)	15 (6.8%)	8 (3.7%)
	Stage 3	5 (21.7%)	27 (25.0%)	34 (38.6%)	36 (34.6%)	48 (40.3%)	44 (39.2%)	60 (36.3%)	38 (23.0%)	72 (34.1%)	56 (25.5%)	61 (28.2%)
	Stage 4	12 (52.1%)	69 (63.8%)	43 (48.8%)	57 (54.8%)	58 (48.7%)	61 (54.4%)	92 (55.7%)	110 (66.6%)	112 (53.0%)	129 (58.9%)	130 (60.1%)

	Stage 4s	3 (13.0%)	5 (4.6%)	7 (7.9%)	8 (7.7%)	7 (5.8%)	4 (3.5%)	10 (6.0%)	6 (3.6%)	9 (4.2%)	8 (3.6%)	11 (5.1%)
Retinoblastoma , n=786												
Stage	Intra-ocular	12 (92.3%)	33 (89.2%)	44 (89.7%)	31 (83.8%)	47 (92.2%)	54 (80.6%)	75 (85.2%)	86 (89.6%)	102 (87.1%)	101 (93.5%)	115 (95.0%)
	Extra-ocular	1 (7.6%)	4 (10.8%)	5 (10.3%)	6 (16.2%)	4 (7.8%)	13 (19.4%)	13 (14.7%)	10 (10.4%)	17 (12.9%)	7 (6.5%)	6 (5.0%)
Laterality (Intra-ocular)	Unilateral	5 (41.6%)	14 (42.4%)	22 (50.0%)	23 (74.2%)	28 (59.5%)	37 (68.5%)	39 (52.0%)	54 (62.3%)	61 (59.8%)	58 (57.4%)	63 (54.7%)
	Bilateral	7 (58.3%)	19 (57.5%)	22 (50.0%)	8 (25.8%)	19 (40.5%)	17 (31.5%)	36 (48.0%)	32 (37.2%)	41 (40.2%)	43 (42.6%)	5 (4.3%)
Renal tumours , n=900 *												
Sub-type	Wilms tumours	17 (94.4%)	32 (94.1%)	59 (81.9%)	65 (92.8%)	64 (79.0%)	81 (80.2%)	68 (86.1%)	97 (87.4%)	97 (88.0%)	96 (88.0%)	87 (80.5%)
	Rhabdoid tumours	*NA*	*NA*	2 (2.8%)	*NA*	4 (4.9%)	7 (6.8%)	1 (1.3%)	4 (4.5%)	5 (4.5%)	*NA*	3 (2.7%)
	Renal Sarcomas	1 (5.6%)	*NA*	*NA*	1 (1.4%)	11 (13.5%)	11 (10.9%)	7 (8.9%)	10 (2.7%)	3 (2.7%)	6 (5.5%)	9 (8.3%)
	Other Renal tumours	*NA*	2 (5.9%)	11 (15.2%)	4 (5.7%)	2 (2.5%)	2 (2.0%)	3 (3.7%)	3 (5.4%)	6 (5.4%)	7 (6.4%)	9 (8.3%)
Stage - Wilms T.	Stage I	4 (22.2%)	13 (38.2%)	20 (27.8%)	22 (32.3%)	16 (18.2%)	20 (20.2%)	11 (14.1%)	13 (11.7%)	11 (10.6%)	11 (11.2%)	6 (6.3%)
	Stage II	2 (11.1%)	8 (23.5%)	10 (13.8%)	7 (10.3%)	4 (4.5%)	16 (16.2%)	10 (12.8%)	17 (15.3%)	13 (12.5%)	14 (14.3%)	20 (21.1%)
	Stage III	7 (38.9%)	5 (14.7%)	24 (13.3%)	13 (19.1%)	33 (37.5%)	35 (35.3%)	32 (41.0%)	50 (45.0%)	54 (51.9%)	51 (52.0%)	43 (45.2%)
	Stage IV	3 (16.7%)	6 (17.4%)	16 (22.2%)	16 (23.5%)	16 (18.2%)	21 (21.2%)	18 (23.1%)	20 (18.0%)	18 (17.3%)	14 (14.3%)	17 (17.9%)
	Stage V	2 (11.1%)	2 (5.8%)	2 (2.7%)	10 (14.7%)	19 (21.6%)	7 (7.1%)	7 (9.0%)	11 (10.0%)	8 (7.6%)	8 (8.2%)	9 (9.5%)
Ewing Sarcoma , n=499												

Stage	Localized	12 (80.0%)	2 (11.7%)	27 (71.0%)	26 (74.3%)	28 (68.2%)	18 (56.2%)	26 (57.7%)	39 (70.9%)	40 (67.8%)	49 (72.1%)	56 (72.8%)
	Metastatic	3 (20.0%)	15 (88.3%)	11 (28.9%)	9 (25.7%)	13 (31.8%)	14 (43.8%)	19 (42.3%)	16 (29.1%)	19 (32.2%)	19 (27.9%)	16 (22.2%)
Osteosarcoma , n=502												
Stage	Localized	7 (53.8%)	21 (77.8%)	23 (58.9%)	18 (50.0%)	26 (68.4%)	26 (63.4%)	32 (59.3%)	30 (63.8%)	51 (67.1%)	46 (65.7%)	41 (67.2%)
	Metastatic	6 (46.2%)	6 (22.2%)	16 (41.1%)	18 (50.0%)	12 (31.6%)	15 (36.6%)	22 (40.7%)	17 (36.2%)	25 (32.9%)	24 (34.3%)	20 (32.8)
Metastatic Site	Lung(+/-LN)	6 (85.7%)	5 (83.3%)	12 (92.3%)	8 (44.4%)	11 (91.7%)	13 (86.7%)	13 (59.1%)	16 (94.1%)	21 (84.0%)	14 (58.3%)	12 (60.0%)
	Bone + Lung (+/-LN)	1 (14.3%)	19 (16.7%)	1 (7.7%)	7 (40.0%)	1 (8.3%)	*NA*	5 (22.7%)	1 (5.9%)	3 (12.0%)	9 (37.5%)	3 (15.0%)
	Bone Only	*NA*	*NA*	*NA*	3 (16.6%)	*NA*	2 (13.3%)	4 (18.2%)	*NA*	1 (4.0%)	1 (4.2%)	5 (25.0%)
Rhabdomyosarcoma , n=523 *												
Risk	Low	2 (13.3%)	8 (20.5%)	8 (23.5%)	4 (12.5%)	3 (7.7%)	1 (2.6%)	3 (6.1%)	5 (7.6%)	4 (6.3%)	5 (7.0%)	8 (11.4%)
	Intermediate	11 (73.3%)	24 (61.5%)	20 (58.8%)	20 (62.5%)	22 (56.4%)	30 (78.9%)	30 (61.2%)	42 (64.6%)	46 (73.0%)	48 (67.6%)	48 (68.6%)
	High	2 (13.4%)	7 (18.0%)	6 (17.6%)	8 (25.0%)	14 (35.9%)	7 (18.4%)	16 (32.7%)	18 (27.8%)	13 (20.6%)	18 (25.4%)	14 (20.0%)
Stage	Stage I	2 (13.3%)	12 (30.8%)	8 (23.5%)	6 (18.7%)	7 (17.9%)	9 (23.7%)	5 (10.2%)	15 (23.0%)	11 (17.5%)	12 (16.9%)	19 (27.2%)
	Stage II	4 (26.7%)	5 (12.8%)	5 (14.7%)	4 (12.5%)	9 (23.0%)	4 (10.5%)	6 (12.2%)	2 (3.1%)	6 (9.5%)	9 (12.6%)	4 (5.7%)
	Stage III	7 (46.7%)	15 (38.4%)	15 (44.1%)	14 (43.8%)	9 (23.0%)	18 (47.3%)	22 (44.9%)	30 (46.2%)	33 (52.3%)	32 (45.1%)	33 (47.1%)
	Stage IV	2 (13.3%)	7 (18.0%)	6 (17.7%)	8 (25.0%)	14 (35.9%)	7 (18.4%)	16 (32.7%)	18 (27.7%)	13 (20.6%)	18 (25.4%)	14 (20.0%)
Other Soft Tissue tumours , n=178												

Risk	Low	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	10 (38.5%)	18 (45.0%)	8 (28.6%)	7 (29.2%)
	Intermediate	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	12 (46.1%)	17 (42.5%)	15 (53.6%)	14 (58.3%)
	High	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	4 (15.4%)	5 (12.5%)	5 (17.8%)	3 (12.5%)
Germ cell tumours , n=247												
Site	Gonadal	6 (85.7%)	7 (41.2%)	4 (28.6%)	7 (50.0%)	8 (40.0%)	10 (41.7%)	10 (45.5%)	19 (57.6%)	17 (51.5%)	10 (52.6%)	21 (48.8%)
	Extra-gonadal	1 (14.3%)	10 (58.8%)	10 (71.4%)	7 (50.0%)	12 (60.0%)	14 (58.3%)	12 (54.5%)	14 (42.4%)	16 (48.5%)	9 (47.4%)	22 (51.2%)
Stage	Stage I	4 (57.1%)	4 (23.5%)	4 (28.6%)	4 (28.6%)	2 (10.0%)	4 (16.7%)	5 (22.7%)	8 (24.2%)	9 (27.3%)	6 (31.5%)	16 (37.2%)
	Stage II	1 (14.3%)	1 (5.8%)	2 (14.3%)	2 (14.3%)	2 (10.0%)	3 (12.5%)	*NA*	7 (21.3%)	6 (18.2%)	2 (10.5%)	5 (11.6%)
	Stage III	1 (14.3%)	7 (41.2%)	3 (21.4%)	6 (42.8%)	10 (50.0%)	9 (37.5%)	14 (63.7%)	14 (42.4%)	14 (42.4%)	6 (31.6%)	15 (34.9%)
	Stage IV	1 (14.3%)	5 (29.5%)	5 (35.7%)	2 (14.3%)	6 (30.0%)	8 (33.3%)	3 (13.6%)	4 (12.1%)	4 (12.2%)	5 (26.4%)	7 (16.3%)
Risk	Good (low risk)	4 (57.1%)	4 (23.5%)	3 (21.4%)	4 (28.6%)	2 (10.0%)	4 (16.7%)	4 (18.2%)	8 (24.2%)	8 (24.2%)	6 (31.5%)	16 (37.2%)
	Intermediate	1 (14.3%)	1 (5.9%)	3 (21.4%)	3 (21.4%)	3 (15.0%)	3 (12.5%)	2 (9.1%)	9 (27.3%)	8 (24.2%)	2 (10.5%)	6 (13.9%)
	Poor(high risk)	2 (28.6%)	12 (10.6%)	8 (57.2%)	7 (50.0%)	15 (75.0%)	17 (70.8%)	16 (72.7%)	16 (48.5%)	17 (51.6%)	11 (58.0%)	21 (48.9%)
Langerhans Cell Histosytosis , n=309												
Risk	Multisystem RO-LR	1 (7.7%)	*NA*	1 (5.3%)	*NA*	*NA*	2 (7.7%)	4 (20.0%)	6 (12.0%)	11 (27.5%)	15 (35.7%)	15 (33.3%)
	Multisystem RO+LR	2 (15.3%)	6 (35.3%)	4 (21.1%)	5 (26.4%)	6 (30.0%)	7 (26.9%)	4 (20.0%)	14 (28.0%)	6 (15.0%)	1 (2.3%)	6 (13.3%)
	Unisystem Multifocal	5 (38.5%)	5 (29.4%)	4 (21.1%)	8 (47.1%)	8 (40.0%)	10 (38.4%)	5 (25.0%)	15 (30.0%)	14 (35.0%)	8 (19.0%)	9 (20.0%)

	Unisystem Unifocal	5 (38.5%)	6 (35.3%)	10 (52.6%)	4 (23.5%)	6 (30.0%)	7 (26.9%)	7 (35.0%)	15 (30.0%)	9 (22.5%)	18 (43.0%)	15 (33.3%)

* In neuroblastoma, 10 patients had NA risk; RMS had 2 NA risk and stage; Wilms tumor had 1 NA stage; CNS had 6 NA subtypes; 5 Hodgkin lymphoma had NA risk;
Abbreviations: CNS: Central Nervous System.

Appendix 3.13. Potential reasons for inferior survival based on discussions with lead paediatric oncologists at CCHE/Egypt.

Childhood Cancer Type	**Potential reason(s) for inferior survival**
Acute Lymphoid Leukaemia	• Higher percent of toxic deaths compared to other settings in HICs. • Delays in high-dose methotrexate cycles as it requires hospitalization, which leads to reduced dose intensity and increased relapse rates, negatively affecting survival. • Limited BMT capacity for children with high-risk ALL as only patients who have a matched sibling donor can perform BMT at CCHE due to unavailability of BMT registry in Egypt and limited capacity of BMT beds at CCHE. • CCHE offers less treatment options as salvage therapy for relapsed/refractory patients, who currently receive CAR-T cell immunotherapy as a standard of care in HICs.
Acute Myeloid Leukaemia	• Higher percent of induction and toxic deaths at CCHE, accounting for 25.0% of AML deaths compared to 2% and 3% as reported by COG and St. Jude, respectively. • Induction/toxic deaths are likely due to delayed diagnosis, high rate of infection (especially multi-drug resistant (MDR) bacteria) and malnutrition at presentation. • Limited BMT capacity for high risk and relapsed AML patients, unlike other HICs who offer haplo-identical and matched unrelated BMT and post-transplant immunotherapy. • Limited hospital capacity to offer second line treatment for relapsed children in second complete remission.
MDS and JMML	• Limited capacity to perform BMT which is the only curative option for MDS and JMML patients; BMT is not offered for all patients; only offered as first line treatment for MDS and JMML with matched sibling donor; not offered as salvage therapy for relapsed patients.
Non-Hodgkin's Lymphoma	• Late referrals and delayed diagnosis, with high tumour burden. • Higher percentage of treatment-related mortality than in HICs. • Poor survival of Burkitt lymphoma at CCHE, due to tumour lysis syndrome and chemotherapy-related toxicities.
CNS tumours	• Delayed diagnosis and late presentation. • Lack of second line treatment for recurrent patients, especially re-surgery due to limited number of beds. • CCHE does not offer BMT for CNS tumours due to limited BMT capacity, unlike other HICs who give multi-modality treatment strategies.

Neuroblastoma	• Delayed referral, advanced disease, poor general condition at presentation. • Inferior survival of high-risk neuroblastoma (34% at CCHE compared to 40–50% in HIC), due to limited BMT capacity. • Unavailability of Anti-GD2 (post-transplant immunotherapy) which is an important therapeutic advance for treating high-risk neuroblastoma and has been recently incorporated as a standard of care in the US, the UK and across Europe.
Retinoblastoma	• Although retinoblastoma survival is significantly inferior than survival in England, it is comparable with survival in the US.
Renal tumours	• Late referral and delayed diagnosis. • Advanced Wilms tumour disease at presentation; stages III and IV (38.2% and 19.6% at CCHE, versus 25% and 10% as reported in literature, respectively). • Higher percentage of bilateral Wilms tumour (9.6% at CCHE compared to 5% in literature). • Limited options for relapsed patients.
Hepatoblastoma	• Late diagnosis and advanced stage at presentation; majority of patients (>70%) present with advanced stages (III and IV), and 95% of patients are in the high-risk group compared to 40% as reported from a HIC setting. • Unresectable tumours; only 66% of the patients at CCHE present with resectable (operable) tumours versus 95% who undergo surgery in SIOPEL; of which 55% undergo resection and 45% make orthotopic liver transplantation. • Unavailability of liver transplant surgery at CCHE (which is needed by 45% of patients with unresectable hepatoblastoma), where liver transplantation is only allowed through live donor not cadaveric in Egypt.
Osteosarcoma	• Advanced metastatic disease at presentation (35.7% of this study cohort compared to18% on average in HICs), where patients with initial bone metastasis are treated on palliative care at CCHE and eventually die. • Inferior survival of localized osteosarcoma at CCHE likely due to the high ratio of poor responders (60% vs. 40% good responders) which is not aligned with data in the literature and negatively affects survival. • Delays in methotrexate cycles due to limited capacity of beds and long waiting list, resulting in reduced dose intensity which leads to higher relapse rates and poor survival.
Rhabdomyosarcoma	• Inferior survival due to advanced stage at initial diagnosis, and very poor survival of metastatic rhabdomyosarcoma (stage IV) at 26.3%

Abbreviations: MDS Myelodysplastic Syndrome; JMMLL Juvenile myelomonocytic leukaemia.

Appendix Chapter 4

Appendix 4.1. The Strengthening Reporting of Observational Studies in Epidemiology (STROBE) checklist

	Item No	Recommendation	Location in thesis where items are reported
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 6, 115
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 6
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 52–55, 115
Objectives	3	State specific objectives, including any pre-specified hypotheses	Page 116
Methods			
Study design	4	Present key elements of study design early in the paper	Page 117
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 117–119
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 117–119
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 120, 121
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 118–121
Bias	9	Describe any efforts to address potential sources of bias	Page 123,
Study size	10	Explain how the study size was arrived at	Page 117
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 123
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 123
		(*b*) Describe any methods used to examine subgroups and interactions	Page 123
		(*c*) Explain how missing data were addressed	NA

		(*d*) If applicable, explain how loss to follow-up was addressed	Page 124
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 124, 125
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 124, 125
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	Page 124, 125
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 131, 132, 139, 140
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 127, 135
		(*b*) Report category boundaries when continuous variables were categorized	Page 125
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 127, 132, 136, 138
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 143, 144
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 147
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 143–147
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 147
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 5

Appendix 4.2. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 checklist

Section/item	Item No.	Section/item	Location in thesis where items are reported
Title and abstract			
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	Page 115
Abstract	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Page 6
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Page 115, 116
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	NA
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Page 117
Setting and location	6	Provide relevant contextual information that may influence findings.	Page 117
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Page 118, 119
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Page 122
Time horizon	9	State the time horizon for the study and why appropriate.	Page 122
Discount rate	10	Report the discount rate(s) and reason chosen.	NA
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Page 118, 120, 121
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	NA
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Page 120, 121
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Page 122, 123
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Page 122, 123
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	NA
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Page 123
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Page 123
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Page 123
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	NA

Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	NA
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Page 127, 130
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Page 341
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	NA
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	NA
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Page 143–149
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Page 5
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	NA

Appendix 4.3. Childhood Cancer types at CCHE based on ICCC-3 diagnostic groups, by age-group distribution, (N=8,886).

ICCC-3 Groups	**No. of patients (% from total)**	**0 – 4 years**	**5 – 9 years**	**10 – 14 years**	**15 – 18 years**
All cancers combined*	8,886	4,319 (48.2%)	2444 (27.5%)	1518 (17.5%)	605 (6.8%)
I. Leukaemia and related cancers	2,357 (26.5%)	1074 (45.5%)	696 (29.5%)	426 (18.1%)	161 (6.9%)
Ia. Acute Lymphoid Leukaemia	1660 (18.7%)	771 (46.1%)	533 (32%)	257 (15%)	99 (6%)
Ib. Acute Myeloid Leukaemia	544 (6%)	238 (43.8%)	126 (23.2%)	134 (24.6%)	46 (8.4%)
Ic. Chronic Myeloid Leukaemia	77 (0.9%)	11 (14.4%)	20 (25.9%)	30 (38.9%)	16 (20.8%)
Id. Myelodysplastic Syndrome	28 (0.3%)	8 (28.6%)	15 (53.6%)	5 (17.8%)	*NA*
Id. JMML	48 (0.5%)	46 (95.8%)	2 (4.2%)	*NA*	*NA*
II. Lymphomas	1344 (15%)	322 (23.9%)	510 (37.9%)	356 (26.4%)	156 (11.6%)
IIa. Hodgkin Lymphoma	709 (8%)	110 (15%)	277 (39%)	222 (31%)	100 (14%)
IIb. Non-Hodgkin Lymphoma	635 (7%)	212 (33.3%)	233 (36.6%)	134 (21.3%)	56 (8.8%)
III Brain and CNS Tumours	1659 (18.7%)	590 (35.5%)	649 (39.1%)	324 (19.6%)	96 (5.8%)
IV.a Neuroblastoma**	967 (10.9%)	831 (85.9%)	115 (11.9%)	16 (1.6%)	5 (0.6%)
V. Retinoblastoma	523 (5.9%)	499 (95.4%)	21 (4.1%)	3 (0.5%)	*NA*
VI. Renal Tumours	521 (5.7%)	393 (75.4%)	107 (20.5%)	20 (3.8%)	1 (0.3%)
VII.a Hepatoblastoma	122 (1.4%)	112 (91.8%)	4 (3.2%)	5 (4.2%)	1 (0.8%)
VIII. Malignant bone tumours	602 (6.2%)	46 (7.6%)	167 (27.7%)	258 (42.9%)	131 (21.8%)
VIIIa Osteosarcoma	305 (3.4%)	6 (2.1%)	61 (20.3%)	150 (49%)	88 (28.6%)
VIIIc Ewing sarcomas	297 (3.3%)	40 (13.5%)	106 (35.6%)	108 (36.4%)	43 (14.5%)
IX. Soft tissue–extra-osseous sarcoma	444 (5%)	224 (50.5%)	108 (24.4%)	69 (15.5%)	43 (9.6%)
IXa. Rhabdomyosarcoma	317 (3.6%)	177 (55.8%)	84 (26.5%)	39 (12.3%)	17 (5.4%)
IXb-d Other soft tissue tumours	127 (1.4%)	47 (37%)	24 (18.9%)	30 (23.6%)	26 (20.5%)
X.a-c Germ Cell Tumours	150 (1.75%)	96 (64%)	19 (12.1%)	26 (17%)	9 (6%)
XII. Other Tumours (LCH)***	197 (2.2%)	132 (67%)	48 (24.1%)	15 (7%)	2 (1%)

Abbreviations. JMML: Juvenile myelomonocytic leukaemia; LCH. Langerhans cell histiocytosis. ***** For all cancers combined, only the primary tumours were included based on ICCC-3 diagnostic groups excluding (Ia.1.) Precursor cell leukaemia – aged <1); (I.e.) Unspecified and other specified leukaemia; (VII.b.) Hepatic carcinomas; (XI.) Other malignant epithelial neoplasms and malignant melanomas. *****Neuroblastoma includes Neuroblastoma and ganglioneuroblastoma. ** XII includes LCH only. NA: patients were not available in this age group.

Appendix 4.4. Main resource use measures at 3-years post diagnosis, by ICCC-3 groups (N=8,886)

ICCC-3 groups	Median (IQR)					
	Inpatient days	No. of All encounters [a]	No. of Inpatient admissions	No. of Outpatient visits	No. of Investigations [b]	No. of Treatment Interventions [c]
All cancers combined *	43 (20-74)	77 (57-118)	7 (3-11)	69 (44-109)	663 (239-1,208)	2,412 (933-4,068)
I. Leukaemia and related cancers	59 (42-101)	119 (68-155)	7 (5-10)	113 (61-147)	1,312 (1,068-1,670)	3,939 (2,981-5,345)
Ia. Acute Lymphoblastic Leukaemia	52 (39-72)	142 (114-167)	7 (5-10)	134 (108-158)	1,255 (1,060-1,565)	3,794 (2,981 – 4,930)
Ib. Acute Myeloid Leukaemia	117 (94-150)	53 (35-71)	8 (6-11)	45 (27-62)	1,546 (1,232-2,014)	4,820 (3,362-6,712)
Ic. Chronic Myeloid Leukaemia	49 (31-78)	59 (44-75)	6 (2-10)	57 (44-72)	334 (269-1,359)	392 (202-3,598)
Id. Myelodysplastic Syndrome	111 (66-131)	74 (57-86)	8 (4-11)	65 (52-78)	1,912 (1,319-2,327)	5,078 (3,956-6,904)
Ie. JMML	64 (43-93)	73 (53-96)	6 (4-11)	66 (44-86)	1,520 (909-2,024)	4,211 (2,423-6,322)
II. Lymphomas	45 (24-71)	54 (43-75)	7 (4-11)	52 (40-69)	382 (192-913)	1,036 (365-2,933)
IIa. Hodgkin's lymphoma	36 (11-68)	53 (43-63)	5 (2-10)	52 (43-62)	200 (170-242)	380 (285-599)
IIb. Non-Hodgkin lymphoma	51 (38-72)	60 (44-100)	8 (6-11)	51 (37-90)	886 (626 -1,298)	2,775 (1,880-4,178)
IIIa-e CNS and Brain Tumours	23 (10-43)	60 (32-105)	4 (2-8)	56 (30-98)	300 (101-554)	1,458 (754-2,586)
IVa. Neuroblastoma**	58 (26-86)	86 (57-115)	12 (5-17)	74 (49-98)	953 (512-1,454)	3,356 (1,762-5,204)
V. Retinoblastoma	33 (9-61)	56 (42-69)	6 (2-11)	54 (42-68)	146 (99-222)	714 (488-1,056)
VI. Renal Tumours	15 (8-36)	63 (49-84)	2 (1-7)	60 (47-77)	309 (212-668)	1,214 (782-2,601)
VIIa. Hepatoblastoma	36 (25-55)	85 (68-102)	11 (8-13)	74 (58-90)	622 (511-876)	2,238 (1,706-3,008)
VIII. Malignant Bone Tumours	54 (22-85)	108 (85-132)	12 (5-20)	96 (72-118)	761 (527-937)	3,036 (2,080-4,287)
VIIIa. Osteosarcoma	80 (57-97)	103 (73-130)	19 (13-23)	84 (57-107)	832 (577-975)	3,752 (2,729-4,680)
VIIIb. Ewing Sarcoma	28 (12-52)	113 (95-133)	6 (3-11)	106 (88-124)	670 (497-865)	2,492 (1,823-3,357)
IX. Soft tissue/extra-osseous sarcoma	27 (10-55)	88 (69-111)	6 (2-10)	84 (61-105)	506 (332-770)	1,956 (1,072-3,076)
IXa. Rhabdomyosarcoma	25 (10-53)	99 (83-118)	5 (3-10)	95 (78-112)	532 (363-847)	2,106 (1,319-3,167)
IXb-d. Other soft tissue tumours	30 (11-60)	59 (35-80)	6 (2-11)	55 (32-71)	386 (137-672)	1,511 (718-2,763)
XI. Germ Cell Tumours	34 (13-55)	43 (26-60)	6 (3-9)	37 (22-54)	406 (177-702)	1,446 (543-2,420)
XII. Langerhans cell histiocytosis***	43 (14-68)	65 (37-88)	6 (2-10)	65 (37-88)	234 (145-328)	574 (324-889)

[a] All encounters include total number of encounters for inpatient admissions and outpatient visits. [b] Investigations include total number of laboratory tests and radiology tests. [c] Treatment interventions include total number of drug doses, radiotherapy sessions, surgeries, and medical supplies. ***** For all cancers combined, only the primary tumours were included based on ICCC-3 diagnostic groups excluding (Ia.1.) Precursor cell leukaemia – aged <1); (I.e.) Unspecified and other specified leukaemia; (VII.b.) Hepatic carcinomas; (XI.) Other malignant epithelial neoplasms and malignant melanomas. ** IVa. Neuroblastoma includes Neuroblastoma and ganglioneuroblastoma. *** XII includes Langerhans cell histiocytosis (LCH) only.

Appendix 4.5. Resource use measures of investigations and treatment interventions at 3-years post diagnosis, (N=8,886)

ICCC-3 groups	Median (IQR)						
	Investigations		Treatment (interventions)				
	No. of Lab tests	No. of Imaging tests	No. of total Drug doses	No. of Chemotherapy doses	No. of Supportive IV drugs doses	No. of Surgeries	No. of Supplies^
All cancers combined *	650 (232 - 1,195)	24 (19-33)	1,016 (360 - 1,840)	147 (57 - 253)	458 (126 - 911)	2 (1 - 4)	1,343 (559 - 2,231)
I. Leukaemia and related cancers	1,298 (1,057 - 1,656)	29 (24-37)	1,849 (1,360 - 2,506)	257 (197 - 317)	783 (534 - 1,186)	2 (1 - 3)	2,063 (1,558 - 2,822)
Ia. Acute Lymphoblastic Leukaemia	1,246 (1,051 - 1,548)	48 (45-53)	1,810 (1,393 - 2,362)	282 (237 - 331)	711 (519 - 1,038)	2 (1 - 3)	1,978 (1,543 - 2,576)
Ib. Acute Myeloid Leukaemia	1,522 (1,213 - 1,994)	44 (38-52)	2,210 (1,471 - 3,128)	188 (157 - 228)	1,118 (763 - 1,599)	3 (1 - 3)	2,576 (1,764 - 3,704)
Ic. Chronic Myeloid Leukaemia	330 (264 - 1,337)	5 (4-7)	218 (124 - 1,766)	162 (55 - 248)	239 (8 - 831)	2 (1 - 4)	173 (56 - 2,060)
Id. Myelodysplastic Syndrome	1,912 (1,309 - 2,327)	38 (34-44)	2,083 (1,530 -2,734)	169 (83 - 266)	1,134 (942 - 1,567)	2 (2 - 3)	2,918 (2,358 - 3,771)
Ie. JMML	1,498 (905 - 1,989)	29 (20-37)	1,616 (894 - 2,132)	196 (101 - 253)	818 (357 - 1,230)	3 (2 - 5)	2,526 (1,574 - 4,032)
II. Lymphomas	378 (188 - 901)	18 (15-23)	464 (171 - 1,375)	74 (47 - 165)	178 (23 - 6970	2 (1 - 3)	518 (182 - 1,508)
IIa. Hodgkin's lymphoma	193 (164 - 238)	14 (12-15)	179 (128 - 287)	53 (40 - 64)	28 (13 - 74)	1 (1 - 3)	193 (138 - 288)
IIb. Non-Hodgkin lymphoma	867 (612 - 1,282)	25 (21-30)	1,305 (854 - 1,916)	158 (125 - 261)	660 (398 - 1,015)	2 (1 - 3)	1,418 (947 - 2,211)
IIIa-e CNS and Brain Tumours	287 (92 - 539)	20 (16-26)	556 (277 - 1,016)	85 (15 - 135)	264 (109 - 538)	2 (1 - 3)	896 (446 - 1,567)
IV-XII. Other solid tumours	505 (230-907)	1 (1-2)	789 (319 - 1,555)	130 (46 - 232)	334 (93 - 854)	2 (1 - 4)	1,124 (534 - 2,025)
IVa. Neuroblastoma**	941 (494 -1,433)	30 (25-36)	1,417 (738 - 2,165)	202 (135 - 306)	735 (309 - 1,244)	2 (1 - 3)	1,858 (1,014 - 2,943)
V. Retinoblastoma	144 (97 - 218)	5 (4-6)	216 (150 - 344)	43 (37 - 58)	52 (18 - 114)	1 (1 -2)	472 (302 - 710)
VI. Renal Tumours	290 (201 -656)	22 (18-29)	483 (271 - 1,031)	38 (32 - 185)	200 (84 - 491)	1 (1 -2)	753 (485 - 1,568)
VIIa. Hepatoblastoma	615 (508 - 841)	40 (36-47)	786 (562 - 1,102)	90 (71 - 109)	374 (227 - 637)	2 (1 - 3)	1,404 (1,068-1,933)
VIII. Malignant Bone Tumours	725 (513-907)	46 (39 – 53)	1,298 (821-1,916)	209 (121-253)	659 (358-1,197)	3 (1-4)	1,662 (1,160-2,328)
VIIIa. Osteosarcoma	799 (557 - 945)	56 (49-65)	1,716 (1,153 - 2,186)	125 (76 - 177)	1,073 (681 - 1,438)	3 (2 - 5)	1,951 (1,348 - 2,694)
VIIIb. Ewing Sarcoma	642 (483 - 851)	41 (37-46)	948 (725 - 1,390)	250 (233 - 294)	417 (282 - 628)	2 (1 - 3)	1,447 (1,032 - 1,911)
IX. Soft tissue/extra-osseous sarcoma	498 (314-755)	23 (19–27)	860 (425-1,437)	127 (98-180)	284 (117-712)	2 (1-3)	1,028 (589-1,723)
IXa. Rhabdomyosarcoma	520 (351 - 823)	25 (22-29)	985 (488 - 1,597)	127 (105 - 162)	319 (126 - 804)	2 (1 - 3)	1,060 (677 - 1,700)
IXb-d. Other soft tissue tumours	375 (124 - 668)	22 (18-26)	583 (246 - 950)	128 (37 - 58)	221 (98 - 490)	2 (1 - 3)	915 (470 - 1,736)
XI. Germ Cell Tumours	390 (166 - 684)	22 (16-28)	554 (192 - 1,024)	167 (75 - 224)	288 (80 - 526)	1 (1 - 2)	787 (343 - 1,415)
XII. Langerhans cell histocytosis***	228 (140 -319)	21 (17-25)	256 (142 - 459)	32 (22 - 92)	44 (12 - 106)	1 (1 - 2)	294 (176 - 473)

***** For all cancers combined, only the primary tumours were included based on ICCC-3 diagnostic groups excluding (Ia.1.) Precursor cell leukemia – aged <1); (I.e.) Unspecified and other specified leukemia; (VII.b.) Hepatic carcinomas; (XI.) Other malignant epithelial neoplasms and malignant melanomas. ** IVa. Neuroblastoma includes Neuroblastoma and ganglioneuroblastoma. *** XII includes Langerhans's cell histocytosis (LCH) only. ^Supplies include total number of medical supplies (syringes, cannulas, needles, etc.) per patient. during treatment.

Appendix 4.6. Trends in resource use at 1-year post-diagnosis, by year of diagnosis [2013–2017], for all cancers combined, and stratified by ICCC-3 groups (N=8,886)

Resource use measure per ICCC-3 groups	Median (IQR)			% change in coefficient ^	*p*-value*
	Year 2013	Year 2015	Year 2017		
All cancers combined					
LOS (days)	41 (17 – 60)	40 (18 – 63)	36 (17 – 57)	-0.7%	0.303
Inpatient admissions	6 (3 – 9)	6 (3 – 10)	6 (3 – 9)	-0.9%	0.186
Outpatient visits	45 (31 – 61)	44 (28 – 63)	46 (28 – 63)	13.4%	0.111
ED visits	5 (2 – 7)	5 (3 – 8)	5 (3 – 9)	3.9%	<0.001*
Lab tests	534 (191 – 868)	525 (176 – 898)	514 (168 – 878)	-0.5%	0.476
Chemotherapy doses	127 (43 – 181)	132 (54 – 195)	120 (52 – 163)	-3.1%	<0.001*
IV supportive drugs	337 (93 – 600)	411 (122 – 790)	501 (175 – 830)	14.1%	<0.001*
Oral supportive drugs	119 (38 – 263)	338 (123 – 655)	95 (33 – 208)	-16.4%	<0.001*
Supplies	1404 (616 – 2164)	1188 (494 – 1824)	958 (394 – 1382)	-10.5%	<0.001*
Leukaemia and related cancers					
LOS (days)	52 (43 – 69)	52 (37 – 90)	48 (36 – 74)	-0.7%	0.214
Inpatient admissions	7 (6 – 8)	6 (4 – 8)	6 (4 – 8)	-4.2%	<0.001*
Outpatient visits	52 (33 – 64)	60 (35 – 72)	57 (34 – 70)	23.0%	0.004*
ED visits	4 (2 – 7)	6 (3 – 9)	6 (3 – 8)	3.2%	0.003*
Lab tests	896 (750 – 1140)	980 (814 – 1294)	924 (766 – 1214)	0.8%	0.207
Chemotherapy drugs	160 (128 – 189)	184 (156 – 216)	156 (137 – 173)	0.6%	0.449
IV supportive drugs	516 (364 – 745)	710 (464 – 1073)	654 (501 – 947)	7.5%	<0.001*
Oral supportive drugs	254 (165 – 423)	688 (500 – 926)	169 (98 – 310)	-18.6%	<0.001*
Supplies	1960 (1495 – 2856)	1734 (1388 – 2292)	1250 (1046 – 1596)	-11.7%	<0.001*
Acute Lymphoblastic Leukaemia					
LOS (days)	50 (42 – 58)	48 (36 – 60)	44 (34 – 54)	-3.3%	<0.001*
Inpatient admissions	7 (6 – 8)	6 (3 – 8)	6 (4 – 7)	-5.6%	<0.001*
Outpatient visits	58 (48 – 68)	69 (59 – 77)	64 (53 – 74)	13.8%	<0.001*
ED visits	5 (3 – 7)	6 (4 – 10)	6 (4 – 9)	5.1%	<0.001*
Lab tests	858 (750 – 1029)	929 (814 – 1095)	873 (751 – 1058)	-0.1%	0.784
Chemotherapy doses	154 (133 – 182)	187 (164 – 216)	154 (137 – 168)	-0.3%	0.631
IV supportive drugs	450 (351 – 649)	618 (448 – 880)	608 (488 – 812)	8.5%	<0.001*
Oral supportive drugs	236 (157 – 331)	642 (508 – 817)	142 (89 – 228)	-21.1%	<0.001*

Supplies	1816 (1478 – 2422)	1632 (1365 – 1968)	1198 (1034 – 1420)	-11.5%	<0.001*
Acute Myeloid Leukaemia					
LOS (days)	101 (76 -122)	109 (81 – 134)	112 (98 – 134)	7.4%	<0.001*
Inpatient admissions	8 (6 – 11)	8 (5 – 9)	6 (5 – 8)	-2.7%	0.049*
Outpatient visits	27 (20 – 33)	27 (16 – 35)	22 (15 – 27)	-15.4%	0.034
ED visits	3 (2 – 5)	4 (2 – 6)	2 (1 – 4)	-7.1%	0.005*
Lab tests	1262 (1040 – 1674)	1454 (1038 – 1729)	1288 (1070 – 1574)	2.9%	0.034*
Chemotherapy drugs	185 (131 – 211)	181 (132 – 220)	168 (145 – 199)	1.5%	0.361
IV supportive drugs	931 (613 – 1428)	1147 (786 – 1526)	956 (667 – 1212)	2.9%	0.107
Oral supportive drugs	477 (280 – 716)	1054 (700 – 1371)	354 (227 – 564)	-11.9%	<0.001*
Supplies	2874 (2272 – 4460)	2481 (1798 – 3377)	1720 (1436–2190)	-13.3%	<0.001*
Chronic Myeloid Leukaemia					
LOS (days)	29 (16 – 44)	21 (6 – 34)	60 (52 – 68)	-15.8%	0.336
Inpatient admissions	2 (1 – 2)	1 (1 – 2)	5 (4 – 5)	12.5%	0.24
Outpatient visits	24 (21 – 35)	30 (26 – 42)	22 (18 – 29)	-6.5%	0.117
ED visits	5 (1 – 5)	3 (2 – 6)	1 (1 – 2)	-5.6%	0.465
Lab tests	181 (127 – 704)	313 (159 – 755)	159 (138 – 194)	-8.7%	0.179
Chemotherapy doses	86 (78 – 104)	107 (67 – 134)	114 (96 – 131)	-6.2%	0.764
IV supportive drugs	368 (188 – 542)	428 (228 – 549)	1204 (1090 – 1318)	15.8%	0.528
Oral supportive drugs	279 (178 – 342)	404 (269 – 464)	364 (313 – 416)	18.8%	0.231
Supplies	136 (72 – 1484)	318 (42 – 1185)	52 (32 – 92)	-28.1%	0.021*
Myelodysplastic Syndrome					
LOS (days)	93 (49 – 113)	102 (74 – 110)	76 (61 – 96)	8.6%	0.554
Inpatient admissions	6 (2 – 8)	6 (6 – 7)	7 (5 – 8)	9.5%	0.314
Outpatient visits	37 (32 – 38)	40 (31 – 45)	50 (45 – 70)	16.6%	0.031
ED visits	5 (2 – 7)	4 (2 – 12)	8 (4 – 21)	21.5%	0.045
Lab tests	1239 (873 – 1673)	1314 (1228 – 1376)	1542 (1378 – 1689)	10.4%	0.195
Chemotherapy doses	140 (100 – 266)	150 (79 – 156)	170 (168 – 171)	-3.4%	0.765
IV supportive drugs	954 (644 – 1042)	1020 (839 – 2088)	940 (888 – 992)	17.1%	0.306
Oral supportive drugs	477 (258 – 823)	479 (425 – 494)	348 (345 – 372)	-2.9%	0.685
Supplies	2607 (1496 – 3362)	1878 (1464 – 2005)	2329 (1844 – 2368)	-0.1%	0.990
Juvenile myelomonocytic leukemia					

LOS (days)	28 (23 – 57)	38 (22 – 80)	36 (26 – 68)	4.6%	0.548
Inpatient admissions	4 (3 – 5)	3 (3 – 6)	4 (3 – 7)	3.1%	0.683
Outpatient visits	26 (21 – 42)	44 (40 – 49)	36 (29 – 38)	12.3%	0.035*
ED visits	4 (3 – 7)	7 (5 – 7)	6 (4 – 11)	8.4%	0.014*
Lab tests	587 (538 – 1166)	612 (368 – 1486)	892 (484 – 1510)	10.6%	0.247
Chemotherapy doses	76 (56 – 120)	114 (70 – 260)	138 (75 – 201)	7.7%	0.233
IV supportive drugs	335 (161 – 505)	252 (106 – 830)	344 (219 – 982)	9.8%	0.401
Oral supportive drugs	72 (40 – 208)	234 (103 – 683)	96 (51 – 360)	-2.7%	0.809
Supplies	1896 (888 – 2582)	970 (550 – 3984)	943 (576 – 2206)	-7.7%	0.338
Lymphoma					
LOS (days)	45 (28 – 65)	47 (31 – 64)	42 (14 – 61)	-9.7%	<0.001*
Inpatient admissions	7 (5 – 9)	7 (4 – 10)	6 (2 – 9)	-2.9%	0.151
Outpatient visits	35 (26 – 43)	34 (26 – 45)	34 (27 – 42)	27.3%	0.016*
ED visits	3 (2 – 6)	4 (2 – 6)	4 (2 – 6)	1.7%	0.018*
Lab tests	324 (134 – 784)	353 (138 – 799)	181 (126 – 723)	-3.1%	0.003*
Chemotherapy doses	53 (32 – 156)	65 (52 – 158)	72 (52 – 139)	4.1%	0.22
IV supportive drugs	91 (24 – 473)	228 (23 – 657)	90 (14 – 617)	1.8%	0.822
Oral supportive drugs	88 (10 – 262)	248 (42 – 555)	66 (6 – 152)	-25.1%	<0.001*
Supplies	521 (181 – 1692)	488 (150 – 1449)	275 (148 – 955)	-10.6%	<0.001*
Hodgkin's lymphoma					
LOS (days)	8 (7 – 26)	6 (2 – 18)	4 (3 – 7)	-23.7%	0.001*
Inpatient admissions	2 (1 – 3)	1 (1 – 3)	2 (1 – 2)	-8.7%	0.038*
Outpatient visits	35 (31 – 41)	36 (30 – 42)	34 (29 – 40)	-17.8%	0.695
ED visits	2 (1 – 4)	3 (2 – 5)	3 (1 – 5)	0.1%	0.992
Lab tests	134 (113 – 160)	140 (120 – 168)	133 (112 – 163)	-1.3%	0.206
Chemotherapy doses	34 (26 – 42)	53 (40 – 60)	60 (48 – 70)	11.8%	<0.001*
IV supportive drugs	24 (16 – 32)	24 (12 – 67)	18 (8 – 56)	6.5%	0.082
Oral supportive drugs	44 (22 – 51)	40 (33 – 82)	28 (14 – 38)	-38.7%	0.438
Supplies	180 (131 – 262)	155 (113 – 209)	170 (116 – 230)	-2.6%	0.149
Non-Hodgkin lymphoma					
LOS (days)	46 (33 – 67)	52 (38 – 70)	48 (35 – 70)	-0.8%	0.704
Inpatient admissions	7 (5 – 9)	8 (6 – 10)	7 (6 – 10)	2.3%	0.190
Outpatient visits	34 (23 – 50)	31 (24 – 52)	33 (24 – 48)	17.5%	0.037*
ED visits	4 (2 – 6)	4 (3 – 7)	5 (3 – 8)	5.0%	0.019*
Lab tests	764 (502 – 1130)	784 (599 – 1016)	792 (533 – 1093)	1.2%	0.452
Chemotherapy doses	154 (109 – 189)	154 (132 – 206)	143 (117 – 182)	0.6%	<0.722
IV supportive drugs	450 (297 – 868)	614 (368 – 832)	678 (435 – 938)	9.9%	0.002*
Oral supportive drugs	136 (66 – 297)	544 (386 – 740)	112 (66 – 217)	-13.6%	<0.001*

Supplies	1609 (1039 – 2810)	1377 (958 – 1930)	1004 (716 – 1403)	-12.1%	<0.001*
Brain Tumours					
LOS (days)	19 (9 – 38)	21 (11 – 38)	17 (8 – 31)	-1.6%	0.375
Inpatient admissions	3 (2 – 7)	3 (2 – 6)	3 (2 – 7)	-0.4%	0.752
Outpatient visits	39 (20 – 70)	38 (19 – 64)	32 (19 – 56)	-12.4%	0.043*
ED visits	4 (2 – 7)	5 (2 – 8)	5 (2 – 8)	3.6%	0.024*
Lab tests	213 (69 – 462)	236 (85 – 410)	152 (74 – 370)	-4.1%	0.028*
Chemotherapy doses	70 (13 – 119)	58 (11 – 91)	50 (3 – 84)	-15.0%	<0.001*
IV supportive drugs	230 (102 – 465)	267 (121 – 525)	288 (120 – 639)	10.9%	<0.001*
Oral supportive drugs	84 (39 – 174)	195 (82 – 438)	38 (14 – 90)	-28.3%	<0.001*
Supplies	906 (581 – 1851)	896 (397 – 1439)	662 (333 – 1100)	-12.3%	<0.001*
Surgeries	2 (1 – 3)	2 (1 – 3)	2 (1 – 3)	-1.7%	0.092
Other solid tumours					
LOS (days)	28 (10 – 58)	34 (13 – 61)	29 (11 – 55)	2.1%	0.062
Inpatient admissions	6 (2 – 12)	7 (3 – 13)	6 (2 – 12)	2.7%	0.004*
Outpatient visits	48 (37 – 61)	44 (33 – 58)	49 (35 – 61)	-10.3%	0.088
ED visits	5 (3 – 8)	5 (3 – 8)	6 (4 – 10)	5.5%	<0.001*
Lab tests	382 (189 – 680)	406 (180 – 729)	402 (196 – 702)	0.8%	0.008*
Chemotherapy doses	116 (41 – 201)	122 (44 – 200)	102 (42 – 163)	-4.0%	<0.001*
IV supportive drugs	195 (59 – 504)	293 (86 – 692)	410 (141 – 834)	24.3%	<0.001*
Oral supportive drugs	56 (15 – 138)	239 (101 – 432)	63 (20 – 153)	-9.8%	<0.001*
Supplies	1182 (564 – 1836)	1000 (471 – 1658)	815 (368 – 1355)	-9.4%	<0.001*
Neuroblastoma					
LOS (days)	53 (18 – 71)	50 (25 – 69)	49 (27 – 66)	3.5%	0.092
Inpatient admissions	11 (4 – 14)	10 (5 – 15)	11 (6 – 14)	3.6%	0.077
Outpatient visits	50 (43 – 59)	48 (32 – 59)	50 (40 – 60)	-24.9%	0.237
ED visits	8 (5 – 10)	6 (4 – 9)	8 (6 -1 3)	3.5%	0.034*
Lab tests	738 (410 – 1032)	766 (419 – 1002)	756 (501 – 998)	0.8%	0.661
Chemotherapy doses	194 (145 – 240)	195 (128 – 265)	156 (114 – 196)	-6.2%	<0.001*
IV supportive drugs	460 (206 – 700)	620 (291 – 946)	866 (556 – 1201)	21.4%	<0.001*
Oral supportive drugs	109 (56 – 222)	358 (230 – 542)	96 (46 – 224)	-12.8%	<0.001*
Supplies	1808 (1140 – 2398)	1581 (939 – 2215)	1373 (842 – 1760)	-7.8%	<0.001*
Surgeries	1 (1 – 2)	2 (1 – 2)	2 (1 – 2)	-0.5%	0.706
Retinoblastoma					
LOS (days)	15 (3 – 38)	6 (4 – 25)	5 (3 – 14)	-7.1%	0.353
Inpatient admissions	4 (1 – 7)	2 (1 – 7)	2 (1 – 5)	-5.9%	0.314
Outpatient visits	36 (30 – 42)	36 (26 – 44)	33 (27 – 33)	-15.4%	0.026
ED visits	4 (2 – 6)	4 (2 – 7)	4 (2 – 7)	3.0%	0.28

Lab tests	104 (82 – 178)	132 (92 – 198)	118 (80 – 175)	-3.7%	0.144
Chemotherapy doses	36 (31 – 44)	43 (38 – 56)	40 (36 – 44)	-1.9%	0.212
IV supportive drugs	20 (11- 50)	64 (22 – 139)	55 (24 – 116)	31.7%	<0.001*
Oral supportive drugs	10 (8 – 13)	74 (57 – 126)	5 (2 – 11)	-19.0%	<0.001
Supplies	451 (339 – 604)	398 (280 – 605)	240 (174 – 332)	-18.2%	<0.001*
Surgeries	7 (5 – 8)	8 (6 – 10)	8 (6 – 10)	3.1%	0.035*
Renal Tumours					
LOS (days)	10 (8 – 18)	14 (8 – 26)	16 (9 – 29)	5.0%	0.049
Inpatient admissions	1 (1 – 4)	2 (1 – 4)	3 (1 – 5)	6.1%	0.029*
Outpatient visits	43 (33 – 51)	38 (30 – 46)	47 (39 – 54)	13.2%	0.136
ED visits	4 (2 – 6)	4 (3 – 7)	6 (3 – 9)	6.1%	0.018*
Lab tests	216 (134 – 388)	211 (144 – 382)	280 (191 – 526)	7.2%	0.003*
Chemotherapy	33 (26 – 163)	36 (31 – 131)	35 (32 – 140)	-2.1%	0.444
IV supportive drugs	77 (50 – 206)	117 (74 – 255)	246 (141 – 550)	30.3%	<0.001*
Oral supportive doses	32 (18 – 54)	189 (79 – 337)	35 (15 – 97)	-13.6%	0.002*
Supplies	785 (554 – 1396)	608 (462 – 1133)	614 (420 – 1081)	-4.9%	0.020*
Surgeries	1 (1 – 1)	1 (1 – 1)	1 (1 – 2)	1.7%	0.137
Hepatoblastoma					
LOS (days)	26 (16 – 34)	42 (28 – 60)	34 (24 – 52)	11.8%	0.002*
Inpatient admissions	7 (4 – 8)	11 (8 – 13)	10 (7 – 13)	12.7%	<0.001*
Outpatient visits	42 (34 – 53)	48 (36 – 56)	53 (50 – 60)	23.3%	<0.001*
ED visits	5 (2 – 8)	5 (4 – 8)	9 (6 – 11)	17.1%	<0.001*
Lab tests	472 (355 – 539)	602 (418 – 790)	496 (428 – 675)	8.3%	0.004*
Chemotherapy doses	83 (42 – 102)	95 (83 – 126)	76 (61 – 84)	1.8%	0.555
IV supportive drugs	160 (99 – 206)	336 (250 – 511)	392 (291 – 580)	32.1%	<0.001*
Oral supportive drugs	78 (49 – 135)	273 (137 – 430)	79 (38 – 108)	-3.8%	0.548
Supplies	1121 (693 – 1618)	1500 (1109 – 2060)	1269 (948 – 1566)	2.9%	0.464
Surgeries	1 (1 – 1)	1 (1 – 2)	1 (1 – 2)	3.2%	0.288
Osteosarcoma					
LOS (days)	64 (51 – 72)	75 (60 – 87)	57 (35 – 66)	-4.3%	0.074
Inpatient admissions	16 (13 – 17)	16 (13 – 20)	14 (10 – 17)	-3.2%	0.120
Outpatient visits	54 (46 – 67)	50 (39 – 64)	49 (44 – 57)	-26.1%	0.010
ED visits	5 (3 – 7)	4 (2 – 6)	7 (3 – 10)	8.1%	0.020
Lab tests	618 (462 – 674)	668 (548 – 798)	541 (434 – 657)	-0.9%	0.648
Chemotherapy doses	120 (94 – 151)	148 (116 – 186)	70 (53 – 83)	-16.6%	<0.001*
IV supportive drugs	684 (458 – 894)	965 (779 – 1306)	908 (622 – 1122)	7.5%	0.007*
Oral supportive drugs	132 (93 – 286)	345 (208 – 500)	174 (115 – 352)	5.8%	0.105
Supplies	1668 (1402 – 1985)	1638 (1210 – 2010)	1174 (951 – 1451)	-9.3%	<0.001*

Surgeries	2 (2 – 3)	2 (2 – 4)	3 (2 – 4)	4.9%	0.042*
Ewing Sarcoma					
LOS (days)	16 (9 – 28)	24 (10 – 50)	24 (9 – 43)	9.9%	0.029*
Inpatient admissions	3.5 (2 – 5)	6 (3 – 13)	5 (3 – 9)	11.9%	0.002*
Outpatient visits	66 (55 – 78)	63 (51 – 74)	71 (65 – 81)	17.3%	0.114
ED visits	5 (3 – 8)	4 (2 – 7)	6 (4 – 10)	7.1%	0.031*
Lab tests	381 (265 – 494)	530 (372 – 702)	502 (404 – 671)	6.4%	<0.001*
Chemotherapy doses	244 (201 – 298)	220 (199 – 250)	204 (188 – 227)	-3.1%	0.002*
IV supportive drugs	176 (76 – 281)	279 (208 – 377)	456 (284 – 670)	27.0%	<0.001*
Oral supportive drugs	48 (26 – 108)	161 (78 – 306)	68 (28 – 153)	-3.1%	0.522
Supplies	1179 (864 – 1566)	1153 (792 – 1424)	1127 (828 – 1380)	-5.4%	0.001*
Surgeries	1 (1 – 2)	1 (1 – 2)	2 (1 – 3)	7.6%	0.003*
Rhabdomyosarcoma					
LOS (days)	9 (7 – 23)	17 (8 – 32)	14 (6 – 23)	1.0%	0.904
Inpatient admissions	2 (2 – 4)	4 (2 – 9)	3 (2 – 5)	2.0%	0.576
Outpatient visits	68 (61 – 78)	66 (58 – 75)	70 (59 – 76)	-25.0%	0.856
ED visits	6 (2 – 9)	6 (4 – 8)	6 (3 – 10)	6.6%	0.046*
Lab tests	348 (259 – 475)	372 (260 – 514)	380 (272 – 554)	3.8%	0.061
Chemotherapy doses	74 (62 – 88)	112 (98 – 131)	114 (100 – 132)	8.6%	<0.001*
IV supportive drugs	120 (92 – 214)	188 (59 – 356)	410 (130 – 665)	27.3%	<0.001*
Oral supportive drugs	26 (9 – 62)	56 (18 – 84)	20 (5 – 44)	-23.6%	<0.001*
Supplies	1028 (495 – 1499)	846 (550 – 1364)	615 (462 – 889)	-7.6%	0.002*
Surgeries	1 (1 – 2)	1 (1 – 2)	1 (1 – 2)	1.7%	0.528
Other soft tissue tumours					
LOS (days)	38 (25 – 51)	31 (8 – 55)	17 (11 – 43)	-9.8%	0.195
Inpatient admissions	8 (6 – 11)	6 (2 – 10)	3 (2 – 8)	-13.9%	0.042*
Outpatient visits	47 (44 – 51)	35 (22 – 42)	36 (29 – 43)	-16.2%	0.309*
ED visits	6 (4 – 7)	5 (2 – 8)	6 (3 – 8)	-0.8%	0.901
Lab tests	550 (343 – 586)	281 (126 – 606)	170 (65 – 413)	-19.0%	0.010*
Chemotherapy doses	164 (89 – 208)	102 (32 – 152)	84 (38 – 146)	-12.6%	0.184
IV supportive drugs	267 (133 – 407)	304 (102 – 450)	337 (216 – 416)	10.7%	0.221
Oral supportive drugs	45 (36 – 72)	195 (123 – 320)	68 (20 – 197)	-7.1%	0.498
Supplies	1572 (850 – 1747)	727 (422 – 1503)	550 (304 – 1091)	-23.7%	0.005*
Surgeries	1 (1 – 3)	2 (1 – 3)	2 (1 – 2)	0.7%	0.860
Germ Cell Tumours					
LOS (days)	37 (28 – 54)	38 (14 – 62)	24 (10 – 40)	-4.8%	0.406
Inpatient admissions	7 (6 – 8)	7 (4 – 10)	5 (1 – 7)	-8.4%	0.082
Outpatient visits	27 (20 – 32)	25 (18 – 30)	25 (16 – 35)	21.6%	0.697

ED tests	4 (2 – 6)	4 (3 - 6)	3 (3 – 6)	3.4%	0.482
Lab tests	401 (276 – 640)	406 (185 – 654)	262 (96 – 483)	-7.1%	0.183
Chemotherapy doses	172 (126 – 227)	176 (93 – 240)	93 (42 – 129)	-17.0%	0.012*
IV supportive drugs	292 (162 – 468)	322 (174 – 571)	363 (183 – 688)	15.2%	0.038*
Oral supportive drugs	76 (49 – 134)	170 (97 – 346)	50 (22 – 192)	-13.5%	0.056
Supplies	1067 (718 – 1519)	1080 (315 – 1492)	541 (300 – 978)	-11.4%	0.028*
Surgeries	1 (1 – 2)	1 (1 – 2)	1 (1 – 2)	<0.1%	0.986
Langerhans cell histiocytosis					
LOS (days)	6 (1 – 19)	16 (8 – 45)	5 (3 – 10)	-10.6%	0.445
Inpatient admissions	1 (1 – 3)	2 (1 – 5)	2 (1 – 2)	-4.4%	0.557
Outpatient visits	46 (32 - 56)	48 (21 – 57)	45 (33 – 55)	-10.1%	0.909
ED visits	3 (1 – 5)	4 (2 – 6)	3 (1 – 6)	4.6%	0.355
Lab tests	187 (163 – 222)	170 (126 – 214)	179 (126 – 228)	-4.2%	0.363
Chemotherapy doses	27 (22 – 33)	21 (18 – 28)	20 (16 – 26)	-8.2%	0.019*
IV supportive drugs	11 (6 – 204)	22 (10 – 60)	50 (20 – 96)	37.1%	0.003*
Oral supportive drugs	55 (3 – 79)	123 (74 – 283)	2 (2 – 22)	-46.3%	<0.001*
Supplies	268 (185 – 404)	230 (145 – 367)	235 (135 – 377)	-10.8%	0.038*
Surgeries	1 (1 – 1)	1 (1 – 1)	1 (1 – 1)	-0.2%	0.906

^ Coefficient of trend obtained from linear regression model with 'Year of diagnosis" as independent variable and log-transformed total costs as outcome variable. % change in coefficient obtained by multiplying anti-log of coefficient by 100. * Statistically significant at $p<0.05$.

Appendix 4.7. Mean (± SD) total costs (USD) for childhood cancers at 1- and 3-years post-diagnosis (N=8,886)

ICCC-3 group	Mean (± SD)	
	1-year post-diagnosis	3 years post-diagnosis
All cancers combined *	$ 17,178 (± 13,532)	$24,232 (± 19,703)
I. Leukaemia and related cancers	23,736 (14,835)	35,185 (21,898)
Ia. Acute Lymphoblastic Leukaemia	$24,299 (± 10,594)	$36,793 (± 18,059)
Ib. Acute Myeloid Leukaemia	$38,477 (± 19,648)	$47,886 (± 28,501)
Ic. Chronic Myeloid Leukaemia	$14,927 (± 13,424)	$35,483 (± 29,418)
Id. Myelodysplastic Syndrome	$31,453 (± 13,983)	$43,853 (± 18,727)
Ie. Juvenile myelomonocytic leukaemia	$22,027 (± 12,292)	$35,318 (± 20,267)
II. Lymphomas	7,542 (12,382)	10,803 (17,404)
IIa. Hodgkin's lymphoma	$5,540 (± 4,594)	$8,739 (± 9,757)
IIb. Non-Hodgkin’s lymphoma	$21,172 (± 13,174)	$26,891 (± 18,991)
III. Brain Tumours	$10,525 (± 8,450)	$14,994 (± 11,879)
IV-X. Other solid tumours	12,601 (11,014)	16,882 (15.965)
IVa. Neuroblastoma**	$20,411 (± 12,498)	$28,124 (± 17,992)
V. Retinoblastoma	$6,360 (± 4,813)	$8,963 (± 6,604)
VI. Renal Tumours	$10,865 (± 7,818)	$15,552 (± 12,421)
VIIa. Hepatoblastoma	$14,661 (± 6,858)	$18,906 (± 8,617)
VIII. Malignant bone tumours	22,272 (9,115)	30,277 (13,801)
VIIIa. Osteosarcoma	$25,045 (± 10,560)	$33,840 (± 15,395)
VIIIb. Ewing sarcoma	$21,455 (± 6,899)	$30,766 (± 11,735)
IX. Soft tissue/extra osseous sarcoma	11,989 (7,637)	16,401 (12,787)
IXa. Rhabdomyosarcoma	$13,516 (± 7,033)	$20,483 (± 12,504)
IXb-d. Other soft tissue tumours	$13,050 (± 9,002)	$17,550 (± 13,290)
Xa-c. Germ Cell Tumours	$10,835 (± 7,990)	$13,600 (± 10,892)
XII. Langerhans cell histiocytosis ***	$6,804 (± 6,812)	$9,577 (± 9,381)

***** For all cancers combined, only the primary tumours were included based on ICCC-3 diagnostic groups excluding (Ia.1.) Precursor cell leukaemia – aged <1); (I.e.) Unspecified and other specified leukaemia; (VII.b.) Hepatic carcinomas; (XI.) Other malignant epithelial neoplasms and malignant melanomas. ** IVa. Neuroblastoma includes ganglioneuroblastoma. *** Hepatic tumours included Hepatoblastoma only. **** XII includes Langerhans cell histiocytosis only.

Appendix 4.8. Total cumulative costs and percent of main cost categories from total costs (USD) at 1-year post-diagnosis, for all cancers combined and by ICCC-3 groups, (N=8,886).

ICCC-3 group	Cost categories (% of cost category from sum of total cost)				Sum of Total costs (100%)
	Personnel costs	Investigation costs	Treatment costs	Overhead costs	
All cancers combined *	55,301,092 (36.3%)	13,521,455 (8.8%)	41,912,497 (27.5%)	41,718,368 (27.4%)	$152,453,412
I. Leukaemia/related cancers	21,765,824 (33.8%)	6,249,775 (9.7%)	19,892,199 (30.9%)	16,419,832 (25.5%)	$64,327,630
Ia. Acute Lymphoblastic Leukaemia	14,855,399 (36.8%)	392,5879 (9.7%)	10,346,817 (25.7%)	11,206,704 (27.8%)	$40,334,799
Ib. Acute Myeloid Leukaemia	6,155,276 (29.4%)	1,928,725 (9.2%)	8,180,935 (39.2%)	4,643,454 (22.2%)	$20,908,389
Ic. Chronic Myeloid Leukaemia	165,280 (14.4%)	152,384 (13.3%)	706,996 (61.5%)	124,685 (10.8%)	$1,149,344
Id. Myelodysplastic Syndrome	253,927 (28.8%)	110,159 (12.5%)	325,025 (36.9%)	191,559 (21.8%)	$880,672
Ie. JMML	335,943 (31.9%)	132,628 (12.6%)	332,425 (31.5%)	253,430 (24.0%)	$1,054,426
II. Lymphomas	6,017,707 (34.7%)	1,882,951 (10.8%)	4,889,548 (28.2%)	4,539,674 (26.2%)	$17,329,880
IIa. Hodgkin's lymphoma	1,329,743 (34.0%)	575,112 (14.7%)	1,008,754 (25.8%)	1,003,139 (25.6%)	$3,916,748
IIb. Non-Hodgkin lymphoma	4,687,965 (35.0%)	1,307,839 (9.8%)	3,880,794 (28.9%)	3,536,535 (26.4%)	$13,413,132
IIIa-e CNS and Brain Tumours	6,967,462 (39.9%)	1,096,718 (6.3%)	4,120,566 (23.6%)	5,256,155 (30.1%)	$17,440,901
IV-XII. Other solid tumours	20,550,098 (38.5%)	4,292,012 (8.1%)	13,010,185 (24.3%)	15,502,706 (29.1%)	$53,355,001
IVa. Neuroblastoma**	7,544,236 (38.3%)	1,743,353 (8.8%)	4,735,978 (24.0%)	5,691,266 (28.9%)	$19,714,834
V. Retinoblastoma	1,358,326 (40.8%)	215,053 (6.5%)	728,018 (21.9%)	1,024,702 (30.8%)	$3,326,099
VI. Renal Tumours	2,357,073 (41.6%)	456,776 (8.1%)	1,067,377 (18.8%)	1,778,143 (31.5%)	$5,659,369
VIIa. Hepatoblastoma	778,959 (43.6%)	158,860 (8.9%)	261,532 (14.6%)	587,636 (32.9%)	$1,786,987
VIII. Malignant Bone Tumours	4,941,480 (35.3%)	821,777 (5.9%)	4,494,720 (32.1%)	3,727,783 (26.7%)	$13,985,760
VIIIa. Osteosarcoma	2,719,439 (35.7%)	454,668 (6.1%)	2,388,046 (31.3%)	2,051,507 (26.9%)	$7,613,659
VIIIb. Ewing Sarcoma	2,222,041 (34.9%)	367,109 (5.8%)	2,106,674 (33.1%)	1,676,277 (26.3%)	$6,372,101
IX. Soft tissue/extra-osseous sarcoma	2,368,358 (39.9%)	554,444 (9.3%)	1,219,585 (20.5%)	1,786,656 (30.3%)	$5,929,043
IXa. Rhabdomyosarcoma	1,744,156 (40.7%)	419,888 (9.8%)	804,963 (18.8%)	1,315,767 (30.7%)	$4,284,774
IXb-d. Other soft tissue tumours	624,202 (38.0%)	134,555 (8.2%)	414,623 (25.2%)	470,889 (28.6%)	$1,644,269
XI. Germ Cell Tumours	670,732 (41.5%)	157,205 (9.7%)	280,414 (17.4%)	505,991 (31.3%)	$1,614,341
XII. Langerhans cell histiocytosis***	530,934 (39.7%)	184,545 (13.8%)	222,560 (16.6%)	400,529 (29.9%)	$1,338,568

* For all cancers combined, only the primary tumours were included based on ICCC-3 diagnostic groups excluding (Ia.1.) Precursor cell leukaemia – aged <1); (I.e.) Unspecified and other specified leukaemia; (VII.b.) Hepatic carcinomas; (XI.) Other malignant epithelial neoplasms and malignant melanomas. ** IVa. Neuroblastoma includes ganglioneuroblastoma. *** XII includes LCH (Langerhans cell histiocytosis) only. **Abbreviations:** RTH: Radiotherapy.

Appendix 4.9. Trends in cost categories (USD) at 1-year post-diagnosis, per ICCC-3 groups, by year of diagnosis (N=8,886)

Cancer Type	Cost Category	Median cost (IQR)			% change in coefficient ^	*p*-value*
		Year 2013	Year 2015	Year 2017		
All Cancers Combined	Personnel costs	5,433 (2,218 – 8,383)	5,865 (2,570 – 9,625)	5,055 (2,371 – 7,441)	2.4%	<0.001*
	Investigation costs	10,848 (5,949 – 17,661)	11,465 (5,721 – 19,410)	14,345 (6,368 – 23,369)	-18.2%	<0.001*
	Treatment costs	21,637 (9,825 – 44,526)	22,385 (9,709 – 54,736)	39,630 (13,702 – 82,814)	-12.3%	<0.001*
	Overhead costs	4,099 (1,673 – 6,324)	4,424 (1,939 – 7,261)	3,813 (1,789 – 5,613)	2.1%	<0.001*
Leukaemia	Personnel costs	8,247 (6,769 – 10,304)	9,646 (7643 – 12,004)	7,468 (6315 – 8,853)	0.2%	0.657
	Investigation costs	2,936 (2,423 – 3,711)	2,906 (2,349 – 3,863)	1,480 (1,240 – 1,890)	-15.6%	<0.001*
	Treatment costs	6,506 (3,756 – 14,890)	6,486 (3,599 – 13,076)	3,961 (2,443 – 8,037)	-12.7%	<0.001*
	Overhead costs	6,221 (5107 – 7,773)	7,277 (5,766 – 9,056)	5,634 (4,764 – 6,678)	0.1%	0.865
Lymphoma	Personnel costs	2,067 (1,153 – 6,390)	3,286 (1,560 – 7,627)	2,022 (1434 – 5,371)	2.5%	0.124
	Investigation costs	1,432 (925 – 2,358)	1,376 (815 – 2,340)	518 (388 – 1,090)	-18.8%	<0.001*
	Treatment costs	2,275 (1,355 – 5,676)	1,926 (983 – 5,434)	773 (490 – 3,100)	-19.2%	<0.001*
	Overhead costs	1,559 (870 – 4,820)	2,479 (1,177 – 5,754)	1,526 (1082 – 4,052)	1.9%	0.189
Brain Tumours	Personnel costs	3,496 (1,520 – 5,840)	3,237 (1,497 – 5,851)	2,868 (1,655 – 4,698)	4.1%	0.020*
	Investigation costs	842 (344 – 1,414)	584 (266 – 953)	266 (145 – 513)	-21.9%	<0.001*
	Treatment costs	2,339 (1,170 – 4,195)	1,623 (958 – 2,756)	1,369 (778 – 2,489)	-8.8%	<0.001*
	Overhead costs	2,638 (1,147 – 4,406)	2,442 (1,130 – 4,414)	2,164 (1,249 – 3,544)	3.6%	0.021
Other Solid Tumours	Personnel costs	4,384 (2,216 – 7,765)	5,347 (2,776 – 8,902)	4,548 (2,583 – 6,804)	3.4%	0.001*
	Investigation costs	1,468 (849 – 2,167)	1,238 (635 – 1,930)	697 (340 – 1,043)	-18.8%	<0.001*
	Treatment costs	2,556 (1,68 – 5,964)	2,377 (1,025 – 6,401)	1,903 (634 – 4,884)	-9.5%	<0.001*
	Overhead costs	3,307 (1,672 – 5,858)	4,034 (2,094 – 6,715)	3,431 (1,948 – 5,133)	3.1%	0.002*

^

Coefficient of trend obtained from OLS linear regression model with 'Year of diagnosis" as independent variable and log-transformed total costs as outcome variable. % change in coefficient obtained by multiplying anti-log of coefficient by 100. * Statistically significant at $p<0.05$.

Appendix 4.10. Contribution of resource use measures to total costs (USD) at 1-year post-diagnosis for the 4 main childhood cancer groups, (N=8,886)

Predictor variable	SD	% change in coefficient* [95% CI]		*p-value* ˜	Adjusted R^2 (Overall *p*-value of the model ˜)
		Standardized coefficients**	Unstandardized coefficients***		
Leukaemia (n=2,357)					
Gender					Adjusted R^2 = 0.752 (p<0.001˜)
Female	--	Ref. group	Ref. group		
Male		-0.5% [-2.5 – 1.4%]	-0.5% [-2.5 – 1.4%]	0.570	
Age at diagnosis (yrs)	4.5	8.4% [7.3 – 9.6%]	1.8% [1.5 – 2.1%	<0.001˜	
Year of diagnosis	--	-10.6% [-11.7 – -9.4%]	-7.5% [-8.3 – -6.7%]	<0.001˜	
LOS (weeks)	5.3	24.8% [21.2 – 28.5%]	4.2% [3.6 – 4.8%]	<0.001˜	
Inpatient admissions	3	0.8% [-0.5 – 2.3%]	-0.1% [-0.2 – 0.7%]	0.240	
Outpatient visits	23	12.0% [10.3 – 13.7%]	0.4% [0.3 – 0.5%]	<0.001˜	
Lab tests (x 100)	4	9.4% [6.1 – 12.9%]	2.1% [1.3 – 2.8%]	<0.001˜	
Supplies (x 100)	11	-4.1% [-5.8 – -2.4%]	-0.3% [-0.5 – -0.2%]	<0.001˜	
Chemotherapy doses (x10)_	51	5.8% [4.4 – 7.4%]	1.1% [0.8 -1.4%]	<0.001˜	
Supportive IV (x 100)	5	10.6% [8.2 – 13.0%]	2.1% [1.7 – 2.6%]	<0.001	
PICU admission					
No	--	Ref. group	Ref. group		
Yes		0.2% [-1.9 – 2.5%]	0.2% [-1.9 – 2.5%]	0.830	
Lymphoma (n=1,344)					
Gender					Adjusted R^2 = 0.807 (p<0.001˜)
Female	--	Ref. group	Ref. group	0.191	
Male		-2.9% [-7.1 – 1.5%]	-2.9% [-7.1 – 1.5%]		
Age at diagnosis (yrs)	4.3	4.5% [2.3 – 6.7%]	1.0% [0.5 – 1.5%]	<0.001˜	
Year of diagnosis	--	-9.4% [-11.6 – -7.1%]	-6.7% [-8.4 – -5.1%]	<0.001˜	
LOS (weeks)	4.5	10.3% [3.0 – 18.1%]	2.2% [0.6 – 3.7%]	0.004˜	
Inpatient admissions	4	10.2% [5.3 – 14.8%]	2.3% [1.2 – 3.4%]	<0.001˜	
Outpatient visits	22	12.3% [10.1 – 14.6%]	0.6% [0.5 – 0.7%]	<0.001˜	
Lab tests (x 100)	4	30.5% [21.5 – 40.2%]	6.1% [4.4 – 7.8%]	<0.001˜	
Supplies (x 100)	11	11.2% [-7.5 – -0.1%]	-0.3% [-0.7 – -0.01]	0.040˜	
Chemotherapy doses (x10)	70	4.1% [0.4 – 8.1%]	0.5% [0.05 – 1.1%]	0.029˜	
Supportive IV (x 100)	5	11.2% [6.0 – 16.5%]	2.1% [1.1- 2.9%]	<0.001˜	
PICU admission					
No	--	Ref. group	Ref. group		
Yes		1.7% [-2.8 – 6.5%]	1.7% [-2.8 – 6.5%]	0.461	
Brain tumours (n=1,659)					
Gender					Adjusted R^2 = 0.694 (p<0.001˜)
Female	--	Ref. group	Ref. group	0.080	
Male		-3.8% [-7.9 – 0.4%]	-3.8% [-7.9 – 0.4%]		
Age at diagnosis (yrs)	4.2	6.1% [3.8 – 8.5%]	1.4% [0.8 – 1.9%]	<0.001˜	
Year of diagnosis	--	0.9% [-1.4 – 3.3%]	0.6% [-1.0 – 2.4%]	0.452	
LOS (weeks)	3.7	24.9% [17.6 – 32.7%]	6.4% [4.6 – 8.2%	<0.001˜	
Inpatient admissions	4	2.4% [-1.2 – 6.3%]	0.6% [-0.3 – 1.6%]	0.202	
Outpatient visits	26	28.1% [24.5 – 31.5%]	0.9% [0.8 – 1.0%]	<0.001˜	
Lab tests (x 100)	4	-0.9% [-5.6 – 4.1%]	-0.2% [-1.7 – 1.2%]	0.711	
Supplies (x 100)	13	9.1% [3.3 – 15.3%]	0.6% [0.2 – 1.1%]	0.001˜	
Chemotherapy doses (x10)	56	10.8% [7.3 – 14.4%]	1.8% [1.2 – 2.4%]	<0.001˜	

Supportive IV (x 100)	5	8.1% [4.1 – 12.2%]	1.5% [0.8 – 2.2%]	<0.001˜	
PICU admission No Yes	--	Ref. group 14.3% [8.1 – 20.9%]	Ref. group 14.3% [8.1 – 20.9%]	<0.001˜	
Predictor variable	**SD**	**% change in coefficient* [95% CI]**		***p*-value ˜**	**Adjusted R^2 (Overall *p*-value of the model ˜)**
		Standardized coefficients**	Unstandardized coefficients***		
Other Solid tumours (n=3,526)					
Gender Female Male	--	Ref. group 2.2% [0.2 – 4.3%]	Ref. group 2.2% [0.2 – 4.3%]	0.031˜	
Age at diagnosis (yrs)	4.8	6.2% [6.1 – 8.3%]	1.5% [1.2 – 1.7%]	<0.001˜	
Year of diagnosis	--	-0.4% [-1.5 – 0.7%]	-0.2% [-1.1 – 0.5%]	0.486	
LOS (weeks)	4.3	19.0% [14.8 – 15.6%]	4.1% [3.2 – 5.0%]	<0.001˜	
Inpatient admissions	6	11.3% [8.7 – 14.0%]	1.8% [1.4 – 2.2%]	<0.001˜	
Outpatient visits	19	17.5% [16.0 – 19.0%]	0.8% [0.7 – 0.9%]	<0.001˜	
Lab tests (x 100)	4	12.1% [8.7 – 15.6%]	3.0% [2.1 – 3.8%]	<0.001˜	
Supplies (x 100)	10	0.4% [-1.7 – 2.7%]	0.05% [-0.2 – 0.2%]	0.677	
Chemotherapy doses (x10)	81	15.8% [14.3 – 17.4%]	1.8% [1.6 – 1.9%]	<0.001˜	
Supportive IV (x 100)	6	2.0% [0.3 – 3.7%]	0.3% [0.06 – 0.6%]	0.018˜	
PICU admission No Yes	--	Ref. group 4.5% [2.2 – 6.8%]	Ref. group 4.5% [2.2 – 6.8%]	<0.001˜	

Adjusted R^2 = 0.816 (p<0.001˜)

*Coefficient obtained from multivariable OLS linear regression with total cost in US$ (log-transformed).
** Standardized coefficients are interpreted in terms of SD (standard deviation) units of the predictor variables as follows; an increase in SD units of the predictor variable results, on average, in an increase of β1 in total costs. *** Unstandardized coefficients are expressed in natural units.
˜ Statistically significant at *p*-value <0.005. Abbreviations: PICU: Paediatric Intensive Care Unit.

Appendix Chapter 5

Appendix 5.1. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 checklist

Section/item	Item No.	Section/item	Location in thesis where items are reported
Title and abstract			
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	Page 157
Abstract	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Page 6
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Page 157, 158
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	NA
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Page 159
Setting and location	6	Provide relevant contextual information that may influence findings.	Page 159
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Page 162
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Page 161
Time horizon	9	State the time horizon for the study and why appropriate.	Page 161
Discount rate	10	Report the discount rate(s) and reason chosen.	Page 163, 164
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Page 161
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Page 162, 163
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Page 162–164
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Page 122, 123, 161, 162
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Page 161
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	NA
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Page 165
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Page 163
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	NA

Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Page 165
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	NA
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Page 169
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Page 168, 169
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Page 169, 170
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	NA
Discussion			
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Page 180–184
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Page 5
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	NA

Appendix 5.2. Detailed DALY calculation method

Utility adjustment for late-effect morbidity was conducted to avoid over-estimation of cost-effectiveness by obtaining the number of YLD per case through multiplying the estimated duration of disability (duration of treatment) by the disability weights for childhood cancers as set by the Global Burden of Disease (GBD) working group.[a,b] Adjustment for late-effect morbidity was made by varying the duration of disability by cancer type, based on duration of therapy at CCHE as follows: 2.5 years for ALL, 6 months for Lymphomas, and 1 year for all other cancer types. I also adjusted duration of disability by stage for cancers that had different duration of therapy by disease stage as per the adopted protocols at CCHE. Additionally, I adjusted for excess late morbidity and mortality among childhood cancer survivors using the Medical Expenditures Panel Survey (MEPS)[c] and Childhood Cancer Survivorship Study (CCSS)[d] methods following the same methodology by *Nickhill et al.* (2013) and *Fuentes-Alabi et al.* (2018). MEPS provides utility weights generalizable to the United States general population, whereas, CCSS provides utility weights for late effects for those who received treatment for cancer in childhood.

References:

a. Murray CJ, Lopez AD, World Health Organization. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Global Burden of Disease and Injury Series, Vol II. Cambridge, MA: Harvard School of Public Health; 1996.
b. World Health Organization. The Global Burden of Disease: 2004 Update. World Health Organization, 2008. Accessed at: http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf
c. Agency for Healthcare Research and Quality (AHRQ). Medical Expenditure Panel Survey. Accessed 07 May, 2022 at: https://meps.ahrq.gov/mepsweb/
d. Oeffinger KC, Mertens AC, Sklar CA, *et al*. Chronic health conditions in adult survivors of childhood cancer. *The New England journal of medicine*. 2006; 355(15):1572–1582.

Appendix 5.3. Cost per DALY averted for childhood cancers, stratified by stage, risk, or subtype (N=8,886)

Cancer Type	Stages, risk, subtypes groups	No. of patients (%)	3-year costs (USD)		5-year overall survival (%)		Cost/DALY averted (3% discount) ^	Ratio of Cost/DALY averted to GDP/Capita (3%)	Cost/DALY averted (6% discount) ^	Ratio of cost/DALY averted to GDP per Capita (6%)
			Median Costs (95% CI)	*p*-value˜	Survival (95% CI)	*p*-value°				
Acute Lymphoid Leukaemia, *n=1,660*										
Risk [a]	Low risk	720	$26,820 (51,023 – 62,825)	<0.001*	92.5 (90.5 - 94.6)	<0.001*	$1,041	0.3	$1,725	0.6
	Standard risk	815	$38,114 (37,256 – 38,977)		76.2 (73.3 - 79.3)		$1,766	0.6	$2,925	1.0
	High risk	125	$57,272 (51,023 – 62,825)		54.5 (45.8 - 65.0)		$3,785	1.3	$6,271	2.1
Acute Myeloid Leukaemia, *n= 544*										
Sub-type [b]	AML	477	$45,165 (42,592 – 47,507)	<0.001*	51.5 (46.8 - 56.7)	0.02	$3,316	1.1	$5,552	1.8
	APL	38	$33,555 (26,491 – 39,637)		76.8 (66.5 - 92.9)		$1,701	0.6	$2,847	0.9
	AML Down Syndrome	29	$39,611 (28,478 – 45,613)		69.1 (54.0 - 88.0)		$1,738	0.6	$2,909	1.0
Risk [c] *NA* ~	Low	165	$42,598 (41,186 – 46,686)	0.003*	73.1 (66.1 - 80.7)	<0.001*	$2,268	0.8	$3,796	1.3
	Intermediate	263	$42,216 (37,963 – 45,165)		46.7 (40.2 - 54.0)		$3,178	1.1	$5,320	1.8
	High	89	$52,909 (44,710 – 59,662)		37.3 (28.3 - 49.1)		$4,544	1.5	$7,607	2.5
Myelodysplastic Syndrome, *n= 28*										
Risk [d]	Low	3	29,168 (*NA*)	0.1	33.3 (6.7 – 100)	0.71	$4,258	1.4	$7,122	2.4
	Intermediate	6	$26,684 (7,722 – 71,669)		66.7 (37.9 – 100)		$1,563	0.5	$2,614	0.9
	High	12	$49,364 (32,974 – 56,116)		32.4 (13.1 - 80.4)		$4,936	1.6	$8,257	2.7
	Very high	7	$52,103 (39,552 – 73,137)		28.6 (8.9 - 92.2)		$6,319	2.1	$10,570**	3.5**
Sub-type [e]	MDR-AML	6	$49,364 (44,783 – 56,116)	0.002*	50.0 (22.5 – 100)	0.66	$3,469	1.1	$5,803	1.9
	RAEB	15	$52,103 (25,487 – 56,116)		38.1 (19.6 - 74.2)		$3,961	1.3	$6,626	2.2
	RC	7	$28,545 (7,722 – 82,245)		33.3 (10.8 – 100)		$3,523	1.2	$5,892	2.0

Did BMT?	Yes	10	$53,296 (25,487 – 70,071)	0.01*	68.6 (44.5 – 100)	0.049*	$2,361	0.8	$3,949	1.3
	No	18	$42,311 (28,545 – 53,356)		23.8 (10.1 - 55.9)		$6,106	2.0	$10,213**	3.4**
Juvenile myelomonocytic Leukaemia, n= 48										
Did BMT?	Yes	25	$36,700 (29,472 – 47,516)	<0.001*	46.4 (31.7 - 75.7)	0.072	$3,303	1.1	$5,925	2.0
	No	23	$22,642 (16,705 – 32,883)		25.4 (9.7 - 49.2)		$4,393	1.5	$7,828	2.6
Chronic Myeloid Leukaemia, *n= 77*										
Sub-type [f]	Chronic phase	72	$27,336 (20,972 – 34,198)	0.01*	94.4 (89.3 - 99.9)	0.87	$1,125	0.4	$1,689	0.6
	Blast crisis	4	$67,950 (*NA*)		100 (100)		$2,371	0.8	$3,558	1.2
	Accelerated	1	$64,354 (*NA*)		100 (100)		$1,983	0.7	$2,976	1.0
Hodgkin Lymphoma, *n= 709*										
Risk [g]	Low	348	$5,123 (4,981 – 5,314)	<0.001*	98.8 (97.7 - 99.9)	<0.001*	$191	0.1	$299	0.1
	Intermediate	153	$6,467 (6,210 – 6,726)		94.3 (90.1 - 98.7)		$301	0.1	$470	0.2
	High	208	$7,310 (6,715 – 7,913)		90.0 (85.6 - 94.7)		$487	0.2	$760	0.3
Non-Hodgkin Lymphoma, (*n= 635)*										
Stage [h]	Stage I	24	$13,865 (5,928 – 18,286)	<0.001*	100 (100)	<0.001*	$500	0.2	$829	0.3
	Stage II	87	$15,400 (13,257 – 16,888)		94.2 (89.4 - 99.3)		$643	0.2	$1,066	0.4
	Stage III	364	$20,436 (19,215 – 22,070)		84.7 (80.9 - 88.7)		$1,053	0.3	$1,746	0.6
	Stage IV	160	$33,281 (30,104 – 35,809)		72.8 (66.2 - 80.1)		$1,691	0.6	$2,803	0.9
CNS tumours, *n= 1,659*										
Subtype [I]	Astrocytoma	482	$12,357 (11,370–13,309)	<0.001*	69.9 (61.2 – 75)	<0.001*	$709	0.2	$1,179	0.4
	Ependymoma	149	$11,009 (10,155–13,516)		66.1 (55.9 - 78.1)		$716	0.2	$1,196	0.4
	Medulloblastoma/ Embryonal	359	$23,082 (21,447 – 24,598)		57.3 (51.4 - 63.9)		$1,524	0.5	$2,544	0.8
	Neuronal & Mixed Neuronal	97	$10,963 (11,370–13,309)		86.7 (79.1 – 95.0)		$514	0.2	$859	0.3
	Optic Gliomas	92	$11,912 (8,465 – 12,434)		85.0 (76.2 - 94.9)		$486	0.2	$812	0.3
	Brain stem lesions	239	$3,481 (3,178 – 3,765)		11.6 (7.6 - 17.8)		$1,273	0.4	$2,125	0.7

	Others***	241	11,217 (3,178 – 3,765)		80.0 (73.3 - 87.4)		$607	0.2	$1,013	0.3
Neuroblastoma (NBL), n= 967										
Risk [j]	Low	72	5,613 (4,353 – 6,338)	<0.001*	96.9 (91.2 – 100)	<0.001*	$303	0.1	$567	0.2
	Intermediate	296	14,599 (13,567 – 15,822)		89.3 (85.7 - 92.9)		$697	0.2	$1,295	0.4
	High	599	34,852 (32,704 – 35,897)		32.8 (28.9 - 37.2)		$4,232	1.4	$7,810	2.6
BMT for HR NBL?	Yes	140	45,924 (32,515 – 43,827)	<0.001	64.4 (18.7 - 27.4)	<0.001*	$2,785	0.9	$5,139	1.7
	No	459	31,119 (23,725 – 27,094)		22.6 (56.2 - 73.8)		$5,595	1.9	$10,325**	3.4**
Stage [k]	Stage 1	35	5,503 (3,928 – 6,284)	<0.001	95.0 (85.9 – 100)	<0.001*	$320	0.1	$600	0.2
	Stage 2	38	5,933 (4,311 – 7,489)		97.2 (92 – 100)		$275	0.1	$514	0.2
	Stage 3	286	19,655 (17,773 – 22,305)		75.5 (70.6 - 80.7)		$1,282	0.4	$2,383	0.8
	Stage 4	565	31,281 (29,829 – 32,515)		37.8 (33.7 - 42.4)		$3,354	1.1	$6,190	2.1
	Stage 4S	43	10,576 (7,417 – 15,200)		76.0 (62.6 - 92.2)		$792	0.3	$1,473	0.4
Retinoblastoma, *n= 523*										
Stage [l]	Intra-ocular	479	7,149 (6,774 – 7,448)	<0.001*	98.4 (97.1 - 99.6)	<0.001*	$304	0.1	$569	0.2
	Extra-ocular	44	20,340 (18,027 – 23,457)		53.9 (40.2 - 72.2)		$1,624	0.5	$3,019	1.0
Intra-ocular	Unilateral	275	6,401 (6,115 – 6,785)	<0.001*	98.0 (96.3 - 99.8)	0.44	$270	0.1	$506	0.2
	Bilateral	204	8,314 (7,797 – 8,664)		98.8 (97.2 – 100)		$349	0.1	$653	0.2
Renal tumours, *n= 521*										
Sub-type	Wilms tumours	445	10,076 (9,718 – 10,567)	<0.001*	85.9 (82.6 - 89.2)	<0.001*	$659	0.2	$1,201	0.4
	Rhabdoid tumour	13	17,639 (9,542 – 27,637)		*X*		*X*	*X*	*X*	*X*
	Clear Cell Sarcoma Kidney	35	24,498 (19,616 – 29,901)		77.9 (64.4 - 94.3)		$1,291	0.4	$2,336	0.8
	Renal Cell Carcinoma	11	4,576 (3,155 – 9,346)		71.6 (48.8 – 100)		$266	0.1	$480	0.2
	Mesoblastic nephroma	17	8,993 (3,186 – 13,066)		94.1 (83.6 – 100)		$225	0.1	$412	0.1
***Wilms t*umours, n=445**										
	Stage I	45	7,955 (6,603 – 9,718)		97.8 (93.6 – 100)	<0.001*	$383	0.1	$702	0.2

Stage [n]	Stage II	68	7,705 (6,957 – 8,504)	<0.001*	96.8 (96.8 - 92.6)		$384	0.1	$705	0.2
	Stage III	202	9,800 (9,157 – 10,388)		87.5 (82.8 - 92.4)		$592	0.2	$1,077	0.4
	Stage IV	87	16,970 (14,278 – 20,037)		78.5 (69.8 - 88.1)		$986	0.3	$1,784	0.6
	Stage V	43	13,295 (10,357 – 22,094)		74.2 (62.1 - 88.6)		$882	0.3	$1,596	0.5
Hepatoblastoma, *n= 122*										
Stage [o]	Stage I	4	7,126 (NA)	0.02*	100 (100)	0.001*	$245	0.1	$450	0.1
	Stage II	1	15,145 (NA)		*X*		*X*	*X*	*X*	*X*
	Stage III	87	17,627 (16,537 – 19,536)		71.1 (61.9 - 81.6)		$1,043	0.3	$1,912	0.6
	Stage IV	30	17,967 (13,036 – 20,480)		35.9 (22.1 - 58.3)		$1,986	0.7	$3,617	1.3
Risk [p]	Very Low	1	5,111 (NA)	0.03*	*X*	0.24	*X*	*X*	*X*	*X*
	Low	5	9,918 (NA)		100 (100)		$429	0.1	$787	0.3
	High	116	17,617 (16,537 – 19,421)		61.4 (52.9 - 71.3)		$1,187	0.4	$2,162	0.7
Ewing Sarcoma, *n= 297*										
Stage [q]	Localized	211	28,638 (27,288 – 30,116)	0.4	77.7 (71.9 - 83.9)	<0.001*	$1,253	0.4	$1,920	0.6
	Metastatic	86	27,780 (24,678 – 30,445)		44.4 (34.3 - 57.4)		$2,158	0.7	$3,309	1.1
Osteosarcoma, (*n*= 305)										
Stage [r]	Localized	199	36,863 (34,372 – 38,162)	0.001*	58.9 (52.1 - 66.4)	<0.001*	$1,798	0.6	$2,554	0.8
	Metastatic	106	27,992 (21,177 – 33,378)		22.2 (15.2 - 32.4)		$3,753	1.2	$5,330	1.8
Rhabdomyosarcoma, *n= 317*										
Risk [s]	Low	25	12,215 (10,568 – 17,325)	0.08	85.8 (75.7 - 97.2)	<0.001*	$643	0.2	$1,109	0.4
	Intermediate	214	17,112 (15,992 – 18,767)		68.8 (63 - 74.9)		$1,073	0.4	$1,852	0.6
	High	78	17,056 (14,948 – 18,923)		26.3 (18.4 - 37.6)		$2,612	0.9	$4,509	1.5
Stage [t]	Stage I	62	14,599 (12,607 – 18,068)	0.3	79.2 (69.3 - 90.5)	<0.001*	$784	0.3	$1,353	0.4
	Stage II	27	17,066 (13,084 – 24,993)		78.4 (62.6 - 98.1)		$1,036	0.3	$1,788	0.6
	Stage III	150	17,153 (15,826 – 19,028)		64.6 (57.2 - 73.0)		$1,019	0.3	$1,760	0.6
	Stage IV	78	17,056 (14,576 – 19,150)		21.2 (13.1 - 34.5)		$3,421	1.1	$5,906	2.0
Other soft tissue tumours, *n= 127*										

Risk [u]	Low	45	6,432 (4,547 – 9,966)	<0.001*	92.9 (85.6 – 100)	<0.001*	$337	0.1	$541	0.2
	Intermediate	63	18,612 (15,450 – 23,108)		84.9 (76.4 - 94.5)		$804	0.3	$1,291	0.4
	High	19	24,491 (14,172 – 34,751)		30.7 (15.4 - 61.1)		$2,729	0.9	$4,381	1.5
Germ Cell tumours, *n= 150*										
Stage [v]	Stage I	44	3,145 (2,698 – 3,803)	<0.001*	100 (100)	<0.001*	$141	<0.1	$248	0.1
	Stage II	20	7,599 (6,586 – 10,424)		89.1 (75.8 – 100)		$403	0.1	$709	0.2
	Stage III	63	16,793 (14,394 – 18,900)		88.7 (81.2 - 96.9)		$759	0.3	$1,335	0.4
	Stage IV	23	17,595 (14,424 – 26,008)		63.8 (46.5 - 87.4)		$1,256	0.4	$2,211	0.7
Risk [w,x]	Low	42	3,109 (2,671 – 3,670)	<0.001*	100 (100)	0.008*	$123	<0.1	$217	0.1
	Intermediate	27	7,991 (6,586 – 11,402)		92.1 (82.2 – 100)		$436	0.1	$767	0.3
	High	81	17,104 (14,733 – 19,084)		81.1 (72. 9 - 90.2)		$886	0.3	$1,559	0.5
Langerhans cell histiocytosis, n= 197										
Risk [y]	Multisystem RO- LR	51	8,924 (8,172 – 10,955)	<0.001*	98.0 (94.31 – 100)	<0.001*	$385	0.1	$690	0.2
	Multisystem RO+ HR	32	7,863 (10,180 – 18,827)		52.3 (37.4 - 73.1)		$1,339	0.4	$2,403	0.8
	Uni-system Multifocal	50	7,863 (6,233 – 9,334)		96.0 (90.7 – 100)		$349	0.1	$626	0.2
	Uni-system Unifocal	64	3,609 (3,609 – 5,124)		98.4 (95.3 – 100)		$186	0.1	$334	0.1

^ Costs and effects (survival) were discounted at 3% (base-case scenario), and 6% on sensitivity analysis. ** Not cost-effective treatment (>3 GDP per Capita). ˜ P-value for difference in costs was obtained from Wilcoxon and Kruskal Wallis tests as appropriate. ° *P*-value for difference in survival was obtained from log-rank test. ** Statistically significant at p<0.005. *** Other CNS/brain tumors include: Other specified and unspecified intracranial and intraspinal neoplasms. *NA* refers to 'not available', defined as patients with undetermined risk at diagnosis, as these patients died before risk determination, as follows: AML risk (n=27, 4.9%). 'X' refers to the sub-groups of patients who did not complete 5 years of follow-up, or had no deaths or survivors within this group, and for which 5-year survival could not be calculated. Abbreviations: APL: Acute Promyelocytic Leukaemia; BMT: Bone Marrow Transplant; RAEB: Refractory anaemia with excess blasts; RC: refractory cytopenia. [a–y] refer to references for definitions of staging, risk stratification and sub-type classifications systems are listed in Appendix 6.

Appendix 5.4. Cost per DALY averted, stratified by relapse/refractory (R/R) or progressive disease (PD) status

Cancer Type	No. of patients (n)	Relapse/refractory or PD status	3-Year Median Costs (95% CI)	*p*-value~	5-year overall survival (95% CI)	*p*-value°	Costs/DALY averted (3% discount)	Ratio of Costs/ DALY to GDP per Capita (3%)	Costs/DALY averted (6% discount)	Ratio of Costs/DALY to GDP per Capita (6%)
Acute Lymphoblastic Leukaemia	166	R/R	50,261 (46,882 – 53,450)	<0.001	0.164 (0.111 – 0.249)	<0.001	$11,014*	3.6*	$18,247*	6.0*
	1,494	No	31,905 (31,248 – 32,700)		0.886 (0.869 – 0.903)		$1,321	0.4	$2,188	0.7
Acute Myeloid Leukaemia	163	R/R	59,519 (55,931 – 64,860)	<0.001	0.099 (0.049 – 0.201)	<0.001	$20,075*	6.6*	$33,439*	11.1*
	381	No	39,540 (37,631 – 41,603)		0.699 (0.654 – 0.747)		$2,150	0.7	$3,599	1.2
Brain and CNS tumours	146	Relapse/PD	20,904 (18,490 – 22,982)	<0.001	0.081 (0.039 – 0.637)	<0.001	$9,710*	3.2*	$16,130*	5.3*
	1,513	No	11,789 (11,163 – 12,490)		0.665 (0.637 – 0.695)		$729	0.2	$1,211	0.4
Chronic Myeloid Leukaemia	6	PD	34,260 (22,341 – 77,353)	0.3	1 (1-1)	0.45	$1,246	0.4	$1,864	0.6
	71	No	27,790 (20,145 – 38,351)		0.944 (0.892 – 0.999)		$1,191	0.4	$1,782	0.6
Ewing Sarcoma	84	Relapse/PD	34,056 (30,973 – 37,526)	<0.001	0.122 (0.060 – 0.250)	<0.001	$9,530*	3.2*	$14,559*	4.8*
	213	No	27,224 (26,025 – 28,392)		0.888 (0.842 – 0.937)		$994	0.3	$1,518	0.5
Germ cell tumours	13	Relapse/PD	16,836 (5,389 – 34,459)	0.3	0.615 (0.400 – 0.946)	<0.001	$1,041	0.3	$1,821	0.6
	137	No	11,503 (8,702 – 13,482)		0.909 (0.860 – 0.959)		$524	0.2	$917	0.3
Hepatoblastoma	42	Relapse/PD	17,362 (13,036 – 21,324)	0.9	0.076 (0.021 – 0.271)	<0.001	$10,199*	3.4*	$19,208*	6.4*
	80	No	17,617 (15,859 – 19,451)		0.899 (0.835 – 0.968)		$808	0.3	$1,533	0.5
Hodgkin Lymphoma	46	Relapse/PD	24,204 (16,149 – 31,052)	<0.001	0.754 (0.620 – 0.918)	<0.001	$1,090	0.4	$1,689	0.6
	663	No	5,821 (5,617 – 5,977)		0.967 (0.952 – 0.982)		$253	0.1	$394	0.1
JMML	10	Relapse/PD	32,014 (25,997 – 52,340)	0.2	1 (0.016 – 0.642)	0.074	$1,711	0.6	$3,297	1.1
	38	No	31,055 (21,720 – 36,971)		0.449 (0.312 – 0.647)		$2,980	1.0	$5,741	1.9
LCH	49	Relapse/PD	13,586 (11,968 – 16,374)	<0.001	0.812 (0.708 – 0.931)	0.021	$851	0.3	$1,517	0.5
	148	No	6,845 (5,728 – 7,542)		0.931 (0.891 – 0.973)		$261	0.1	$468	0.2
Myelodysplastic Syndrome	19	PD	39,552 (28,545 – 53,356)	0.3	0.140 (0.041 – 0.480)	<0.001	$10,284*	3.4*	$17,115*	5.7*
	9	No	54,488 (27,882 – 58,060)		0.875 (0.673 – 1)		$1,876	0.6	$3,138	1.0
Neuroblastoma	143	Relapse/PD	37,984 (34,180 – 40,425)	<0.001	0.156 (0.101 – 0.243)	<0.001	$9,662*	3.2*	$17,955*	5.9*
	824	No	23,161 (21,730 – 24,457)		0.623 (0.590 – 0.659)		$1,635	0.5	$3,061	1.0

Non-Hodgkin Lymphoma	43	Relapse/PD	48,700 (39,570 – 63,171)	<0.001	0.416 (0.291 – 0.594)	<0.001	$4,542	1.5	$7,453	2.5
	592	No	20,436 (19,215 – 21,792)		0.867 (0.839 – 0.896)		$982	0.3	$1,627	0.5
Osteosarcoma	104	Relapse/PD	38,076 (34,680 – 40,579)	<0.001	0.222 (0.149 – 0.333)	<0.001	$4,939	1.6	$7,015	2.3
	201	No	32,149 (28,633 – 34,981)		0.574 (0.507 – 0.649)		$1,615	0.5	$2,300	0.8
Other soft tissue tumours	35	Relapse/PD	21,181 (14,172 – 26,602)	0.001	0.39 (0.248 – 0.614)	<0.001	$1,940	0.6	$3,100	1.0
	92	No	12,881 (9,966 – 17,365)		0.934 (0.898 – 0.993)		$547	0.2	$878	0.3
Renal Tumours	58	Relapse/PD	29,419 (25,054 – 35,279)	<0.001	0.303 (0.201 – 0.457)	<0.001	$3,889	1.2	$7,082	2.3
	463	No	9,876 (9,354 – 10,277)		0.901 (0.873 – 0.928)		$569	0.2	$1,043	0.3
Retinoblastoma	10	Relapse/PD	22,626 (15,960 – 39,964)	<0.001	--	<0.001	--	-		-
	513	No	7,282 (7,047 – 7,711)		0.969		$353	0.1	$673	0.2
Rhabdomyosarcoma	137	Relapse/PD	23,801 (22,148 – 26,711)	<0.001	0.146 (0.091 – 0.233)	<0.001	$6,657	2.2	$11,427*	3.8*
	180	No	13,485 (12,553 – 15,088)		0.910 (0.869 – 0.953)		$591	0.2	$1,020	0.3

Progressive disease (PD) was defined as cancer that is growing, spreading or getting worse (at least a 20 percent growth in the size of the tumour or spread of the tumour since the beginning of treatment). * Not cost-effective treatment (> 3 times GDP per Capita, $3,019).

˜ P-value for difference in costs was obtained from Wilcoxon and Kruskall Wallis as appropriate.

° *P*-value for difference in survival was obtained from log-rank test. * Statistically significant at p<0.005.

Appendix 5.5. Cost per DALY averted for relapsed acute leukaemia (ALL/AML), by disease characteristics and BMT status

Cancer Type		No. of patients (n)	3-Year Median Costs (95% CI)	*p*-value~	5-year Overall Survival (95% CI)	*p*-value°	Costs/DALY averted (3% discount)	Ratio of Cost/DALY to GDP per Capita (3%)	Costs/DALY averted (6% discount)	Ratio of Cost/DALY to GDP per Capita (6%)
Relapsed/refractory ALL (n=166)										
Initial Risk	Low	35	40,157 (29,135 – 50,353)	<0.001	0.404 (0.245 – 0.629)	<0.001	$3,749	1.2	$6,212	2.1
	Standard	97	52,385 (46,808 – 56,771)		0.094 (0.045 – 0.198)		$18,751*	6.2*	$31,065*	10.3*
	High	34	57,853 (48,091 – 66,280)		0.136 (0.0514 – 0.361)		$16,404*	5.4*	$27,178*	9.0*
Subtype	T-cell	48	56,486 (46,882 – 67,069)	0.006	0.109 (0.046 – 0.294)	<0.001	$18,068*	6.0*	$29,934*	9.9*
	B-cell	118	49,191 (44,905 – 52,981)		0.191 (0.121 – 0.295)		$8,947	3.0	$14,823*	4.9*
Relapsed ALL (n=163)										
Site of relapse	Haematological or combined	101	49,634 (45,528 – 52,983)	0.1	0.058 (0.021 – 0.160)	<0.001	$30,717*	10.2*	$50,889*	16.9*
	Isolated extra medullary	62	54,467 (46,763 – 59,527)		0.326 (0.216 – 0.493)		$5,696	1.9	$9,436*	3.1
Risk of relapse**	Low-risk	27	50,170 (46,882 – 54,163)	0.5	0.462 (0.291 – 0.732)	<0.001	$4,489	1.5	$7,437	2.5
	High-risk	136	47,593 (37,103 – 60,355)		0.089 (0.047 – 0.171)		$20,146*	6.7*	$33,376*	11.1*
BMT for high-risk relapse ALL	Yes	10	91,359 (44,522 – 111,583)	<0.001	0.312 (0.102 – 0.955)	0.054	$7,053	2.3	$11,685*	3.9*
	No	126	49,535 (46,563 – 52,983)		0.077 (0.038 – 0.160)		$22,865*	7.6*	$37,882*	12.5*
Relapsed/refractory AML (n=163)										
Initial Risk ***	Low	25	65,546 (57,449 – 82,856)	<0.001	0.42 (0.252 – 0.693)	0.003	$5,809	1.9	$9,677	3.2
	Intermediate	97	53,087 (45,665 – 59,875)		0.26 (0.187 – 0.383)		$6,419	2.1	$10,692	**3.5***
	High	41	64,860 (57,939 – 72,736)		0.11 (0.04 – 0.354)		$21,183*	7.0*	$35,283*	11.7*
BMT	Yes	25	92,511 (72,674 – 101,347)	<0.001	0.39 (0.218 – 0.727)	<0.001	$8,061	2.7	$13,428*	4.4*
	No	138	55,250 (47,706 – 58,623)		0.03 (0.005 – 0.162)		$59,265*	19.6*	$98,715*	32.7*

***** Not cost-effective treatment (> 3 times GDP per Capita, $3,019). ˜ *P*-value for difference in costs was obtained from Wilcoxon and Kruskall Wallis as appropriate. ° *P*-value for difference in survival was obtained from log-rank test. * Statistically significant at p<0.005. ** Low-risk of relapse includes B-cell with isolated extra-medullary relapse, who relapse within 18 months from date of diagnosis. All patients not meeting these criteria are high-risk relapsing patients. *** For relapsed/refractory AML by risk groups, only 3-year OS was calculated as the high-risk group did not complete 5 years follow-up.

Appendix 5.6. Change in cost (in USD and EGP) per change in survival (ICER) between patients diagnosed in 2013 and 2017

Cancer type	3-year Costs in EGP (USD) (2013–2017)				3-year Overall survival (OS) (%)				ICER * (USD)	ICER * (EGP)
	Costs in 2013 EGP (USD)	Costs in 2017 EGP (USD)	Percent of change in cost (EGP%)	*p*-value [a]	OS (2013)	OS (2017)	Diff. OS	*p*-value [b]	Δ Cost / Δ OS	Δ Cost / Δ OS
All cancers combined	316,228 ($22,117)	395,302 ($16,409)	-25.8% (+25.0%)	<0.001*	74.1	78.7	4.6	<0.001*	(1,241)	17,190
I. Leukaemia	561,615 ($37,953)	642,547 ($26,822)	-29.3% (+14.4%)	<0.001*	74.5	82.8	8.3	<0.001*	(1,341)	9,751
Ia. Acute Lymphoid Leukaemia	526,062 ($35,291)	621,270 ($25,938)	-26.5% (+18.1%)	<0.001*	80.8	87.7	6.9	0.007*	(1,356)	13,798
Ib. Acute Myeloid Leukaemia	727,116 ($52,052)	768,337 ($31,559)	-39.4% (+5.7%)	<0.001*	56.6	67.9	11.3	0.090	(1,814)	3,648
Ic. Chronic Myeloid Leukaemia	659,469 ($46,579)	400,420 ($17,078)	-63.3% (-39.3%)	0.8	76.9	93.3	16.4	0.210	(1,799)	-15,796
Id. Myelodysplastic Syndrome	715,699 ($50,136)	777,906 ($32,330)	-35.5% (+8.7%)	0.003*	50.1	20.1	-30.0	0.672	594	-2,074
Ie. Juvenile myelomonocytic Leukaemia	337,140 ($21,488)	481,838 ($20,456)	-4.8% (+42.9%)	<0.001*	58.3	53.8	- 4.5	0.721	229	-32,155
II. Lymphomas	169,760 ($12,222)	174,237 ($7,029)	-42.5% (+2.6%)	<0.001*	86.9	94.8	7.9	<0.001*	(657)	567
IIa. Hodgkin Lymphoma	89,629 ($6,035)	117,920 ($4,914)	-18.6% (+31.6%)	<0.001*	97.2	98.2	1.0	0.330	(1,121)	28,291
IIb. Non-Hodgkin Lymphoma	356,426 ($24,564)	405,375 ($16,661)	-32.2% (+13.7%)	<0.001*	77.6	90.3	12.7	0.004*	(622)	3,854
III. Brain Tumours	217,627 ($15,333)	229,396 ($9,596)	-37.4% (+5.4%)	<0.001*	64.2	69.9	5.7	0.12	(1,007)	2,065
IV. Other Solid Tumours	243,722 ($17,206)	349,040 ($14,514)	-15.6% (+43.2%)	<0.001*	72.3	73.1	0.8	0.65	(3,365)	131,648
IV.a Neuroblastoma	411,318 ($27,855)	548,786 ($23,079)	-17.1% (+33.4%)	<0.001*	66.7	55.4	-11.3	0.045*	423	-12,165
V. Retinoblastoma	103,388 ($6,873)	130,657 ($5,498)	-20.0% (+26.4%)	<0.001*	91.6	97.3	5.7	0.058	(241)	4,784
VI. Renal Tumours	145,679 ($9,911)	233,742 ($9,779)	-1.3% (+60.5%)	<0.001*	89.7	85.9	- 3.8	0.510	35	-23,175
VII.a Hepatoblastoma**	186,139 ($13,020)	359,388 ($15,145)	16.3% (+93.1%)	<0.001*	52.8	80.2	27.4	0.018*	78	6,323
VIIIa Osteosarcoma	528,464 ($37,198)	534,598 ($22,256)	-40.2% (+1.2%)	<0.001*	45.2	43.1	- 2.1	0.490	7,115	-2,921
VIIIc Ewing sarcomas	403,408 ($27,379)	567,453 ($23,231)	-13.0% (+40.7%)	<0.001*	58.1	77.6	19.5	0.012*	(182)	8,413
IXa. Rhabdomyosarcoma	219,125 ($14,963)	340,411 ($13,969)	-6.6% (+55.4%)	<0.001*	68.1	63.8	- 4.3	0.810	231	-28,206
IXb-d Other soft tissue tumours	334,523 ($23,792)	236,667 ($9,681)	-59.3% (-29.3%)	0.5	87.5	74.1	-13.4	0.291	1,053	7,303
X. a-c Germ Cell Tumours	216,988 ($14,736)	202,156 ($8,574)	-41.8% (-6.8%)	0.1	81.5	89.5	8.0	0.401	(770)	1,854
XII. Other Tumours (LCH)***	114,713 ($7,970)	146,934 ($5,894)	-26.0% (+28.1%)	<0.001*	85	88.4	3.4	0.690	(610)	9,477

*****ICER was calculated as incremental costs (difference between median costs of patients diagnosed in 2017 compared with those diagnosed in 2013) divided by the incremental survival (difference between the 3-year overall survival of patients diagnosed in 2017 compared with those diagnosed in 2013).

[a] P-value for difference in costs was obtained from Wilcoxon**.** [b] *P*-value for difference in survival was obtained from log-rank test.

Appendix 5.7. Disease-related characteristics for patients diagnosed in 2013 versus 2017

Cancer type	**Cancer stage/risk/subtype at initial diagnosis**	**Patients diagnosed in 2013**		**Patients diagnosed in 2017**		**Diff. in Percent (2017 – 2013)**
		No.	**Percent**	**No.**	**Percent**	
I. Leukaemia						
Ia. Acute Lymphoid Leukaemia – Risk	Low risk	128/276	46.3%	203/460	44.1%	-2.20%
	Standard risk	121/276	43.8%	226/460	49.1%	5.30%
	High risk	27/276	9.7%	31/460	6.7%	-3.00%
Ib. Acute Myeloid Leukaemia – Risk	Low	28/81	34.5%	39/128	30.4%	-4.10%
	Intermediate	37/81	45.6%	70/128	54.7%	9.10%
	High	16/81	19.7%	19/128	14.8%	-4.90%
Ic. Chronic Myeloid Leukaemia – Subtype	Chronic phase	13/13	100%	14/15	93.3%	-6.70%
	Blast crisis	0/13	0%	1/15	6.6%	6.60%
	Accelerated	0/13	0%	0/15	0%	0.00%
Id. Myelodysplastic Syndrome – Risk	Low	1/8	12.5%	1/6	16.6%	4.10%
	Intermediate	2/8	25%	1/6	16.6%	-8.40%
	High	3/8	37.5%	2/6	33.3%	-4.20%
	Very high	2/8	25%	2/6	33.3%	8.30%
II. Lymphomas						
IIa. Hodgkin Lymphoma – Risk	Low	53/109	48.6%	93/175	53.1%	4.50%
	Intermediate	20/109	18.3%	34/175	19.4%	1.10%
	High	36/109	33.0%	48/175	27.4%	-5.60%
IIb. Non-Hodgkin Lymphoma – Stage	Stage I	6/121	4.9%	6/136	4.4%	-0.50%
	Stage II	17/121	14.0%	17/136	12.5%	-1.50%
	Stage III	61/121	50.4%	74/136	54.4%	4.00%
	Stage IV	37/121	30.6%	39/136	28.7%	-1.90%
III. CNS/Brain Tumours – Subtype	Astrocytoma	66/233	28.3%	99/397	24.9%	-3.40%
	Ependymoma	24/233	10.3%	45/397	11.3%	1.00%
	Medulloblastoma/Embryonal	50/233	21.4%	82/397	20.6%	-0.80%
	Neuronal & Mixed Neuronal	15/233	6.4%	23/397	5.8%	-0.60%
	Optic Gliomas	3/233	1.3%	23/397	5.8%	4.50%

	Brain stem lesions	42/233	18.0%	58/397	14.6%	-3.40%
	Others**	33/233	14.1%	67/397	16.8%	2.70%
Other Solid Tumours						
IV.a Neuroblastoma – Risk	Low	3/161	1.8%	14/217	6.4%	4.60%
	Intermediate	60/161	37.2%	54/217	24.8%	-12.40%
	High	98/161	60.9%	149/217	68.6%	7.70%
Neuroblastoma – Stage	Stage 1	3/161	1.8%	6/217	2.7%	0.90%
	Stage 2	0/161	0%	8/217	3.6%	3.60%
	Stage 3	60/161	37.3%	63/217	29.0%	-8.30%
	Stage 4	89/161	55.3%	129/217	59.4%	4.10%
	Stage 4s	9/161	5.6%	11/217	5.1%	-0.50%
V. Retinoblastoma – Stage	Intra-ocular	75/87	86.2%	115/118	97.4%	11.20%
	Extra-ocular	12/87	13.8%	3/118	2.5%	-11.30%
VI. Renal Tumours – Subtype	Wilms tumours	68/79	86.1%	87/108	80.5%	-5.60%
	Rhabdoid tumour	1/79	1.3%	3/108	2.7%	1.40%
	Clear Cell Sarcoma Kidney	7/79	8.8%	9/108	8.3%	-0.50%
	Renal Cell Carcinoma	1/79	1.3%	3/108	2.7%	1.40%
	Others*	2/79	2.5%	6/108	5.5%	3.00%
Renal Tumours – Stage	Stage I	11/79	13.9%	6/108	5.5%	-8.40%
	Stage II	10/79	12.6%	20/108	18.5%	5.90%
	Stage III	32/79	40.5%	43/108	39.8%	-0.70%
	Stage IV	19/79	24.0%	17/108	15.7%	-8.30%
	Stage V	7/79	8.9%	9/108	8.3%	-0.60%
VII.a Hepatoblastoma – Stage	Stage I	1/22	4.5%	1/31	3.2%	-1.30%
	Stage II	0/22	0%	1/31	3.2%	3.20%
	Stage III	15/22	68.2%	22/31	70.9%	2.70%
	Stage IV	6/22	27.3%	7/31	22.6%	-4.70%
VIIIa Osteosarcoma – Stage	Localized	32/54	59.3%	41/61	89.1%	29.80%
	Metastatic	22/54	40.7%	20/61	32.8%	-7.90%
VIIIc Ewing sarcomas – Stage	Localized	26/44	59.1%	56/72	77.7%	18.60%
	Metastatic	18/44	40.9%	16/72	22.2%	-18.70%
IXa. Rhabdomyosarcoma – Stage	Stage I	5/49	10.2%	19/70	27.1%	16.90%

	Stage II	6/49	12.2%	2/70	2.8%	-9.40%
	Stage III	22/49	44.9%	33/70	47.1%	2.20%
	Stage IV	16/49	32.6%	14/70	20.0%	-12.60%
IXb-d Other soft tissue tumours – Risk	Low	2/8	25%	7/24	29.2%	4.20%
	Intermediate	4/8	50%	14/24	58.3%	8.30%
	High	2/8	25%	3/24	12.5%	-12.50%
X. a-c Germ Cell Tumours – Risk	Low	2/22	9.1%	16/43	37.2%	28.10%
	Intermediate	2/22	9.1%	6/43	13.9%	4.80%
	High	16/22	72.7%	21/43	48.8%	-23.90%
X. a-c Germ Cell Tumours – Stage	Stage I	5/22	22.7%	16/43	37.2%	14.50%
	Stage II	0/22	0%	5/43	11.6%	11.60%
	Stage III	14/22	63.6%	15/43	34.8%	-28.80%
	Stage IV	3/22	13.6%	7/43	16.3%	2.70%
XII. LCH***	Multisystem RO- LR	4/20	20.0%	15/45	33.3%	13.30%
	Multisystem RO+ HR	4/20	20.0%	6/45	13.3%	-6.70%
	Uni-system Multifocal	5/20	25.0%	9/45	20.0%	-5.00%
	Uni-system Unifocal	7/20	35.0%	15/45	33.3%	-1.70%

***** Other CNS/brain tumours include: Other specified and unspecified intracranial and intraspinal neoplasms. NA refers to 'not available', defined as patients with undetermined risk at diagnosis, as these patients died before risk determination, as follows: AML risk (n=27, 4.9%). 'X' refers to the sub-groups of patients who did not complete 5 years of follow-up, or had no deaths or survivors within this group, and for which 5-year survival could not be calculated. Abbreviations: APL: Acute Promyelocytic Leukaemia; BMT: Bone Marrow Transplant; RAEB: Refractory anaemia with excess blasts; RC: refractory cytopenia. a–y refer to references for definitions of staging, risk stratification and sub-type classifications systems are listed in Appendix 3.3.

Appendix Chapter 6

Appendix 6.1. PRISMA checklist

Section and Topic	Item no.	Checklist item	Location in thesis where items are reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 196
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 6
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 56, 196, 197
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 197
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 199
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 198, 199
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 365
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 200
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 200
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 370
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 370
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers	Page 201

Section and Topic	Item no.	Checklist item	Location in thesis where items are reported
		assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 201
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 201
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 201
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 201
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 201
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 201
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 201
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 201
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 202, 203
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	NA
Study characteristics	17	Cite each included study and present its characteristics.	Page 202–205
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 204–206, 371, 372
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 208, 209
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 204, 205
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of	Page 213

Section and Topic	Item no.	Checklist item	Location in thesis where items are reported
		statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 214–216
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 2017, 377, 378
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 371
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 371
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 217
	23b	Discuss any limitations of the evidence included in the review.	Page 222, 223
	23c	Discuss any limitations of the review processes used.	Page 222, 223
	23d	Discuss implications of the results for practice, policy, and future research.	Page 223, 224
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 198
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 198
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 5
Competing interests	26	Declare any competing interests of review authors.	NA
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 370

Appendix 6.2. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 checklist

Section/item	Item No.	Section/item	Location in thesis where items are reported
Title and abstract			
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	Page 196
Abstract	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Page 6
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Page 196, 197
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	NA
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Page 199
Setting and location	6	Provide relevant contextual information that may influence findings.	Page 199
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Page 199, 200
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Page 200
Time horizon	9	State the time horizon for the study and why appropriate.	Page 200
Discount rate	10	Report the discount rate(s) and reason chosen.	Page 200
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Page 199
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Page 199
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Page 199, 200
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Page 201
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	NA
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	NA
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Page 201
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Page 201
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	NA
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Page 201

Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	NA
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Page 208
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Page 213
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Page 206, 371
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	NA
Discussion			
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Page 217–223
Other information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Page 5
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	NA

Appendix 6.3. Detailed Search strategy

I searched Medline (OvidSP) [1946-present], Embase (OvidSP), Cochrane Database of Systematic Reviews & Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley)[Issue 8 of 12, August 2021], Database of Abstracts of Reviews of Effects, NHS Economic Evaluation Database (NHS–EED) & Health Technology Assessment Database (Centre for Reviews & Dissemination https://www.crd.york.ac.uk/CRDWeb/HomePage.asp) [inception to 31/03/2015], Science Citation Index & Social Citation Index (Web of Science Core Collection) [1900-present] and Cost Effectiveness Analysis Registry - Basic Search (http://healtheconomics.tuftsmedicalcenter.org/cear2n/search/search.aspx). The search strategy consisted of title/abstract keywords and subject headings to describe the key concepts of children, leukaemia and relapse.

A methodological filter for economic studies was adapted from the NHS EED filter available at https://www.crd.york.ac.uk/crdweb/searchstrategies.asp.

The search was restricted to English language; no publication limits were applied. Results were exported to Endnote X9 where duplicates were removed. Remaining references were exported into EXCEL for screening of articles.

Appendix 6.4. Full electronic search strategy

S3.1. MEDLINE database

No.	Searches
1	adolescent/ or exp child/ or infant/
2	Pediatrics/
3	(infan* or baby* or babies or toddler* or preschooler? or pre-schooler? or kid or kids or child* or schoolchild* or boys or girls or adolescen* or juvenil* or youth* or teen* or minors or underage* or "under-age*" or pubescen* or pediatric* or paediatric* or peadiatric*).ti,ab,kw.
4	1 or 2 or 3
5	exp Leukemia/
6	leuk?emi*.ti,ab,kw.
7	5 or 6
8	Recurrence/ or Neoplasm Recurrence, Local/
9	exp treatment failure/
10	(recur* or relaps* or refractor*).ti,ab,kw.
11	((treatment or therap* or induction) adj5 (fail* or resistan*)).ti,ab,kw.
12	Disease Progression/ or Disease Resistance/
13	8 or 9 or 10 or 11 or 12
14	4 and 7 and 13
15	"Value of Life"/
16	quality-adjusted life years/
17	("Value of life" or "value for money" or "quality adjusted life year*" or qaly* or qald* or qale* or "disability adjusted life year*" or daly*).ti,ab.
18	Economics/
19	exp "costs and cost analysis"/
20	Economics, Dental/
21	exp economics, hospital/
22	Economics, Medical/
23	Economics, Nursing/
24	Economics, Pharmaceutical/
25	(economic$ or cost or costs or costly or costing or pharmacoeconomic$).ti,ab.
26	expenditure$.ti,ab.
27	"willingness to pay".ti,ab.
28	budget$.ti,ab.
29	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30	((energy or oxygen) adj cost).ti,ab.
31	(metabolic adj cost).ti,ab.

32	((energy or oxygen) adj expenditure).ti,ab.
33	30 or 31 or 32
34	29 not 33
35	exp animals/ not humans/
36	34 not 35
37	14 and 36
38	limit 37 to english language

S3.2. EMBASE database

No.	**Searches**
1	exp adolescent/ or exp child/
2	Pediatrics/
3	(infan* or baby* or babies or toddler* or preschooler? or pre-schooler? or kid or kids or child* or schoolchild* or boys or girls or adolescen* or juvenil* or youth* or teen* or minors or underage* or "under-age*" or pubescen* or pediatric* or paediatric* or peadiatric*).ti,ab,kw.
4	1 or 2 or 3
5	exp Leukemia/
6	leuk?emi*.ti,ab,kw.
7	5 or 6
8	cancer growth/ or cancer recurrence/ or deterioration/ or recurrent disease/ or relapse/ or tumor growth/ or tumor recurrence/
9	(recur* or relaps* or refractor*).ti,ab,kw.
10	((treatment or therap* or induction) adj5 (fail* or resistan*)).ti,ab,kw.
11	8 or 9 or 10
12	4 and 7 and 11
13	leukemia relapse/
14	4 and 13
15	12 or 14
16	socioeconomics/
17	disability-adjusted life year/ or quality adjusted life year/
18	("Value of life" or "value for money" or "quality adjusted life year*" or qaly* or qald* or qale* or "disability adjusted life year*" or daly*).ti,ab.
19	Health Economics/
20	exp Economic Evaluation/
21	exp Health Care Cost/
22	Pharmacoeconomics/
23	(economic$ or cost or costs or costly or costing or pharmacoeconomic$).ti,ab.
24	expenditure$.ti,ab.
25	"willingness to pay".ti,ab.

26	budget$.ti,ab.
27	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28	((energy or oxygen) adj cost).ti,ab.
29	(metabolic adj cost).ti,ab.
30	((energy or oxygen) adj expenditure).ti,ab.
31	28 or 29 or 30
32	27 not 31
33	(animal/ or exp animal experiment/ or nonhuman/) not (exp human/ or human experiemnt/)
34	32 not 33
35	15 and 34
36	limit 35 to english language

S3.3. NHS–EED

No.	Searches
	((infan* or baby* or babies or toddler* or preschooler? or pre-schooler? or kid or kids or child* or schoolchild* or boys or girls or adolescen* or juvenil* or youth* or teen* or minors or underage* or under-age* or pubescen* or pediatric* or paediatric* or peadiatric*)) AND (leukemia* OR leukaemia*)

S3.4. Web of Science (WoS)

1	TS=(leukaemia* OR leukemia*) AND TS=(infan* OR baby* OR babies OR toddler* OR preschooler* OR pre-schooler* OR kid OR kids OR child* OR schoolchild* OR boys OR girls OR adolescen* OR juvenil* OR youth* OR teen* OR minors OR underage* OR under-age* OR pubescen* OR pediatric* OR paediatric* OR peadiatric*) AND TS=(relaps* OR refract* OR recur* OR ((treatment OR therap* OR induction) NEAR/5 (fail* OR resistan*)))
2	TS=("Value of life" OR "value for money" OR "quality adjusted life year*" OR qaly* OR qald* OR qale* OR "disability adjusted life year*" OR daly*) OR TS=(economic* or cost or costs or costly or costing or pharmacoeconomic*) OR TS=(expenditure* OR "willingness to pay" OR budget*)
3	1 AND 2
4	1 AND 2 - limited to English

S3.5. Cochrane database

ID	Search
#1	MeSH descriptor: [Adolescent] explode all trees
#2	MeSH descriptor: [Child] explode all trees
#3	MeSH descriptor: [Infant] this term only
#4	MeSH descriptor: [Pediatrics] explode all trees
#5	(infan* or baby* or babies or toddler* or preschooler* or pre-schooler* or kid or kids or child* or schoolchild* or boys or girls or adolescen* or juvenil* or youth* or teen* or minors or underage* or "under-age*" or pubescen* or pediatric* or paediatric* or peadiatric):ti,ab,kw

#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Leukemia] explode all trees
#8	(leukemia* OR leukaemia*):ti,ab,kw
#9	#7 or #8
#10	MeSH descriptor: [Recurrence] this term only
#11	MeSH descriptor: [Neoplasm Recurrence, Local] explode all trees
#12	MeSH descriptor: [Treatment Failure] explode all trees
#13	(recur* or relaps* or refractor):ti,ab,kw OR (((treatment or therap* or induction) NEAR/5 (fail* or resistan*))):ti,ab,kw
#14	MeSH descriptor: [Disease Progression] this term only
#15	MeSH descriptor: [Disease Resistance] explode all trees
#16	#10 or #11 or #12 or #13 or #14 or #15
#17	#6 and #9 and #16
#18	MeSH descriptor: [Economics] this term only
#19	MeSH descriptor: [Economics, Hospital] explode all trees
#20	MeSH descriptor: [Economics, Medical] explode all trees
#21	MeSH descriptor: [Value of Life] explode all trees
#22	MeSH descriptor: [Health Care Costs] explode all trees
#23	MeSH descriptor: [Quality-Adjusted Life Years] explode all trees
#24	(pharmacoeconomic* OR price* OR pricing):ti,ab,kw OR (((cost or economic) NEAR/2 (evaluation* or analy* or study or studies or effect* or benefit* or util* or consequence* or comparison* or identificat*))):ti,ab,kw OR (cost OR costs OR economic*):ti
#25	#18 or #19 or #20 or #21 or #22 or #23 or #24
#26	#17 and #25

S3.6 CEA Registry

Basic search

1	leukemia	Methods	73
2	leukaemia	Methods	21

Appendix 6.5. Data extraction form

Study ID:
Publication (Authors, Year):
Country
Main intervention
Comparator
Study perspective
Currency unit
Study design
Setting
Target population
Sample size
Model specification/assumptions
Time horizon
Measures of clinical effectiveness
Measures of cost-effectiveness
Price year
Costs categories
Main cost drivers
Opportunity cost
Excluded costs
Willingness-to-pay (Cost-effectiveness threshold)
Discount rate
Sensitivity analysis (uncertainty analysis)
Funding source
Conclusion/other comments

Appendix 6.6. Detailed CHEERS checklist scoring for included studies

Item no.	Section/item	Lin (2010)	Lin (2018)	Whittington (2018)	Sarkar (2019)	Santasusana (2020)	Thielen (2020)	Furzer (2020)	Yang (2020)	Maser (2020)	Schulthess (2021)	Wakase (2021)	Moradi-Lakeh (2021)	Item scores (out of 12)
1	Title	1	1	0.5	1	1	1	1	0.5	1	0.5	1	1	10.5
2	Abstract	1	1	1	1	1	1	1	1	1	0.5	1	0.5	11
3	Background and objectives	1	1	1	1	1	1	1	1	1	1	1	1	12
4	Target population & subgroups	1	0.5	1	1	1	0.5	0.5	0.5	1	0.5	0.5	1	9
5	Setting and location	1	1	1	0.5	1	1	1	1	1	1	1	1	11.5
6	Study perspective	1	1	1	1	1	1	1	1	1	0.5	1	1	11.5
7	Comparators	1	0.5	1	0.5	1	0.5	1	0	1	1	1	1	9.5
8	Time horizon	1	0.5	1	1	0.5	1	1	1	1	1	1	0.5	10.5
9	Discount rate	0	0.5	1	0.5	1	1	1	0	1	1	1	1	9
10	Choice of health outcomes	1	1	0.5	1	1	1	1	1	1	1	1	1	11.5
11	Measurement of effectiveness	0.5	1	1	0.5	1	1	1	1	1	1	1	1	11
12	Measurement and valuation of preference-based outcomes	1	1	0.5	1	1	1	1	0	1	1	0	1	9.5
13	Estimating resources and costs	1	1	1	1	1	1	0.5	1	0.5	0.5	1	1	10.5
14	Currency, price date and conversion	1	1	1	1	0	0.5	0.5	0.5	0	0	1	0.5	7
15	Choice of model	0	0.5	0.5	1	0.5	0.5	0.5	0.5	0.5	1	0.5	0.5	6.5
16	Assumptions	NA	1	1	1	1	1	1	1	1	0.5	1	1	10.5
17	Analytic methods	1	1	1	1	0.5	0.5	1	0	1	0	0	1	8
18	Study parameters	1	1	0.5	0.5	1	1	1	0.5	1	0.5	1	0.5	9.5
19	Incremental costs and outcomes	1	1	1	0.5	1	1	1	0.5	0.5	1	1	0.5	10
20	Characterizing uncertainty	1	1	1	1	1	1	1	0.5	1	1	1	1	11.5
21	Characterizing heterogeneity	1	1	0.5	0	1	0	0	0.5	0.5	1	0.5	1	7

22	Study findings, limitations, generalizability, and current knowledge (Discussion)	1	1	1	1	1	0.5	1	1	1	1	1	0.5	11
23	Source of funding	0.5	1	1	1	1	0.5	1	0	0	0.5	0.5	0.5	8.5
24	Conflicts of interest	1	0.5	1	0.5	1	0	1	0	0.5	0.5	0.5	1	7.5
Overall scoring (out of 24)		**19.5**	**21**	**21**	**19.5**	**21.5**	**19**	**21**	**15.5**	**19.5**	**17.5**	**19.5**	**19.5**	

Abbreviations: CHEERS: Consolidated Health Economic Evaluation Reporting Standards.

Appendix 6.7. Key model input parameters, cost categories, and main cost drivers

Author (Year)	Key model input parameters			Cost categories	Main cost drivers
	Clinical evidence	Utilities (quality of life)	Drug(s) list price		
Lin *et al.* (2010)	Clinical outcomes reported from real-world data analysis	NR	Retrospective micro-costing approach	• Cost categories: days in hospital, outpatient visits, IV treatments, nuclear medicine, laboratory and diagnostic services, radiotherapeutic and surgical procedures, blood products, medications, and emergency room visits. • PBSC costs: laboratory tests and donor collection fees but do not include costs of processing stem cell products in lab.	Room and board accounted for 50% of total costs, pharmacy accounted for ~28% of total costs. Other major cost items: blood products, lab and radiology services.
Maser *et al.* (2020)	Literature review; Raetz 2008[1]; Gamis 2014[2]; Ammann 2015[3]; Gupta 2015[4].	0.81 (Kwon *et al*. 2018)[5]	Drug Benefit Formulary[6]	Only included costs of Levofloxacin prophylaxis.	NR
Lin *et al.* (2018) ***	• Tisa-cel: Maude *et al*[7], • Blina: von Stackelberg *et al*[8], • Clo-M: Jeha *et al*[9] • HSCT: von Stackelberg *et al*[8], Hijiya *et al*[10], Locatelli *et al.*[11], Miano *et al.* [12], Crotta *et al*[13]	• Tisa-cel: 0.78 (Tengs).[14] • Blina: 0.78 (Delea[15]; van Litsenburg[16]). • Clo-C and Clo-M: 0.71 (Furlong).[17].	Costs in US$ • Tisa-cel: $475,000 (Red Book[18]) • Blina: $44,000 (CMS[19]) • Clo-C: $67,000 (CMS[19]) • Clo-M: $47,000 (CMS[19])	• Direct health care costs: drugs (including tisa-cel), therapy administration, AE, HSCT, and follow-up. • Related costs: pre-infusion chemotherapy, administration, and complications. • Follow-up costs after tisa-cel assume 5 years of B-cell aplasia with monthly IV immunoglobulin infusions for patients in remission.	NR
Whittington *et al.* (2018)	ICER[20], Jeha et al[9]	Kelly et al[21]	Acquisition cost (with markup) in $ • Tisa-cel: $575,000 • Clo-C: Clofarabine (264 per mg/mL), Cyclophosphamide (0.74 per mg/mL), Etoposide (0.09 per mg/mL) Red book[18]	• Cost categories: drugs, other chemotherapy, healthcare use costs (cost per hospital day, cost per ICU Day, office visits, IV administration, hematology panel, liver function tests).	NR

Sarkar *et al.* (2019)	CAR–T cell transition probability: Maude et al[7]; FDA Drug Advisory Meeting[22]	Sung et al., 2003,[23] Furlong et al., 2012[24] Hettle et al., 2017,[25] Aristides et al., 2015,[26] Beauchemin et al., 2016[27] Cuthbertson et al., 2005[28]	Costs in US$ • Tisa-cel: $475,000 (Bach et al. [29]) • Standard of care: (Clo-C): 51,286 (AWP[8,12,22,30,31,32]; followed by HSCT: successful: 299,987; failed: 459,682 (Lin et al., [33])	•Cost of drug (tisa-cel), cost of toxicity, cost of end-of-life care (for 1 month for patients who died after relapse).	NR
Santasusana *et al.* (2020)	•Tisa-cel: ELIANA, ENSIGN, and B2101J trials.[7,34,35,36,37] •FLA-IDA: Von Stackelberg *et al*.[8]	•Utility in the EFS state: 0.91; utility in the PD/RL state: 0.75 (Kelly *et al*[21]). •Disutility associated with tisa-cel or FLA-IDA: − 0.42 (Sung *et al*.).[23]	•Tisa-cel: € 320,000 (discounted € 307,200). •FLA-IDA: Fludarabine 25 mg/mL, 1 vial, 2 mL (€ 49.77); Cytarabine 1 g, 1 vial, 10 mL (€ 14.380); and Idarubicin 5 mg, 1 vial, 5 mL) (€ 40.90).	•Cost categories: pharmacological treatments and costs derived from health resource use. •In infused patients, based on the clinical trial results, costs of the use of the following resources were considered: bridging chemotherapy, lymphodepleting chemotherapy (96% of patients), tisa-cel infusion, hospitalization, management of AE, HSCT, follow-up and terminal care. •In non-infused patients, costs of salvage chemotherapy (one FLA-IDA cycle), hospitalization, AE management, follow-up and terminal care were considered. •For the comparator, the pharmacological costs of salvage chemotherapy (FLA-IDA), hospitalization costs, costs of the management of AE, costs of HSCT, follow-up and terminal care costs were considered.	In the case of tisa-cel, the main cost determinant was the pharmacological cost while, in the case of FLA-IDA, it was the cost derived from HSCT.
Thielen *et al.* (2020) ****	•Tisa-cel: duration of benefit in months: 60 •EFS vs OS ratio for all Comparators: 0.69 (Van den Berg *et al.* 2011).[38]	•Utility for EFS: 0.83 and for PD: 0.68 (ELINA trial). [34] •Disutility for tisa-cel, Clo-M, Clo-C, Blina: -0.20 (Kwon *et al*. (utility value)[5]; Gaynon (duration Clo-M)[39]; Hijiya (duration (Clo-C)[40]; von Stackelberg (duration Blina).[8]	•Pretreatment cost for lymphodepleting regimen: €521 (ELIANA trial) [34] •Tisa-cel €320,000 •Clo-M: €71 020 •Clo-C: €35 453 •Blina: €117 934 (Dutch Z-index public list price, Jeha 2006, Hijiya 2011, von Stackelberg 2016). [8,9,40]	•Costs of pretreatment, treatment, AE, follow-up period, subsequent HSCT, and future medical costs. •Tisa-cel included costs for drug acquisition and administration, outpatient and inpatient days.	Main cost driver was the much higher drug acquisition costs for tisa-cel, compared to other drugs.

Furzer *et al.* (2020)	Clinical outcomes reported from Canadian population-based registry.	• Tisa-cel: 0.80 (Short-term utility assumed equivalent to HSCT without GVHD).[41] • HSCT: 0.73 (Ontario Ministry of Health and Long Term Care13; Kurosawa *et al*[41])	• Tisa-cel: CaD $625,000 (Bach *et al.*, 2018). [29] • HSCT: CAD $112,582 (Ontario Ministry of Health and Long Term Care13; Kurosawa *et al*.) [41]	• Costs associated with in-hospital treatment and follow-up care for both treatment strategies. • For patients infused with tisa-cel,, additional nonproduct costs applied for cell infusion, monitoring and management of adverse events, and associated hospitalizations.	For those who received tisa-cel, the most significant cost component was the product itself. .
Yang *et al.* (2020)	NR	NR	• Tisa-cel: $475,000 (RED BOOK.[18] CMS Physician Fee Schedule).[42] Pre-treatment regimens: • Regimen A: Fludarabine $281.23; Cyclophosphamide $817.47 (RED BOOK) [18] • Regimen B: Cytarabine $11.40; Etoposide $42.40 (RED BOOK) [18]	• Cost components included leukapheresis, lymphodepleting chemotherapy, tisa-cel infusion and hospital administration, inpatient and ICU admissions, medical professional visits, laboratory tests and procedures, for medical professional visits and management of major AE (resource estimates based on ELIANA trial).	Top 3 drivers of "additional cost" were AE management (51.6%), inpatient and ICU admissions not attributed to AE (42.1%), and laboratory tests and procedures (3.8%).
Schulthess *et al.* (2021)	Clinical evidence from RWD from EHR	NR	• Tisa-cel: US$475 000 • HCT: US$303,065	• Internal costs within the hospital, the cost of CAR-T infusion and follow-up (excluding price cost of CAR-T cell therapy).	80% of the cost is due to the purchase price of the drug itself.
Wakase *et al.* (2021)	• Tisa-cel: ELIANA, ENSIGN, and B2101J trials.[34,35,36] • Blina: von Stackelberg,[8] Gore *et al*[43] • Clo-C: Miano *et al*, Hijiya *et al.*, Locatelli *et al*.[11,12,40]	• Tisa-cel (infused patients): -0.42; 32 d • Blina: -0.42; 61 d • Clo-C: 0.42; 47 d (Sung *et al*.;[23] (disutility) ELIANA study;[34] (duration for Tisa-cel) von Stackelberg *et al.* (duration for Blina); [8] Hijiya *et al*.(duration for Clo-C). [40]	Costs including drug and administration costs: • Tisa-cel: JPY 40,276,340 • Blina: JPY 11,872,596 • Clo-C: JPY 2,984,104 596	• Costs categories: pretreatment costs, treatment costs, AE costs, follow-up costs, subsequent HSCT costs, and terminal care costs.	NR

Moradi-Lakeh *et al.* (2021)	•Tisa-cel: ELIANA, ENSIGN, and B2101J trials. [34,35,36] •Comparators: Hijiya 2011; Jeha 2006; Kuhlen 2018; Locatelli 2009; Miano 2012; von Stackelberg 2016, von Stackelberg 2011.[40,9, 44,11,12, 8, 45]	• Utility for EFS (0.91) and for PD (0.75) Treatment disutility • Tisa-cel: (infused patients): -0.03 • Clo-C: -0.03 •Blina: -0.02 •Salvage chemo: -0.04	•Tisa-cel: CHF 329,367 •Blina: CHF 127,816 •Clo-C: CHF 51,284 •FLA-IDA: CHF 3,600	•Costs categories: pre-treatment leukapheresis, bridging chemotherapy and lymphodepleting costs for tisa-cel arm, drug and procedure acquisition costs for tisa-cel and comparators, associated drug administration costs, associated hospitalization and ICU costs, adverse event costs, sub- sequent SCT costs, other follow-up and monitoring costs, and terminal care costs.	NR

Abbreviations: CCG: Children's Cancer Group; **NR:** Not reported; **PBSC:** Peripheral blood stem cell; **HSCT:** haematopoietic stem cell transplantation; **tisa-cel:** tisagenlecleucel; AE: adverse events; **Blina:** Blinatumomab; **Clo-C:** Clofarabine combination therapy; **Clo-M:** Clofarabine monotherapy; **ICER:** Institute for Clinical and Economic Review; **PD:** progressive disease; **RL:** relapse. **NR:** Not reported; **RWD:** Real-world data. Clofarabine combination therapy includes clofarabine, cyclophosphamide, and etoposide. FLA-IDA salvage chemotherapy includes combination of fludarabine, cytarabine and idarubicin. Reference list is included in Additional References (below in this document).

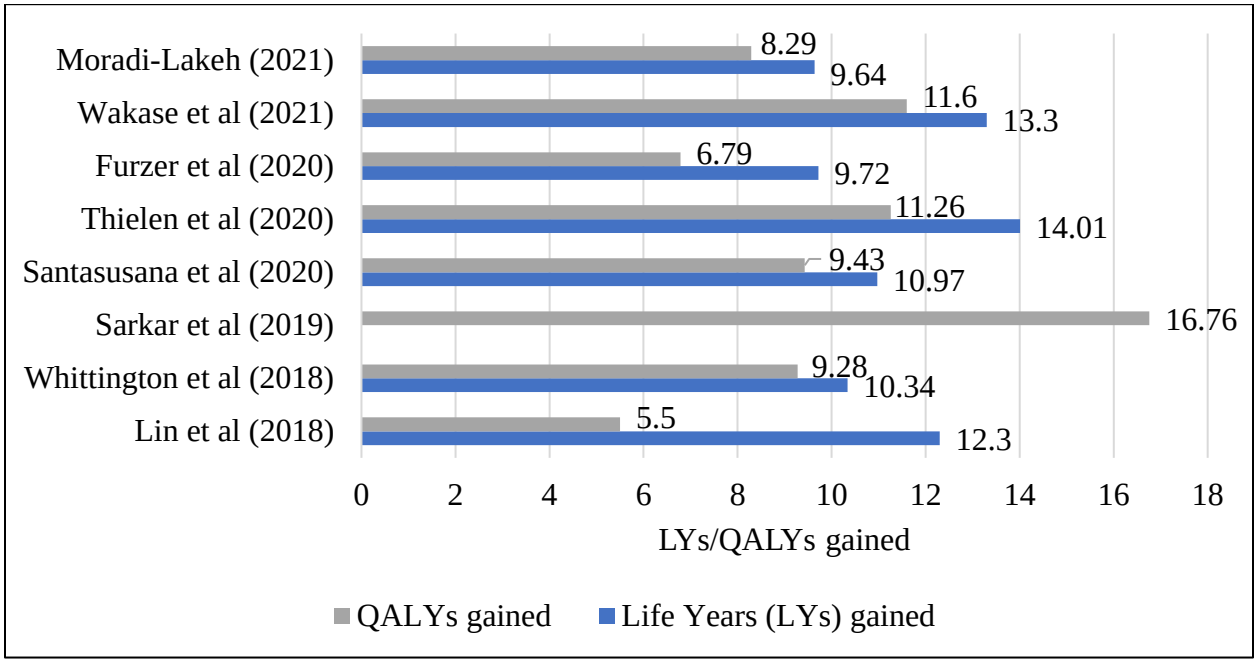
Appendix 6.8. Sensitivity (uncertainty) analysis

Author (Year)	Method of sensitivity (uncertainty) analysis	Results of sensitivity (uncertainty) analysis
Lin *et al.* (2010)	One-way and probabilistic sensitivity analysis	• There was a higher probability that PBSCT was less effective and more costly, and 19% probability for PBSCT being less costly, but also less effective. • There is a 36.8% probability that PBSCT would be less costly but also less effective compared with BMT. • PBSCT has an equivalent opportunity (24%) of being the dominant option or being the dominated choice over BMT. • Overall, there is no clear preference for either treatment method, because of the large degree of uncertainty in the results. • The ICER was reduced to $1.41 million in the analysis of high-risk patients, with BMT more expensive and more effective than PBSCT.
Maser *et al.* (2020)	One-way deterministic, probabilistic (Monte Carlo simulation), and threshold analysis.	• Levofloxacin prophylaxis remained cost-effective within the predetermined range of values for all parameters. • Levofloxacin prophylaxis became a nondominant alternative at daily levofloxacin costs of ≥$21.55 but remained cost effective throughout the range tested, using a willingness-to-pay threshold of $50 000/QALY.
Lin *et al.* (2018) ***	One-way deterministic and probabilistic sensitivity analysis	• In one-way sensitivity analyses, two model parameters rendered tis-cel cost-effective by assuming modest long-term outcomes: reductions in price and a low discount rate. • In a bridge- to-transplantation scenario, increasing the proportion of patients who receive a transplantation (and achieve remission) from 0.55 to 0.75 improved tis-cel's economic value, but it would not make it cost-effective. • Tis-cel's economic value was substantially worse if costs and benefits were over 15 years rather than lifespan. • Several parameters moderately worsened tis-cel's economic value: standardized mortality ratio after long-term remission, cost of care after long-term remission, and cost of care for grade 4 cytokine release syndrome. • In probabilistic sensitivity analyses, tis-cel at a 5-year RFS rate of 40% was cost-effective in 99.3%, 98.7%, and 6.0% of simulations at WTP thresholds of $150,000, $100,000, and $50,000, respectively. • Tis-cel at a 5-year RFS rate of 20% was cost-effective in 53.1%, 6.5%; at a 5-year RFS rate of 0% and in the absence of transplantation, Tis-cel consistently produced inferior outcomes to Blinatumomab at a higher cost.
Whittington *et al.* (2018)[5]	Probabilistic sensitivity analysis and scenario analyses.	• Study results were robust to probabilistic sensitivity analyses. • Across scenario analyses that included more conservative assumptions regarding long-term relapse and survival, the incremental cost-effectiveness ratio ranged from $37,000 to $78,000 per QALY gained.
Sarkar *et al.* (2019)	One-way deterministic and probabilistic sensitivity analyses	• CAR-T was cost-effective in 94.8% of iterations at a WTP of $100,000/QALY. • CAR-T therapy would be cost effective 94.8% of the time at a WTP threshold of $100,000 per QALY. • Base-model assumed a 76.0% 1-year survival, if this decreased to 57.8%, then CAR-T is no longer cost-effective. • If the complete remission rate of CAR-T recipients decreased from 81% to 56.2%, or if the health utility of disease-free survivors decreased from 0.94 to 0.66, then CAR-T was no longer cost-effective.
Santasusana *et al.* (2020)	Deterministic sensitivity analyses	• Sensitivity analysis showed that model results were robust, since all variations result in an ICUR below €50,000/QALY.

	and scenario analysis	• Changes in parameters that most affected the results were those made in the discount rate for costs and benefits (0–5%; 3% base case), the pharmacological cost of tis-cel (± 25%) and age of onset (1–25 years; 12 years base case). • All modifications resulted in an ICUR below € 40,000/QALY. • In scenario analysis, the modification of the time horizon (20 years; vs lifetime in the base-case) and different OS parametric functions are the most influential variations in results, resulting in an ICUR below € 50,000/QALY.
Thielen *et al.* (2020)****	Deterministic and probabilistic sensitivity analyses	• Results showed that 98% of the iterations in the probabilistic sensitivity analysis were cost-effective. • None of the scenarios of choosing different survival parameters exceeded the WTP threshold of 80,000 EURO/QALY. • Variation of starting age of the simulated cohort was the most influential factor for the ICER in all three comparators. • Scenario analyses, assuming a time horizon of 20 years had the highest impact on the ICER. In this scenario, the ICERs per QALY gained increased to 60 859 EUR, 63 341 EUR, and 53 698 EUR for Clo-M, Clo-C, and Blina, respectively. This implies that tisa-cel is less cost-effective with a shorter time-horizon.
Furzer *et al.* (2020)	One-way and probabilistic sensitivity analyses	• Results were robust across 1-way and structural sensitivity analyses • Increasing proportion of patients receiving IV immunoglobulin treatment, removing the value-based pricing structure and increasing standardized mortality ratio or decreasing estimated time horizon all increased the estimated ICUR. • While lowering the assumed treatment age and assuming all patients reach infusion lowered the ICUR. • The probabilistic sensitivity analysis demonstrated some overlap on expected QALYs between tisa-cel and standard care, although the incremental effect was largely in favor of tisa-cel (95%CI, 0.37-4.73QALYs gained). • Across all Monte Carlo iterations, incremental tisa-cel cost was more than standard care (95% CI, 422000-530000). • Cost-effectiveness acceptability curve indicated a 32% probability of tisa-cel being cost-effective at 150000 per QALY
Yang *et al.* (2020)	Scenario analyses	• In the scenario analyses, the total costs ranged from $483,169 (tisa-cel treatment in the outpatient setting without adverse events) to $672,373 (tisa-cel treatment in inpatient setting with grade 3/4 cytokine release syndrome and B-cell aplasia). • Under the scenario that all patients received tisa-cel treatment in the outpatient setting and did not experience any AEs during follow-up, the model calculated a cost of $8,026 aside from the tisa-cel procedure and administration. Under the scenario that all patients received tisa-cel in the inpatient setting and experienced grade ¾ CRS and B-cell aplasia, the model calculated a cost of $197,230 aside from the t tisa-cel procedure and administration
Schulthess *et al.* (2021)	Not done.	Not done.
Wakase *et al.* (2021)	Deterministic and probabilistic sensitivity analyses	• Model results remained robust to alternative model assumptions and inputs. • Across all scenarios, the incremental costs per QALY gained ranged from tisa-cel being dominant to <2,885,485 compared with a blinatumomab, and from tisa-cel being dominant to <3,756,251 compared with a Clo-C.
Moradi-Lakeh *et al.* (2021)	Deterministic and probabilistic sensitivity analyses	• Tisa-cel had a 100% probability of being cost-effective versus all comparators using a WTP threshold of CHF 100,000. • Highest impact was including productivity gains which ended up with dominancy of tisa-cel over competitors. • Tisa-cel was more effective and cheaper than all standard treatments, cost-effective under all scenarios and assumptions.

Abbreviations: PBSCT: Peripheral stem cell transplantation; BMT: bone marrow transplant; NA: Not applicable; tisa-cel: tisagenlecleucel; RFS: relapse-free survival; WTP: willingness-to-pay; OS: overall survival; ICER: incremental cost-effectiveness ratio; ICUR: Incremental cost-utility ratio; DSA: Deterministic sensitivity analysis.

Appendix 6.9. Clinical benefit (effects/outcomes) of CAR-T cell therapy: LYs gained and QALYs gained*



Abbreviations: LYs: Life years; QALYs: Quality adjusted life years. * LYs gained and QALYs gained were included as absolute effects/outcome of CAR–T cell therapy, not incremental values compared to other treatment interventions.

Appendix Chapter 7

Appendix 7.1. The Consolidated Criteria for Reporting Qualitative Research (COREQ): 32-item checklist

No. Item	Guide questions/description	Location in thesis where items are reported
Domain 1: Research team and reflexivity		
Personal Characteristics		
1. Interviewer/facilitator	Which author/s conducted the interview or focus group?	Page 236
2. Credentials	What were the researcher's credentials? e.g. PhD, MD	Page 236
3. Occupation	What was their occupation at the time of the study?	Page 236
4. Gender	Was the researcher male or female?	Page 236
5. Experience and training	What experience or training did the researcher have?	Page 236
Relationship with participants		
6. Relationship established	Was a relationship established prior to study commencement?	Page 238
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	Page 238
8. Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	Page 238
Domain 2: study design		
Theoretical framework		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? *e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis*	Page 239
Participant selection		
10. Sampling	How were participants selected? *e.g. purposive, convenience, consecutive, snowball*	Page 238
11. Method of approach	How were participants approached? e.*g. face-to-face, telephone, mail, email*	Page 238
12. Sample size	How many participants were in the study?	Page 238
13. Non-participation	How many people refused to participate or dropped out? Reasons?	Page 240
Setting		
14. Setting of data collection	Where was the data collected? e.*g. home, clinic, workplace*	Page 238, 239
15. Presence of non-participants	Was anyone else present besides the participants and researchers?	Page 238, 239
16. Description of sample	What are the important characteristics of the sample? *e.g. demographic data, date*	Page 238

Data collection		
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Page 238, 391
18. Repeat interviews	Were repeat interviews carried out? If yes, how many?	Page 238
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	Page 239
20. Field notes	Were field notes made during and/or after the interview or focus group?	Page 239
21. Duration	What was the duration of the interviews or focus group?	Page 240
22. Data saturation	Was data saturation discussed?	Page 238
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	NA
Domain 3: analysis and findings		
Data analysis		
24. Number of data coders	How many data coders coded the data?	Page 239
25. Description of the coding tree	Did authors provide a description of the coding tree?	NA
26. Derivation of themes	Were themes identified in advance or derived from the data?	Page 239, 241, 242
27. Software	What software, if applicable, was used to manage the data?	Page 239
28. Participant checking	Did participants provide feedback on the findings?	NA
Reporting		
29. Quotations presented	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? e.*g. participant number*	Page 245–247
30. Data and findings consistent	Was there consistency between the data presented and the findings?	Page 241
31. Clarity of major themes	Were major themes clearly presented in the findings?	Page 241, 242
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Page 248

Appendix 7.2. Ethics approval by Oxford Tropical Research Ethics Committee (OxTREC)

Oxford Tropical Research Ethics Committee

University of Oxford
Research Services, Research Governance, Ethics & Assurance
Boundary Brook House, Churchill Drive, Oxford OX3 7GB
Tel. +44 (0)1865 (2)82106
E-mail: oxtrec@admin.ox.ac.uk



7 January 2022

Ranin Soliman
DPhil student in Evidence-based Healthcare
Department for Continuing Education, University of Oxford
c/o Maadi Degla, street 233, building 9, apartment 22,
Cairo, Egypt

Dear Ms Soliman

Full Title of Study: Barriers and facilitators to implement cost-effective childhood cancer treatment in Egypt based on evidence

OxTREC Reference: 569-21

Thank you for your email of 21 December 2021, and for your updated minimal risk application form and study documents.

I am pleased to confirm that approval has now been granted for this study. This is valid for the first five years and is subject to receiving the local ethical approval (if this approval has not yet been received).

The documents approved for this study are as follows:

Documents:	Version:	Date:
OxTREC participant information sheet Soliman R	2	21 Dec 2021
OxTREC consent form Soliman R	2	21 Dec 2021
Recruitment material Soliman R	2	21 Dec 2021
Interview guide Soliman R	1.1	30 Nov 2021
OxTREC minimal risk application form	2	21 Dec 2021

Any subsequent changes to the application must be submitted to the Committee as an Amendment. This should include a letter to give the reasons for the proposed modifications and all revised documents with changes tracked.

Please ensure that you submit a completed Annual Report form on every anniversary of this approval and a final End of Study Report. The relevant forms can be found on the OxTREC website: https://researchsupport.admin.ox.ac.uk/governance/ethics/apply/oxtrec.

Finally, please note the following **important information**:

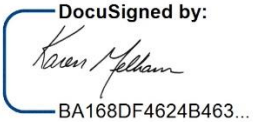
Data safety—all studies
It is the responsibility of the PI to ensure that all data collected during the course of the study is

stored and transferred safely and securely. Further guidance and advice is available from the Research Data Team.

Only studies that will involve storing human tissue samples in Oxford
If you are planning to import the samples into England, you will need to make arrangements before the samples are transferred to store them under the governance of a Human Tissue Authority (HTA) licence. It is a legal requirement that any tissue or fluid made up of or containing human cells to be used for the purpose of research is stored on premises licensed by the HTA unless covered by an exemption. OxTREC approval is not a recognised exemption. Further information may be found on the University's human tissue governance web pages: https://researchsupport.admin.ox.ac.uk/governance/human-tissue.

Yours sincerely

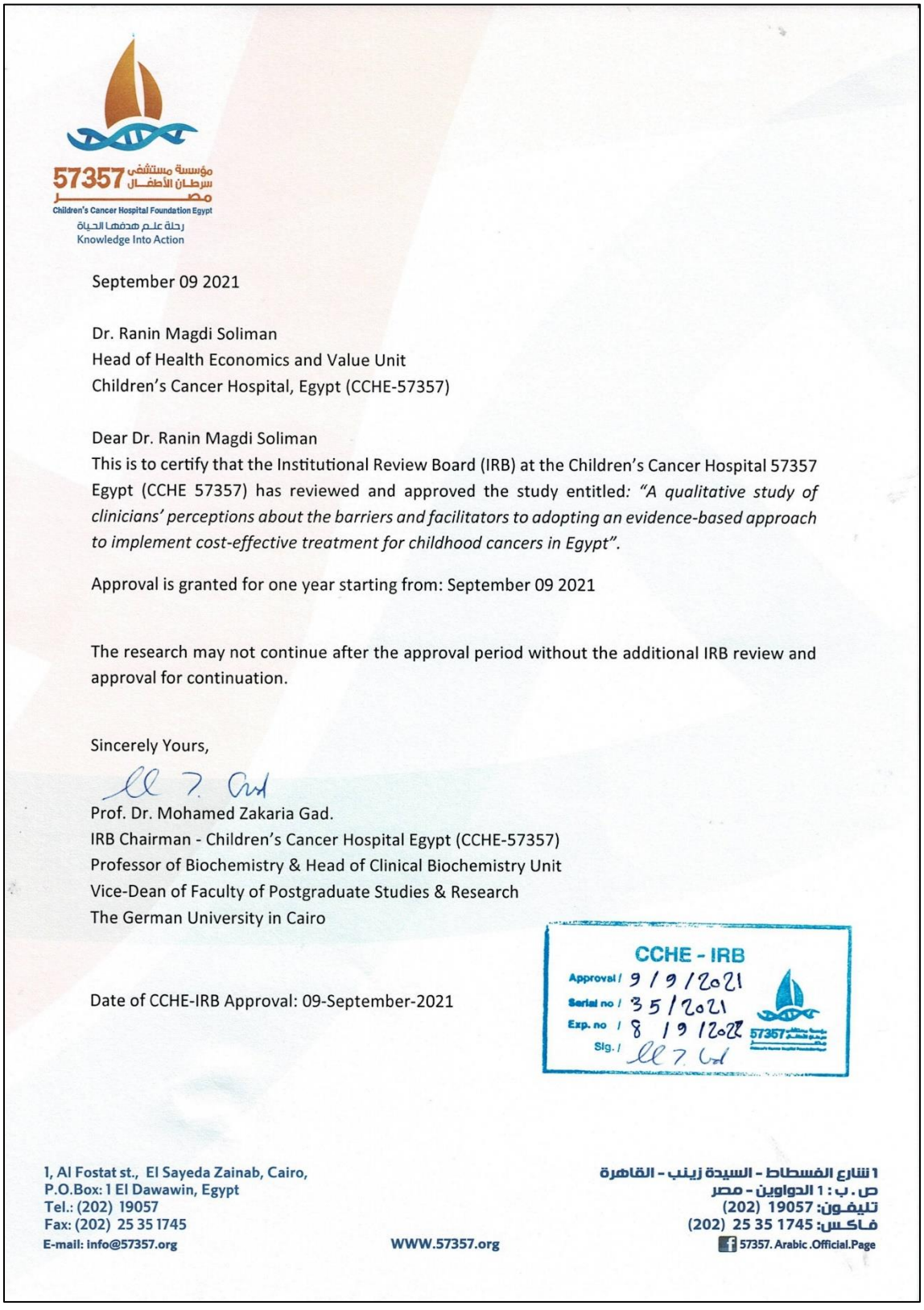
DocuSigned by:



BA168DF4624B463...

Dr Karen Melham
Sponsorship and Ethics Lead
for
Research Ethics Manager, OxTREC

Appendix 7.3. Ethics approval granted by institutional review board (IRB) at CCHE



57357 مؤسسة مستشفى سرطان الأطفال مصر
Children's Cancer Hospital Foundation Egypt
رحلة علم هدفها الحياة
Knowledge Into Action

September 09 2021

Dr. Ranin Magdi Soliman
Head of Health Economics and Value Unit
Children's Cancer Hospital, Egypt (CCHE-57357)

Dear Dr. Ranin Magdi Soliman
This is to certify that the Institutional Review Board (IRB) at the Children's Cancer Hospital 57357 Egypt (CCHE 57357) has reviewed and approved the study entitled: *"A qualitative study of clinicians' perceptions about the barriers and facilitators to adopting an evidence-based approach to implement cost-effective treatment for childhood cancers in Egypt".*

Approval is granted for one year starting from: September 09 2021

The research may not continue after the approval period without the additional IRB review and approval for continuation.

Sincerely Yours,

Prof. Dr. Mohamed Zakaria Gad.
IRB Chairman - Children's Cancer Hospital Egypt (CCHE-57357)
Professor of Biochemistry & Head of Clinical Biochemistry Unit
Vice-Dean of Faculty of Postgraduate Studies & Research
The German University in Cairo

CCHE - IRB
Approval / 9/9/2021
Serial no / 35/2021
Exp. no / 8/9/2022
Sig. /

Date of CCHE-IRB Approval: 09-September-2021

1, Al Fostat st., El Sayeda Zainab, Cairo,
P.O.Box: 1 El Dawawin, Egypt
Tel.: (202) 19057
Fax: (202) 25 35 1745
E-mail: info@57357.org

WWW.57357.org

١ شارع الفسطاط - السيدة زينب - القاهرة
ص.ب: ١ الدواوين - مصر
تليفون: 19057 (202)
فاكس: 1745 35 25 (202)
57357. Arabic .Official.Page

Appendix 7.4. OxTREC Consent form

Consent Form

Version 1.0 November 2021

Title of Study: A qualitative study of clinicians' perceptions about the barriers and facilitators to adopting an evidence-based approach to implement cost-effective treatment for childhood cancers in Egypt

Study researcher: Ranin Soliman

OxTREC reference number: **569-21**

Participant Identification Number for this study:

1. I confirm that I have read the information sheet for the above study, (version.....). I have had the opportunity to consider the information and ask questions, and have had these answered satisfactorily.	Yes / No
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my clinical or administrative roles being affected.	Yes / No
3. I understand that the information collected from me will be used to support the research project and will be shared anonymously	
4. I give consent for my data to be stored/shared overseas.	Yes / No
5. I consent to being audio-recorded and data to be transcribed anonymously.	Yes / No
6. I agree to take part in this study.	Yes / No

Name of participant	Date	Signature
Name of person taking consent	Date	Signature

Appendix 7.5. Consent form approved by IRB at CCHE

CONSENT FORM

Participant Identification Number for this study:





Title of Study: A qualitative study of clinicians' perceptions about the barriers and facilitators to adopting an evidence-based approach to implement cost-effective treatment for childhood cancers in Egypt

Name of Researcher: Ranin Soliman

Please check box

1. I confirm that I have read the information sheet dated..... (version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my clinical or administrative roles being affected. ☐
3. I understand that the information collected from me will be used to support the research project and will be shared anonymously. ☐
4. I understand that the information obtained during the interview will be anonymously analysed in a qualitative manner, and that results of the research study will be published in a journal. ☐
5. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person seeking consent	Date	Signature

Appendix 7.6. Recruitment material

Barriers and facilitators to adopting an evidence-based approach to implement cost-effective treatment for childhood cancers in Egypt: A qualitative study

IRB Approval Reference: [35/2021]

Participants NEEDED FOR interview



The treatment of children with cancer is resource intense and expensive, and CCHE would greatly benefit from providing cost-effective treatments that provide greatest value for money (improved health outcome relative to costs). Implementation of cost-effective treatment based on evidence requires knowledge about the factors affecting its use.

We are looking for senior clinicians (senior paediatric oncologists who are the study team leads, senior surgeons, and senior radiation oncologists) to give their opinions and views about the barriers and facilitators to adopting an evidence-based approach to implement cost-effective treatment for childhood cancers. You are invited to participate in this study through being interviewed for about 50–60 minutes.

If you are interested and would like more information, please contact Dr. Ranin Soliman at the Health Economics and Value Unit, on 01003263399 or by email at ranin.soliman@kellogg.ox.ac.uk. There is no obligation to take part.

Thank you!

Appendix 7.7. Participant Information Sheet

Participant Information Sheet (PIS)

Version 1.0 November 2021

Title of Study: A qualitative study of clinicians' perceptions about the barriers and facilitators to adopting an evidence-based approach to implement cost-effective treatment for childhood cancers in Egypt

Study researcher: Dr. Ranin Soliman

OxTREC reference number: **569-21**

1. What's the purpose of this research?

This study aims to understand clinicians' perceptions about the barriers and facilitators of adopting an evidence-based approach to implement cost-effective treatment interventions for children with cancer in Egypt at CCHE. Getting your voices and opinions heard about the potential barriers and facilitators affecting the use of cost-effective treatment based on evidence at CCHE will help translate the knowledge into practice, and make better informed decisions in patient care.

2. Why have I been invited to take part?

You were invited to take part in this study owing to your role as a senior clinician (study team lead or senior consultant) who is involved in the decision-making process of evaluating and choosing the treatment interventions that patients receive at CCHE. We need your clinical expertise and experience to understand your views and perceptions of implementing cost-effective treatment intervention for children with cancer, in an evidence-based approach. Your valuable contribution would be much appreciated to address the gap between evidence and practice, and to translate the knowledge into action in the clinical setting.

3. What's involved for me?

If you agree to take part as a participant in this study, you will be interviewed about your opinions, views, and perceptions as a senior clinician regarding the adoption of an evidence-based approach to implement cost-effective treatment interventions at CCHE. The interview will take place as either face-to-face, online through video/audio conference on MS. Teams, or through the phone. The interview will be audio-record for verbatim transcription used in qualitative data analysis, and is expected to last between 50–60 minutes. You are encouraged to ask any questions you have before the interview, and we ask you to complete the informed consent at least 24 hours before it.

4. What will happen to my data?

Research data that is collected as part of the study will include audio-recording of the interviews. Confidentiality of the participants will be maintained through de-identification and anonymously transcribing the audio-recorded interviews into anonymous text, and anonymously coding the participants into de-identified unique participant identification ID for the study.

Data will be stored with the study PI (Dr. Ranin Soliman) using the de-identified participants' study ID, and will be shared anonymously with other study investigators and overseas with the supervisors at the University of Oxford to ensure confidentiality of data. The audio-recorded files will not be shared with any of the study investigators at CCHE or at the University of Oxford. Data will not be shared with other researcher not working on the study. The use of personal data in the study will be minimised as much as possible, and personal data will not be retained for future research studies.

5. Are there any risks in taking part?

There are no potential risks to the participants Confidentiality of the participants will be maintained through de-identification and anonymously transcribing the audio-recorded interviews into anonymous text, and anonymously coding the participants into de-identified participant identification ID for the study.

Data will be stored with the de-identified participants' study ID, and will be shared with the supervisors and other study investigators anonymously to ensure confidentiality of data. The audio-recorded files will not be shared with my supervisors or any of the investigators.

6. What are the benefits of taking part?

Potential benefits of the study to the participants include: having the opportunity to express their views and opinions to help translate evidence into practice, and how to practically apply this at CCHE. This will enable developing a mechanism and a system for the implementation of cost-effective treatment interventions based on evidence, from the clinicians' perspectives.

7. Do I have to take part?

Participating in this study is voluntary (not mandatory) and it is their choice whether to take part or not and this choice will not affect the clinical or administrative roles of the clinicians. The potential participants can ask questions about the study before deciding whether to take part, and if they agree to take part, they can withdraw from the study without penalty at any time.

8. Has the study been reviewed by an ethics committee?

The study was approved by the Institutional Review Board (IRB) ethics committee at CCHE on 09/09/2021 (serial number 35/2021). The study will also seek the research ethics approval at the University of Oxford for research conducted outside the UK/EU (OxTREC).

9. What if I have any questions or want to raise a concern?

Potential participants may ask any questions or raise any concerns at any time. If you have any questions about participating in this study, please contact the researcher who organize it and is responsible for communication with the participants on behalf of the research team: Dr. Ranin Soliman **on 01003263399.**

10. Data protection

The University of Oxford is the data controller with respect to your personal data, and as such will determine how your personal data is used in the study. The University will process your personal data for the purpose of the research outlined above. Research is a task that is performed in the public interest. Further information about your rights with respect to your personal data is available from http://www.admin.ox.ac.uk/councilsec/compliance/gdpr/individualrights/.

The University of Oxford is responsible for ensuring the safe and proper use of any personal information you provide, solely for research purposes.

Appendix 7.8. The interview guide: topics and example questions

Interview Guide
Version 1.0 November 2021

57357

UNIVERSITY OF OXFORD

Title of Study: Barriers and facilitators to adopting an evidence-based approach to implement cost-effective treatment for childhood cancers in Egypt: A qualitative study

Study researcher: Dr. Ranin Soliman

This study involves conducting semi-structured interviews, which will be guided by some pre-defined topics and example guiding interview questions as below. However, the main focus will be to elicit issues of importance to the participants. The questions below may or may not be asked in their entirety and may not be asked in a specific sequence (based on the interview dynamics). These are some predefined topics and example guiding questions that are not necessarily asked in the same order.

Interview topics	Example questions
Decision-making process regarding treatment options	• Can you describe the process of decision-making regarding the treatment of children with cancer? - Prompts: Who is involved? What role do you play? What happens? How are decisions made? Who is responsible for making the ultimate decision? How is the decision-making process governed and held to account?
Experiences and implementation of evidence-based practice	• What are the main sources of knowledge (evidence) that you use to make clinical decisions about the treatment of children with cancer?
Knowledge about costs and benefits of treatment interventions	• How does your knowledge of costs of treatment (relative to outcomes) affect your decision-making process in the clinical setting? How important is this to you?

Barriers and facilitators to implement cost-effective treatment based on evidence	• From your experience, what do you think are the barriers or challenges to adopt cost-effective interventions based on evidence in clinical practice? - How can these barriers be overcome? • What are some of the facilitators or enablers? - How can they be more effectively used to improve the decision-making process? - How can they be more effectively used to improve outcomes for children?
Suggestions to help implement cost-effective evidence-based treatment	• What skills could be useful in supporting the adoption of cost-effective treatment interventions based on evidence? • What additional mechanisms could be useful in supporting the adoption of cost-effective treatment interventions based on evidence? Who is responsible for implementing these? • What policies could be useful in supporting the adoption of cost-effective treatment interventions based on evidence? • How do you see your own role in supporting the use of evidence in clinical practice? • What advice would you give to other clinicians about using evidence in clinical practice?