The impact of dose intensity in the adolescent and young adult cancer population

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Submitted in accordance with the requirement for the degree of Doctor of Philosophy

The University of Leeds

School of Medicine

December 2023

Intellectual Property and Publication Statement

I confirm that the work submitted is my own, except where work which has formed part of jointly authored publications has been included. My contribution and the other authors to this work has been explicitly indicated below. I confirm that appropriate credit has been given within the thesis where reference has been made to the work of others.

This thesis has been written as an alternative format thesis. This method has enabled the research to be disseminated promptly, whilst the work is still relevant. It has also given me excellent experience of scientific writing for which I have gained invaluable feedback not only from co-authors but also through peer- review. This has enhanced the research I have carried out and the publications I have produced.

In Chapter 1 the aims and objectives of the thesis are listed. Chapter 2 provides a review of the background literature with Chapter 3 describing the methods used. My published review paper can be found in Appendix A providing a summary of the challenges faced in managing adolescents and young adults with cancer. Chapters 4-6 each contain a scientific paper, two of which have been published and one which will be submitted in the coming months. Each paper is briefly introduced and contains an individual set of references. Supplementary material for each paper is included in appendices B to D and the reader signposted to this content at relevant points in the text. Appendix E contains unpublished analysis investigating the impact of RDI on survival in bone tumours. Appendix F summarises variation in achieved RDI by sociodemographic characteristics. A description of the data cleaning required for Chapter 4 is provided in Appendix G. Chapter 7 brings together the research summarising the main findings of the thesis, the strengths and limitations of the research and areas for future work identified.

Publications

Hughes, NF, Cromie, KJ, Feltbower, RG, McCabe, MG, Stark, D. Delivered relative dose intensity in adolescent and young adult germ cell tumours in England: Assessment of data quality and consistency from clinical trials compared to national

cancer registration data. *International Journal of Cancer*. 2023; 1-14. doi:10.1002/ijc.34762

Contributor's statement: The study was conceived by Nicola Hughes, Dan Stark and Richard Feltbower. Nicola Hughes performed the analysis with statistical support from Kirsten Cromie. Nicola Hughes, Dan Stark, Richard Feltbower, Kirsten Cromie and Martin McCabe contributed to the interpretation of the analysis. Nicola Hughes wrote the article with contributions from all other authors. All authors have read and approved the final manuscript for publication.

Hughes, N.F., Fern, L.A., Polanco, A., Carrigan, C., Feltbower, R.G., Gamble, A., Connearn, E., Lopez, A., Bisci, E. and Kathy Pritchard-Jones. Patient and public involvement to inform priorities and practice for research using existing healthcare data for children's and young people's cancers. *Research Involvement and Engagement* **9**, 71 (2023). https://doi.org/10.1186/s40900-023-00485-8

Contributor's statement: All authors contributed to the conception, design and completion of the workshops. Angela Polenco produced the workshop schedules. Nicola Hughes wrote the manuscript. All authors provided feedback and approved the final manuscript.

Hughes N and Stark D. The management of adolescents and young adults with cancer. Cancer Treatment Reviews. 2018 June; 67: 45-53.

Contributor's statement: Nicola Hughes wrote the manuscript. Dan Stark provided feedback. Both authors decided on the focus of the review. All authors provided feedback and approved the final manuscript.

Conference presentations

Understanding data for children's and young people's cancers: a participatory study. **Hughes N**, Feltbower R, Pritchard-Jones K, Fern L, Gamble A, Carrigan C, Connearn E, Polanco A. 54th Congress of the International Society of Paediatric Oncology (SIOP 2022), October 2022, Barcelona, Spain (poster).

The impact of chemotherapy dose intensity on survival in Ewing's sarcoma. A study in Teenagers and Young Adults (TYA) using the Systemic Anti-Cancer Treatment (SACT) dataset. **Hughes N**, Feltbower R and Stark D. Advances in Ewings Sarcoma, Leeds UK (poster).

The use of healthcare datasets to investigate the impact of dose intensity in the adolescent and young adult cancer population. **Hughes N,** Feltbower R and Stark D.

International Population Data Linkage Network Conference, September 2022, Edinburgh, UK (poster).

Acknowledgements

This work uses data provided by patients and collected by the NHS as part of their care and support. This PhD would not be possible without these data so many thanks to all involved in making it accessible.

Thank you to the Candlelighters Trust and the NIHR for funding me to carry out this work.

I would like to thank my supervisors Dan Stark and Richard Feltbower for their invaluable support, guidance and feedback during this project. I cannot thank them enough for steering me down this AYA path.

Thank you to Kirsten Cromie for her statistical support and for being a constant soundboard and friend throughout. I would also like to thank the YSRCCYP and PICANET teams for their friendship, advice, support and the many, many laughs. It has been a pleasure working with you all.

An additional thank you to the co-authors of the published papers contributing to this thesis for their input and critical revisions of the manuscripts: Martin McCabe, Lorna Fern, Angela Polanco, Chris Carrigan, Ashley Gamble, Emily Connearn, Angela Lopez, Ellen Bisci and Kathy Pritchard-Jones.

Thank you to Mark for always being there during the highs and lows of this PhD and to my gorgeous girls Georgie, Bea and Clemmie for their constant supply of cuddles.

Finally, I would like to thank my lovely Dad. He might not be here to see me finish this PhD but I know he would be very proud. I will be forever grateful for his unwavering love and belief. Nil satis nisi optimum.

Abstract

Survival rates for Adolescent and Young adults (AYA) with cancer lag behind those of some children and many older adults with the same cancers. The reason for this is multifactorial but this study focuses on variation in treatment received. For many cancers common in AYAs there is the evidence that maintaining dose intensity (DI) improves outcomes. This can be problematic as the more intense regimes carry greater toxicity. In AYA there is both poor recruitment and access to available clinical trials. The use of routinely collected healthcare data in this cohort is therefore appealing to investigate the efficacy of treatments.

In this study data was utilised from sources spanning regional, national and international population datasets and registries. The utility of each dataset was reviewed and described. Kaplan-Meir survival estimation was used to describe survival over time and cox proportional hazards regression methods used to determine the adjusted effect of DI on mortality risk.

Linked national data was used to investigate the impact of chemotherapy DI on survival in patients with germ cell and bone tumours. In germ cell comparisons were made to treatment received within international clinical trials. Variations in DI received in trials compared to routine care were seen alongside variations across tumour types. The impact on survival of toxicity induced modifications of treatment (TIMT) in patients receiving chemotherapy for bone tumours was investigated using linked regional data. Differences were seen in TIMT across age categories and sex. TIMT were positively associated with survival. Patient and public involvement and engagement was conducted to identify existing barriers to trust in the use of existing healthcare data for research purposes. Recommendations for changes to practice and research priorities were ascertained through use of thematic analysis.

The findings of this study have identified a patient group for which dose de-escalation of treatment may be possible and provide evidence for further research into sex and age differences in chemotherapy efficacy.

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List of Abbreviations

ABVD	Doxorubicin, bleomycin, vinblastine and dacarbazine
AE	Adverse Event
ALCL	Anaplastic Large Cell Lymphoma
ALL	Acute Lymphoblastic Leukaemia
ALT	Alanine transaminase
AML	Acute Myeloid Leukaemia
AUC	Area under the curve
AYA	Adolescence and Young Adult
BEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone.
BEP	Bleomycin, etoposide and cisplatin chemotherapy
BL	Burkitt Lymphoma
CAG	Confidentiality Advisory Group
CCA	Complete case analysis
CCNU	Cisplatin, cyclophosphamide, vincristine and lomustine
COG	Children's Oncology Group
COJEC	Cisplatin, vincristine, carboplatin etoposide and cyclophosphamide
COSD	Cancer Outcomes and Services Dataset
CTCAE	Common Terminology Criteria for Adverse Events
COPP	Cyclophosphamide, vincristine, procarbazine and prednisone
CYP	Cytochrome P450
DAG	Directed Acyclic Graph
DI	Dose Intensity
DLBCL	Diffuse large B-cell lymphoma

EE2012	Euro Ewing 2012
EFS	Event Free Survival
EGFR	Epidermal growth factor receptor
EOI	European Osteosarcoma Intergroup
EP	Etoposide and cisplatin chemotherapy
EpSSG	European paediatric soft tissue sarcoma Study Group
FFTE	Freedom from treatment failure
G-CSF	Granulocyte-colony stimulating factor
GCT	Germ cell tumour
GDPR	General Data Protection Regulation
GHSG	German Hodgkin Lymphoma Study Group
HL	Hodgkin's lymphoma
HRA	Health Research Authority
IE/VC	Ifosfamide, etoposide, vincristine, cyclophosphamide
ITCC	Innovative Therapies for Children with Cancer
LL	Lymphoblastic lymphoma
LTHT	Leeds Teaching Hospitals NHS Trust
MAR	Missing at random
MCAR	Missing completely at random
MNAR	Missing not at random
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NCRAS	National Cancer Registration and Analysis Service
NCRI	National Cancer Research Institute
NDRS	National Disease Registration Service
NHL	Non-Hodgkin's lymphoma
NHS	National Health Service

NICE	National Institute of Clinical Excellence
NIHR	National Institute of Health Research
OJEC	vincristine, carboplatin, etoposide and cyclophosphamide
OPEC	vincristine, cisplatin, etoposide and cyclophosphamide
ORR	Objective Response Rate
OS	Overall Survival
PBCR	Population-based cancer registries
PFS	Progression Free Survival
PHE	Public Health England
PNET	Primitive neuroectodermal tumours
PPIE	Patient and public involvement and engagement
RCT	Randomised Control Trial
RDI	Relative Dose Intensity
REC	Research Ethics Committee
RTDS	Radiotherapy dataset
RWD	Real World Data
RWE	Real World Evidence
SACT	Systemic Anti-Cancer Therapy
SDI	Standard dose intensity
SEER	Surveillance, Epidemiology and End Results Programme
SIOPE	The European Society for Paediatric Oncology
TIMT	Toxicity Induced Modification of Treatment
TYA	Teenage and Young Adult
VAC	Vincristine, dactinomycin and cyclophosphamide.
VAI	Vincristine, dactinomycin and ifosfamide.

VDC/IE	Vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide.
VIDE	Vincristine, ifosfamide, doxorubicin and etoposide.
WHO	World Health Organisation
YSRCCYP	Yorkshire Specialist Register of Cancer in Children and Young People

Chapter 1. Introduction

1.1 Background

The age range defined by the term Adolescent and Young Adult (AYA) varies according to purpose and is discussed in more detail later in this chapter. Here it refers to individuals aged 15-39 years to enable comparison with international research. Cancer in the AYA population is rare, accounting for less than 1% of new cancer diagnoses in England (1) and 7% of new cancers globally (2). Despite its rarity cancer is the highest cause of disease related death in this population (3)(4) and incidence rates have increased by more than a quarter since the 1990s (5). In the UK mortality rates are worse in AYA than for many other European countries (6) and survival rates lag behind those of most children and many older adults with the same types of cancers (5,7). Improving the survival of AYAs is an important clinical and societal priority, due to the loss of social structure and productivity that is associated with poor outcomes in these patients compared to cancers occurring in older adults near the end of their natural lives. Improving the quality of the survival for these patients is also paramount.

There are a number of factors that contribute to worse outcomes in AYAs. Pathways to diagnosis, variation in cancer biology (8), compliance issues (9), poor recruitment to clinical trials (10), psychological state (11) and treatment environment (12) (i.e. specialist versus non-specialist centre) all play a part. It is variation in chemotherapy treatment received that this study focuses upon.

1.2 Study rationale

Chemotherapy remains an important and potentially curative treatment for many AYA cancers including germ cell tumours and tumours of the bone. Here, the dose is critical if the cancer is to be cured. It is vital to ensure that a sufficient dose is given to kill the cancer cells, but not so much as to cause unacceptable toxicity and at worst, preventable and early excess deaths. Dose intensity is the quantity of a chemotherapy drug (e.g. mg per m^2) administered per unit time (e.g. weeks). For

some AYA cancers the evidence suggests that maintaining dose intensity (DI) improves outcomes (13–18). The literature surrounding DI in the AYA population however is limited and relies on clinical trial data, often retrospectively. This is problematic due to AYA having both poor recruitment and less access to available clinical trials (19) meaning the findings may not be true in everyday practice. For this reason, the use of existing health datasets holds much potential in addressing the impact of DI in AYA.

This project will contribute to improving cancer outcomes among AYAs, aligning to a number of identified areas of need:

- The NHS Long Term Plan sets out strategies to improve outcomes for children and young people with cancer (20).
- In 2005, the National Institute of Clinical Excellence (NICE) identified the treatment of AYA cancers as an area of need and published guidelines on 'Improving outcomes for cancer in children and young people (21)'.
- In 2014, NICE supplemented their guidance with seven statements prioritising areas for service improvement (22), one of which was the introduction of electronic chemotherapy prescribing in the paediatric and AYA setting.
- In January 2018, the James Lind Alliance Priority Setting Partnership released their top 10 living with and beyond cancer research priorities for teenagers and young adults with cancer, two of which cover treatment-related side effects (23).
- A report by The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) (24) examined deaths in patients up to the age of 24 years receiving Systemic Anti-Cancer Therapy (SACT). The key recommendations include improved assessment of toxicity throughout treatment and the availability of all SACT prescriptions on hospital IT systems.
- Embracing the power of data as outlined by the United Kingdom (UK) government in their policy "Data saves lives: reshaping health and social care with data (25).

- The CRUK research strategy announced in 2022 “Unleashing the power of data to beat cancer” (26).

By demonstrating where DI influences survival outcomes and identifying barriers to patients receiving optimal chemotherapy this study hopes to inform healthcare interventions to improve patient care. In addition, this research will demonstrate the potential utility of routinely collected health data for AYA cancer research and use the voice of patients and the public to improve research practices and identify research priorities.

1.3 Research questions

1. Is the dose intensity of chemotherapy received by AYA cancer patients causally associated with their survival?
2. Does the toxicity experienced by AYA receiving chemotherapy differ according to patient characteristics and is there in a causal association between toxicity experienced and survival?
3. What are the strengths and weaknesses of existing data sets at a regional, national and international level in answering these questions? Where weaknesses exist, what improvements can be recommended?
4. What current barriers exist to the use of healthcare data for research from a patient and public perspective and how could these be overcome?

1.4 Aims

1. To determine the causal association between survival outcomes of AYAs with cancer receiving chemotherapy and the dose intensity of treatment that they have received, accounting for and exploring the effects of external demographic and clinical factors.
2. To describe the toxicity experienced by AYA receiving chemotherapy and whether this differs according to age and sex.
3. To explore the utility of existing health datasets; those routinely collected in the NHS and in prospective clinical trials, to address aims 1 and 2.

4. To use patient and public involvement to improve research practice and inform future research questions.

1.5 Objectives

1.5.1 Primary objectives

For the regional, national and clinical trials datasets within the study, the objectives were to:

1. Identify existing datasets suitable for analysis.
2. Request and receive data from source.
3. Extract, clean, code, classify and examine the data.
4. Analyse these data to quantify, characterise and interpret the relationship between chemotherapy dose intensity and survival outcomes.
5. Compare the quality and completeness of the datasets and their utility for AYA research.

1.5.2 Secondary objectives

1. Review the datasets for data items relating to toxicity, comparing the quality and completeness.
2. Extract the available data items and analyse these data to compare experienced toxicity by age and sex and the relationship between toxicity and survival.
3. Carry out Patient and Public Involvement and Engagement (PPIE) to identify barriers to trust in the use of existing healthcare data and data linkage methodology for research.

1.6 Thesis outline

Chapter 2 contains a review of the existing evidence surrounding chemotherapy dose intensity in AYA, identifying gaps in the current literature. This is supplemented by Appendix A which contains a detailed review of the challenges faced in the management of AYA with cancer. In Chapter 3 the data sources and

statistical methods used throughout are discussed. Chapter 4 contains the relative dose intensity (RDI) analysis carried out for patients with a Germ Cell Tumour (GCT) using a clinical trials dataset and data from the English national cancer registry. In Chapter 5 the toxicity of patients receiving chemotherapy for bone tumours in investigated using linked data from a regional cancer register and electronic patient records. Chapter 6 describes the PPIE work carried out with young people and their carers. Chapter 7 brings together the research summarising the main findings of the thesis. The strengths and limitations of the research are discussed along with implications for research and clinical practice and areas for future work identified. Appendices B to D contain supplementary material for Chapters 4, 5 and 6. Appendix E contains unpublished analysis investigating the impact of RDI on survival in bone tumours. Appendix F summarises variation in achieved RDI by sociodemographic characteristics. Appendix G provides a more detailed description of the data cleaning carried out for this thesis and further information of some of the statistical modelling performed.

Chapter 2. Background and review of the literature

2.1 Introduction

In this chapter a background is provided into the use of dose intense chemotherapy for cancer in the AYA population. The theory and scientific basis of chemotherapy DI is described along with how it is implemented in AYA cancers. Challenges in achieving DI are highlighted and the existing gaps in the literature outlined.

My published literature review provided the background to this thesis and is included in Appendix A. It provides a detailed overview of cancer in the AYA population, the unique challenges that arise and discusses the different age ranges used to define this population. This thesis uses the term AYA throughout, referring to individuals aged 15 to 39 years and chosen to align with that used internationally. The age ranges investigated in each Chapter of this thesis however differ according to study design and are clarified in the inclusion criteria.

2.2 Classification of AYA tumours

The International Classification of Diseases in Oncology (ICD-O) codes cancers according to their topography (anatomical site), morphology and behaviour (e.g., malignant, benign, in situ or metastatic). The ICD-O is currently in its 3 edition, (ICD-O-3), and is an extension of the tenth revision of the International Classification of Diseases (ICD-10), which describes the anatomical site only.

In children the International Classification of Childhood Cancer, currently in its 3rd edition, is used (ICCC-3). This classification system comprising 12 diagnostic groups and 47 subgroups is based more on morphology than site. Whilst it can be useful when applied to AYA cancers the distribution of cancers seen in this age group differs to that seen in younger children. For example, the germ cell cancers seen predominately in AYA cancer are much less predominant within childhood cancers.

In adults, classification tends to be described according to the anatomical site of the tumour (topography). In AYAs it was recognised that for the cancers common in this age group morphology was more important than site, for example Ewing sarcomas or germ cell tumours can occur (with similar cancer biology and requiring similar treatment protocols) throughout the body. So, as for many AYA cancers, classifying a cancer as Ewing sarcoma provides more useful information than naming it a chest wall cancer. The most accurate description being provided by both site and morphology (e.g. 'Ewing Sarcoma of chest wall primary site').

In order to take into account the distinct profile of cancers seen in the AYA population, a separate classification system was developed. The Birch classification(28), also based on ICD-O, comprises of 10 main diagnostic groups containing 32 sub-divisions. This enables maximum allocation of codes to specific categories, reducing the number of malignancies falling within the "other" category. Malignant germ cell tumours form their own group and carcinomas are separated in more detail. In situ tumours and cancers if uncertain behaviour occurring outside of the CNS are excluded.

2.3 Chemotherapy in AYA cancers

The development of novel anti-cancer agents targeting cell signalling pathways, and agents killing through the host immune system has seen improvements in outcomes for some cancers in AYAs such as metastatic melanomas. Despite this cytotoxic chemotherapy which kills cancer cells by damaging DNA replication remains an important component of cancer treatment in the AYA population. This is due to tumours common in this age group being chemo sensitive, meaning targeting cell replication is effective at reducing the tumour burden and improving survival. The survival gap between AYAs in comparison to both children and adults and the lack of new efficacious agents being discovered for some cancers such as osteosarcomas has led to clinical research focus being placed on adapting existing chemotherapy protocols. This includes altering the DI of the agents received.

2.4 Chemotherapy dose intensity

The concept of DI was first introduced over 30 years ago and since then a number of studies both in adult and childhood cancers have demonstrated its benefit in improving survival. DI is defined as the quantity of a chemotherapy drug (e.g., mg per m^2) administered per unit time (e.g., weeks). Standard dose intensities (SDI) are defined by clinical trial protocols or clinical guidelines. In practice, however, the desired DI isn't always reached due to patient toxicity requiring dose modifications. A more accurate calculation is therefore that of relative (or sometimes referred to as received) dose intensity (RDI), the ratio of the DI of chemotherapy actually delivered compared to the SDI (29). RDI can be calculated for individual or all agents within a regime. The most popular method of calculating RDI is that described by Hryniuk (13,30) which calculates DI as the total dose of chemotherapy delivered divided by the total time taken to complete chemotherapy. Miller et al. used an alternative approach in which DI is calculated for all participants per cycle thus preventing analysis according to individual patient characteristics for example age, gender, stage or grade of the tumour (31).

Historically RDI was used in the adjuvant setting (when there is no visible cancer remaining, but there is a risk of the cancer returning), where protocols were standardised and the regimes of set durations. Difficulties arise in the metastatic setting where chemotherapy is administered more according to response, progression and toxicity. Patients with metastatic disease are also likely to have had previous chemotherapy or radiotherapy which may influence the quantity of further chemotherapy they can receive. In addition, more advanced disease is likely to be accompanied by a lower general health (measured as performance status), deranged biochemistry and more comorbidities meaning lower doses can be delivered. Patients with metastatic disease are also more likely to die during treatment making comparisons of DI received more difficult.

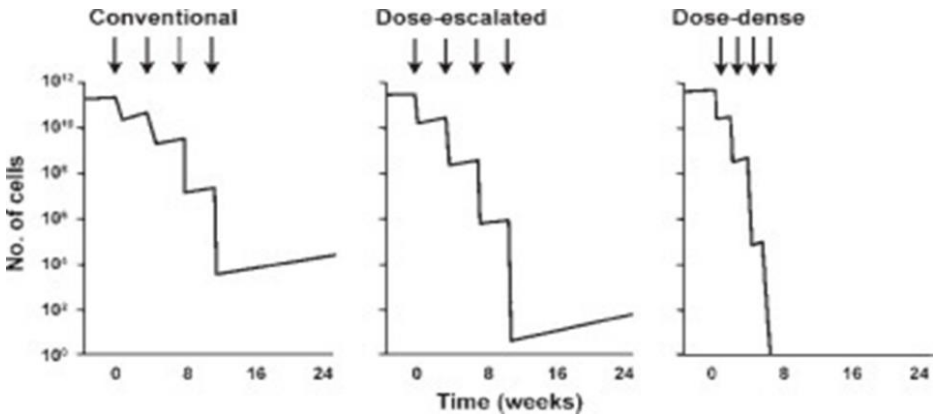
2.5 The science behind dose intensity

The tumour cell growth of most cancers follows a Gompertzian curve (32). This demonstrates a characteristic initial rapid growth of tumour cells followed by a reduction in doubling rate as the tumour size increases and approaches the limits of

space. The Norton-Simon hypothesis (33–35) is based on these Gompertzian kinetics of growth hypothesising that small tumours grow faster. As a result, tumour growth is fastest when tumour size is reduced, including after cytoreductive chemotherapy. Therefore, by reducing the time interval between chemotherapy doses and delivering more chemotherapy during this period of rapid growth, better outcomes should be seen. Figure 1.1. demonstrates how dose-dense chemotherapy is more effective at reducing tumour cell number and rate of growth compared to conventional and dose-escalated regimes.

The Goldie-Coldman (36) hypothesis follows a somatic mutation model of drug resistance, suggesting that spontaneous drug-resistant mutations arise most frequently when the tumour burden is high. Based on this theory using the highest possible doses of effective chemotherapeutic agents early prevents the emergence of resistance and has the greatest chance of eradicating the tumour.

Figure 1.1: Tumour cytoreduction and regrowth after conventional, dose-escalated and dose-dense chemotherapy (37).



2.6 Dose intensity in the AYA cancer population

2.6.1 Acute lymphoblastic leukaemia

Historically AYA patients received their treatment either in a paediatric or adult oncology setting, with chemotherapy regimes in the former being of a higher

intensity. In the mid-2000s, a number of international groups compared the outcomes of AYA patients with acute lymphoblastic leukaemia (ALL) who were treated with adult versus paediatric protocols (38–43). Findings demonstrated superior complete response, event-free and overall survival (OS) rates for patients treated on paediatric protocols with higher dose intensities. Increased use of dose intense protocols following this has led to improvement in AYA ALL survival rates (44) and has been adopted across other tumour types in AYA as discussed below. It should be noted that of equal importance to the chemotherapy regime was the treatment setting in which it was received, with paediatric protocols being delivered in departments accustomed (through research and protocolisation) and resourced to safely manage with the associated higher toxicities.

2.6.2 Germ cell tumours

GCT are amongst the success stories of AYA cancers with 5-year survival rates of over 95% in localised tumours and 70-90% in those that have metastasised (45). Bleomycin, etoposide and cisplatin (BEP) chemotherapy administered three weekly for four cycles remains the gold standard care for intermediate and poor prognosis patients and has been since its introduction in the 1980s (46). Attempts to improve survival in these patients have focused on intensifying this standard regime. Nichols *et al*. looked at doubling the dose of cisplatin from 20mg/m^2 to 40mg/m^2 (47). deWit and colleagues investigated the effect of adding in paclitaxel (48). A number of studies have compared the standard treatment to high dose ifosfamide (49,50) or cyclophosphamide (51) containing regimes. The finding of these studies all failed to demonstrate a survival advantage from the alternative regime and produced greater toxicity. A current phase 3 trial P3BEP is currently investigating whether accelerating standard BEP chemotherapy from 3 weekly to 2 weekly is superior in the treatment of intermediate and poor prognosis patients (52).

2.6.3 Osteosarcoma

The introduction of effective adjuvant and neo-adjuvant chemotherapy, along with improved surgical techniques has improved the 5-year survival estimates for localised high-grade osteosarcoma from 20% to 50-70%. Little further

advancement in survival however has been achieved. Current treatment regimes focus on cisplatin, doxorubicin, high-dose methotrexate and ifosfamide (53).

A number of retrospective studies have suggested that DI has potential benefits in outcomes in osteosarcoma. Smith *et al.* (54) demonstrated the importance of doxorubicin DI in osteogenic sarcoma. This is supported by findings of the European Osteosarcoma Intergroup (EOI) Study 80831, which compared six cycles of doxorubicin and cisplatin (doxorubicin DI of 25 mg/m^2/week) with four cycles of cisplatin, doxorubicin and methotrexate (doxorubicin DI of 15 mg/m^2/week). Five-year disease-free survival was 57% for the arm with higher doxorubicin DI compared to 41% in the lower DI arm (55). Two reviews looking at the impact of methotrexate DI have shown it to be an important predictor of prognosis (56,57).

In the EOI retrospective analysis looking at the impact of dose intensification of the conventional three weekly two drug regime of cisplatin and doxorubicin no significant survival benefit was seen from increasing the DI. Overall survival and progression free survival however were both lower in the patients receiving the lowest dose intensities (58).

Lewis *et al*. (53) compared conventional treatment of six 3 weekly cycles of cisplatin (100 mg/m^2 by 24-hour infusion) and doxorubicin (25mg/m^2 by 4 hour infusion for 3 days) to the intensified treatment which compared the identical doses of cisplatin and doxorubicin, planned as six 2 weekly cycles supported with granulocyte-colony stimulating factor (G-CSF). Whilst a good histological response (>90% tumour necrosis) was observed in 50% of the DI group compared to 36% in the conventional group there was no increased in overall survival or progression free survival.

2.6.4 Ewing sarcoma

Ewing sarcoma is the second most common bone cancer in AYA characterised by the 11;22 translocation present in more than 95% of cases (59). Current 5-year survival rates for localised Ewing sarcoma are 82% falling to 71% for regional

disease and 39% for metastatic disease(60). Chemotherapy regimes focus on actinomycin D, doxorubicin, etoposide, cyclophopsamide, vincristine and ifosfamide.

In a review of 16 studies, including the second Intergroup Ewing's Sarcoma Study, Smith *et al*.(54) found doxorubicin DI to be an important determinant of favourable outcomes in Ewing sarcoma. Granowetter *et al*. (61)looked at whether interval compression of alkylating agents alone had the same positive effect but found that this increased toxicity with no improvement in efficacy. Smith *et al*. (54) also suggested that increasing the DI of dactinomycin had a negative effect on outcome due to it limiting the amount of doxorubicin that could be delivered. This provides an example of how increasing the DI of a less active agent has a negative impact through limiting the amount of the more active agent that can be administered.

In the US Children's Oncology Group (COG) AEWS0031 trial, patients with localised Ewing received alternating cycles of vincristine-doxorubicin-cyclophosphamide and ifosfamide-etoposide (VDC/IE) as induction chemotherapy with alternating cycles of ifosfamide-etoposide and vincristine-cyclophosphamide (IE/VC) as consolidation chemotherapy. Randomisation was to either the standard 3 weekly cycles arm or the 2 weekly experimental arm. A significantly improved event free survival (EFS) rate of 73% was seen in the compressed arm compared to 65% in the standard arm (p=0.048). Overall survival (OS) was also better with 83% versus 77% (p=0.056) (18). This then became the standard treatment.

The pinnacle trial in Europe was the Euro Ewing 2012 trial comparing the European regimen of VIDE (vincristine, ifosfamide, doxorubicin and etoposide) induction and VAI or VAC (vincristine, actinomycin D and ifosfamide or cyclophosphamide) consolidation with the US regimen of compressed VDC/IE induction and IE/VC consolidation. The more dose intense US regime was shown to be superior in terms of EFS and OS with no excess toxicity (62) and is now standard practice internationally.

2.6.5 Hodgkins Lymphoma

The alternating chemotherapy regime of cyclophosphamide, vincristine, procarbazine and prednisone (COPP)/ doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) regime was introduced in the mid-1970s and became the standard treatment for intermediate and advanced Hodgkin's lymphoma (63).

In 1990 the German Hodgkin Lymphoma Study Group (GHSG) used data from animal models, the mathematical effective dose model and retrospective clinical trials data to predict that more rapid administration of chemotherapy could improve disease free survival by 3 percent and an additional 10 percent by dose escalations(64,65). As a result, they developed the effective intensified regime BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone). This regime replaced vinblastine and dacarbazine with etoposide and also rearranged the regime so that the most myelotoxic agents (cyclophosphamide, doxorubicin and etoposide) were administered on days 1-3, enabling G-CSF to be given from day 8 onwards and reducing the treatment duration from 4 to 3 weeks (66). Further increasing the doses of cyclophosphamide, etoposide, and doxorubicin to 192%, 200%, and 140% of the standard regime in BEACOPPescalated was investigated in the HD9 trial (67). A significant improvement in freedom from treatment failure (FFTF) was seen at 24 months for the escalated regime 84% verses 75%, however the toxicity was higher with the escalated regime and long-term effects such as fertility and secondary neoplasms worse.

2.6.6 Non-Hodgkin's lymphoma

The four most common subtypes of Non-Hodgkin's lymphoma (NHL) in AYAs and children are high grade lymphomas: Burkitt lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), lymphoblastic lymphoma (LL) and anaplastic large cell lymphoma (ALCL) (68).

Dose-dense chemotherapy with G-CSF support has been shown to be advantageous in aggressive NHL in a number of studies. The Lymphoma Study

Group in Japan compared standard 14-day CHOP with dose-escalated 14-day CHOP and found higher 3-year PFS rates of 60 verses 51% (69). The Southwest Oncology Group treated 88 previously untreated patients with dose-escalated CHOP chemotherapy at a DI 1.8 times higher than standard CHOP and also found a 14% survival improvement at 5 years (70).

The characteristic high growth fraction and short doubling cells of mature B-cell lymphoma results in DI being an important component of NHL treatment. An analysis of doxorubicin-based regimes in DLCL found a doxorubicin RDI of greater than 75% to be an important prognostic indicator of survival(71). Similarly in aggressive NHL those receiving less than 70% DI of anthracycline regimes had lower 2-year OS rates 61% vs 72% (72). Subsequent focus has turned to a more risk stratified approach of reserving the more intense treatments for those with a higher tumour burden (73) thus reducing late effects of treatment where possible.

High-dose methotrexate combined with leucovorin is an important component in many treatment regimes for B-cell tumours in children and teenagers. Whilst the use of methotrexate has shown favourable outcomes, the toxicity associated with these therapies are high. The NHL-BFM95 trials looked at whether shortening the 5g/m2 infusion to 4 hours as opposed to 24 hours would reduce toxicity without affecting response rates. The study showed worse progression-free survival (PFS) for those who received the infusion over 4 hours in the higher risk groups (74) suggesting that the duration of exposure is important in methotrexate as opposed to simply the total dose.

Myeloablative high-dose chemotherapy (HDT) with stem cell transplantation has been shown to be effective in relapsed aggressive lymphoma in patients under 60 years old(75,76). It's use in aggressive NHL however is less clear (77–79).

2.6.7 Carcinomas

Breast cancer was the first tumour site in which the theory of RDI was investigated (80). An early randomised control trial (RCT) reported that patients receiving

greater than 85% of RDI had significantly better survival outcomes than those receiving less than this cut off(81). A recent meta-analysis of trials in adjuvant chemotherapy for breast cancer showed dose-intense versus standard chemotherapy reduced the risk of 10-year recurrence and 10-year breast cancer mortality, without increasing the mortality from other causes (82). Interval compression from 3 to 2 weeks was shown to be superior and with less toxicity in the C9741 trial (83).

The incidence of colorectal cancer in young people is increasing (84). These patients tend to present with more advanced disease but despite this 5-year survival rates remain comparative to the rest of the colorectal cancer population. In advanced colorectal cancer the backbone of treatment consists of fluoropyrimidine (i.v. 5-FU or oral capecitabine) in combination with oxaliplatin or irinotecan plus or minus epidermal growth factor receptor (EGFR). The impact of the dose intensity of these chemotherapy agents is uncertain. A review of 28 randomized and one non-randomized trials found an increase of 10mg/m^2/ week of i.v. 5-FU increased the response rate in previously untreated patients from 20 to 29% (13). A phase II clinical trial and review of five other studies by Cascinu *et al*. (85) found no significant effect. The FOLFOX7 regime showed that intensification of oxaliplatin dose provided a significant improvement in response rate and PFS without increasing toxicity (86). Maintaining RDIs of at least 80% has been suggested as a predictor of disease control in irinotecan-based regimes (87).

In ovarian cancer a retrospective analysis of 325 of patients with epithelial ovarian cancer receiving multi-agent chemotherapy found delivered RDIs of <85% to be associated with shorter overall survival (29).

2.6.8 Medulloblastoma

From a patient database of 2434 patients from 30 clinical trials Smith *et al*. (88) estimated the effect of prescribed chemotherapy DI on survival in childhood medulloblastoma. Chemotherapy agents investigated included cisplatin, cyclophosphamide, vincristine and lomustine (CCNU). For both standard and high-risk patients a positive relationship was found between DI of cisplatin and

cyclophosphamide and 5-year OS. A weaker relationship was seen for vincristine and a negative relationship for CCNU. All relationships were stronger for standard-risk patients in comparison to high-risk.

In 2008 the Milan strategy was published by Gandola *et al* for the treatment of patients with metastatic medulloblastoma (89). This single centre study of only 33 patients included intensive post operative chemotherapy followed by, in some cases, myeloablative chemotherapy. A favourable outcome was demonstrated in terms of overall survival and in response treatment guidelines were published and implemented across the UK. Attempts at replicating the success of this regime in the UK however were unsuccessful for a number of possible reasons including less selection bias in the patient population in the UK and also variation in treatment delivery (90). This highlighted the need for careful guideline development concerning intensive chemotherapy particularly when implementing the findings of a single centre study.

2.6.9 Dose intensity of immunotherapy

Although outside of the scope of this thesis the effect of immunotherapy DI is worthy of brief consideration. Melanoma accounts for 8% of malignancies in AYA(91) and the incidence is increasing in the US and across Europe (92,93). The introduction of immunotherapy agents including nivolumab and ipilimumab has improved survival rates although due to their infancy little data exists on the optimal dosing frequency of these therapies. This is of particular importance for attempting to minimise the high toxicity of these treatments. The MOIO protocol study is a non-inferiority randomized phase 3 trial to investigate this in adult cancers (94).

2.7 Barriers to maintaining dose intensity in AYA

2.7.1 Environment of care

Despite the evidence in favour of maintaining DI for some cancers that are frequent in AYA, many AYAs have been found to be receiving inappropriate initial treatment (95). The variation in environment of care, as discussed in the review paper (96),

may partly explain this. Maintaining DI can be problematic and costly to both the patient and NHS. Short-term barriers include high levels of toxicity which can require input to reduce the symptom burden and in severe cases be life threatening resulting in admission to a higher level of care. When the cancer is cured, higher dose intensities of treatment may result in higher rates of irreversible end-organ damage which will negatively impact long-term health and quality of life. Non-specialist centres treating AYA may lack the experience and infrastructure required to support the toxicity of dose intense treatments, such as sufficient clinician experience, lack of treatment protocolisation outside of clinical trials, and the required multidisciplinary team.

2.7.2 Clinical pharmacology and toxicity

Evidence suggests that age and sex-dependent pharmacological differences exist in the processing of chemotherapy drugs(97). During the normal process of puberty and the years that follow, several changes occur in the body which can influence the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs throughout the body. These include hormonal changes (98), changes in body fat and muscle composition (99,100) and organogenesis of the liver and kidneys. Clearance capacity of the kidneys is thought to increase through the AYA age range (101) as is the volume of the liver, which can have differing effects on drugs depending on their metabolic pathway (102).

The age of onset of these changes varies in each individual patient and is different in males and females. Extremes of weight, experimentation with drugs and alcohol and concomitant medications can also influence the PK and PD of drugs (97). Different chemotherapy drugs, including those commonly used in AYA, can be affected in different ways. For example, AYA exhibit an oral clearance of methotrexate that is only half that of children (103). Dose capping of actinomycin D (104) results in lower Area under the Curve (AUC) exposure in AYA than children. Drug dosing in AYA patients may therefore be more complex than in older adults and younger children.

There is a suggestion that treatment related toxicity experienced by patients reflects systemic exposure to chemotherapy. A study in Ewing sarcoma found adults experienced less toxicity than children (105). Similarly, older AYA treated for rhabdomyosarcoma had less toxicity reported by their clinical teams than in younger children (106). The degree of myelosuppression seen in patients after chemotherapy has also been shown to correlate with outcomes (107–110). Poorer outcomes in AYA patients may therefore be related to lower systemic exposure to chemotherapy even if DI is similar. This might be manifest as less myelosuppression despite similar doses. Work in osteosarcoma (111) supports this with findings that within the same chemotherapy protocols in clinical trials, AYA patients are receiving lower doses of chemotherapy, fewer toxicities and worse cancer outcomes.

2.8 Gaps in the literature of dose intensity in AYA

Whilst the literature discussed earlier in this chapter shows that maintaining DI is beneficial in many cancers common in AYA, it is derived from clinical trials. This is problematic in this patient group due to the known poor recruitment rates of AYA to trials, with participation rates of only 5-34% compared to over 90% in children (19,112,113). The evidence suggesting that the clinical pharmacology of chemotherapy drugs may differ at different stages of the AYA age range and by patient sex was discussed in section 2.8.2. These findings limit the ability to extrapolate results from trials in adults and children. Due to these factors data related specifically to RDI in AYA patients is limited.

In addition, it is also known that patients who are treated in clinical trial active institutions have a survival benefit (114–116). This is of particular relevance in rarer tumours, such as those common in AYA, where research active institutions are more likely to have the clinical experience required to deliver dose intense treatments and manage the accompanying toxicity. Through the analysis of real-world data, we can observe treatment delivered and associated survival outcomes from centres that may not have such skills and infrastructure. In addition, the impact of sociodemographic factors can also be investigated in the real world setting whereas this data is not routinely collected within clinical trials.

To make further progress in survival outcomes, the knowledge of the impact of dose intensity in AYA needs to be expanded to include treatment received in routine care. This is the focus of this thesis.

Chapter 3. Methods and data sources

3.1 Introduction

This Chapter introduces the data sources used in this thesis. The advantages and disadvantages of the datasets are described along with the data items available in each. The ethical and data security processes required are detailed as are the data flows. I then describe the statistical methods chosen for data analysis, including how missing data will be managed. Finally, the importance of including Patient and Public Involvement and Engagement (PPIE) in this research is described and how thematic analysis will be utilised.

3.2 Identification of data sources

Routinely collected health data is defined as data collected for the primary purpose of individual patient care, without specific research questions developed prior to utilisation for research (117). It is collected every day in primary and secondary care within the NHS and other healthcare systems. Also referred to as real-world data (RWD), it can be analysed to provide real-world evidence (RWE) (118). Whilst randomised controlled trials (RCTs) remain the gold standard for assessing treatment efficacy, RWE can inform where there is some suggestion of efficacy, or evidence is underpowered, as in the case of DI in the AYA population. The quality of RWD varies, mainly in terms of data field completion rates. The quality of data in local databases (such as single hospital electronic health records) may be different from the quality of the subsets of data that are exported by hospital administrative teams to national datasets for the purpose of public health monitoring. RWD might be improved in either of these settings by experienced clinical interpretation. RWD has demonstrated utility in other areas of oncology, such as bladder(119), breast (120)and bowel cancers (121), though its use restricted by governance frameworks as outlined in the 2022 Goldacre report (122).

Preliminary work for this thesis involved reviewing available datasets for use in the analysis. Table 3.1 describes the data items available in regional and national sources, comparing and contrasting them with those present in clinical trials data.

Table 3.1: Comparison of the data items available in regional, national and clinical trials datasets.

Data field	Regional	National	Clinical trial
Patient demographics			
Patient identifiers (NHS number, DOB)	Yes	Yes*	No
Age at diagnosis	Yes	Yes*	Yes
Sex	Yes	Yes	Yes
Ethnicity	Yes	Yes	No
Socioeconomic status	Yes	Yes	No
Postcode	Yes	Yes*	No
Co-morbidity	Yes – via additional linkage to HES.	Yes - Charlson co-morbidity index score and via HES	Often excluded in trial criteria.
Patient numbers (using GCT as example)	137	1454	808 (across 4 trials)
Cancer details			
Diagnosis date	Yes	Yes*	Yes
Route to diagnosis	No	Yes	No
Stage a diagnosis	Yes	Yes	Yes
Site of metastatic disease	No	No	Yes
Radiology results	Incoming	No	Yes
Vital status	Yes	Yes	Yes (within trial follow up only)
Date of death	Yes	Yes*	Time to death
Cause of death	Yes	Yes	Yes
Details of diagnosing/ treating hospital	Yes	Yes*	No
Tumour markers	Incoming	No	Yes
Data availability time frame	From 1984 to current	1995 to average two-year lag (at time of data request)	Variable
Data availability – age range	0-29 years	All ages	Trial dependent
Treatment data			

Drug name	Yes	Yes	Yes
Regimen	Yes	Yes	Yes
Dose	Yes	Yes	Yes
Date of administration	Yes	Yes*	Yes
Treatment intent	Yes	Yes	Yes
Consultant speciality code	Yes	Yes	No
Height and weight	Yes	Yes	Yes
Performance status	Yes	Yes	Yes
Clinical trial indicator	Yes	Yes	Yes
Chemo-radiation indicator	Yes	Yes – improved via linkage to RTDS	Yes
Regimen modification indicator	Yes	Yes**	Yes
Pathology results	Yes	No	Yes
Toxicity data	Yes	Limited	Yes
Availability	2012 to current	April 2012 to NCRAS dependent lag	Trial dependent

*may be subject to data minimisation principles (General Data Protection Regulation Article 5 (1)(c))

** only available in some versions of SACT.

Abbreviations: DOB; Date of Birth, HES; Hospital episode statistics, GCT; germ cell tumour, NCRAS; National Cancer Registration and Analysis Service, NHS; National Health Service, RTDS; Radiotherapy dataset.

3.2.1 Cancer registries

The role of population-based cancer registries (PBCR) is to record all new cases of cancer within a defined population (123). The population is normally defined geographically, and a defined set of core variables collected for each case. PBCR play an important role in monitoring trends in incidence, mortality and survival rates over time which facilitates the planning of cancer services (123).

Cancer registration began in England in the 1920s, initially with regional registers before national standardised coverage was introduced in 1971 by the organisation now known as the National Cancer Registration and Analysis Service (NCRAS).

3.2.2 National Cancer Registration and Analysis Service

Formally held within Public Health England (PHE) and now part of the National Disease Registration Service (NDRS) within NHS England, NCRAS collects data on all cases diagnosed or treated in or funded by the NHS in England to produce the national cancer registration dataset (124). Data are collected according to the Cancer Outcomes and Services Dataset (COSD) which includes both generic cancer and site-specific items(125). The provision of these specified and selected data items, by extraction from medical notes by administrators in NHS trusts, has been mandatory since January 2013 and data sources include pathology reports, multidisciplinary team meetings, hospital activity records (126) and benchmarks such as hospital waiting times (124). They are not routinely subject to clinical verification at source but extracted clerically. Death details are provided via linkage to the Office for National Statistics (ONS)(128).

A strength of the NCRAS data is its national population coverage enabling national epidemiological studies for cancer to be conducted. This is of particular benefit in AYA cancers where patient numbers can be smaller than many adult cancers such as colorectal. The data undergoes quality assurances to resolve inconsistencies and for many cancers the completeness of data items such as formal systematic cancer stage estimation has greatly improved over recent years, with this aspect specifically evaluated for AYA cancers in this study. As demonstrated in this thesis, a further strength of the cancer registration data is that it can be linked to other datasets such as the Systemic Anticancer Therapy (SACT) dataset and the Radiotherapy Dataset (RTDS), providing detailed patient-level treatment data. Linkage to datasets such as inpatient and outpatient Hospital Episode Statistics (HES)(126) provides insight into a patient's broader health both before and after a cancer diagnosis.

A limitation of the NCRAS data however is the lack of availability of data items relating to causal risk factors for diseases and outcomes, such as smoking, alcohol intake and other lifestyle factors. Whilst this could, in part, be overcome through linkage to primary care data, this data source is not available on a national level. Collection is also known to be incomplete from the private healthcare sector, although the impact of this is likely to be minimal due to our state funded healthcare in England. Changes in clinical and coding definitions over time also need to be taken into account to ensure data accuracy as well as the impact on data completeness caused by a possible lag time to receiving some new cancer registrations. People receiving NHS care are permitted to ask for their data not to be included in this process; the ability to 'opt out'. The effect opt-outs can have on cancer registration data in discussed in more detail below in the ethics section 3.2.

3.2.3. Regional Cancer Registration

The research in Chapter 5 is derived from data sourced from the Yorkshire Specialist Register of Cancer in Children and Young People (YSRCCYP) at the University of Leeds. The YSRCCYP is a unique population-based database of children and young people (aged 0-29 years) diagnosed with cancer whilst living in the Yorkshire and Humber region (129). It currently holds data on over 11,000 patients. A distinctive feature of the register is that patients have been followed up every 2 years to provide data on recurrence, second malignancies, any subsequent treatment and health status. The register also contains detailed treatment histories since 1990 (preceding this detail being mandated by public health for national data, and before data linkage to prescribing systems were available). A strength of register is the ability and approval to link to existing local and national datasets. The main limitation being the rarity of many cancers in AYA which hinders the ability to perform detailed subgroup analyses. A detailed description of the YSRCCYP is provided in the profile paper to which I personally contributed to the sections related to SACT and ChemoCare and led on establishing these data linkages (129).

3.2.4 National Chemotherapy Prescribing Data - Systemic Anti-Cancer Therapy (SACT) dataset

The SACT dataset, previously held by PHE now the NDRS, collects systemic anti-cancer therapy activity from all NHS England providers. The dataset covers SACT treatments in both adult and paediatric patients delivered in secondary or tertiary settings. All treatments are given with the intention of improving survival, delaying further cancer progression or development or to improve disease-free survival. Treatments such as steroids and bisphosphonates, which can also commonly be given for symptom control should only be recorded on SACT when they are prescribed with the intent of modifying the disease, rather than only the side effects.

Collection of the SACT dataset began in April 2012 with a phased implementation. Mandatory monthly data submissions then began in April 2014 and are mandatory for all Trusts in England, therefore providing a comprehensive national database of prescribing data. The population level capture of this data limits selection-bias of the data and increases the validity of studies using it (130). SACT also enables comparisons to be made between findings from clinical trials and routine care (131), a strength this study will utilise.

As with all RWD, SACT is entered at the point of care and is therefore susceptible to user error, limiting data completeness. For example, in a busy clinic clinicians may omit entering data which is known to them if the process of entering it slows clinical care, and the data is not mandated for the key action of treatment prescribing. They may not have all the information they require in the form the database requires (such as if a precise TNM stage is requested but in practice a simpler 'localised versus advanced' classification determines care decisions). Some entries may be estimated with a degree of uncertainty e.g., performance status. Data relating to cycle number is also known to be incomplete. SACT data collection is dependent on the use of chemotherapy prescribing systems which were not universal in paediatric cancer centres during the early years of SACT collection. As a result, ascertainment is known to be poorer for childhood and teenage cancers in the early years of these datasets. It is expected that an improvement in this will be seen with increased uses of electronic chemotherapy prescribing systems. Ascertainment is also problematic for long-established oral anti-cancer agents that may be prescribed

non-electronically e.g. endocrine therapies for breast and prostate cancers. These are likely to represent only a small proportion of the AYA population however it is important to be mindful of this during analysis (132).

3.2.5 Regional chemotherapy prescribing data

As described in the profile paper (129), the YSRCCYP receives a flow of data from the electronic patient notes system at Leeds NHS Teaching Hospitals Trust (LTHT). This system, Patient Pathway Manager (PPM), also records data from the electronic chemotherapy prescribing system ChemoCare. In the UK a move towards electronic chemotherapy prescribing happened in response to patient safety concerns surrounding poorly written chemotherapy prescriptions (24). This has successfully improved the quality and accuracy of chemotherapy prescriptions (133). In addition, it has led to electronic datasets from which information can be extracted less labour intensively and with more precision than from paper prescriptions, thus facilitating clinical research and audit (134). It has been discussed above how these systems contribute to the mandated data items in the SACT dataset. A wider range of data however is collected in ChemoCare and it is the toxicity data from this source that is utilised in Chapter 5 of this thesis.

3.2.6 Clinical trials data

Clinical trials recruit a subset of patients and collect a very comprehensive and tightly quality-assured dataset, including clinical review before submission to the dataset. These datasets however are held by the study sponsor, for whom they may contain valuable intellectual property, and are not always shared. The advantages of sharing patient level clinical trials data are numerous and include ethical, economic and scientific benefits (135). Ethically, data sharing recognises the trial participants who contributed their time, increasing the utility of the data they provided. From an economic perspective it prevents new studies from having to be carried out and increases the value of the initial investment. Scientifically it enables new hypotheses to be tested, previous conclusions to be re-examined and either verified or corrected. Combining data from different trials can also enable a larger patient population to be examined or new meta-analyses to be performed. The last 20 years has seen a change in practice relating to clinical trials data sharing due to

the growing recognition that data from clinical research should be easily accessible (136).

It was therefore possible to obtain data from the European Organisation for Research and Treatment (EORTC) collected in four germ cell clinical trials. The inclusion criteria for these trials are described in supplementary material for Chapter 4, located in Appendix B. Permission was provided for the analysis and publication of data outputs from these trials.

3.3 Ethics and data security

Data for both the YSRCCYP and the national cancer registration dataset are collected under the provisions of Section 251 of the NHS Act 2006, which forms a legal basis on which identifiable patient level data can be collected on cancer patients, for specific purposes without consent. Individuals do however have the right to opt out of their health records being shared for purposes other than direct care. In rarer cancers, such as those common in AYA, even small numbers choosing to opt out can influence the generalisability of the data.

Data collection by the YSRCCYP is reviewed annually by the Health Research Authority (HRA) Confidentiality Advisory Group ((CAG), study reference 20CAG0133) and the North East–York Research Ethics Committee (reference 00/3/001). Obtaining the chemotherapy treatment data from LTHT required amendments to existing Data Sharing Agreements (ODR1819_163A4). Existing patient information leaflets and posters were updated, ensuring the research was General Data Protection Regulation (GDPR) compliant.

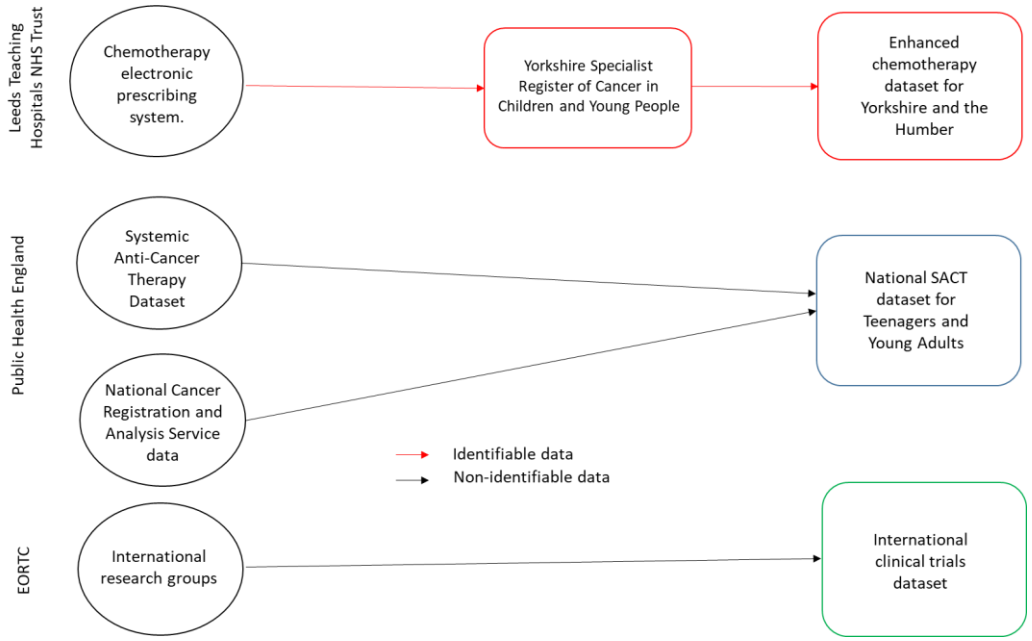
The national SACT data was requested as a pseudonymised dataset and ethical approval obtained from the Yorkshire and The Humber- Bradford Leeds Research Ethics Committee (reference 19/YH/0121).

All data are stored within the University of Leeds secure MS Azure cloud in LASER (https://lida-data-analytics-team.github.io/laserdocs/docs/laser_info/laser.html) and accessed only by authorised personnel. No identifiable data is ever published and to avoid potential disclosure of patient information, case numbers fewer than five are supressed.

3.4 Data Flows

The data flows are summarised in Figure 3.1. Linkage of the LTHT data to the YSRCCYP was carried out using the patient identifiers NHS number, date of birth, postcode and sex. Data linkage of the COSD and SACT data was carried out in house at PHE/NCRAS prior to the data being released for this study.

Figure 3.1: Dataflow of the datasets used in this thesis.



3.5 Statistical methods

3.5.1 Adoption of a Causal inference framework

The statistical analyses in this thesis have been undertaken within a causal inference framework. The use of this methodology is growing in health and epidemiological research where the research questions often investigate the consequences of an exposure such as an intervention (for example a new treatment) or individual characteristic (such as ethnicity or socioeconomic status) on an outcome. Based on counterfactual thinking causal inference enables statistical analysis of non-randomized and observational studies to be performed and unbiased causal effect estimates to be produced through full adjustment for confounding. This allows justified claims to be made such as if we make changes to exposure X it will improve outcome Y in our patients or the public (137).

Counterfactual exposures are ones which did not happen. For example, if we are looking at the outcomes from two different treatments A compared to B, if a patient only receives A then the outcome for B does not happen for that patient. Outcome B is therefore termed the 'counterfactual' outcome (the one that did not happen) and outcome A the 'factual' outcome (that did happen). The term 'potential' outcome is used to describe the outcome before a treatment is allocated. Only one outcome can therefore be observed per patient, and this demonstrates why causal effects cannot be estimated at individual levels, only at group levels (135).

In order to estimate a causal effect in group a number of assumptions need to be met (136). One assumption is of exchangeability, which refers to individuals having equal likelihood of outcomes, in this thesis, survival. Positivity refers to it being possible for individuals to get all possible variations of the exposure, in this thesis for example RDI. There should be consistency in that the potential outcome from the potential exposure should be equal to the factual outcome from the factual exposure. Lastly there should be no interference between individuals. In this thesis for example one patient's outcome does not affect that of another.

Directed acyclic graphs (DAGs) can be used in causal inference to visualize and define *a priori* all causal relationships. DAGs are created using the online tool

DAGitty (139) and consist of nodes (which represent variables) connected via a set of arrows representing a path. Paths within a DAG must be acyclic and arrows only unidirectional. Included variables are commonly identified from existing literature and/or informed by clinical experience, as was done in this thesis. Even if a variable of interest is not present within the dataset it can still be included as an unobserved variable. The path under investigation in causal inference is that between the exposure of interest and the defined outcome. "Back door" paths are alternative paths between these two variables and the presence of at least one of these paths results in confounding if they are left open. A confounding variable is one which lies on one of these "back door" paths between the exposure and outcome of interest. Controlling for this confounding variable closes the back door path and reduces confounding (138).

Other variables to be aware of in causal inference include mediators. These lie on the causal path of interest causing an indirect causal pathway. They should not be controlled for as doing so closes the indirect causal pathway, limiting the ability to make observations about the association between the exposure and outcome of interest. Colliders are other variables which should not be controlled for. These variables are caused by two or more other variables, controlling for them introduces collider bias through the opening of a back door pathway (139).

DAGs identify the minimum sufficient adjustment set of confounders for each analysis, enabling the exposure-outcome relationship to be estimated with minimal confounding. This is important as the presence of confounding can result in the finding of an incorrect causal relationship if not controlled for appropriately.

Strengths of DAGs include the promotion of transparency, giving the reader insight into assumptions made by the analyst and also enhancing the reproducibility and replicability of analyses. They are also flexible, aiding the researcher at all stages of the research cycle from defining the research question to interpretation of the findings. DAGs can also aid sample selection either in terms of the dataset selected for use in an analysis or as in the case of prospective data collection, helping to determine which data items need to be collected. Limitations of DAGs include the competency of the analyst and the thought processes used in creating them.

Deciding which relationships exist and do not exist between variables, and indeed in which direction, can be problematic. In this thesis this has been minimised by the clinical and epidemiological knowledge of both myself, and my supervisors and also in consultation with the literature. Including all possible variables and causal pathways in DAGs can make them complex, difficult to interpret and prone to error(140). This can be limited by using tools such as DAGitty (137) used in this thesis.

The strengths and limitations of DAGs were considered when deciding whether to use them in this thesis. It was felt that they provided both an accessible and robust method of reducing bias in the study with the acknowledgment that in practice removing all possible unobserved confounding is impossible. Whilst I am aware that other methods of variable selection are available, such methodology was outside the scope of thesis. Through using DAGitty software and gaining advice from experts in the field I was confident that the limitations could be minimised. In addition, causal inference methodology use is currently limited in medical research leading to potential bias in studies. Through promoting its use through this thesis it was hoped to make others more aware of the use of causal inference in the analysis of observational data.

3.5.2 Survival models – Kaplan-Meier

Kaplan-Meier survival estimates define the probability of surviving a given length of time, in which time is considered in many small intervals. The assumptions made using this analysis are that:

- The survival probabilities are the same for those who enter the study early as those who enter late.
- The event of interest happens at a specific time.
- Censoring is not dependent on the survival outcome. Patients who are censored have the same likelihood of survival as those who continue in the study.

The survival probability is calculated by the formula:

$$S_t = \frac{\text{(Number of subjects living at the start – Number of subjects that died)}}{\text{Number of subjects living at the start}}$$

Using this formula survival probability is calculated for each time interval by dividing the number of patients surviving by the number of patients at risk at the start of the time interval. The total probability of surviving until the time interval of interest is then calculated by multiplying all the probabilities of survival from the preceding time intervals (134).

Kaplan-Meier estimates have been utilised in this study to estimate survival times at 1, 2 and 5 years. These estimates were calculated overall and also according to patient variables of interest in each paper.

3.5.3 The Cox Proportional Hazards Regression Analysis

Cox proportional hazards multivariable regression analysis can be used to investigate the effect of several variables on survival at one time. This is a semi-parametric approach in that no particular distribution is assumed for the survival times. The effects of the different variables on survival however are assumed to be multiplicative on a linear scale and constant over time. Another important assumption is that survival times between individuals in the cohorts are independent.

In this analytical model the hazard rate is the measure of effect and provides the risk of suffering the event of interest, in this study death, given the individual has survived up to a given time. The hazard ratio is then used to compare the hazard rate of two groups. If the hazard ratio is greater than 1 then the exposure is associated with a higher risk of death. Close to 1 then the exposure has little effect and if less than 1 the effect is deemed to be protective (141,142).

In this thesis these models will be used for survival analysis to estimate hazard ratios for the exposure of interest in each paper, for example RDI or toxicity, on risk of death. The results of unadjusted models and models adjusted according to the minimum adjustment set provided by the DAG will be presented for comparison purposes.

3.5.4 Multiple imputation

Missing data is common in RWD, often occurring across multiple variables in a dataset. Ideally all participants with missing data would be excluded and only individuals with complete data analysed, referred to as complete case analysis (CCA). However, doing so could lead to loss of a substantial proportion of participants, reducing the power of the study. It could also lead to introduction of bias as those with missing data may carry data important to the outcome e.g. those with missing data may have worse outcomes. There are a number of possible methods of overcoming missing data including random effects models (143), inverse probability weighting (144) and maximum likelihood estimation (145) however it is multiple imputation (MI) that has been chosen for use in this thesis. MI is a popular solution to missing data and involves the generation of data where missing values exist, considering relationships and distributions in the observed dataset (146). MI is now available in standard statistical software packages including Stata, as used in this thesis, and R.

MI relies upon certain assumptions being made about the data which are classified according to Rubin's assumptions. Under these assumptions data are classed as being missing completely at random (MCAR), missing at random (MAR) or missing not at random (MNAR). For MCAR the probability of a data item being missing does not depend on the unobserved value of the data item or the observed values of other data items. Being missing is unrelated to any inference we wish to draw. In MAR the probability of the data item being missing depends marginally on observed data values, but also given that the observed data is conditionally independent of the missing data values. MNAR, where the probability of the data being missing does depend on the unobserved value of the data item, even given the observed data. The assumption required for MI is MAR (146,147). In addition, it requires the data to be normally distributed. Other methods of good practice in MI include using

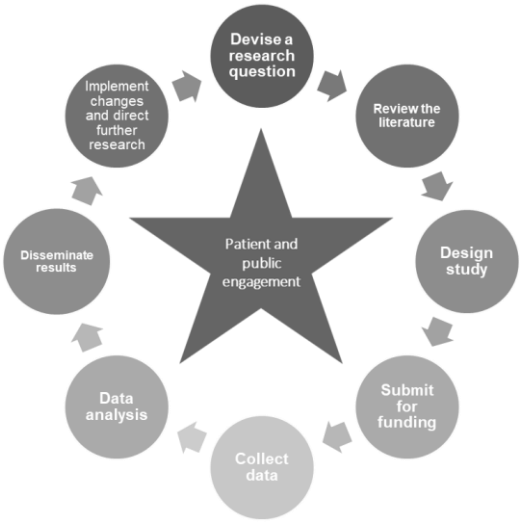
a wide range of variables in the multiple imputation models, including those which may be predictive of the missing variable itself. Bias may be introduced if a large percentage of missing data is present, in these cases a higher number of imputations may need to be made (146,147). In order to maximise the validity of the imputed dataset analysis should also be run on the non-imputed dataset to check for any discrepancies.

3.6 Patient and Public Involvement and Engagement in AYA

Patient and Public Involvement and Engagement (PPIE) in research is defined as research carried out with or by members of the public rather than to, about or for them. The public can include patients, carers, family members and individuals who use or represent health and social care services. Since the late 1990s there has been a move towards involving patients and the public more in UK health research. Facilitated by the launch of 'INVOLVE' by the NIHR in 1996 (148), PPIE has now become a prerequisite for many funding bodies, providing the public with a say in how public funds are spent. It is also required by research governance bodies such as the HRA CAG (149,150).

'Involvement' can occur at all stages of the research cycle as demonstrated in Figure 3.2 below and has been described as improving the relevance of research, ensuring the right priorities are focused upon and using acceptable research processes. For reasons described in my review article (96), young people are often seen as "hard to reach" (151) but this does not mean that their involvement in research is not as vital as in the adult population. Initiatives such as the James Lind Alliance (152) and BRIGHTLIGHT(151) have shown the benefit that involving young people can have. PPIE of young people and their carers surrounding the use of existing healthcare data for research use has therefore formed an important component of the thesis and is described in Chapter 6.

Figure 3.2: The research cycle.



3.6.1 Thematic analysis

Thematic analysis will be used to analyse the transcripts from the PPIE activity carried out for this thesis. This will enable conclusions to be drawn and learnt from. Thematic analysis is a method of describing a dataset that involves familiarisation with the data, the identification and generation of codes and the construction of themes (153). It is seen as a flexible analytical model accessible to novice researchers (154). Of relevance to this thesis is that it is considered a robust method when the intention is to understand a set of thoughts within a dataset (155).

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Chapter 4.

In this Chapter the analysis of linked COSD and SACT data from NCRAS to investigate the impact of delivered RDI on survival is described through my published research in the International Journal of Cancer. This work addresses Aims 1 and 3 of this thesis. The focus of this research is GCT which enabled comparisons to be made between patients treated within the routine NHS setting and those treated within clinical trials. The supplementary tables and figures to this publication can be found in Appendix B. Appendix G contains a description of the data cleaning carried out for this analysis.

The results of unpublished analysis carried out in patients with the bone tumours osteosarcoma and Ewing sarcoma can also be found in Appendix E. The limitations of this analysis where the chemotherapy regimes are more complex is discussed at the end of this Appendix, with comparisons made across the three tumour types.

Title. Delivered relative dose intensity in adolescent and young adult germ cell tumours in England: assessment of data quality and consistency from clinical trials compared to national cancer registration data.

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4.1 Novelty impact of the work

We compare the impact of relative dose intensity (RDI) on survival in Adolescent and Young Adult (AYA) patients with germ cell tumours treated in clinical trials compared to routine practice. Our findings suggest that maintaining chemotherapy RDI is associated with improved survival outcomes in both settings but with a stronger effect in clinical trials. With more follow up this data could be used to identify possible safe parameters for dose reduction in these patients.

4.2 Unstructured abstract

Adolescent and Young Adults (AYA) with germ cell tumours (GCT) have poorer survival rates than children and many older adults with the same cancers. There are several likely contributing factors to this, including the treatment received. The prognostic benefit of intended dose intensity is well documented in GCT from trials comparing regimens. However, evidence specific to AYA is limited by poor recruitment of AYA to trials and dose delivery outside trials not being well examined.

We examined the utility of cancer registration data and a clinical trials dataset to investigate the delivery of relative dose intensity (RDI) in routine National Health Service practice in England, compared to within international clinical trials.

Linked data from the Cancer Outcomes and Services Dataset (COSD) and the Systemic Anti-Cancer Therapy (SACT) dataset, and data from four international clinical trials were analysed. Survival over time was described using Kaplan-Meier estimation; overall, by age category, International Germ-Cell Cancer Collaborative Group (IGCCCG) classification, stage, tumour subtype, primary site, ethnicity and deprivation. Cox regression models were used to determine the fully adjusted effect of RDI on mortality risk.

The quality of both datasets was critically evaluated and clinically enhanced. RDI was found to be well maintained in all datasets with higher RDIs associated with improved survival outcomes. Real-world data demonstrated several strengths, including population coverage and inclusion of sociodemographic variables and co-morbidity. It is limited in GCT however, by the poor completion of data items enabling risk classification of patients and a higher proportion of missing data.

4.3 Background

Germ cell tumours (GCT) are the most common malignancy in the male adolescent and young adult (AYA) cancer population, aged 15-39 years, constituting approximately 10% of all tumours (1). They are often considered the success story of young onset cancers with five-year survival rates of over 95% in localised tumours and 70-90% in those that have metastasised (2). Despite this overall achievement, adolescents with GCT have worse outcomes compared to younger children and older young adults. A recent study using retrospective clinical trials data found adolescent males (11-18 years) to have a 5-year event free survival (EFS) of 72% compared to children aged 0-10 years (90%) and young adults aged 18 to 30 years (88%)(3). The unique biological, clinical and social needs of AYA have been well documented as contributing factors to the survival lag seen in these patients (4). However, research focusing upon the treatment delivered has had less attention.

The cisplatin-based bleomycin, etoposide and cisplatin (BEP) chemotherapy regime (5) remains the gold standard of treatment in adult GCT. Within the adult population randomised controlled trials (RCTs) have compared regimes with high dose intensity (DI) to lower DI and found higher DI regimes to be more effective in all clinical risk groups and for each chemotherapy drug (6,7). DI is defined as the quantity of a chemotherapy drug (e.g. mg per m^2) administered per unit time (e.g. weeks) and is defined by clinical trial protocols or clinical guidelines. In practice however, the desired dose intensity is not always reached due to patient toxicity requiring dose delays or reductions. A more accurate assessment is relative dose intensity (RDI), described by Hryniuk as the ratio of the DI of chemotherapy that is actually delivered, compared to the standard DI defined by trial protocol (8,9). There are studies in other AYA cancers indicating that reduction in RDI may be associated

with poorer outcomes (10,11). Maintaining dose intensity can be problematic and costly to both the patient and health services. Short-term barriers include high levels of toxicity, which can be life threatening and require admission to high-level care. In the long term, there is the need to avoid irreversible end organ damage, which will negatively impact long-term health and quality of life. It is crucial therefore, that treatment is delivered by experienced clinical teams (12)

Clinical trial recruitment has long been problematic for the AYA population (13), in part due to these patients falling between the age cut offs of paediatric and adult trials. Participation rates of AYA in clinical trials is estimated at between 5% to 34% compared to over 90% in children (14). Underrepresentation of AYA in GCT trials was evidenced by Shaikh *et al*. who pooled all paediatric trials from North America and the UK over the last 30 years and found only 109 male adolescent participants with metastatic GCT (3).

The use of routine health data for research purposes has been gathering momentum in recent years. Within the field of oncology cancer registration data holds great potential, especially when linked to other, more detailed, datasets. Given the complexities of the AYA population and the poor representation in clinical trials, we set out to explore the utility of cancer registration data to investigate the delivery of RDI in routine practice within the National Health Service (NHS) in England. Through comparison to a clinical trials dataset, we aimed to assess the quality and extent of data items available, strengths of the datasets, limitations of use and areas for improvement.

4.4 Methods

4.4.1 Data sources

4.4.1.a National Cancer Registration and Analysis Service

Data from the Cancer Outcomes and Services dataset (COSD)(15) and the Systemic Anticancer Therapy dataset (SACT) (16), both held by the National Cancer Registration and Analysis Service (NCRAS) were linked to create a dataset of patients diagnosed in England with a GCT when aged 12 to 29 years. COSD

holds patient details of all cancers diagnosed and resident in England, whilst the SACT dataset comprises chemotherapy prescribing data from all treating NHS hospital trusts in England.

Inclusion criteria were:

- Patients registered with a malignant GCT in the NCRAS dataset and diagnosed aged 12-29 years between 1st April 2014 and 31st December 2018. This period reflected the most up to date SACT data available at the time of data extraction.
- Only patients who had received first line treatment recorded in SACT were included, defined as individuals who received chemotherapy within 60 days of diagnosis.
- Patients who had received BEP (bleomycin, etoposide, cisplatin), EP (etoposide, cisplatin) and CBOP/ BEP (vincristine, cisplatin, bleomycin, etoposide, carboplatin) chemotherapy, enabling comparison of bleomycin, etoposide and cisplatin delivery to that within clinical trials.
- Only male patients to improve comparability with the clinical trials dataset.

Exclusion criteria included:

- Any registration record missing both height and weight at the start of treatment.
- Patients where administration dose of drug, number of days to administration of drug or drug name were missing.
- Those who had received less than one cycle of treatment.
- Patients who had received first line carboplatin. These patients were excluded from analysis due to carboplatin dosing using area under the curve (AUC) methods. AUC requires an estimated glomerular filtration rate (eGFR) value, which was not available in the dataset.

4.4.1.b Clinical trials

Patient level data was obtained from four international European Organisation for Research and Treatment (EORTC) clinical trials: 30873, 30895, 30974 and 30983, examining mainly intermediate and poor prognosis patients. The inclusion criteria of

the trials (Table B.1) and characteristics of patients recruited to each trial (Table B.6) were examined and deemed to have adequate clinical heterogeneity to combine the trials data and compare to the real-world dataset. Patients were excluded if the required data items for RDI calculation were missing. The trials combined recruited from 1987 to 2009, therefore there was no overlap in patients between the two cohorts.

4.4.2 Patient and treatment related variables

The linked NCRAS data were explored and data for patient sex, age at diagnosis (years), stage, ethnicity, deprivation, year of diagnosis, region where the patient was living when the tumour was diagnosed, treating speciality and whether or not the treatment regime was adjusted according to co-morbidity were extracted. Germ cell subtype was categorised using International Classification of Diseases for Oncology version 2 (ICD) morphology codes. Stage was derived from TNM imaging, TNM pathology in COSD and stage at the start of treatment in SACT, to maximise completeness. Ethnicity was provided by category as per the 2001 Census (17). Treating specialty codes were provided in accordance with the NHS data dictionary (18) and labelled as either adult or paediatric. Population weighted quintiles of the English Index of Multiple Deprivation (IMD) 2015 (19) were provided by NCRAS as the measure of socio-economic deprivation. Vital status at the time of censoring, the number of days from diagnosis to vital status and year of death were extracted to enable survival analysis.

Where available the same data items were extracted from the clinical trials dataset with the addition of data items required for the International Germ Cell Consensus Classification (IGCCC) (20–22). This risk classification is based on age, histological subtype, primary site, site of metastases and tumour marker levels. Within the NCRAS cohort, only age, histological subtype and primary site were available to request. Whilst the presence of lymph node and visceral metastases were given as part of the TNM pathology data this was poorly completed and did not provide information regarding the site, as required for the IGCCC. We therefore estimated the risk classification of patients in the NCRAS cohort according to the protocol treatment they commenced. Patients were classed as good risk if they had received between one and three cycles of BEP or up to four cycles of EP;

intermediate risk if they received more than three cycles of BEP; and poor risk if they received CBOP/BEP chemotherapy (2,21,22). Stage was provided according to Royal Marsden classification system in one trial and in line with the American Joint Committee on Cancer (AJCC) system in the remaining three. To provide consistency in the dataset all staging data was converted to the AJCC.

4.4.3 Treatment toxicity

Data related to toxicity of treatment was explored and summarised. Toxicity data in the clinical trials dataset were given for each individual chemotherapy drug. Whilst details relating to organ specific toxicity as per Common Terminology Criteria for Adverse Events (CTCAE) grade were available, only data relating to dose reduction, treatment delay and early cessation of treatment were extracted. This enabled comparison with the NCRAS cohort where toxicity data were limited to binary variables of regime modifications; dose reduction, treatment stopped early and treatment delay with outcomes yes, no or missing possible. Cause of death was extracted from both cohorts as a marker of toxicity, derived either from the trial follow-up data or from the Office for National Statistics (ONS)(17) death certificate data for the NCRAS cohort. Censor date for the ONS data was 28th February 2020.

4.4.4 RDI calculation

The treatment variables used for RDI analysis were those providing treatment regime, drug name, numbers of days from diagnosis to administration date of chemotherapy, actual dose of drug per administration and cycle number. Patient height and weight at the start of regimen were used to calculate an individual's body surface area. Patients missing both height and weight were excluded. In instances where data on either height or weight were unavailable, these were assumed to be missing at random and imputed using predictive mean matching. This enabled calculation of the standard dose of chemotherapy a patient would have received as per the relevant protocol, without dose adjustments. Treatment data were reviewed by a clinician to ensure adequacy of data quality. Actual doses per administration were converted to standard units where required; mg/m^2 for cisplatin and etoposide, IU for bleomycin.

The RDI of chemotherapy received by each patient was calculated by dividing the actual dose intensity (ADI) of treatment received by the expected standard dose intensity (SDI). The ADI was the actual total dose of chemotherapy received divided by the number of weeks it was given over. The SDI was calculated by dividing the standard dose that individual should have received, assuming no toxicity, by the time over which it should have been given, as determined either by the trial protocol (Table B.1) or that which is received as per standard care (23). RDI was expressed as a decimal with 1.0 indicating that treatment had been received 100% in accordance with protocol. RDI was categorised into those that had received less than 0.75, 0.75-0.84, 0.85-0.94 and greater than 0.95. Within the literature there is variation as to what constitutes an adequate RDI. The cut offs used were chosen to align with those used in previous studies(24–28). The majority of patients (93.9%) in the NCRAS cohort were treated within an adult speciality and therefore all patients were analysed in comparison to standard adult chemotherapy protocols.

4.4.5 Statistical analysis

Overall survival over time was described using Kaplan-Meier estimation (29) at 1-, 2- and 5- years post-diagnosis. Survival rates were examined overall and by age category, IGCCG risk classification, stage, tumour subtype, primary site, ethnicity and deprivation. Cox regression models (30) were used to determine the total effect of RDI as a continuous variable on mortality risk, in the two cohorts separately. The models were adjusted for confounding using the minimal sufficient adjustment set as informed by causal inference methods (31) using directed-acyclic graphs (Figure B.1) within DAGitty software (32). For the NCRAS dataset the model adjusted for age at diagnosis, whether the dose was adjusted for co-morbidity, ethnicity, deprivation quintile, sex and region treatment received in. In the clinical trials dataset adjustment was for IGCCCG classification and age at diagnosis. Age was included as a continuous variable but all others as categorical variables due to how they were provided in the datasets. Only patients with complete data for the required variables were analysed. Goodness-of-fit testing using Bayesian Information Criterion (33) was performed to confirm that presenting RDI as a continuous variable was more optimal that a categorical variable. Schoenfeld and

scaled residuals (34,35) were used to assess the Cox proportional hazard assumption. The Stata command estat phtest was used to test the proportionality of the model as a whole; and by specifying the detail option it was possible to examine whether the proportional hazards assumption held for each variable included the model. The plot extension of the stphtest command produced graphical representation of the scaled Schoenfeld assumption, enabling visual verification of whether the models satisfied the assumption of proportionality. None of the tests in the table reached statistical significance, indicating that the predictors did not violate the proportionality assumption. All statistical analysis was performed using Stata 16 (36).

4.5 Results

4.5.1 Patient characteristics

Data for 1503 GCT patients were received from NCRAS. Of these patients, 138 were excluded for missing treatment data, 107 due to missing both height and weight, 226 were excluded as they had received carboplatin first line and 73 received a first line regime other than those under investigation. There were 90 patients excluded as they had received less than one cycle of chemotherapy and 48 female patients excluded. A total of 817 patients therefore met the inclusion criteria from the NCRAS data. From the clinical trials data 799 patients were included, and nine excluded for missing treatment data. The patient characteristics of both cohorts and case numbers can be found in Table 4.1. The flow of patients in both datasets are shown in Figure 4.1.

Table 4.1: Germ cell patient characteristics within the clinical trials and NCRAS datasets.

		Clinical trials n (%)	**NCRAS n (%)**
Total number patients		799	817
Total number of deaths		151 (18.9)	35 (4.3)
Age at diagnosis	17 or under	31 (3.9)	33 (4.0)

(years)	18-23	228 (28.5)	282 (34.6)
	24-29	268 (33.5)	502 (61.4)
	30 or over	272 (34.1)	
Tumour subtype	**Seminoma**	**27 (3.4)**	**75 (9.2)**
	Non-seminoma	**580 (72.6)**	**260 (31.8)**
	Yolk Sac		13
	Embryonal		164
	Choriocarcinoma		13
	Teratoma		70
	Mixed	113 (14.1)	387 (47.4)
	Other		95 (11.6)
	Unknown/ missing	79 (9.9)	-
Stage[£]	1	1 (0.1)	78 (9.5)
	2	139 (17.4)	175 (21.4)
	3	648 (81.1)	46 (5.6)
	4	0 (0)	147 (18.0)
	Missing	11 (1.4)	371 (45.4)
IGCCC risk classification [a#]	Good	11 (1.4)	668 (81.8)
	Intermediate	470 (58.8)	108 (13.2)
	Poor	296 (37)	19 (2.3)
	Not possible	22 (2.8)	22 (2.7)
Primary site	Abdomen/retroperitoneal	40 (5)	4 (0.5)
	Testis	684 (85.6)	803 (98.3)
	Mediastinal	39 (4.9)	10 (1.2)
	Other	22 (2.8)	-
	Missing	14 (1.8)	0
Site metastatic disease			
Lymph nodes			
Mediastinal	Yes	218 (27.3)	*
	No	566 (70.8)	*
	Missing	15 (1.9)	*
Supraclavicular			
	Yes	125 (15.6)	*
	No	660 (82.6)	*
	Missing	14 (1.8)	*
Abdominal			
	Yes	444 (55.6)	*

	No	341 (42.7)	*
	Missing	14 (1.7)	*
Visceral	Yes		
Lung	No	479 (60)	*
	Missing	314 (39.3)	*
		6 (0.7)	*
	Yes		
	No	74 (9.3)	*
Other	Missing	708 (88.7)	*
		16 (2)	*
Tumour markers	HCG (IU/L)		
	<5000	492 (61.6)	*
	≥5000 & ≤50,000	192 (24)	*
	>50,000	115 (14.4)	*
	AFP (ng/ml)		
	<1000	2 (0.2)	*
	≥1000 & ≤ 10,000	59 (7.4)	*
	>10,000	738 (92.4)	*
	LDH		
	<1.5 x ULN	237 (29.7)	*
	≥1.5 x ULN ≤ 10 x ULN	416 (52.1)	*
	>10 X ULN	146 (18.3)	*
Ethnicity	White/ White Irish	*	696 (85.2)
	Other	*	117 (14.3)
	Missing	*	4 (0.5)
Socioeconomic status (IMD quintile)[b]	1	*	139 (17)
	2	*	133 (16.3)
	3	*	164 (20.1)
	4	*	180 (22)
	5	*	201 (24.6)

* data item not available

[a] International Germ-Cell Cancer Consensus Classification[20].

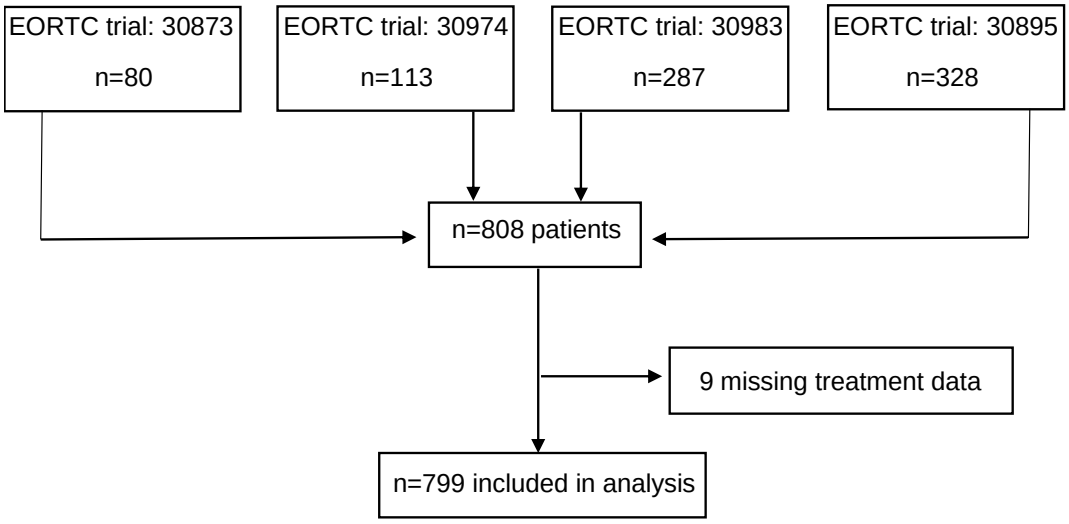
[b] English Index of Multiple Deprivation (IMD) 2015[19].

[£] Different staging systems applied in trials and NCRAS data.

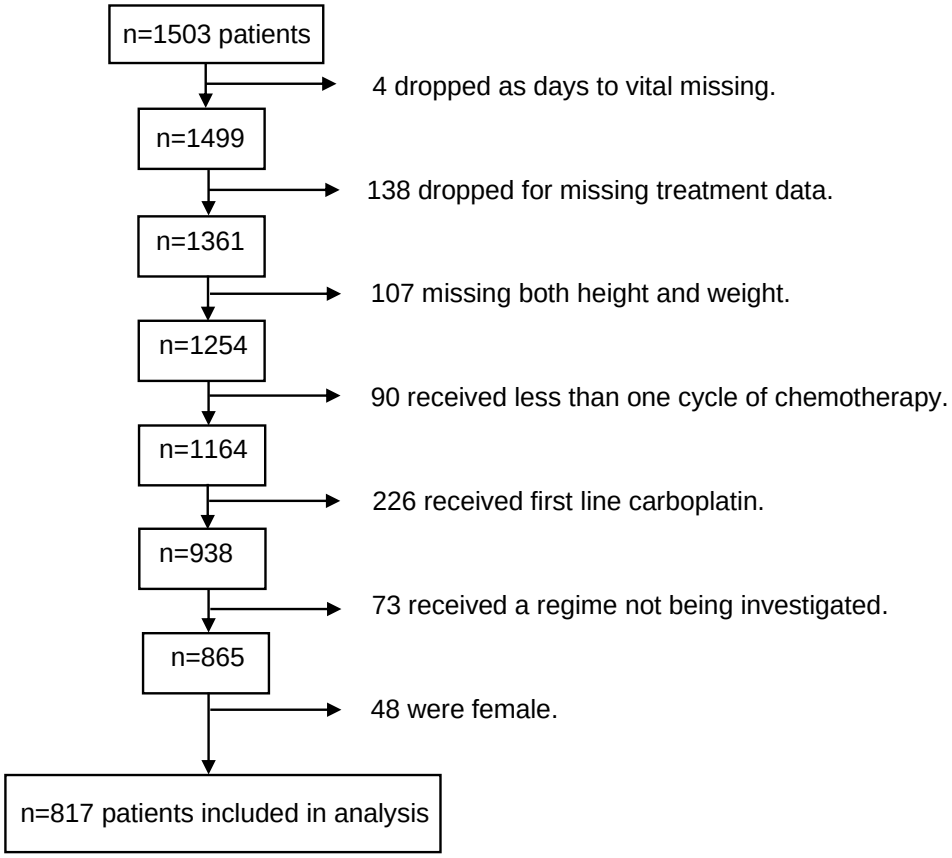
coded according to treatment received as in methods.

Figure 4.1: Consort diagrams demonstrating patient flow in the clinical trials cohort (a) the NCRAS cohort (b).

(a)



(b)



The median age at diagnosis in the clinical trials dataset was 26.7 years (IQR, 22.5 – 31.4) compared to 25.0 years (IQR, 22-27) in the NCRAS cohort. The age range was 14.8 to 39.8 years in the clinical trials data and 12-29 years for the NCRAS cohort. Mixed was the most common histological subtype in the NCRAS cohort (47.4%) compared to non-seminoma in the clinical trials patients (72.6%). Testis was the most common primary site (85.6% and 98.3%) in the clinical trials and NCRAS cohorts respectively.

There was a higher proportion of missing data for stage in the NCRAS cohort (45.4%) compared to the clinical trials data (1.4%). Within the clinical trials data, 11 (1.4%) patients were classified as good prognosis according to the IGCCC, 470 (58.8%) intermediate prognosis and 296 (37%) poor prognosis. 668 (81.8%) patients in the NCRAS cohort were classified as good prognosis, 108 (13.2%) as intermediate prognosis and 19 (2.3%) as poor prognosis.

Patient ethnicity and deprivation status were not recorded in the clinical trials data. In the NCRAS cohort white ethnicity was the most common group (85.2%). The highest proportion of patients fell into the most deprived fifth of the IMD (24.6%).

4.5.2 Treatment toxicity and cause of death

For the analysis of toxicity, the clinical trials were treated as individual datasets and summarised in Table B.2. Two clinical trials provided dose reductions, recording 67.5% and 41.3% respectively compared to 3.1% in the NCRAS data. NCRAS data had a higher proportion of missing data for this item (23.3%) than clinical trials (0%, 1% respectively). All four clinical trials provided treatment delay data, occurring in 20%, 6.8%, 17.8% and 13.1% of patients compared to 6.4% in NCRAS, although there was a higher level of missing data in the NCRAS cohort (39%) limiting interpretation. Treatment stopped early data was provided in trial 30895 and reported in 19.3% of cases compared to 10.4% in the NCRAS cohort; levels of missing data were 3% and 14.9% respectively.

Thirty-five patients (4.3%) died in the NCRAS cohort with a cause of death provided on ONS death certificate for 33 (94%) patients. Of these, 89% (n=24) were recorded as being directly related to malignancy, and one death from complication post procedure. Three patients died of accidental causes. There were 6 causes of death attributed to toxicity including neutropenic sepsis (n=2), pneumonia (n=3) and liver failure (n=1). Only three deaths occurred within 30 days of the last recorded chemotherapy, all of which were recorded as being cancer related. There were 151 (18.9%) deaths in the clinical trials dataset; malignant disease was recorded as the cause of death for 78.8%, toxicity for 13.9% and other for 4.7%.

4.5.3 Achieved RDI and survival analysis

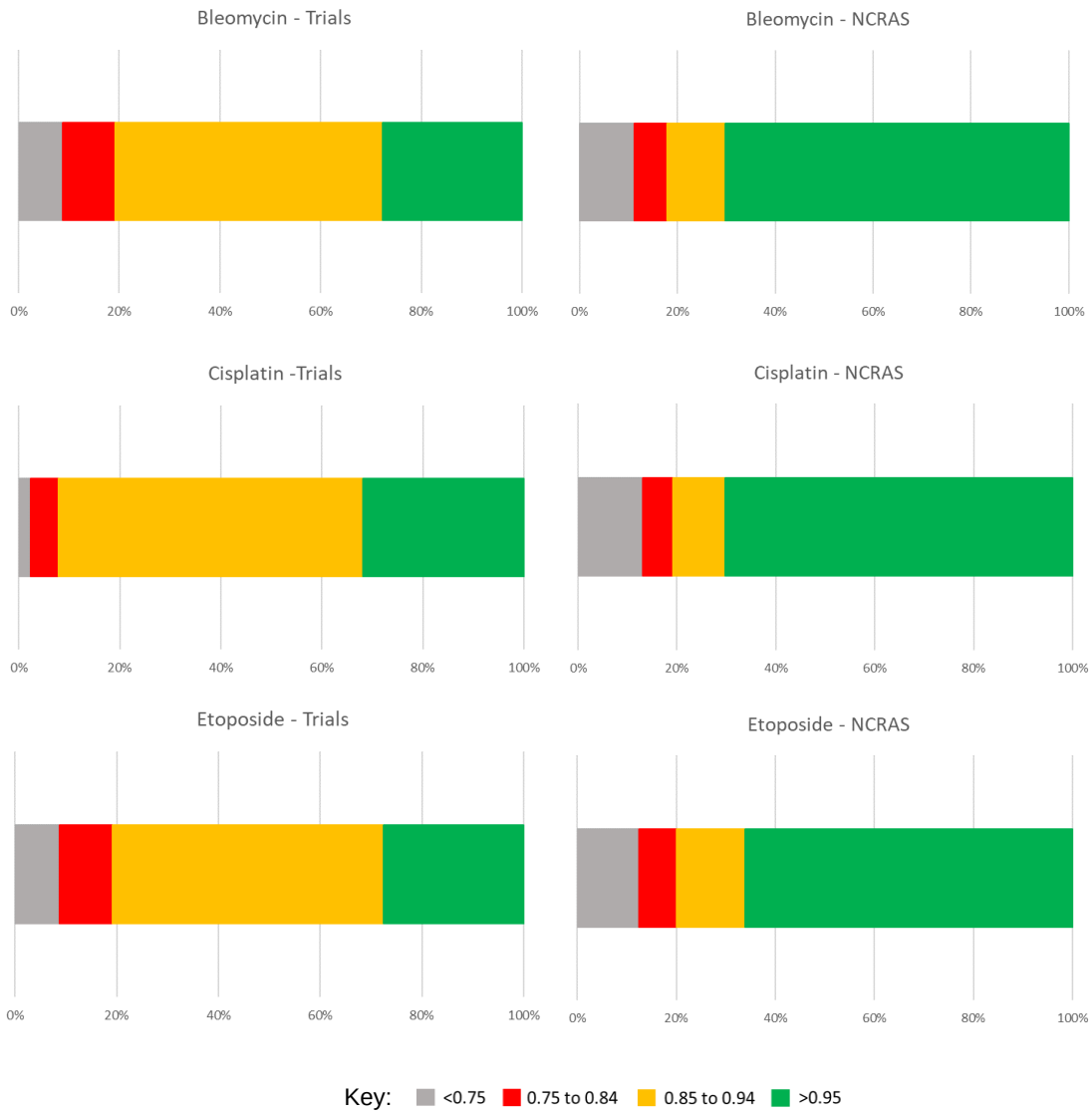
Comparison of median achieved RDIs (Table 4.2) showed high RDIs were delivered in both the clinical trials and NCRAS cohorts for each drug (bleomycin: clinical trials 0.97 (IQR: 0.85-1.0) vs. NCRAS 1.02 (IQR: 0.90-1.06), cisplatin: clinical trials 0.98 (IQR: 0.93-1.0) vs. NCRAS 1.01 (IQR: 0.92-1.08), etoposide: clinical trials 0.96 (IQR: 0.88-1.0) vs. NCRAS 1.00 (IQR: 0.89-1.06). Within the clinical trials cohort a

higher proportion of patients received an RDI of 0.85-0.94 (Figure 4.2) in comparison to the NCRAS cohort for all drugs (bleomycin; 53.2% vs 11.2%, etoposide; 53.4% vs 13.9%, cisplatin 60.3% vs 10.6%). A lower proportion of patients in the clinical trials cohort however received a RDI greater than 0.95, compared to the NCRAS cohort (bleomycin; 27.6% vs 70.2%, etoposide; 27.6% vs 66.%, cisplatin 32% vs 70.3%).

Table 4.2: The median achieved relative dose intensity and associated interquartile range (IQR) within the clinical trials and National Cancer Registration and Analysis Service datasets.

	Clinical trials		**NCRAS**	
	Median RDI achieved	**IQR (25%-75%)**	**Median RDI achieved**	**IQR (25%, 75%)**
Bleomycin	0.97	0.85 to 1.0	1.02	0.90 to 1.06
Cisplatin	0.98	0.93 to 1.0	1.01	0.92 to 1.08
Etoposide	0.96	0.88 to 1.0	1.00	0.89 to 1.06

Figure 4.2: Bar charts demonstrating the proportion of patients achieving each category of relative dose intensity.



Median survival time for those that died in the clinical trials cohort was 0.95 years (IQR: 0.50-1.62 years) with an overall median follow up time of 4.85 years (IQR: 3.75-6.5 years). In the NCRAS cohort median survival time for those that died was 1.14 years (IQR, 0.62-1.62 years), with an overall median follow up time of 4 years (IQR: 2-5 years).

Overall survival (OS) was lower in the clinical trials dataset (1 year 90% and 5 year 80%) compared to NCRAS (1 year 98% and 5 year 95%) (Table 4.3). In the clinical trials dataset those aged 30 years or over had the lowest 5-year survival (78%) followed by 18–23-year-olds (80%). In the NCRAS cohort 5-year survival was highest in those 17 years and under (97%) with no difference seen in patients aged 18-23 (95%) or 24–29-year-olds (95%). These differences are demonstrated in the Kaplan-Meier survival estimates (Figure B.2). When age was categorised into under 18 years and over 18 years, to enable comparison with the literature, 5-year survival was higher for those under 18 years compared to those over 18 years in both the NCRAS cohort; (97% vs 95%) and in the clinical trials data; (84% vs 81%) (Table B.3).

Table 4.3: Kaplan Meier one, two and five-year survival estimates presented for clinical trials and National Cancer Registration and Analysis Service cohorts, both overall and by clinical and demographic variables.

	Clinical trials % (95% CI)			**NCRAS % (95% CI)**		
	1 year	**2 years**	**5 years**	**1 year**	**2 years**	**5 years**
Overall	90 (88-92)	84 (81-86)	80 (77-83)	98 (97-99)	96 (95–97)	95 (93 – 96)
Age category at diagnosis (years)						
17 or under	97 (79-100)	97 (79-100)	84 (61-94)	100	97 (80-100)	97 (80-100)
18-23	88 (82-92)	82 (76-87)	80 (73-85)	98 (95-99)	95 (91-97)	95 (91-97)
24-29	91 (88-94)	85 (80-89)	83 (78-87)	98 (96-99)	97 (95-98)	95 (92-97)
30 or over	89 (85-92)	82 (77-86)	78 (73-83)	-	-	-
IGCCC risk						
Good	100	100	-	99 (98-100)	98 (97-99)	97 (95-98)
Intermediate	95 (93-97)	92 (89-94)	89 (86-92)	96 (90-99)	92 (85-96)	92 (85-96)
Poor	82 (77-86)	71 (66-76)	67 (60-72)	84 (59-95)	68 (42-84)	51 (17-77)
Stage						
1	100	100	100	100	99 (91-100)	99 (91-100)
2	99 (94-100)	96 (90-98)	95 (89-97)	99 (96-100)	98 (95-99)	98 (95-99)
3	88 (85-90)	81 (77-84)	77 (73-80)	98 (86-100)	96 (86-100)	94 (78-99)
4	-	-	-	98 (94-99)	91 (85-95)	89 (82-94)

Tumour subtype						
Seminoma	93 (74-98)	85 (65-94)	77 (55-89)	100	99 (91-100)	99 (91-100)
Non-seminoma	91 (88-93)	84 (81-87)	81 (77-84)	97 (94-99)	96 (93-98)	95 (91-97)
Mixed	78 (51-91)	72 (46-88)	72 (46-88)	99 (98-100)	98 (96-99)	98 (96-99)
Other	-	-	-	95 (88-98)	85 (76-91)	78 (63-88)
Unknown/missing	77 (64-86)	70 (57-80)	68 (54-78)	-	-	-
Primary site						
Abdomen/ retroperitoneal	85 (70-93)	77 (61-88)	75 (58-85)	75 (13-96)	75 (13-96)	-
Testis	93 (91-95)	87 (84-89)	84 (81-87)	99 (97-99)	97 (95-98)	95 (93-97)
Mediastinal	57 (39-71)	45 (29-60)	37 (21-54)	80 (41-95)	64 (23-87)	-
Other	73 (49-87)	57 (34-75)	-	-	-	-
Missing	100	100	100	100	100	-
Ethnicity*						
White	-	-	-	98 (97-99)	97 (95-98)	95 (93-97)
Mixed	-	-	-	100	100	-
Asian	-	-	-	96 (85-99)	86 (72-94)	86 (72-94)
Black	-	-	-	100	100	-
Other	-	-	-	98 (88-100)	98 (88-100)	98 (88-100)
Deprivation quintile* #						
1 - least deprived	-	-	-	98 (93-99)	96 (91-98)	96 (91-98)
2	-	-	-	99 (94-100)	96 (91-98)	94 (87-97)
3	-	-	-	96 (91-98)	96 (91-98)	96 (91-98)
4	-	-	-	100	98 (95-99)	96 (90-99)
5 - most deprived	-	-	-	99 (95-100)	95 (91-97)	93 (88-96)

*Ethnicity and deprivation quintile were not provided for the clinical trials cohort.

Deprivation indicator is the English Index of Multiple Deprivation (IMD) 2015[19].

a International Germ-Cell Cancer Consensus Classification[20].

Poorer survival rates were seen at all time points with an increase in IGCCC risk category within the NCRAS patients (1 year; good 99%, intermediate 96%, poor 84%, 2 years; good 98%, intermediate 92%, poor 68%, 5 years; good 97%, intermediate 92%, poor 51%). These findings were also seen in the clinical trials patients (Figure B.2), providing some validation for the clinical estimation of risk grouping we applied.

There was a trend of lower survival estimates associated with increasing stage in the NCRAS data at 1 year (stage 1; 100%, stage 2; 99%, stage 3; 98%, stage 4; 98%) and 5 years (stage 1; 99%, stage 2; 98%, stage 3; 94%, stage 4; 89%).

Ethnicity and socioeconomic status data were only available within the NCRAS cohort. Evidence was seen of lower survival in patients of Asian ethnicity (1 year 96% and 5 years 86%). No clear effects were seen by level of deprivation.

Multivariable regression showed that increasing RDI was associated with a lower risk of death (Table 4.4) in both datasets. In the clinical trial dataset those patients who received higher RDI had a lower risk of death for; bleomycin (HR: 0.21, 95% CI 0.08-0.54), cisplatin (HR: 0.09, 95% CI 0.02-0.44) and etoposide (HR: 0.18, 95% CI 0.06 – 0.55). In the NCRAS cohort the same pattern was noted with a similar effect for bleomycin; (HR: 0.26, 95% CI 0.07-1.04) but less strongly for cisplatin (HR: 0.87, 95% CI 0.44-1.72) and etoposide (HR: 0.88, 95% CI 0.33 – 2.34). This pattern remained when only the intermediate and poor risk patient subsets were analysed in the NCRAS dataset, enabling comparison with the trials data; the association strengthened for etoposide (HR: 0.75, 95% CI 0.18 – 3.20), weakened for bleomycin (HR: 0.57, 95% CI 0.13-2.49) and remained unchanged for cisplatin (HR: 0.86, 95% CI 0.35-2.13). Further sensitivity analyses can be found in Table B.4.

Table 4.4: Hazard ratios (HRs) and 95% confidence intervals (CIs) from Cox regression models presenting the association between RDI received and risk of death in germ cell tumour patients within the clinical trials and National Cancer Registration and Analysis Service cohort.

Clinical trials							**NCRAS (all risk categories)**							**NCRAS (intermediate and poor prognosis only)**						
Chemotherapy drug	**Adjusted***			**Unadjusted**			**Chemotherapy drug**	**Adjusted****			**Unadjusted**			**Chemotherapy drug**	**Adjusted****			**Unadjusted**		
	HR	**95% CI**	**P value**	**HR**	**95% CI**	**P value**		**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**		**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Bleomycin (n=652)	0.21	0.08-0.54	0.00	0.13	0.05-0.31	0.00	Bleomycin (n=769)	0.26	0.07-1.04	0.06	0.27	0.07-1.04	0.06	Bleomycin (n=154)	0.57	0.13-2.49	0.46	0.65	0.16-2.64	0.55
Cisplatin (n=739)	0.09	0.02-0.44	0.00	0.06	0.01-0.31	0.00	Cisplatin (n=794)	0.87	0.44-1.72	0.69	0.86	0.44-1.69	0.67	Cisplatin (n=145)	0.86	0.35-2.13	0.75	0.75	0.28-1.99	0.56
Etoposide (n=730)	0.18	0.06-0.55	0.00	0.17	0.05-0.59	0.00	Etoposide (n=798)	0.88	0.33-2.34	0.80	0.88	0.34-2.26	0.79	Etoposide (n=144)	0.75	0.18-3.20	0.70	0.68	0.16-3.00	0.62

* Adjusted for age and IGCCCG classification.

** Adjusted for age, dose adjusted for co-morbidity, ethnicity, deprivation quintile, sex and region treatment received in.

4.6 Discussion

This is the first study to compare prescribing practice and data quality within clinical trials and routine care with regards to RDI in GCT and evaluate the impact on survival outcomes. Whilst other population-based studies have looked at treatment delivered (37–39) few have calculated the actual DI delivered using population level data. We have found that chemotherapy RDI is being maintained in patients within NHS care in England at similar levels to those seen in clinical trials and other single centre studies, but with greater variation (39). This is a positive reflection of the specialist network of AYA centres in England put in place in response to the publication of "Guidance on Improving Outcomes in Children and Young People with Cancer" by the National Institute of Clinical Excellence (NICE) in 2005 (40). The formation of regional MDTs for GCT, which include individuals with expertise in AYA, is another likely contributing factor (41). Our results show some variation in treatment received. Fewer patients received an RDI over 0.95 in clinical trials compared to routine practice. This may reflect dose reductions being driven by strict trial protocols as opposed to clinical experience alone and is supported by a greater number of treatment modifications being recorded in the clinical trials cohort compared to the NCRAS cohort. It may also be the result of clinical trials excluding patients due to co-morbidities (Table B.1). A higher overall proportion of patients received an RDI of over 0.75 in clinical trials. One possible reason for this is that support given when participating in clinical trials may enable patients to tolerate higher dose intensities (42). In addition, within the busy NHS setting, treatment timings may need to be altered according to the availability of resources. Although we tried to identify and exclude patients with missing treatment data in the analysis, the possibility of incomplete treatment data should also be considered as a cause of the higher proportion of patients receiving an RDI of less the 0.75 in the NCRAS cohort. The historical nature of some of the trials should be noted with the earliest trial included starting in 1987. We are aware that more contemporary trial comparators are now available, for example through the MaGIC data commons. The EORTC trials data utilised however were more easily obtainable with the required DSA agreements already in place. The BEP protocol has changed little over this time with limited effect on efficacy (43). G-CSF however achieved United States Food and Drug Administration (FDA) approval in 1991 which could explain some of the variations seen between the two cohorts, alongside an emerging recognition of the unique needs of AYA patients. Whilst we are satisfied that the clinical trials dataset provides a valid comparison to the real-world data caution is

required when making comparisons to historical trials (44). In keeping with other research findings (6,7), an association of maintaining dose intensity with survival was demonstrated for all drugs in both patient cohorts. The hazard ratios were suggestive of a stronger association in the clinical trials cohort, compared to those in the NCRAS cohort, most of these patients received an RDI in the category of 0.85 to 0.94 (Figure 4.2). A similar population-based study found patients to have 5-year OS rates of 95% despite 44% receiving dose modifications (38), it may therefore be that RDIs within this range have the greatest survival benefit.

A strength of this study is our utilisation of data linkage between COSD and SACT data to create a detailed treatment dataset for AYA patients. Whilst the utility of SACT data in the research of adult solid tumours has been demonstrated (45) poorer ascertainment of the treatment data in children, teenagers and young adults (CTYA) is a known limitation (16,46). This is the first published research we know of to detail the analysis possible with SACT data alongside structured clinical interpretation. In addition, we have demonstrated the many strengths that the NCRAS data holds for research purposes. Firstly, the availability and completeness of socio-demographic details provides the ability to investigate health inequalities in the AYA population, such as ethnicity as we have shown. Not only is this data lacking in the clinical trials data but is also limited by difficulties in the recruitment of certain patient subgroups to trials (13). Cancer registration data also enables the impact of co-morbidities, often excluded from trial participation, on treatment delivered to be assessed. Within NCRAS data, a co-morbidity adjustment indicator indicates whether co-existing comorbidities were considered for dose or regime. This, along with ECOG performance status, provides data on how patients ineligible for a trial are treated. Further linkage to Hospital Episode Statistics (HES) admissions and primary care data can extend this in future (47) and although outside the scope of his paper, will be beneficial for research in the increasing number of older patients developing GCT. A further strength of the NCRAS data is that cause of death data is captured directly from the ONS (17), providing almost complete ascertainment, which is not always possible in clinical trials due to loss to follow-up.

Our study has some weaknesses, which we considered in our interpretation. The two datasets differ in some areas, notably the greater proportion of good prognosis

patients in the NCRAS cohort. This is the result of comparing a population dataset (NCRAS) to more focused clinical trials datasets and is a likely reason for the better survival outcomes seen in the real-world dataset. We found that the available NCRAS data has limitations for use in AYA-specific cancers, particularly in relation to data for risk stratification. Only histological subtype and primary site are available for request from the NCRAS dataset, limiting IGCCC risk classification. Whilst further required data items, such as lymphovascular invasion, are present in COSD, completion rates are low. Stage also had a high proportion of missingness in the NRCAS data. This may be because clinicians use IGCCC classification, not stage, to make decisions. We compared the completeness of stage in GCT patients with that of FIGO staging in cervical cancer patients of the same age and found a missingness of 46.2% compared to 4.8%, highlighting the difference in comparison to a common carcinoma in adulthood where stage more directly determines treatment. We have demonstrated how the lack of risk stratification data can, in part, be overcome with clinical interpretation but acknowledge that this is still imperfect. Standard treatment for intermediate and poor prognostic adult testicular cancer remains four cycles of BEP chemotherapy (23). It was not possible to separate out these patients from the NCRAS data using our algorithm, therefore some poor prognosis patients will have been misclassified as intermediate. In our cohort the number of patients categorised as good risk was 81.3% compared to that in the literature of 45% (3). It is therefore likely that some patients classified as good risk are in fact intermediate or poor prognostic risk patients who did not complete four cycles of chemotherapy. The immaturity of SACT data, which became available from 2014 onwards, means only a limited period of follow-up of patients is available. This restricts the survival analysis possible where initial survival rates are high, resulting in high right censoring rates for this early data (in our case a censor rate of 95.6%). We attempted to compare the survival rates of the NCRAS cohort with both the clinical trials data and the findings by Shaikh et *al*. and found the NCRAS 5-year survival to be much higher (Table B.3), likely due to both the censoring, a higher proportion of good prognosis patients and the data being more contemporary. Toxicity data in the NCRAS cohort was limited to binary outcomes at regimen level. Whilst this could be enhanced by calculating the percentage dose reduction using the available data items it would still lack the detail provided in clinical trials which provides insight into the barriers faced in delivering each chemotherapy agent.

We have identified a number of areas for further work. Requesting the data in accordance with data minimisation practice meant that we could not investigate the impact of treatment setting on received RDI in the population data, as treatment centre identities were pseudonymised. This is an important area for future consideration as variations may exist between specialist and non-specialist AYA centres. The latter less likely to have been involved in clinical trials and to have experience of treating patients with rare presentations. Decisions around dose modifications may therefore be different, with specialised AYA cancer services able to provide greater supportive care, maintaining survival in poor risk cases (48,49). This is supported by the work by Collete which found GCT patients treated in centres that entered fewer than five patients in clinical trials had poorer survival outcomes(50). In this data those aged over 18 years had the poorest 5-year survival rates. The potential for pharmacokinetic differences across the AYA age range to influence chemotherapy efficacy has been described (51). Exploration of the potential benefits that therapeutic drug monitoring and individualised dosing may bring to AYA warrants further investigation. A stronger association between survival benefit and RDI was seen in the clinical trials dataset, where most patients received an RDI of 0.85 to 0.94 compared to over 0.95 in the NCRAS data. We reported recorded cause of death as a marker of toxicity; 17% of deaths within the NCRAS data were likely due to toxicity and 14.3% in the clinical trials. Given the high proportion of good prognosis patients in the NCRAS cohort, it could be considered whether improvements might be gained from trials of lower dose-intensity approaches in these patients. Dose reduction to reduce toxicity and maintain survival may not be feasible in intermediate and poor prognosis disease but analyses such as these can inform the design of future dose de-escalation trials in cohorts such as the good prognosis GCT patients (52).

AYA cancers are important but rare, so small patient numbers can restrict the analysis of datasets and the meaningfulness of findings produced. Here we have analysed a substantial population level dataset of 817 patients taken from one country over a four-year period, limited from 1503 by our own inclusion criteria. This is comparable to the 799 patients achieved from four international clinical trials. Whilst we appreciate that GCT is within the most common tumour types in AYA, the use of population-based registries to enhance research in this field holds great possibility. Several global initiatives are embracing this including the MaGIC consortium(53) for GCTs who are amalgamating data sets trials into ‘data

commons.' The STRONG-AYA (54) initiative is a European Union funded consortium using new data analysis initiatives such as federated data analysis to compare outcomes for AYA with cancer. Although the limited follow up time restricted the survival analysis possible in our study, with time follow up duration available will become a strength of the NCRAS dataset, greater than possible in clinical trials. Linkage to other datasets such as HES could enable the long-term toxicity of treatments, both within trials and routine practice, to be monitored. There are potential mutual benefits to be gained from the linkage of clinical trials and NCRAS data. The former gaining through better socio-demographic data and longer follow up, the latter by more detailed stage, dose and toxicity data. For this to be effective adequate resources, capacity and training are required to improve data completeness. In addition, patient consent needs to be obtained in clinical trials to enable linkage of data for research purposes in order to help overcome the information governance legislation currently preventing this (55).

4.7 Conclusion

We have demonstrated that delivered dose intensity is associated with improved survival in routine NHS care of AYA with GCT. Careful cleaning, interpretation and analysis maximised the utility of the linked SACT and COSD data, enabling high level analysis, albeit limited in GCT by data completeness for robust risk classification and staging. The ultimate potential of this data can only be harnessed by improving completeness and overcoming existing barriers to data sharing.

4.8 Declarations

Author contributions

The study was conceived by Nicola Hughes, Dan Stark and Richard Feltbower. Nicola Hughes performed the analysis with statistical support from Kirsten Cromie. Nicola Hughes, Dan Stark, Richard Feltbower, Kirsten Cromie and Martin McCabe contributed to the interpretation of the analysis. Nicola Hughes drafted the article with contributions from all other authors. All authors have read and approved the final manuscript for publication. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

Acknowledgements

We would like to acknowledge the EORTC for providing the clinical trials data set.

Funding

Nicola Hughes is funded by the National Institute of Health Research (NIHR) [Doctoral Research Fellowship (NIHR300693)]. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Data availability statement

The NCRAS dataset consists of patient-level information collected by the NHS. This data is collated, maintained and quality assured by the NCRAS team, part of NHS digital. The data that support the findings of this study are available from the authors, following permission from NHS digital and the EORTC.

Conflict of interest

Dan Stark holds programmatic research grant funding from the Teenage Cancer Trust. The other authors have no conflict to disclose.

Ethics statement

Ethical approval for this study was obtained from the Yorkshire and The Humber-Bradford Leeds Research Ethics Committee (REC reference 19/YH/0121).

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Chapter 5.

In this Chapter novel data linkage between regional cancer registration data and electronic chemotherapy prescribing records is utilised to investigate the impact of toxicity induced modifications of treatment (TIMT) on survival. The analysis focuses on patients aged 0-29 years receiving first line chemotherapy for Ewing and osteosarcoma in Leeds Teaching Hospitals. Variations in TIMT according to age and sex are explored and the utility of the data sources for research purposes described. Supplementary tables and figures can be found in Appendix C. This paper will be submitted for publication in the coming months.

Title: Toxicity induced modifications of treatment in AYA patients treated for bone cancers: a single centre study using linked cancer registration and existing healthcare data.

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5.1 Abstract

Purpose

This single centre study uses a novel data linkage approach to investigate the impact of toxicity induced modifications of treatment (TIMT) on survival in patients aged 0-29 years receiving first line chemotherapy for Ewing and osteosarcoma.

Variations in TIMT according to age and sex were explored and the utility of the data sources for research purposes described.

Methods

Linked data from the Yorkshire Specialist Register of Cancer in Children and Young People (YSRCCYP) and electronic chemotherapy prescribing systems were analysed. Survival rates were estimated over time using Kaplan-Meier estimation, overall and according to patient and tumour characteristics. Cox regression models were used to determine the fully adjusted effect of TIMT on survival.

Results

Variation in TIMT were seen across the age categories and between the different sexes. Receiving at least one TIMT was found to be associated with a lower risk of death when compared to those who had no TIMT in both Ewing (HR 0.43, 95% CI 0.14-1.35) and osteosarcoma (HR 0.36, 95% CI 0.11-1.20). In patients who received TIMT, an increasing number was associated with a slight benefit in Ewing (HR 0.87, 95% CI 0.64-1.17) and a negative association in osteosarcoma (HR 1.50, 95% CI 1.21-1.85).

Conclusion

This study supports the theory that differences in chemotherapy handling exist between males and females and across the age categories within children and young people. Evidence is provided for the suggestion that toxicity may be a marker of treatment efficacy.

5.2 Introduction

Primary bone cancers are rare, accounting for only 0.2% of all malignant tumours (1). The incidence of bone tumours peaks in the adolescent and young adult (AYA) population, representing 5.5% of new cancers in 15 to19 year-olds and 2.3% in 15-24-year-olds (2,3). Osteosarcoma and Ewing sarcoma are the most commonly occurring subtypes, both with a slightly higher incidence in males (4,5). Whilst

survival rates for many cancers in AYA have improved over recent decades (6,7), those for bone tumours have remained relatively stagnant with current 5-year relative survival rates of approximately 65% in osteosarcoma and 54% in Ewing. As in other tumour types there is evidence to suggest that adolescents have poorer survival rates compared to younger children (7–9). A sex discrepancy in survival has also been reported with males having worse outcomes compared to females (8,10).

Potential reasons for these observations are well described and include tumour biology, poor clinical trial recruitment, psychosocial factors and treatment received (11). Chemotherapy remains a core part of treatment for many cancers common in AYA, including bone tumours for which patients receive intensive multidrug regimes. There is a growing body of literature to suggest that the physiological changes that occur during and following the normal pubertal processes of adolescence (12–18) affect the handling of chemotherapy agents. These changes occur at different times in different individuals and can influence the absorption, distribution, metabolism and excretion (ADME) of drugs. Further investigation of these differences however are limited due to the rarity of pharmacokinetic (PK) and pharmacodynamic (PD) studies in AYA (18).

In an attempt to improve outcomes in AYA, there has been a move to towards more dose dense chemotherapy regimes which can cause high levels of treatment related toxicity. A meta-analysis of prospective clinical trials data in osteosarcoma reported differences in toxicity experienced between children, AYA and older adults and also between males and females. The authors, along with Khamly *et al.* suggest that higher levels of toxicity are associated with better observed survival outcomes (8,15). These differences may therefore in part contribute to the poorer survival seen in AYA.

The use of routinely collected healthcare data has been gathering momentum over recent years and is particularly appealing in patients such as AYA who have poor recruitment and access to available clinical trials. Whilst toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) is methodically collected in clinical trials, this is not the case in busy routine clinical practice.

Assessment of toxicity is therefore often based on retrospective review of medical notes which can be subjective. In order to standardise the assessment of toxicity in real world data the use of "Toxicity-induced modifications of treatment" (TIMT) (19) has been suggested. TIMT can include dose reductions, dose delays and discontinuation of treatment.

In this study we use linked regional cancer registration and chemotherapy electronic prescribing data to investigate the acute toxicity experienced by children and young people (CYP) (aged 0-29 years) receiving chemotherapy for primary bone tumours in Leeds Teaching Hospitals NHS Trust (LTHT), UK. We explored the impact of TIMTs on survival outcomes and any differing trends due to age or sex. The utility of existing healthcare data available at a regional level to address these research questions is also assessed.

5.3 Methods

5.3.1 Data linkage

Cases were extracted from the Yorkshire Specialist Register of Cancer in Children and Young People (YSRCCYP). The YSRCCYP is a regional population-based database containing detailed demographic, diagnostic and clinical information on children under 15 years diagnosed with cancer since 1974, and young adults (15-29 years) diagnosed with cancer since 1990. The inclusion criteria were individuals aged 0-29 years, with a diagnosis of malignant osteosarcoma or Ewing sarcoma (ICD-O-3 morphology codes 9180/3 and 9260/3, site codes C40-C41) whilst resident in the Yorkshire & Humber region (United Kingdom). The age range 0-29 years was chosen to identify any differences in toxicity across children and AYA. Individuals with previous malignancies were excluded.

The YSRCCYP data were linked to the electronic patient notes system (Patient Pathway Manager, PPM) at LTHT which contains chemotherapy electronic prescribing data from the ChemoCare system since 1996. Of the 492 patients in the YSRCCYP who met the initial inclusion criteria, 292 had a match within PPM and 192 had chemotherapy prescribing data in ChemoCare. Four patients were

excluded due to first line chemotherapy not being available and four due to the chemotherapy data being incomplete.

5.3.2 Patient and tumour variables

All patients were proactively followed up to ascertain their vital status with minimal loss to follow up via linkage between the YSRCCYP and the Office for National Statistics (ONS) mortality register. No cases were ascertained by death certificate data only. Each registered case was censored for follow-up on 31st December 2021 or if appropriate at the time of earlier death, resulting in all cases having a potential follow-up period of at least 1 year.

Sex, age at diagnosis (years), stage at presentation, ethnicity, deprivation score, tumour site, date of diagnosis, vital status, referring treatment centre and date of death (where applicable) were extracted. Assignment of ethnic group was based primarily on linked inpatient hospital episode statistics data, which records ethnic group based on 2001 Census categories (20). Ethnicity was assigned as either south Asian, white or other and was missing for 23% of cases (n=43). Population weighted quintiles of the English Index of Multiple Deprivation (IMD) 2015 (21) were used as a measure of deprivation for each individual. Referring centre was categorised into either a specialist centre or peripheral hospital. Patients were categorised into three age groups comprising those diagnosed when aged 12 years or under, 13 to 17 years and 18 to 29 years. Age groupings were chosen to enable comparison with existing literature (8).

As in previous studies using existing healthcare data, a high proportion of staging data was missing (91%). Multidisciplinary (MDT) reports contained within the YSRCCYP were therefore reviewed for information related to the presence or absence of metastatic disease and this variable was used as a proxy for stage.

5.3.3 Toxicity and treatment data

Chemotherapy regime was extracted for each patient and the linked dataset explored for data related to toxicity in first line chemotherapy only. TIMT were defined as any dose reductions, dose deferrals or episodes of treatment being withheld for any chemotherapy agent within the first line of treatment received. The number of TIMT for each patient was calculated and the associated organ specific toxicity recorded in ChemoCare extracted. Where no reason was provided for the TIMT or it was described generically e.g. “toxicity” or “other toxicity”, free text annotations and bloods tests within ChemoCare were reviewed for additional information. The results of blood tests taken prior to each cycle of chemotherapy were analysed and any bone marrow, hepatic or renal toxicity detected in the bloods, in accordance with the Euro Ewing 2012 (10) and EURAMOS-1 trial (22) protocols, extracted.

5.3.4 Statistical analysis

Survival over time was described using Kaplan-Meier estimation at 1, 2 and 5-years post-diagnosis. Unadjusted survival estimates were examined overall and by age category, sex, ethnicity, deprivation fifth, presence of metastatic disease at diagnosis and primary site. Survival rates were also examined according to presence of individual toxicities.

Cox multivariable regression models were used to determine the effect of TIMT as both a continuous and binary variable on overall survival from diagnosis. Here the continuous variable was the total number of TIMT experienced and the binary variable whether or not a patient had received any TIMT. The models were adjusted for confounding using the minimal sufficient adjustment set informed by causal inference methods using Directed-Acyclic Graphs (DAGs) within DAGitty software (23)(Figure C.1). The models were therefore adjusted for age at diagnosis (as a continuous variable) and the categorical variables sex, ethnicity, deprivation, presence of metastatic disease and referring treatment centre as described in section 5.3.2. Only complete cases were analysed (Ewing n=68, 93%; osteosarcoma n=103, 93%). Schoenfeld and scaled residuals were used to assess

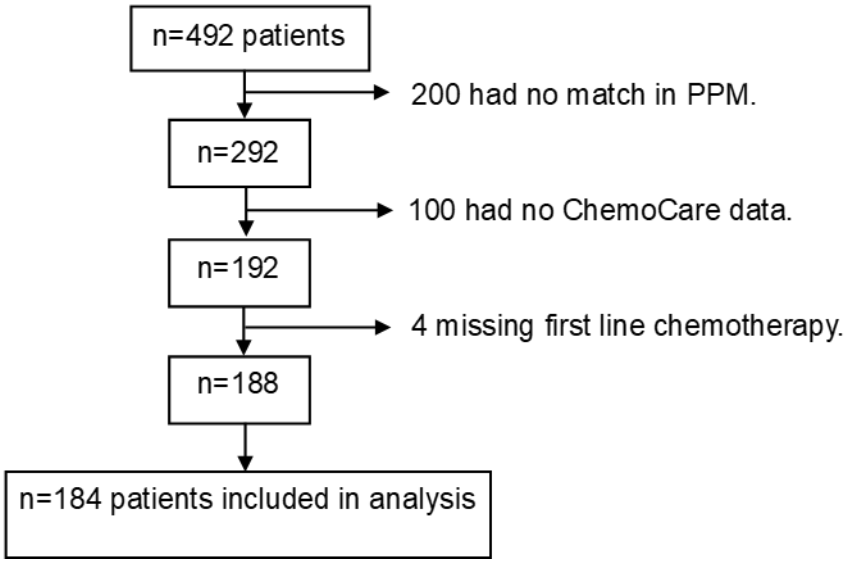
the Cox proportional hazard assumption, with no violation of the proportionality assumption found (24). Statistical analysis was performed using Stata 18 (25)

5.4 Results

5.4.1 Patient characteristics

A total of 184 patients were included in the analysis (Figure 5.1): 111 with a diagnosis of osteosarcoma and 73 with Ewing. The patient characteristics are described in Table 5.1. Median age at diagnosis in Ewing was 15.5 years (range 1.57 to 26.6 years) and 16.0 years (range 6.5 to 26.7 years) in osteosarcoma. There was a higher proportion of males compared to females in both tumour types (Ewing 62% vs 38% and osteosarcoma 59% vs 41%). Being of white ethnicity was most common ethnic category in both Ewing (89%) and osteosarcoma (74%). Presence or absence of metastatic disease at diagnosis was complete in 69% of cases compared to only 9% completeness for stage. Evidence of metastatic disease at diagnosis was recorded in 37% of patients with Ewing and 24% percent of patients with osteosarcoma. Axial and lower limb were the most common primary sites in Ewing (32% and 36%) whilst lower limb tumours were the most common in osteosarcoma (77%). Other potential prognostic factors such as tumour size and tumour markers were reviewed although levels of completeness were too low for inclusion in the analysis (<10%).

Figure 5.1: Flow diagram of the study sample included in the bone cancer analysis.



Methotrexate, doxorubicin and cisplatin (MAP) chemotherapy was the most common regime being received for all patients overall (54%) and for osteosarcoma alone (90%). In patients with Ewing 54 (74%) received vincristine, ifosfamide, doxorubicin and etoposide (VIDE) chemotherapy and 19 (26%) received vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide (VDC/IE).

Table 5.1: Patient characteristics.

		Bone combined n(%)	Ewing n(%)	Osteosarcoma, n (%)
Total		184	73 (40)	111 (60)
Total number of deaths		81 (44)	34 (47)	47 (42)
Sex	Male	110 (60)	45 (62)	65 (59)
	Female	74 (40)	28 (38)	46 (41)
Age category	<12 years	41 (22)	19 (26)	22 (20)
	13-17 years	87 (47)	30 (41)	57 (51)
	18-29 years	56 (31)	24 (33)	32 (29)
Ethnicity	White	147 (80)	65 (89)	82 (74)
	South Asian	12 (7)	4 (5.5)	8 (7)
	Other	15 (8)	0 (0)	15 (14)
	Missing	10 (5)	4 (5.5)	6 (5)
Deprivation fifth	1 (least deprived)	41 (22.3)	17 (23)	24 (22)
	2	35 (19)	17 (23)	18 (16)
	3	31 (16.8)	15 (20.5)	16 (14)
	4	28 (15.2)	8 (11)	20 (18)
	5 (most deprived)	48 (26)	15 (20.5)	33 (30)
	Missing	1 (0.5)	1 (1)	
Metastatic disease at diagnosis	Yes	50 (27)	27 (37)	27 (24)
	No	77 (42)	23 (31.5)	50 (45)
	Missing	57 (31)	23 (31.5)	34 (31)
Primary site	Lower limb	111 (60)	26 (36)	85 (77)
	Upper limb	22 (12)	8 (11)	14 (13)
	Axial	32 (17)	23 (32)	9 (8)
	Pelvis	16 (9)	14 (19)	2 (2)
	Other	3 (2)	2 (3)	1 (1)
Chemotherapy regime	VIDE	54 (29)	54 (74)	-
	VDC/IE	19 (10)	19 (26)	-
	MAP	100 (54)	-	100 (90)
	Ifosfamide/ etoposide/ methotrexate/ doxorubicin	11 (6)	-	11 (10)

Abbreviations: MAP; methotrexate, doxorubicin, cisplatin, VIDE; vincristine, ifosfamide, doxorubicin and etoposide, VDC/IE; vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide.

5.4.2 TIMT

At least one TIMT was made in 89% of patients with 83% of patients experiencing at least one treatment deferral. 43% of cases had at least one episode of treatment being withheld and 31% at least one dose reduction. Median number of TIMT was 2 (IQR: 1-3) in both tumour types. Additional information relating to organ specific toxicities causing the TIMT was available in free text annotations in 21 patients and additional data on 51 toxicities were obtained from blood results.

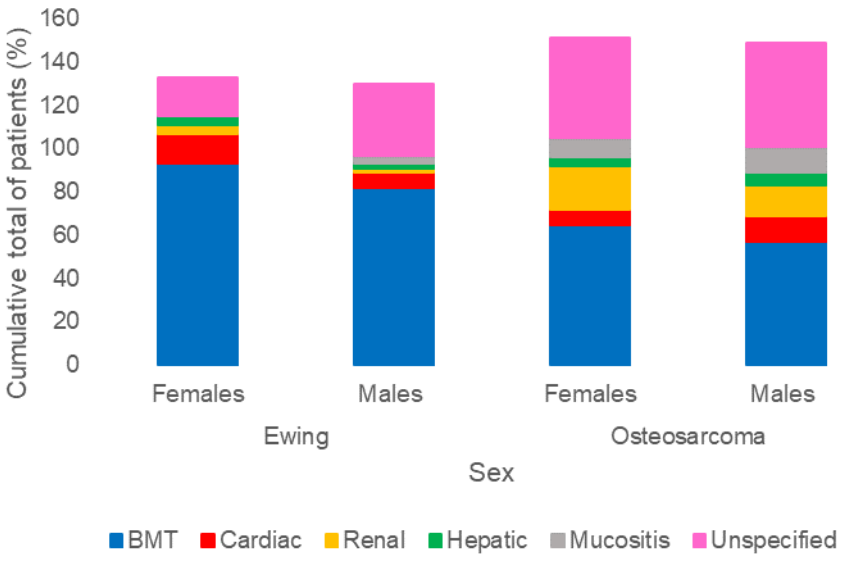
Within the osteosarcoma cohort 72% of patients overall experienced at least one TIMT, with a lower proportion occurring in males (68%) than females (78%). TIMT were more frequent in Ewing, occurring in 90% of patients; 89% males and 93% of females. There was a high proportion of TIMT across all age categories, with the highest percentage seen in those 12 years and under and lowest in patients aged 13-17 years when looking at bone tumours combined (12 years and under: 83%, 13-17 years: 76% and 18-29 years: 82%) (Table 5.2).

Table 5.2: Percentage of TIMT recorded according to sex and age category for bone cancers combined, Ewing and osteosarcoma.

	Bone combined, n (%)		**Ewings, n (%)**		**Osteosarcoma, n (%)**	
			TIMT			
	Yes	**No**	**Yes**	**No**	**Yes**	**No**
Sex						
Males	84 (76)	26 (24)	40 (89)	5 (11)	44 (68)	21 (32)
Females	82 (84)	12 (16)	26 (93)	2 (7)	36 (78)	10 (22)
Age category						
< 12 years	34 (83)	7 (17)	18 (95)	1 (5)	16 (73)	6 (27)
13 -17 years	66 (76)	21 (24)	28 (93)	2 (7)	38 (67)	19 (33)
18-29 years	46 (82)	10 (18)	20 (83)	4 (17)	26 (81)	6 (19)

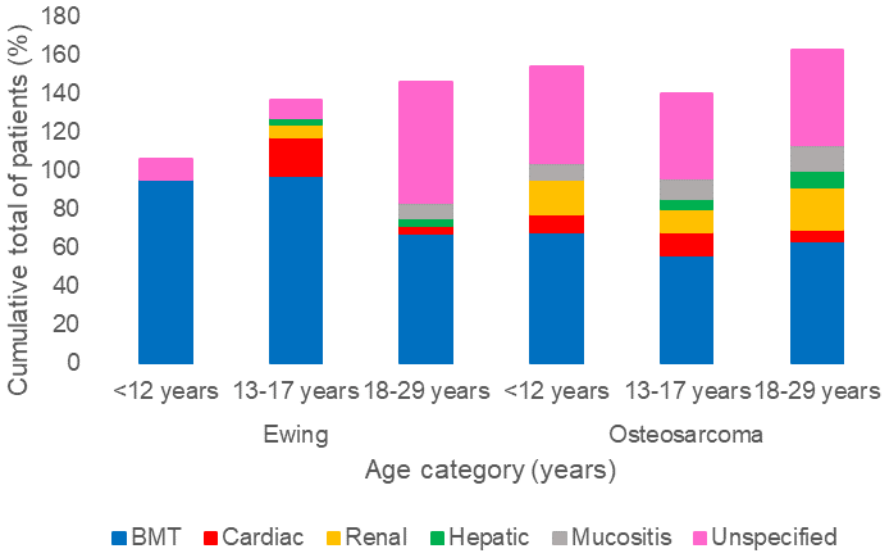
Bone marrow toxicity (BMT) was the most frequently recorded reason for the TIMT in both Ewing (88%) and osteosarcoma (60%). In osteosarcoma this was followed by renal toxicity (16%), oral mucositis (11%) and cardiotoxicity (10%). In Ewing, cardiotoxicity was the second most common (10%) followed by hepatic (3%), oral mucositis (3%), neurotoxicity (3%) and renal toxicity (3%) (Table C.1). A higher proportion of females compared to males had a recorded TIMT for BMT in both Ewing (females: 93% vs males: 82%) and osteosarcoma (females: 65% vs males: 57%). Oral mucositis was more common in males in both tumour types; Ewing (females: 0% vs males: 4%), osteosarcoma (females: 9% vs males: 12%). Cardiotoxicity was more common in females in Ewing (females:14% vs males:7%) but males in osteosarcoma (females: 7% vs males: 12%). Renal toxicity induced TIMTs were seen most frequently in females (Ewing; females:4% vs males:2% and osteosarcoma; females: 20% vs males: 14%) as were TIMTs due to neurotoxicity (Ewing; females:4% vs males: 2% and osteosarcoma; females: 7% vs males: 0%) (Table C.2 and Figure 5.2).

Figure 5.2: The cumulative total of patients who had a toxicity induced modification of treatment for bone marrow toxicity (BMT), cardiotoxicity, renal toxicity, hepatic toxicity, mucositis or unspecified toxicity. Presented for Ewing and osteosarcoma according to sex.



Adolescents aged 13-17 years were most likely to have cardiac toxicity recorded in both tumour types (Ewing; 20%, osteosarcoma; 12%) compared to younger (Ewing; 0%, osteosarcoma; 9%) and older (Ewing; 4%, osteosarcoma; 6%) patients. There was little difference in proportion of patients aged 12 years and under at diagnosis and 13-17 years having BMT recorded in Ewing (95% and 97% respectively) compared to older cases aged 18-29 years (67%). In osteosarcoma the highest proportion was seen in patients aged 12 and under (68%) compared to 13-17 (56%) and 18–29-year-olds (63%). Oral mucositis was more common in the oldest age category in osteosarcoma (Ewing; 8% and osteosarcoma; 13%) compared to those 12 and under (Ewing; 0% and osteosarcoma; 9%) and 13-17 years (Ewing; 11% and osteosarcoma; 0%). Neurotoxicity became more common with increasing age in Ewing and was lowest in 13–17-year-olds in osteosarcoma: 12 years and under (Ewing; 0% and osteosarcoma; 9%), 13-17 years (Ewing; 3% and osteosarcoma; 2%) and 18-29 years (Ewing; 4% and osteosarcoma; 6%). Renal toxicity was more common in those aged 13-17 years in Ewing (12 and under 0%, 13-17 years 7% and 18-29 years 0%) and 18-29 years in osteosarcoma (12 and under 18%, 13-17 years 12% and 18-29 years 22%) (Table C.3 and Figure 5.3).

Figure 5.3: The cumulative total of Ewing and osteosarcoma patients, respectively, experiencing toxicity induced modification of treatment for: bone marrow toxicity (BMT), cardiotoxicity, renal toxicity, hepatic toxicity, mucositis or unspecified toxicity, by age category at diagnosis.



5.4.3 Survival

Descriptive analysis

Females had superior 5-year survival rates than males in osteosarcoma: 66% (95% CI 50-78) vs 55% (95 %CI 42-67), while in Ewing 5-year survival rates were slightly higher in males (58%; 95% CI 42-71) vs females (51%; 95% CI 30-69). Table 5.3 presents the Kaplan-Meier survival estimates according to the different demographic variables by bone tumour type and combined.

Children with Ewing sarcoma aged 12 years and under had superior 5-year survival rates (88%; 95% CI 59-97) compared to those aged 13-17 years and 18-29 years respectively (45%; 95% CI 25-62 and 43%; 95% CI 22-62). In osteosarcoma children aged 12 years and under had the lowest 5-year survival (55%; 95% CI 32-72) compared to those aged 13-17 years and 18-29 years respectively (59%; 95% CI 44-71 and 43%; 65% CI 45-79). Presence of metastatic disease at presentation was associated with lower 5-year survival rates when considering the tumour types individually and combined (40%; 95% CI 27-54 vs 73%; 95% CI 61-82). In the tumours combined those with a pelvic tumour had the lowest 5-year survival rates (41%; 95% CI 13-69) according to site, compared to lower limb (59%; 95% CI 49-68), upper limb (57%; 95% CI 33-75) and axial (62%; 95% CI 42-76) (Table 5.3).

Patients with at least one TIMT recorded due to BMT had superior survival rates at all time points compared to those who did not in both tumour types (osteosarcoma; 1 year 99% vs 89%, 2 years 77% vs 73%, 5 years 60% vs 59%, Ewing's; 1 year 90% vs 80%, 2 years 68% vs 60%, 5 years 56% vs 50%) (Table 5.4, Figure C.2.). Patients who had a TIMT for cardiotoxicity or oral mucositis had worse overall survival compared to those who did not (osteosarcoma: cardiotoxicity; 1 year 91% vs 95%, 5 years 55% vs 60%, oral mucositis; 1 year 92% vs 95%, 5 years 39% vs 62%. Ewing: cardiotoxicity; 1 year 71% vs 91%, 5 years 57% vs 55%, oral mucositis; 1 year 50% vs 90%, 5 years 50% vs 55%) (Table 5.4, Figure C.2).

Multivariable analysis

Receiving at least one TIMT was found to be associated with a lower risk of death when compared to those who had no TIMT in both Ewing (HR 0.43, 95% CI 0.14-

1.35) and osteosarcoma (HR 0.36, 95% CI 0.11-1.20). In patients who received TIMT, an increasing number of TIMTs had little effect on survival in Ewing (HR 0.87, 95% CI 0.64-1.17) but was negatively associated in osteosarcoma (HR 1.50, 95% CI 1.21-1.85) (Table 5.5).

Table 5.3: Kaplan-Meier one, two and five-year survival estimates presented by demographic variables for bone cancers combined, Ewing and osteosarcoma.

	Bone combined			Ewing			Osteosarcoma		
	1 year	**2 years**	**5 years**	**1 year**	**2 years**	**5 years**	**1 year**	**2 years**	**5 years**
Overall	92 (87-95)	71 (65-78)	58 (50-65)	89 (68-99)	67 (55-77)	55 (42-66)	95 (88-98)	75 (66-82)	60 (50-68)
Age category									
<12 years	98 (83-100)	82 (66-91)	68 (51-81)	95 (68-99)	95 (68-99)	88 (59-97)	100	73 (49-87)	55 (32-72)
13-17 years	90 (81-94)	70 (59-79)	54 (42-64)	83 (63-92)	65 (44-79)	45 (25-62)	93 (82-97)	73 (59-83)	59 (44-71)
18-29 years	93 (82-97)	67 (53-78)	56 (41-68)	92 (71-98)	48 (27-66)	43 (22-62)	94 (77-98)	81 (63-91)	65 (45-79)
Sex									
Male	95 (89-98)	67 (57-75)	56 (46-65)	91 (78-96)	66 (50-78)	58 (42-71)	98 (90-100)	68 (55-78)	55 (42-67)
Female	88 (78-93)	79 (68-87)	61 (48-71)	85 (66-94)	70 (49-84)	51 (30-69)	89 (76-95)	85 (71-92)	66 (50-78)
Ethnicity									
White	91 (85-95)	72 (63-78)	57 (48-65)	89 (79-95)	65 (52-76)	53 (39-64)	93 (84-97)	76 (66-84)	61 (49-70)
South Asian	100	92 (54-99)	83 (48-96)	100	100	100	100	88 (39-98)	75 (31-93)
Other	100	72 (42-89)	58 (29-78)	-	-	-	100	72 (42-89)	58 (29-78)
Deprivation fifth									
1 (least deprived)	95 (81-99)	72 (56-84)	54 (37-68)	88 (59-97)	63 (35-81)	47 (21-69)	100	79 (57-91)	58 (36-75)
2	94 (79-99)	79 (61-90)	69 (50-82)	94 (65-99)	69 (41-86)	69 (41-86)	94 (67-99)	89 (61-97)	70 (41-86)
3	97 (79-100)	83 (65-93)	59 (39-74)	93 (59-99)	79 (47-93)	63 (32-83)	100	88 (59-97)	56 (30-76)
4	89 (70-96)	60 (39-75)	55 (35-72)	88 (39-98)	58 (18-84)	44 (10-74)	90 (66-97)	60 (36-78)	60 (36-78)

5 (most deprived)	88 (74-94)	66 (50-77)	56 (40-69)	80 (50-93)	60 (32-80)	51 (24-74)	91 (74-97)	69 (49-82)	58 (39-73)
Metastatic disease at diagnosis									
Yes	86 (73-93)	58 (43-70)	40 (27-54)	83 (60-93)	47 (25-65)	37 (17-56)	89 (69-96)	67 (46-81)	43 (24-61)
No	95 (87-98)	84 (74-91)	73 (61-82)	93 (74-98)	85 (65-94)	65 (43-80)	96 (85-99)	84 (70-92)	77 (63-87)
Missing	95 (84-98)	67 (53-78)	52 (37-65)	90 (67-98)	65 (40-82)	65 (40-82)	97 (81-100)	69 (50-82)	45 (27-62)
Primary site									
Lower limb	96 (90-98)	76 (67-83)	59 (49-68)	92 (73-98)	72 (50-86)	64 (42-79)	96 (89-99)	77 (67-85)	58 (46-67)
Upper limb	95 (72-99)	68 (44-83)	57 (33-75)	100	63 (23-86)	31 (4-64)	93 (59-99)	71 (41-88)	71 (41-88)
Axial	81 (63-91)	66 (47-79)	62 (42-76)	83 (60-93)	70 (47-84)	64 (41-80)	78 (36-94)	56 (20-80)	56 (20-80)
Pelvis	88 (59-97)	64 (34-83)	41 (13-69)	86 (54-96)	61 (29-82)	38 (11-66)	100	100	-
Other	100		-	100	-	-	100	-	-

Table 5.4: Kaplan-Meier one, two and five-year survival estimates presented by recorded organ specific toxicity resulting in TIMT for Ewing and osteosarcoma.

	Ewing						Osteosarcoma					
Toxicity	**Yes**			**No**			**Yes**			**No**		
	1 year	**2 years**	**5 years**	**1 year**	**2 years**	**5 years**	**1 year**	**2 years**	**5 years**	**1 year**	**2 years**	**5 years**
Organ specific toxicity												
Bone marrow	90 (80-96)	68 (55-78)	56 (42-68)	80 (41-95)	60 (25-83)	50 (18-75)	99 (90-100)	77 (64-85)	60 (46-71)	89 (75-95)	73 (57-83)	59 (43-72)
Cardio	71 (26-92)	71 (26-92)	57 (17-84)	91 (81-96)	67 (53-77)	55 (41-67)	91 (51-99)	73 (37-90)	55 (23-78)	95 (88-98)	76 (66-83)	60 (50-69)
Renal	100	100	100	89 (78-94)	66 (54-76)	54 (41-65)	94 (67-99)	83 (57-94)	60 (33-78)	95 (88-98)	74 (63-81)	60 (49-69)
Neuro	100	-	-	89 (78-94)	69 (57-79)	57 (44-68)	100	67 (5-95)	33 (0.9-77)	94 (88-97)	75 (66-83)	60 (50-69)
Mucositis (oral)	50 (0.6-91)	50 (0.6-91)	50 (0.6-91)	90 (80-95)	68 (55-77)	55 (42-67)	92 (54-99)	67 (34-86)	39 (12-65)	95 (88-98)	76 (67-84)	62 (51-71)
Hepatic	50 (0.6-91)	50 (0.6-91)	50 (0.6-91)	90 (80-95)	68 (55-77)	55 (42-67)	100	83 (27-97)	83 (27-97)	94 (88-97)	75 (65-82)	58 (48-67)

Table 5.5: Hazard ratios (HRs) and 95% confidence intervals (CIs) from Cox regression models presenting the association between Toxicity Induced Modifications of Treatment (TIMT) and survival for bone cancers combined, Ewing and osteosarcoma.

	Bone combined						Ewing						Osteosarcoma					
	Adjusted*			Unadjusted			Adjusted*			Unadjusted			Adjusted*			Unadjusted		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Treatment-induced modifications of treatment (TIMT)																		
TIMT (binary)	0.44	0.19-1.01	0.05	0.68	0.34 - 1.36	0.27	0.43	0.14-1.35	0.15	0.62	0.22-1.77	0.37	0.36	0.11 - 1.20	1.10	0.71	0.28-1.80	0.47
TIMT (continuous)	1.20	1.02-1.41	0.03	1.14	1.00 - 1.30	0.05	0.87	0.64-1.17	0.36	0.98	0.76-1.27	0.87	1.50	1.21 - 1.85	0.00	1.34	1.14-1.57	0.00

* Adjusted for age at diagnosis, sex, ethnicity, deprivation, presence of metastatic disease and referring treatment centre.

5.4.4 Cause of death

Cause of death was available for 58 of the 81 patients (72%) who had died. No causes of death were attributable to toxicity.

5.5 Discussion

In this paper we have investigated the incidence of acute chemotherapy toxicity in CYP receiving treatment for Ewing and osteosarcoma. We have considered TIMT, the organ specific toxicities causing them, variations according to age and sex and the impact these factors have on overall survival.

We found a higher proportion of females had at least one TIMT compared to males. This is in keeping with evidence from other studies (8,13,15,18) which have shown higher rates of toxicity and dose modifications in females. As females have better survival outcomes (8,26) it has previously been suggested that toxicity is a potential indicator of superior outcomes. In our study females had superior survival at 2 and 5 years compared to males in osteosarcoma and bone cancers combined but not in Ewing. This may in part be due to the small number of patients in the study. The lowest rates of TIMT were seen in patients aged 18 – 29 years in Ewing and 13-17 years in osteosarcoma. This was associated with worse survival at 2 and 5 years in Ewing and 1 and 2 years in osteosarcoma when compared to the other age categories. Studies looking at the impact of age on toxicity have shown conflicting results and are complicated by inconsistencies in the age ranges compared. Studies in osteosarcoma found higher toxicity in younger children (8,17), whereas a study in Ewing found no effect (18). The many changes that occur in the body during puberty and beyond can influence the PK and PD of drugs throughout the body. These include hormonal changes(27), changes in body fat and muscle composition (28,29) and organogenesis of the liver (30) and kidneys (31). The resulting biological differences between the sexes may affect chemotherapy efficacy and contribute to the survival differences seen. Doxorubicin for example has been shown to have faster clearance in males (32). Further research is needed to investigate these potential PK differences. If confirmed, a move towards therapeutic drug monitoring (TDM) might be more appropriate in the AYA population and may improve outcomes for these patients in the future (33,34).

Regarding organ specific toxicity thrombocytopenia has been associated with better patient outcomes (8). A limitation of our study is that we were unable to break BMT down further into thrombocytopenia and neutropenia for all of our patients due to the way the toxicity was coded and blood tests not being available for all patients. In our cohort however BMT was associated with better 1-, 2- and 5-year survival compared to patients with no BMT. In addition to thrombocytopenia, grade 3 and above mucositis has also been associated with superior survival outcomes (8). These findings were not seen in our study although the number of patients with a recorded TIMT for mucositis was low (n=14). Neurotoxicity occurred more frequently in females in our cohort. Studies investigating the impact of age and sex on ifosfamide related encephalopathy found no evidence of age as a causal factor and insufficient evidence for sex (35,36) with biochemical abnormalities and concomitant cisplatin administration more likely to be associated with toxicity. Renal toxicity was recorded in 11% of patients, a similar proportion to that seen in other studies (17).

Overall, 89% of our patients experienced at least one TIMT. Whilst the percentage of dose modifications were not been reported from EE2012 and EURAMOS-1, data were provided on the number of patients completing chemotherapy. In EURAMOS-1 the percentage of patients receiving at least 80% of planned doses ranged between 65% and 88% depending on the drug and the treatment arm. In EE2012 whilst there was a high percentage of patients completing induction chemotherapy (VIDE group 95%, VDC/IE group 91%), the percentage of patients completing all cycles of consolidation chemotherapy was much lower (VIDE group 58%, VDC/IE group 75%). These findings along with 91% of patients in EE2012 and over 94% of patients in EURAMOS-1 experiencing at least one toxicity grade 3-5 toxicity suggests that our findings are comparable.

We found that patients who received at least one TIMT had a lower risk of death than those who did not (HR: 0.44, 95% CI 0.19 to 1.01). This finding, accompanied by the high percentage of patients receiving a TIMT, suggests that adherence to protocol guided dose modifications is an important component of treatment for these tumours. Increasing the number of dose modifications was shown to have little effect in Ewing patients but a small negative association in osteosarcoma patients.

Maintaining dose intensity may be of greater importance in osteosarcoma than it is in Ewing.

As suggested by *Kok et al*. (19) we have used TIMT to investigate toxicity in real world data. Their definition of a TIMT excludes treatment modifications for personal reasons. In this study we found four patients had a treatment delay related to personal reasons and five a treatment delay described as administrative related. These reasons, whilst small in number, are important considerations in the treatment of AYA, especially in regimes where dose intense regimes have been shown to improve outcomes and there is a pressure to maintain such treatment intensity. Treatment delays for personal reasons need to be considered from a psychosocial point of view. These are particularly important in adolescence where individuals are starting to develop autonomy and maintain a 'normal' life alongside a serious illness. Treatment within AYA specialist centres, where healthcare professionals are equipped to address the unique needs of this patient group, is also of paramount importance to facilitate patients receiving the optimal cancer treatment. The impact of administrative delays is relevant in a currently overstretched health service and needs to be considered by service providers.

A strength of this study is the novel use of linked cancer registration and electronic chemotherapy prescribing data. We have previously described the limited toxicity data available in the national SACT dataset (37). The toxicity data available in this linked dataset is superior to the national data providing details of organ specific toxicity and the opportunity to analyse associated blood tests. The possibility of improving the national collection of toxicity data from sources such as ChemoCare is an area for consideration but will be limited by the time and resource constraints of the personnel collecting the data.

We acknowledge that our study has some limitations. Being a single centre study and utilising electronic chemotherapy prescribing data introduced only in 1996, restricted our sample size. The patient characteristics, including primary site and the proportion presenting with metastatic disease, were however similar to those of other larger studies (10,38–40) giving us confidence our cohort is representative. Data items which aid risk stratification of patients notably tumour size and tumour

markers were poorly collected and therefore could not be used in this analysis. This is a known problem of using routinely collected data in this population (37) and an area in which clinical trial datasets are superior as they collect the required tumour specific variables. We attempted to overcome this problem of missing data by reviewing MDT proformas. Whilst this improved the completeness of whether or not metastatic disease was present at diagnosis it was not beneficial for tumour size which was not commonly recorded. The YSRCCYP now has ethical approval to collect tumour markers through linkage to PPM and this will benefit future research. Linkage to radiology data would also enhance research datasets in bone cancers and is an area to explore in future research. We were unable to consider histological subtype, although the prognostic impact of gene-fusion on survival outcomes was recently investigated by Desandes *et al*. (38)who concluded that other clinicopathological factors were more likely to contribute to the poorer outcomes seen in the AYA population. In comparison to clinical trials a strength of real-world data is the ability to investigate differences according to sociodemographic variables. Due to the small numbers in this cohort, we were unable to take advantage of this. In our analyses we have looked at toxicity overall as opposed to per individual chemotherapy agent due to limited patient numbers. Due to the different ways in which chemotherapy agents are metabolised and the many factors which vary during in adolescence including body fat composition, hormonal imbalances, and changes to metabolic enzymes, this is an important area for future work (12,41) on a larger dataset.

5.6 Conclusions

Our findings provide further evidence to support the theory that differences in chemotherapy handling exist between males and females and across the age categories within CYP. This highlights the need for age and sex to be considered when designing, analysing and interpreting the findings of clinical trials. Whilst a high percentage of patients experienced dose modifications due to toxicity, experiencing at least one TIMT was associated with a lower risk of death compared to those who did not. This is in keeping with the suggestion that toxicity may be a marker of treatment efficacy and emphasises not only the need for patients to be supported through treatment toxicities but also the importance of dose adjusting accordingly.

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Chapter 6.

This Chapter contains the published work detailing the PPIE workshops carried out to address Aim 4 of this thesis. This paper describes the rationale behind the workshops, the methods used and findings of the work. Supplementary material providing more detail of the thematic analysis undertaken can be found in Appendix D (Table D.5 and D.6).

Title: Patient and public involvement to inform priorities and practice for research using existing healthcare data for children's and young people's cancers.

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6.1 Plain English summary

Everyday data is collected on all patients treated within the National Health Service, including children and young people with cancer (CYP). This data is used routinely to improve how services are run and with special permissions, can also be used for research. Negative reporting in the media about this use of data can lead to mistrust and some people choosing not to share their data. This can reduce the quality and accuracy of research looking at rare diseases or populations with small numbers. In addition, many barriers exist to researchers when trying to access this data such as laws around data sharing, making it difficult and sometimes impossible to carry out such research. We invited CYP and carers to two workshops to:

- Learn about how healthcare data is used for research.
- Consider ways to increase public and patient confidence in this use of healthcare data.
- Describe areas of research importance to CYP and their carers using healthcare data.

Ten young people and six carers attended the first workshop. Four young people and four carers returned for workshop two. Workshops consisted of interactive presentations, case studies and group discussions.

Overall participants felt that lack of awareness and negative media reporting led to mistrust in data use for research. It was believed that greater education about how the data is used, including positive examples of the benefits of the research, was needed to improve public confidence. Key research priorities for data use included late-effects, social and educational outcomes and rare tumours.

6.2 Abstract

Background

In the United Kingdom, healthcare data is collected on all patients receiving National Health Service (NHS) care, including children and young people (CYP) with cancer.

This data is used to inform service delivery, and with special permissions used for research. The use of routinely collected health data in research is an advancing field with huge potential benefit, particularly in CYP with cancer where case numbers are small and the impact across the life course can be significant.

Patient and public involvement (PPI) exercise aims:

- Identify current barriers to trust relating to the use of healthcare data for research.
- Determine ways to increase public and patient confidence in the use of healthcare data in research.
- Define areas of research importance to CYP and their carers using healthcare data.

Methods

Young people currently aged between 16-25 years who had a cancer diagnosis before the age of 20 years and carers of a young person with cancer were invited to take part via social media and existing networks of service users.

Data was collected during two interactive online workshops totalling 5 hours and comprising of presentations from health data experts, case-studies and group discussions. With participant consent the workshops were recorded, transcribed verbatim and analysed using thematic analysis.

Results

Ten young people and six carers attended workshop one. Four young people and four carers returned for workshop two.

Lack of awareness of how data is used, and negative media reporting were seen as the main causes of mistrust. Better communication and education on how data is used were felt to be important to improving public confidence. Participants want the ability to have control over their own data use. Late effects, social and education

outcomes and research on rare tumours were described as key research priorities for data use.

Conclusions

In order to improve public and patient trust in our use of data for research, we need to improve communication about how data is used and the benefits that arise.

6.3 Background

Large amounts of data are collected every day in the routine care of patients with or surviving from cancer. This includes data collected in primary and secondary National Health Service (NHS) care, educational and social settings and covers a wide range of information including details relating to the patient, (e.g. age at diagnosis and ethnicity), their cancer (e.g. size and spread at diagnosis) and information about any health conditions occurring after treatment. The use of routine healthcare data to improve patient outcomes has been gathering momentum over the past few years, though its use is restricted by governance frameworks as outlined in the recent Goldacre report (1). The COVID-19 pandemic demonstrated the power and efficacy of timely data collection, access, linkage, analysis and reporting. In the United Kingdom (UK) the government intends to continue to embrace the power of data as outlined in their policy “Data saves lives: reshaping health and social care with data” (2). Cancer Research UK also plan to utilise the enormous potential held in data driven research with the release of their research strategy “Unleashing the power of data to beat cancer” (3).

Cancers occurring in children and young people (CYP) are rare, but despite this remain a leading cause of death in these age groups. Nationally, approximately 1,645 new cases are diagnosed annually in 0 -14 year olds and approximately 2,110 in 15-24 year olds (4). CYP also experience rarer cancers (5), for example, lymphomas, brain cancers, sarcomas and germ cell tumours, compared to older adults where breast, colorectal, prostate and lung dominate (6). Therefore, data sharing is crucial to improve our knowledge of CYP cancers and to strengthen the research being carried out. This includes sharing information safely and securely between institutions in the UK and also internationally.

In England, routine healthcare data is collected for research purposes without patient consent under section 251 of the NHS Act 2006. Individuals do however have the right to opt out of their health records being shared for purposes other than direct care. In June 2021, there was widespread reporting in the media of the NHS "data grab" from General Practitioner (GP) records, a scheme in which GP health data for patients in England would become more readily available for research and health service planning (7). This resulted in a significant increase in individuals opting out of data sharing with numbers almost doubling from 1,652,082 to 3,220,803 over a three-month period (8). For rare diseases such as CYP cancers even small numbers of individuals opting out can have a significantly disproportionate effect on the generalisability of research results. To minimise the numbers of people opting out, the population must trust those using the data to do so safely in order for healthcare data to reach its potential.

As part of the British Science Associations (BSA) Future Forum 2020, 14 young people aged 14-18 years were asked about the use of medical data. More than half, (61%) felt they did not know much or anything about how medical data gets used. With 70% reporting they trusted the NHS to process their data, this fell to 31% for universities/ academic institutions, 23% for Government and 18% for pharmaceutical companies (9). Although this report represents the views of a small sample, it suggests a lack of knowledge about data collection amongst young people and varying levels of trust regarding the use of medical data. We invited CYP and their carers to a patient and public involvement (PPI) workshop to learn how their healthcare data is used and to:

- Identify current barriers to trust regarding the use of healthcare data for research.
- Determine ways to increase public and patient confidence in the use of healthcare data in research.
- Define areas of research importance to CYP and their carers using healthcare data.

6.4 Methods

Two workshops were carried out in January and April 2022 each lasting 2.5 hours. Participants were recruited to the initial workshop following advertisement via DATA-CAN, use MY data, the Children's Cancer and Leukaemia Group (CCLG), the Teenage Cancer Trust (TCT), Candlelighter's Trust and the research teams' social media accounts. Adverts were circulated two weeks prior to workshop 1. Young people currently aged between 16-25 years who had a cancer diagnosis before the age of 20 years, and carers of a young person diagnosed with cancer before the age of 20 years were invited to take part. A £50 incentive was offered in return for taking part in each workshop. We selected an upper age eligibility criteria of 20 years as this was in keeping with the age eligibility criteria of the International Benchmarking of childhood cancer survival by stage (BENCHISTA) project (10). Participants from workshop 1 were invited back to workshop 2. The workshops were facilitated by experienced qualitative researchers AP (CCLG) and LF (UCLH). The research team consisted of KPJ (University College London (UCL) and DATA-CAN), CC (DATA-CAN), RF and NH (Yorkshire Specialist Register of Cancer in Children and Young People (YSRCCYP) and University of Leeds), EC (DATA-CAN), AL (UCL) and AG (CCLG).

6.4.1 Workshop format

Due to COVID-19 restrictions the workshops were held online via a secure Zoom account. The workshops were recorded, transcribed verbatim and stored in line with the University of Leeds data security procedures. All participants provided informed consent prior to taking part using an online consent form. The workshop schedules and case studies are available in Appendix D (Tables D.1 and D.2).

Workshop 1

Workshop 1 started with an interactive presentation (CC) covering; how patient data is generated in the healthcare system, what data this includes and the different levels of identifiability. The collection, storage, and use of data by cancer registries and clinical trials was described along with consent and the data opt out policy.

Participants were then divided randomly into two break-out rooms to discuss two different case studies relating to a young person diagnosed with cancer (Table D.3). The groups were asked to consider what data might be collected and when and who might have access to this data.

RF presented research carried out by the YSRCCYP, which had used linked NHS datasets, to improve survival rates for childhood and young peoples' cancers. NH presented the research cycle, and how data is used and shared throughout.

Participants were invited to ask any questions and feedback their views following each presentation. The final discussion focused on asking the participants to consider ways in which awareness of data use for research purposes could be improved.

Workshop 2

In workshop 2 examples of anonymised primary care, hospital and cancer registration records were used to show participants what data records look like (CC). These examples were then used to explain the difference between data linkage and data sharing, covering aspects including data minimisation and data security measures (CC). A presentation of the BENCHISTA(10) project (KPJ/AL) provided an example of research which requires international data sharing. This facilitated a discussion regarding the legislative barriers faced by such projects and gave participants the opportunity to feedback their thoughts.

A presentation (RF and NH) was given covering the use of social outcome measures in cancer research, why it is important, and barriers faced in accessing the data. A discussion surrounding the use of these data sources followed (LF).

Prior to the workshop participants had been provided with three newspaper articles reporting on use of patient data. Participants were invited (CC) to discuss their thoughts on the articles in relation to data sharing and how such articles may be perceived by the public. The workshop ended with a discussion of key learning points from the workshops and areas for future work. (AP).

6.4.2 Analysis

The workshop transcripts were analysed using thematic analysis (11). This involved familiarisation with the data, generation of codes and examining, reviewing, and defining themes. The initial generation of codes was carried out and agreed by NH and LF, draft themes were then reviewed and finalised by the wider team. Subthemes were then devised by NH and agreed by the wider team. The supporting quotes presented in the results section were selected as they were felt to succinctly represent identified themes and are presented using intelligent verbatim. YP denotes a quote from a young person and C from a carer. Our findings are reported in line with the GRIPP2 checklist (Table D.4).

6.5 Results

Ten young people currently aged 16-25 years and diagnosed with cancer under the age of 20 years, and six carers of young people with cancer responded to the advert and all took part in workshop 1. Four young people and four carers took part in workshop 2. The participants did not know each other prior to the workshops. Participant characteristics are shown in Table 6.1.

Table 6.1: The characteristics of workshop one participants.

	Workshop 1 n (%)			Workshop 2 n (%)		
Characteristic	**Total (n=16)**	**YP (n=10)**	**C (n=6)**	**Total (n=8)**	**YP (n=4)**	**C (n=4)**
Sex						
Female	13 (81)	8 (80)	5 (83.3)	5 (62.5)	2 (50)	3 (75)
Male	3 (19)	2 (20)	1 (16.7)	3 (37.5)	2 (50)	1 (25)
Ethnicity						
White	12 (75)	8 (80)	4 (66.7)	5 (62.5)	2 (50)	3 (75)
Asian/ Mixed	4 (25)	2 (20)	2 (33.3)	3 (37.5)	2 (50)	1 (25)
Current age (years)						
16-25	10 (60)	10 (100)	0 (0)	4 (50)	4 (100)	0
Over 25	6 (40)	0 (0)	6 (100)	4 (50)	0	4 (100)
Cancer type of CYP*						
Solid tumour	4 (40)	4 (40)	-	2 (50)	2 (50)	-
Haematological	6 (60)	6 (60)	-	2 (50)	2 (50)	-
Current country of residence						
England	14 (87.5)	9 (90)	5 (83.3)	7 (87.5)	3 (75)	3 (75)
Scotland	2 (12.5)	1 (10)	1 (16.7)	1 (12.5)	1 (25)	1 (25)

* This data is only reported for young people as understandably some bereaved parents did not want to share this information.

Three main themes were identified; existing barriers to trust in healthcare data use for research, ways to improve public and patient confidence and research priorities for data use. These are discussed in turn with appropriate quotes form participants.

6.5.1. Existing barriers to trust in healthcare data use for research

This theme encompassed the sources of mistrust and how a lack of awareness about healthcare data use presents barriers to trust.

Lack of awareness

Participants were generally unaware of the level of healthcare data that is collected about them, or that this occurs during primary care and secondary care appointments and during follow up. This was particularly true for young people who had their parents advocating for them during treatment as children. There was even less awareness around the collection of social and educational outcomes.

"I didn't really have any idea of all the data collected. Especially when I was going through treatment ... I just didn't have any part in that area … I just got my Mum to sort everything. So it's quite eye opening." YP-6

"Same for me. You just don't really think about it and it's so in depth as well." YP-3

Whilst some participants knew they were consenting for a procedure such as the collection of a tissue sample, they were unaware that this would produce data which would be collected and used.

"Sometimes it's not obvious data gets produced from something. My child had a tissue sample taken… there would have been digital data produced and that's quite difficult to imagine … that's not something I'd visualised before." C-1

"I certainly wasn't ever told about what my data was going to be used for. I suppose before surgeries, and all that sort of stuff you always got told what was going to happen but certainly not what the results were going to be used for." YP-5

Sources of mistrust

Negative portrayal of data use by the media, such as stories about patient health care records being sold to private companies were seen as lowering public confidence in data sharing. Experiences of receiving "spam" advertising via email

or text were also described as lowering confidence and demonstrated a lack of awareness of different types of data sharing, for example the difference between data sharing for marketing purposes and data sharing for research.

"How the media portrays it (data use)… has negative impacts and it does put you off data sharing." YP-2.

"*I think part of the problem is that when we talk about data and research, a lot of us start thinking about how we get adverts for things because we've clicked on something*." C-2.

6.5.2 Ways to increase public and patient confidence

This included providing more information about data collection and use and giving young people more responsibility for their own data.

More information about data use in research

Participants felt that having more information available about how data is used for research and safety measures that exist, for example data security and anonymisation of data, would improve public confidence.

"I think it's quite important to highlight that the data is very well organised and very well protected". YP-1

"*You just have to get it out there somehow like, get it on the internet and things. I feel like people are worried about having really identifiable information about themselves, distributed to loads of different companies. To kind of reassure people that really most of this data is not identifiable …no one can connect it to you… it would actually be hugely reassuring."* YP-7

Dissemination of positive outcomes from research using healthcare data were seen as an important way of improving awareness of, and therefore trust in, data use. Additionally, embedding data use in the current curriculum was described as a way to raise awareness of collection for research purposes and of security measures in place to protect the data and anonymity.

"I do wonder whether, case studies of positive uses of data and research need to be a little bit more embedded in school curriculum, so that we can develop skills as a society to differentiate." C-2

"There are multiple positive impacts that I feel aren't shared as loudly and it's just the way it's presented to the public. I think it's important to try and show the benefits that can be achieved." YP-2

"How the information is presented, that is key here. If it's explained to you clearly and that it's in the best interest of the public, and yourself … there won't be barriers." C-6

Ability to take responsibility for own data

Some of our participants were diagnosed as children, meaning their parents or carers advocated for them in decisions regarding healthcare data sharing. These individuals described a transition of responsibility for their data. Initially when diagnosed they were happy for their parents to take charge but now with increased age and distance from treatment, they want to be able to make those decisions for themselves.

"There's an assumption that we can't have those conversations (about data use)… with young people." C-4

"Being so young, when I was diagnosed, my parents made most of those decisions for me about data and so I didn't really comprehend that anything was going to be

shared… as an adult now, I'd like to feel like I had control of the data or at least continued the consent to use it." YP-1

There was a general consensus that there is a need for increased awareness regarding the use of healthcare data to enable individuals to take responsibility for their own data. However, there was uncertainty around the best time to provide this information. Most participants felt that providing this information at the time of diagnosis was inappropriate. There was concern that for some individuals unexpectedly receiving this information sometime after treatment may be triggering of emotions felt during treatment.

"I'm in two minds about it. On the one hand, I feel if I just received a random letter in the post saying here's how your data has been used in the past … years since your diagnosis, I'd feel obliged to read it, but knowing that, that could very easily trigger my brain. Almost blissful ignorance is better, like I gave you my data that's yours now. I don't particularly want to think about that time I had the biopsy or that time that I had that treatment. Whereas with this (workshop), I was invited to do this, I'm mentally prepared for it. That's totally cool. But if that information was then sprung on me, I don't think I'd be ready for that." YP-1

"When I was first diagnosed, I think if you'd sat me down and said all your data is going to be used for X Y, Z, I probably wouldn't have cared less. My whole attitude towards the entire thing was, let's just get the treatment. Let's get it done. But certainly now and certainly after I've had all my surgeries, all the chemo and all that sort of stuff, it would be interesting to go back and say, oh, yeah, your data was used for this, this this. So I think maybe at the end of the treatment." YP-7.

6.5.3 Research priorities for data use

Participants described late effects, social and educational outcomes and rare cancers as areas of research importance.

Late effects

Research into the late effects of cancer and the treatment was important to participants. Some gave examples where they felt they had directly benefitted from such research.

"*To pick up on the point about gathering data after treatment finishes. I've always been really grateful about knowing about the long-term side effects that my child might have. People used to say, once you finish their treatment within six months they'll feel a lot better, they'll get their energy back, be able to play sport just like a normal child. And that hasn't happened. Because people have allowed their data to be used, because of the research that's happened, we've been able to see that actually, they might have long term side effects and their mobility might continue to be affected. We might not have known that if people hadn't done the research into long term side effects."* C-2

"I think it's really important that especially information on late effects is available. When I was diagnosed I was 13, fertility was just not mentioned to me. That was something that I had to go out and seek for myself. So if it weren't for that information and that data being out there…, I would never have known that I could go and ask somebody about my fertility and … seek help on that aspect." YP 1

Social and educational outcomes

Participants felt that research using social outcomes data would be valuable, particularly as social outcomes can impact children and young people more than older adults due to the amount of time lost in education or work.

"It's really important, I think, often, the social outcomes side can be really neglected, with people obviously focused on health. But that (social outcomes) can have a massive impact on people's lives in other ways." YP-7

"I'm someone who struggled with education and employment… I think it's really important. I think it's something that's not really looked into enough. So yeah, I'm all for it". YP-4

Despite the support for research around social outcomes it was, however, acknowledged that this type of data could be seen to be more sensitive than healthcare data.

"I think it is a more personal area as you don't really have a choice on your cancer, like what your diagnosis is, but you have a choice about how you act with it afterwards. I wouldn't mind giving my data, I feel like other people would feel more judged based on the data they're providing." YP-4

"I think it is more sensitive than some of the health data just because I think for some people, it seems more personal than scientific stuff that feels out of your control." YP-7

Rare tumours and outcomes

The importance of data sharing, including internationally, in young onset cancers, particularly where certain tumours and outcomes can be rare, was described by participants. They could see the value data sharing could have for rare tumours and felt it was important their data was shared for these reasons.

"If someone else finds themself in the same situation as you, it can help massively with research and helping outcomes and treatment for children and young people. We've all in a way got a responsibility to do our bit." YP-9

"I think it's very important, not just for rare diagnoses, but also for diagnoses that are quite common in a certain particular group but other people get them too. My diagnosis, it's very common in elderly. I got it when I was very, very young." YP-2

"I was just thinking that, if you have got something like an anomaly … the more data you have, there might be more anomalies that then spark ideas for new research. Those sort of pathways are kind of shut off without sharing." YP-1

6.5.4 Implementation of findings

The key findings from the workshops are summarised in Table 6.2 alongside actions taken by our research teams to improve public and patient trust in our research and inform our research strategy. These actions include continuing to work with workshop participants, embedding the patient and public voice into our research.

Table 6.2: Key findings from the workshops and actions taken by the research teams.

Key learning point	Action taken
Increasing public and patient trust	
Improved awareness of how the data is used including positive outcomes of data use.	• Public engagement events e.g. Be Curious at University of Leeds. • Conference presentations including parent and young persons' and carer representatives. • Easily accessible websites written in plain English. • Patient information resources at sites of data collection e.g. cancer outpatient clinics, teenage cancer wards. • Incorporation of infographics showing research outputs into posters. • Newsletters. • Twitter.
Enable young people to take responsibility of own data.	• Having information about our data use available for those who want to learn more. • Continuing to provide the option to opt out of data sharing and

	stating this on information resources.
Research priorities for CYP using healthcare data	
Late effects	• Successful in a Teenage and Young Adult Cancer (TYAC) grant to look at the risk of kidney injury in TYA using healthcare data. The research advisory group for this project includes three participants from these workshops. • PhD project looking at cardiometabolic late effects. • Collection of Patient Reported Outcome Measures (PROMs) which patients can view and use to make informed treatment decisions.
Social and educational outcomes	• YSRCCYP continue to pursue these datasets as part of ongoing research objectives.
Data sharing in rare tumours	• BENCHISTA has successfully gained approval for international data sharing through population-based cancer registries to compare tumour stage at diagnosis of childhood cancers.

6.6 Discussion

We report on the first consultation exercise between CYP with cancer, their carers and researchers on the use of their healthcare data for cancer research purposes. Participants reflected a range of cancer types, ages and experiences. Our results reflect the findings of the BSA future forum (9) that there is a lack of knowledge about how healthcare data is used.

Participants were clear they wanted the opportunity to have control over their healthcare data. This is in keeping with healthcare policy “no decision about me,

without me" (12) where adolescent and young adult cancer patients have demonstrated that they want to be involved in decisions about their care (13,14). Currently individuals aged 13 years and over are able to set a national data opt-out(15). It is therefore important that we provide young people with the information required to make an informed decision. This needs to be communicated in a balanced way to avoid negative portrayal often provided through the media. For those diagnosed as children, where decisions are generally driven by parents or legal guardians, additional support and information needs to be provided to those transitioning to adolescence from paediatric services, enabling them to start to take on control of their own decisions around healthcare and social data sharing.

The most appropriate time along the cancer pathway to inform CYPs and their families about routine data collection is unclear and is likely to differ between patients and circumstances. Participants pointed out patients newly diagnosed with cancer are likely to be in a high state of anxiety and unable to comprehend all that is being said to them. However, participants felt that an unexpected notification about how their cancer data is being used after the event may be triggering of negative emotions felt during the time of diagnosis and treatment. This is an area that needs sensitive consideration and for which we are receiving valuable input from CYP and their carers along with specialist healthcare professionals to find the optimal solution.

Whilst we have taken action to improve communication about our research, we acknowledge that this is only part of the picture. As suggested in our workshop, building education surrounding data use into the school curriculum may be one possible way forward. Over time this would help to normalise the use of healthcare data for research purposes and build trust within the general public. As researchers we must continue to be transparent in our use of the data and ensure that appropriate resources are there for people who want to find out more. This includes promotion of the good achieved through research using healthcare related data.

Participants in our workshop were supportive of data sharing in CYP cancers. This may reflect the known altruistic behaviour demonstrated by cancer patients and their families(16,17). Research into social and educational outcomes was seen as

an area of importance by participants. Whilst progress is being made linking education data (18,19), linkage of employment data from the Department for Work and Pensions is more difficult. The recently published top ten priorities for children's cancer by the James Lind Alliance include improving long-term outcomes for survivors, adding further support to the importance of this area of research (20). Internationally, the introduction of European Union General Data Protection Regulation (GDPR) has exacerbated difficulties in international sharing of health and research data, impacting CYP cancer research (21). Organisations are calling for a harmonised interpretation of the regulations. We need to harness the patient voice, as heard in our workshops, to help break down these legislative barriers both within and outside of the UK.

6.6.1 Strengths and limitations

A strength of our study is that it was nationally accessible enabling patients from across England and Scotland to participate. The online setting allowed individuals to attend who normally may have been unable to for health reasons or due to educational or work commitments. Participants were able to attend both workshops, enabling them to expand their own knowledge through our highly experienced multidisciplinary research team. We have invited all participants to continue working with us and a number have taken this opportunity, which has benefited our ongoing research (Table 6.2).

Despite the strengths of our workshop, we acknowledge there are limitations. The participants were a self-selecting cohort and therefore may not reflect the views of all young onset cancer survivors and carers. There was under representation of males which is common in patient and public consultations. A number of strategies have been attempted to increase the number of males participating in PPI including targeting male specific charities and targeted social media campaigns, neither of which have been successful (22). We must continue to consider ways of increasing the accessibility and attractiveness of our PPI exercises in a bid to include underrepresented groups such as males. One tested method is for the team to attend existing groups where males attend such as testicular cancer support groups (23). However, our workshops were held when most NHS institutions had restrictions on face-to-face meetings. We were unable to determine the true uptake

of the workshops due to the snowballing method of recruitment via social media. Both recruitment for the workshops and the workshops themselves were carried out online. This excludes those without access, who may have different opinions. While online workshop formats support national representation of participants, there are some groups for which online may present barriers. For example, those who are unable to operate the technical aspects of participating online although this is likely to be less of an issue with young people. Young people however may not have unlimited data mobile phone contracts or a private space to connect to Wi-Fi. To overcome this issue, we offered to reimburse any participants who had to purchase additional data to participate. As with many PPI activities, educational status and health literacy influences the willingness and ability to participate, as a team we spent numerous hours creating and reviewing content to ensure accessibility and using illustration/pictures where possible.

6.7 Conclusions

It is clear from our patient and public engagement exercise that within CYP and their carers a lack of awareness relating to data collection and its use is a leading cause of mistrust within public and patients. Our research groups have implemented these findings into our practice improving the transparency of our research. Listening to the input of CYP and their carers has enabled us to shape our research strategies to ensure our outputs are important and acceptable to those that matter most.

6.8 Declarations

Funding

NH is funded by the National Institute of Health Research (NIHR) [Doctoral Research Fellowship (grant number: NIHR300693)]. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

AL is funded by Children with Cancer UK (grant number: 20-329. International Benchmarking of childhood cancer survival by stage (BENCHISTA).

AL is also funded in part by Children's Cancer and Leukaemia Group (CCLG)/Little Princess Trust (grant number: CCLGA 2019 27B). The Little Princess Trust Wilms Tumour Knowledge Bank.

KPJ is funded in part by the National Institute for Health Research GOSH University College London Biomedical Research Centre, Great Ormond Street Hospital (GOSH). Grant number: N/A.

LF is funded by the Teenage Cancer Trust. Grant number: N/A.

Competing interests

The authors have no competing interests to declare.

Authors' contributions

All authors contributed to the conception, design and completion of the workshops. AP produced the workshop schedules. NH wrote the manuscript. All authors provided feedback and approved the final manuscript.

Availability of data and materials

An anonymised version of the datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Acknowledgements

We would like to thank our participants for their invaluable time and input on this project. We would also like to thank DATA-CAN and use MY data for their support.

Ethics Statements

Patient consent for publication

Participants gave written consent for the use of anonymised quotes in publication.

Ethics approval

As this was patient and public involvement, formal ethical approvals were not required but research ethical standards were adhered to. All participants agreed to an online conduct policy prior to taking part and were monitored for signs of distress throughout. Participants knew they could leave the workshop at any time. Following the workshops, participants were contacted by a team member (EC) to ensure the content had not elicited any psychological distress.

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Chapter 7. Discussion

7.1 Introduction

In this thesis the use of existing healthcare datasets to investigate the impact of delivered chemotherapy relative dose intensity in the AYA population has been investigated. The utility of linked chemotherapy prescribing data and cancer registry data on regional and national levels has been explored and described in comparison to each other and that available in international clinical trials.

The aims of this thesis are described in Chapter 1. The background literature was described in Chapter 2 including a published review paper which formed the foundation of this work. In Chapter 3 a description of the methods and data sources used is provided. Chapters 4 to 6 contain three original manuscripts of the research carried out for this study, each with its own detailed discussion, two of which have been enhanced through the peer review process then accepted for publication. Appendices B to D contain supplementary material for these papers. Appendix E provides further detail on the utility of the national dataset and methods used in this thesis in other tumour types. Appendix F contains analyses investigating the impact of sociodemographic factors on treatment received.

In this final Chapter the novel findings of this thesis are summarised in relation to the original aims. The strengths and weaknesses of the work are described along with the research and clinical implications and areas for future work suggested.

Aim 1: To determine the causal association between survival outcomes of AYAs with cancer receiving chemotherapy and the dose-intensity of chemotherapy that they have received, accounting for and exploring the effects of external demographic and clinical factors.

The relationship between delivered RDI and survival was investigated in GCT using linked COSD and SACT data from NCRAS and compared to that delivered in a dataset comprising four international clinical trials. Causal inference methodology

was used alongside descriptive Kaplan-Meier survival estimates and multivariable Cox proportional hazard regression analysis. The findings of this analysis (Chapter 4) demonstrate a positive causal effect between delivered RDI and survival outcomes with a stronger effect being observed within clinical trials.

The analysis was repeated for the bone tumours osteosarcoma and Ewing sarcoma (Appendix E) and whilst a survival advantage was seen with increasing RDI in osteosarcoma for doxorubicin and cisplatin a negative association was identified for methotrexate and many chemotherapy agents used in Ewing. Whilst this work has been presented it has not been written up for publication at present but has been included as an appendix to this thesis as an example of how the utility of the existing healthcare data differed between tumour types.

In Chapters 4, 5 and in Appendix E the effects of the external demographic factors ethnicity and deprivation on survival are described. In Appendix F the effects of these factors on achieved RDI are also described along with the impact of sex, age and region treatment was received in.

Aim 2: To describe the toxicity experienced by AYA receiving chemotherapy and whether this differs according to age and sex.

The toxicity data available in the linked NCRAS dataset and the clinical trials data is described in Chapter 4. Due to the male preponderance within the GCT cohorts and the limited toxicity data available within the NCRAS data, this aim was addressed using a linked regional dataset (Chapter 5). The focus was on osteosarcoma and Ewing sarcoma to enable comparison with the existing literature (1). Using linked data from the YSRCCYP and chemotherapy electronic prescribing data from LTHT this study looks at associations between toxicity induced modifications of treatment (TIMT) and survival. The results found female AYA experienced higher rates of TIMT, notably due to bone marrow suppression, and had better survival outcomes than male AYA in osteosarcoma and for bone tumours combined.

Aim 3: To explore the utility of existing health datasets; those routinely collected in the NHS and in prospective clinical trials to address aims 1 and 2.

The utility of the datasets in relation to answering research questions is considered in detail in Chapters 4, 5 and Appendix E. Recommendations for change have been suggested including those to policy and legislation.

Aim 4: To use patient and public involvement to improve research practice and inform future research questions.

To address this aim two patient and public involvement workshops were carried out and the results analysed using qualitative research methods. Current barriers to trust in the use of healthcare data for research purposes were described including a lack of awareness and mistrust in the mainstream media. Ways to improve trust in this use of data, including providing more accessible information to the public and the ability of young people to take control over their own data were considered. Research into late effects, social and educational outcomes and rare tumours were identified as areas of research importance to participants. A number of changes to research practice have been made as a result of this and are outlined in Chapter 6.

7.2 Originality of the study findings

The review of the literature in Chapter 2 identified a paucity of evidence relating to the real-world impact of delivered RDI in AYA patients. Whilst at the start of this study publications using SACT data had been published, no other research had used it for in-depth analysis as carried out in this study. A key finding of the paper published in Chapter 4 is the identification of a patient group, those with good prognosis, in which a trial of chemotherapy dose de-escalation may be feasible. Chapter 5 uses novel data linkage to investigate the impact of TIMT on survival. This research has shown an association between having at least one TIMT and better survival when compared to patients who had no TIMT.

Whilst the work in this thesis has demonstrated the great potential of data linkage and analytics in AYA research it has also highlighted the current limitations in this patient population. Notably the lack and incompleteness of data for variables which enable appropriate risk stratification of patients.

At the outset of this thesis, the field of real-world data was gathering momentum. Despite this, little consideration had been given to how the young people themselves felt about this use of their data. The COVID-19 pandemic and the NHS "data grab" (2) saw data use receiving more public attention and posed a risk to research in rarer tumours such as AYA through data opt-outs. The PPIE work in this thesis was the first to directly address this with CYP and their carers. From this we have laid the foundations of good practice for data use not only for the future research of our team but others in the field.

7.3 Strengths and limitations

A strength of this work is the use of the linked national cancer registry and SACT data which provide population-wide coverage, enabling an insight to be obtained as to the impact of DI throughout England. Unlike in other countries where patients require some level of health insurance, the NHS provides the majority of cancer care in England. It should be acknowledged however that some patients may have received chemotherapy in the private health sector and therefore may not be included in this analysis. These patient numbers are likely to be small, may have received a different level of care and are therefore outside the scope of this work. The NCRAS data also provides socio-demographic data for patients with a high level of completeness. This data is not currently collected in clinical trials and thus enables potential health inequalities to be investigated as demonstrated in Appendix F. Linkage to the ONS means death data has almost complete ascertainment which can be a limitation of clinical trials data due to losses to follow up. Data quality is assessed by the SACT team before the data is provided for analysis, but it must be acknowledged that it is still real-world data collected in a busy NHS setting and therefore may be subject to errors for example in cycle number. I am satisfied that my clinical interpretation of the data minimised these errors.

The study in Chapter 5 uses data from the YSRCCYP, a high-quality regional dataset with minimal loss to follow up. Linkage to LTHT data meant that detailed treatment data was received for all patients for whom there was an electronic chemotherapy prescribing record using the identifiers of NHS number and PPM unique identifier. I must acknowledge that incorrect linkage may have been carried out although the linkage was validated via sense checking treatment received with tumour details and no errors were found. Data linkage between the COSD data and SACT was carried out by NHS Digital and again, there is the possibility of linkage errors. Mismatches (i.e., the wrong patient linked to the wrong treatment record) may have occurred or there may be missing linkages. Beyond the validity checks carried out for the regional dataset however there is no way of assessing this.

One of the main limitations of this work is the incompleteness of data items available in the NCRAS data to enable risk stratification of patients. This not only includes stage but also the variables required for IGCCC risk classification (tumour markers and site of metastatic disease) in the GCT dataset and for the bone tumours grade, site, size of the primary tumour and genetic phenotype of the tumour.

Patient height and weight were required for the RDI analysis in Chapter 4 and Appendix E. Using both weight at the start of treatment and weight at the start of the cycle, this variable was 100% complete. In the GCT analysis height, however, was missing in 3% of patients; this was deemed to be missing at random and imputed by using predictive mean matching. Whilst it is acknowledged that using imputation has the potential to introduce bias, I felt that its use was appropriate for the small number of missing values and enabled patient numbers in the analysis to be maximised. Sensitivity analysis was performed to confirm this did not alter the trends seen. For the confounding variables identified in the DAG to control for in the multivariable regression modelling, all were 100% complete apart from ethnicity (missing in 0.28%) and co-morbidity adjustment score (22% missing). The decision was made not to adjust for either of these; ethnicity as the missing proportion was too low and the latter as the missing proportion too high with the potential to introduce bias. There was also concern that these variables may not be missing a random because some individuals may be reluctant to disclose this information. The proportion of missing data for stage was considered too high (in the GCT cohort

46.2% missing stage) to be appropriate for multiple imputation methods without introducing bias. Stage was therefore only included in the DAG as an unobserved variable.

The immaturity of the SACT dataset resulted in only a limited period of follow up being available for the cohort. This is a limitation particularly of the GCT cohort where survival rates are high and resulted in a high rate of right censoring. It also causes problems in AYA where patient numbers are already small. This limited the subgroup analysis that could be performed in this study.

Whilst a co-morbidity adjustment indicator was provided in the NCRAS data according to whether dose or regimen adjustments were made due to existing comorbidities, no other data relating to the patient's health was available in this dataset. This meant that detailed consideration of the impact of co-morbidities could not be performed in this analysis. By limiting analysis to first line chemotherapy the impact of preexisting health complaints may have been minimised in these young patients. This assumption could be validated in future by linkage to the Admitted Patient Care and Outpatient HES datasets as discussed in more detail below. There was no data available on lifestyle factors such as smoking, alcohol use and recreational drug taking. These are factors which could influence the metabolism of chemotherapy agents. They are however included in the DAG as unobserved variables and therefore accounted for in the underlying causal structure of the models. Looking at the impact of these factors on patient outcomes is an area of possible future work.

The strengths and limitations of the PPIE workshops are discussed in detail in the publication (Chapter 6). The main strength of the work was it took place in an online setting which increased to accessibility of the workshops to those throughout England and Scotland. This also minimised the disruption caused by taking part, for example in relation to education and employment, and reduced any morbidity-related barriers to participation that may be associated with travelling. The online setting however may have restricted participation to some patient groups e.g. those of lower socioeconomic status, although this is likely to be less of a barrier in younger participants.

7.4 Implications of the findings

The findings of the studies have a number of potential implications for both clinical and research practice.

7.4.1 Implications for research

The findings of this thesis highlight the advantages that can be gained from using existing health data. In Chapter 4 the potential benefit of linking clinical trials data to cancer registration data is described. This would enable patients to be followed up routinely following a clinical trial providing a longer follow-up time at low cost and research burden and reducing loss to follow up. In addition, linkage to datasets such as HES would capture data on any subsequent health problems that develop in survivorship beyond the end of the trial. Such detailed follow up data could then be used to risk stratify patients at the end of treatment according to their risk of subsequent morbidity. This would then enable the appropriate healthcare services and support required to be introduced for those at highest risk, maximising quality of life and health in survivorship. Data linkage between clinical trials and NCRAS would require appropriate data sharing agreements and consent processes to be put in place.

Despite patients being supportive of their healthcare data being used for research, as demonstrated in Chapter 6, legislative and data sharing barriers exist to researchers when accessing this data. This is further complicated by high costs to obtain the data and lengthy application processes. The work done in this thesis has improved data flow on a regional level through the implementation of data sharing agreements and appropriate ethical approvals, which will benefit future research. On a national level it is more challenging but something which is being addressed by organisations such as CRUK and something which the patient voice can be used to help improve.

As described earlier in this Chapter, data completeness and availability of data items specific to AYA cancers were a limitation of this work. This is of relevance to researchers, clinicians and data custodians and highlights a requirement for the

unique data collection needs of AYA to be considered. Whilst some of the required data items, for example tumour markers in GCT, are collected, the level of completion is too low to provide any clear research benefit. Incomplete data reflects the challenges faced by cancer registration systems which are often reliant upon overstretched clinicians and clerical staff for data extraction and coding. Through research such as that contained in this thesis, gaps in the data can be identified and steps made towards improving it. Regionally we are making steps to improve data collected through MDT proformas, improvements nationally would require either educating clinical teams on the importance of accurate and complete data, funding for dedicated data collection staff or offering funding incentives to trusts for more complete data collection. The emerging role of microRNA (3) in the detection, risk stratification and monitoring of GCT needs to be monitored closely and the need to collect such data if introduced in routine practice considered. This would ensure these datasets continue to be relevant and useful with changing practice.

It was clear from work in Chapter 6 that CYP and their carers are supportive of data use for research purposes but that there is a need for researchers to improve awareness and communication of this process. As researchers steps to improve this include patient information leaflets, websites, conference presentations and public engagement work. These efforts however will only reach a certain subset of the population. In the digital world that we now inhabit and with the use of healthcare data gathering momentum for all health conditions not only cancer there is much to be gained from building the use of healthcare data into the curriculum, as suggested in the workshops. This will provide individuals with the ability to distinguish between the different types of data sharing and help address any concerns they may have about the use of healthcare data. The recent NHS England contract with Palantir to implement a federated data platform (4) will once again bring data sharing into the public spotlight. Clear communication and maintaining the trust of patients and the public will be of great importance to reduce the number of opt-outs.

In both the PPIE work conducted for this thesis and the James Lind Alliance priority setting partnership workshops (5), research into social and educational outcomes were identified as a priority. Despite this, barriers exist to researchers in England when trying to access the datasets required for this work. Work in other countries

have shown such projects are possible and we must work with the government to overcome these stringent legislative barriers whilst ensuring data privacy is maintained.

7.4.2 Clinical implications

In Chapter 4 of this thesis evidence is provided for the survival benefit of maintaining RDI in the treatment of GCT. This is an important finding for patients and their families giving them further motivation for the need to undergo such intensive treatment. For healthcare professionals treating and caring for patients receiving such regimes it provides further evidence for both the prescribing practice and also the importance of supporting patients through the toxicity associated with maintaining dose intensity. The findings in Chapter 4 also identify a subgroup of patients in whom dose de-escalation of chemotherapy could be considered. De-escalation of treatment could help reduce the common late effects associated with treatment for GCT including second malignancies, cardiovascular disease, neuropathy, nephrotoxicity, ototoxicty and hypogonadism. Whilst a focus of this thesis was considering the impact of puberty on delivered chemotherapy in AYA we can also infer that maintaining RDI is beneficial in post-pubertal patients. This is evidenced in Chapter 4 by the 5-year survival rates in the 24-29 age group being consistent with those in the lower age ranges. Sensitivity analysis performed on the clinical trials dataset (Appendix B) also showed the positive effect of maintaining RDI on survival remained when patients aged over 30 were included.

Whilst the findings in Chapter 4 highlighted the need to maintain dose intensity in GCT the findings for bone tumour presented in Appendix E were less convincing, particularly in Ewing. If we compare the chemotherapy regimens investigated, BEP chemotherapy in GCT is of shorter duration than MAP and both regimes investigated in the EE2012 trial. This may mean that it is easier to maintain DI in these patients as opposed to in the bone tumours where the cumulative burden of the chemotherapy starts to take its toll. In addition, GCT have better survival rates, it may therefore be the case in bone tumours that disease progression in some patients during chemotherapy limits the amount of chemotherapy that can be given. Interpreting these findings alongside those in Chapter 5 provides further insight into the toxicity of these chemotherapy regimens and treatment modifications made as a

result. The most common achieved RDI in the Ewing patients was 0 to 0.74 and for all drugs apart from vincristine and dactinomycin increasing RDI was associated with worse overall survival. The findings in Chapter 5 showed a protective association between having at least one TIMT and survival. For patients receiving chemotherapy for Ewing an increasing number of TIMT was found to be associated with a lower risk of death (HR: 0.87) whereas in osteosarcoma an increasing number was found to have a negative association (HR: 1.5). This in keeping with the RDI analysis done in Ewing (Appendix E) where higher RDIs were associated with an increased risk of death for many drugs. In addition, lower overall RDIs were achieved in Ewing. This suggests that, particularly in Ewing whilst maintaining dose intensity is important, so too is adhering to the toxicity guided dose modifications defined in protocol. In routine clinical practice and outside of clinical trial this relies upon treating clinicians having the necessary knowledge and clinical experience of such requirements. Overall, these findings highlight the need for outcomes from clinical trials to analysed by both age and sex.

Chapter 5 describes the toxicity associated with the treatment of osteosarcoma and Ewing sarcoma and how this differs according to patient characteristics, notably age and sex. This knowledge is beneficial to patients, enabling them to make informed decisions about their treatment. In PPIE work I carried out for a project outside of this thesis young people expressed a wish to be provided with information about what to expect from treatment prior to starting. This equips them with the ability to help manage their health and side effects during treatment, providing them with a sense of control.

The findings of Chapter 5 also add support to the suggestion that within AYAs, chemotherapy drugs are metabolised differently resulting in different levels of toxicity and effects on survival outcomes. Many of the findings in this study mirror those of clinical trials. With the rising call for a personalised approach to cancer treatment we need to consider a move towards therapeutic drug monitoring (TDM) in our patients. This is discussed in more detail later in this Chapter but will require adequate funding and resources within cancer services. Further research is therefore required to assess the feasibility of this. In the shorter term the knowledge of which patient groups are experiencing higher levels of toxicity will enable support to be put in place for patients at the greatest risk.

Investigation of associations between socio-demographic factors and treatment received found no common factors associated with patients receiving lower RDIs. When looking at doxorubicin, cisplatin and etoposide, which were given in at least two tumour types investigated, patients who were treated in the south of England consistently received lower RDIs. Further research into inequalities in treatment in AYA however are required.

The toxicity data available in the national and regional datasets in Chapters 4 and 5 was inferior to that collected in clinical trials where toxicity according to the CTCAE (6) is methodically collected. The importance of toxicity experienced in the real-world healthcare setting has been highlighted in this thesis. Improved routine collection of toxicity data would enable a deeper understanding to be obtained of the impact of toxicity on delivered treatment in AYA.

7.5 Future research

The study in Chapter 5 describes the objective toxicity experienced according to clinical assessment, recorded within blood results and resulting in treatment modifications. This could be enhanced with Patient Reported Outcome Measures (PROMs). Integrating PROMs into routine care has been shown to improve symptom control, reduce emergency admissions during treatment and improve survival (7–9). Currently NHS Digital/ NHS England only routinely collect PROMs data related to some surgical outcomes, not related to cancer patients and they are poorly collected within clinical trials. Having information about the experiences of other young people receiving chemotherapy would provide individuals with further evidence on which they can make an informed decision about treatment choices, enhancing their sense of autonomy. This is an important area of future research in AYA and one which is being addressed by our research team under the European STRONG-AYA project (10). Collecting PROMs has the potential to provide insight into not only the acute toxicity experienced by patients during treatment but also the quality of life (QoL) experienced in survivorship. Just as we consider survival rates at 1, 2 and 5 years, QoL at these time points could also be assessed. This data

could also add support to potential future de-escalation trials in appropriate patient groups.

Research into the late effects of treatment was identified as a research priority by young people and their carers in Chapter 6. The use of detailed data from electronic prescribing systems such as PPM at LTHT holds the potential to investigate the development of late effects in more detail. If we take the example of renal late effects in AYA, important due to many chemotherapy agents commonly used in AYA being nephrotoxic, the data could be used to consider trends over time. This could identify which patients are most at risk of renal late effects, when they manifest and with what clinical presentation. This knowledge could then inform the best way of following up these patients and identify patients for whom early intervention could help prolong kidney function, protect future health and maximise QoL.

One of the limitations of data use in AYA described in Chapters 4 and 5 of this thesis is that of small patient numbers limiting subgroup analysis. A possible solution to this is amalgamating data from institutions both within the same country and internationally. Currently data protection regulations such as GDPR and ethical principles pose barriers to data sharing, particularly outside of the UK. To overcome this, research groups in other rare cancers such as anal (11) and oral cavity (12) cancers have utilised a privacy preserving approach called federated or distributed learning. Using this approach data is pooled in participating centres but no patient-level data leaves the site, only aggregated statistics. Federated learning algorithms then integrate the data locally before sending the results for use in one overall summary model. This approach will help to identify inequalities and discrepancies that exist between institutions and countries, ultimately identifying areas for improvement in patient care with the hope of improving patient outcomes. The work from this thesis will be built on using this federated learning as part of the STRONG-AYA European collaborative (10).

The findings in Chapter 5 are in agreement with existing literature(13–18) which suggest sex and age differences exist in the PK and PD of chemotherapy drugs with a potential impact on experienced toxicity and survival outcomes. There are many

factors that can influence this in adolescents including differences in body fat and muscle composition affecting drug distribution and plasma drug concentrations (19,20). Rising hormone levels, experimentation with drugs and alcohol and other physiological changes such as organogenesis also play a part (21). Add in a cancer diagnosis which can further influence drug processing through changes to nutritional status, tumour related influences and the effects of concomitant medications and it is clear why PK and PD may be complex in these patients. Psychosocial difficulties in AYA can lead to extremes in weight including obesity and malnourishment from eating disorders. Malnourishment can lead to reduced circulating plasma proteins which, for highly protein bound drugs such as cisplatin and etoposide, could result in a higher plasma concentration of unbound drug (22). Being underweight can also result in lower renal perfusion and therefore lower excretion of some drugs (22). Cisplatin excretion has been found to be increased in obese patients suggesting increased tubular secretion (23). Other studies have suggested a reduced clearance of doxorubincinol, the toxic metabolite of doxorubicin, in patients with a higher percentage body fat (24). Findings from adult tumours suggest obese patients have worse outcomes and this has also been found in some paediatric patient groups including sarcoma patients and those receiving cisplatin-based regimes (25–27). Obesity presents the additional challenge of whether to dose according to actual or ideal body weight, the latter of which may risk underdosing. The impact of extremes in weight on treatment in AYA therefore remains an important area for further investigation and one for which datasets used in this thesis could be used to address.

One potential way of overcoming these pharmacological differences is a move from the traditional flat dosing of chemotherapy based on BSA to individualised dosing methods such as TDM. TDM involves individualising drug dosage by maintaining plasma or blood concentrations within a targeted therapeutic range (28), the aim being to optimise the dose to achieve the best survival outcome with minimal toxicity. Many of the drugs commonly used in AYA cancers exhibit the three prerequisites for using TDM approaches: inter-patient variation in exposure with standard dosing, a narrow therapeutic window and a relationship between drug exposure and a clinical endpoint such as reduced neutrophils at nadir (29). It's success has been demonstrated in carboplatin (30) and methotrexate with research into the latter demonstrating that monitoring is not required for efficacy but to minimise toxicity (31). Despite this TDM remains underused due to a number of

challenges; multi-drug regimens require a large number of samples to be taken, pro-drugs such as ifosfamide add complexity to the analysis and there is a lack of therapeutic data from clinical trials. The logistical barriers to TDM also need to be considered including costs, laboratory facilities and having individuals required to take and interpret the samples. All remain areas for future work toward implementing TDM and may be facilitated by the collection of PK samples in clinical trials.

Pharmacogenetics also have a part to play in individualised drug dosing, the aim of such studies being to identify pharmacogenes which affect the ADME of chemotherapy drugs. Success has been seen in the development of genotype and phenotype tests which identify patients deficient in dihydropyrimidine dehydrogenase (DPD) the main enzyme responsible for metabolising 5-FU and capecitabine(32). This has led to the implementation of DPYD screening to identify patients deficient in the enzyme and who therefore have an increased risk of toxicity, enabling these individuals to therefore receive a lower dose of the drug. Identifying such targets in AYA common cancers will help to reduce treatment related toxicity.

In the UK cancer incidence rates have increased in 25 to 49-year-olds by 22% between the early 1990s and 2018 (33). Initial research has suggested the reason for this rise is multifactorial (34) and the need for further research focused on this patient group is apparent. As a result, and to align with the global definition of the AYA age range, the YSRCCYP is increasing its upper age range to 39 years. The relevance of this to the work in this thesis may be limited as we would expect those aged 29-39 years to have completed puberty and therefore their physiology and PK profiles to be the same as adults (20). There are many potential benefits however to be obtained from epidemiological research in these patients particularly via linkage to biological and genetic data.

The increasing incidence of early-onset cancers such as breast and colorectal cancer and the emerging use of immunotherapy earlier on in the cancer setting of these tumours is exposing a growing number of AYA to these therapies (35). Investigation into the toxicity and any differences in the efficacy of immunotherapy in

AYAs is an important consideration and an area in which the work in this thesis could be built upon. A Phase I study of ipilimumab (36) in patients with solid tumours aged 21 years and under found young people to have a similar toxicity and PK profile to adults. A survival advantage in those who experienced toxicity compared to those who did not was also seen. A similar study of nivolumab (37) found similar results regarding PK and toxicity but with a survival benefit only seem in lymphoma. Real world datasets could provide longer term follow up of immunotherapy not only in terms of survival but also the long-term effects. An area of particular importance to AYA is that of fertility and birth outcomes due to the known potential endocrinological (38) and pathological risks (39) of immunotherapy. Linkage to the maternal HES dataset could provide new insights into this topic. An additional area of consideration is that early phase trials of immunotherapy are carried out in patients with advanced disease who have been pretreated, often considerably, with chemotherapy. Use of linked SACT and COSD data as utilised in this thesis could enable the impact of such pretreatment on immunotherapy to be investigated.

7.6 Conclusions

This thesis aimed to investigate the association between received chemotherapy RDI and survival in AYA with cancer at the same time assessing the utility of existing healthcare datasets in answering this research question. A survival benefit was seen between higher RDIs in GCT, a mixed association in osteosarcoma and a predominantly negative association in Ewing. Treatment toxicity was found to differ according to patient age and sex with varying survival implications. The strengths and limitations of the different datasets used have been described, notably the lack of data items enabling risk stratification. The results provide an evidence base on which future dose de-escalation trials in GCT could be designed and highlight the need for further research into sex and age differences in chemotherapy efficacy. In addition, changes to practice for researchers using healthcare data in CYP have been suggested.

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Appendix A.

Title: A review article: The management of adolescents and young adults with cancer

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Keywords: Adolescent, Young Adult, Cancer, Epidemiology, Survival, Psychosocial, Clinical Trials, Biology, Training, Palliative Care, Late Effects, Survivorship.

A.1 Abstract

Adolescents and Young Adults (AYA) with cancer are young people developing serious illness when at the interface between the responsibilities of paediatric and adult cancer services. Personally, they are in a period of transition both biologically and in major social roles (1). For these and other reasons they present a unique set of clinical challenges in their management. Over the last 20 years the requirement for specific services to address their needs has been identified and this has become a growing field of research. Despite this survival rates still lag behind those of children and older adults with cancer (2).

Why do AYA patients have worse outcomes? The observation is that the reason is multifactorial with path to diagnosis, unique cancer biology, uncertainty of treatment protocol, compliance issues and poor recruitment to clinical trials all playing a part. In this review we will discuss the unique challenges faced by healthcare

professionals when managing AYA patients who are commonly and accurately described as being in an 'interface' position.

A.2 The Adolescent and Young Adult (AYA) population

The age classification of adolescent and young adults (AYAs) encompasses different age groups depending on purpose. Adolescence is defined to range from 10 to 19 years (3). For the purpose of active treatment this increases to the mid 20s, up to 30 years for epidemiological studies and 40 years for clinical follow up (4). In the UK we focus on teenagers (13-18 years) and young adults (19- 24 years) forming the Teenage and Young Adult (TYA) patient group. Although some may find this lack of consensus unnerving, maintaining flexibility enables the needs of this patient population to be met more freely. Thus reducing the risk that such patients fall into gaps between services, an outcome which AYA services are trying to avoid (5). In this review the term AYA will encompass the age range 15-39 years as proposed by the National Cancer Institute and supported by ENCCA (6).

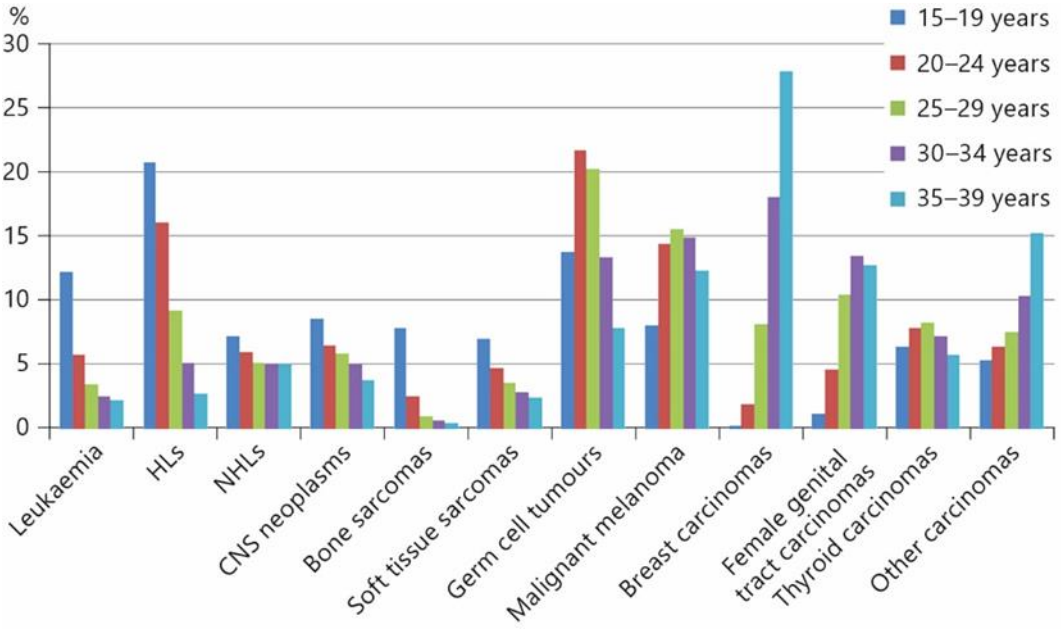
A.3 Epidemiology

Cancer is the leading cause of disease-related death in people aged 15-24 years old, exceeded only by cardiovascular disease in 25-39 year olds. Throughout Europe it is the third most significant cause of mortality in young people, behind road traffic injuries and suicide(3). Globally the annual incidence of cancer in 15-39 year olds is estimated at one million, with approximately 66,000 cases in Europe per year (7). Across North America and Western Europe the overall incidence of AYA cancers is slowing increasing. The rates differ between cancer types and may be partially attributed to external factors, for example the increase in Thyroid cancer in North America may be due to evolving diagnostics. Projections in the UK are that rates will continue to rise particularly within germ cell tumours in men and carcinomas in females (8).

The most commonly occurring cancers types in AYAs are; haematological malignancies (mostly Hodgkins's lymphoma (HL) and non-Hodgkin's lymphoma), carcinomas (notably breast, thyroid, melanoma and gynaecological) and germ cell

tumours (7). The distribution of cancer types across the AYA age group is demonstrated in Figure A.1 (7).

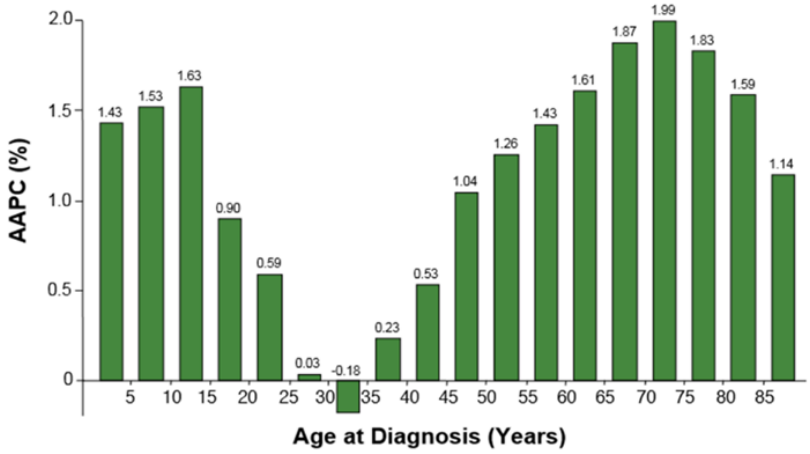
Figure A.1: The distribution of cancer types among different age groups in AYA patients (7).



The aetiology of AYA cancer remains relatively unknown and understudied. Germline mutations account for less than 5% of cases. It has been considered that they are caused by a combination of congenital and prenatal factors, seen in childhood cancers and environmental cancers seen in adult cancers, although with different latencies (9). Other causative factors may be attributable to puberty and the stage of life. For example, the incidence of osteosarcoma rises after puberty in long bone sites that undergo rapid growth at this time, the earlier onset of pubertal growth in females is also demonstrated (10).

Traditionally survival rates for AYA's have been poor and improvements have lagged behind that of paediatric oncology patients. Analysing US SEER data Bleyer *et al*. showed that improvement in survival rates for patients aged 15-45years old was a fraction of that in children in older adults. For those aged 25-35 years there was no evidence of any improvement (see Figure A.2) (11).

Figure A.2: Average Annual Percent Change (AAPC) in 5-Year relative Survival for All Invasive Cancer, SEER 1975-1997. (11)



An increased interest in the field of AYA oncology and the identification of the need to recognise this group of patients as a distinct cohort with their own unique needs has improved outcomes. In their European study looking at survival of teenagers and young adult cancers Trama *et al*. showed 5 year relative survival for all cancers combined to have improved from 79% in 1999-2001 to 82% in 2005-2007 (12). EUROCARE-5, a population-based cancer registry study, looked at the 5-year relative survival of AYA patients in comparison to childhood and adult cancers. This showed that the overall five year survival for all cancers in AYA patients is now greater than 80% in high-income countries. Survival rates however were still lower than in children for eight cancers: Acute Lymphoblastic Leukaemia (ALL), Acute Myeloid Leukaemia (AML), HL, non-HL, astrocytomas, Ewing sarcoma and rhabdomyosarcoma (12). AYAs survival rates for fibrosarcomas, soft tissue sarcoma and acute myeloid leukaemia remained stable.

A.4 Cancer Biology

AYA patients and their cancers both display specific biological characteristics (13) which influence their response to treatment and thus prognosis. This can be a positive factor, for example melanomas with BRAF mutations are more prevalent in the AYA population and thus are more likely to respond to a BRAF inhibitor (14). Less favourably, triple negative breast cancer is more prevalent in patients under 40

years and is associated with increased mortality partly due to fewer treatment options (15). In comparison to children, AYA patients with ALL have a higher proportion of unfavourable genetic abnormalities such as Ph-1 and a lower proportion of those which are treatment responsive. The TEL-AML1 translocation in ALL has a favourable response to treatment and is found in only 10% AYA cases as opposed to 50% of childhood cases (16). AYA patients with rhabdomyosarcoma are more likely to have the more aggressive alveolar subtype (17). Studies in synovial sarcoma (18) and rhabdomyosarcoma (19) have demonstrated the potential to use identifiable genetic differences within cancer subtypes as decision aids in clinical management to identify those in need of high risk treatment. As the molecular characterisation of cancers advances the hope is that patients will be able to be treated with more individualized protocols which may improve outcomes in AYA patients and develop AYA-specific clinical trials.

A.5 Model of care

AYA patients were historically treated in either a paediatric setting or an adult oncology setting. The former takes a family centred approach and threatens the AYA's autonomy, impacting upon emotional wellbeing. The adult setting focuses on the disease and not the complex psychosocial needs of the AYA, impacting upon concordance with treatment. AYAs are at an age where they are developing very rapidly in areas such as independence from the family unit. Each individual patient will vary in how far along their transition to independence they are at any one time and this will change during their cancer management, often quite dramatically. Thus presenting their own evolving and fluctuating challenges in terms of information, communication and decision-making preferences. A model of care is required that keeps the best of the two traditional approaches for AYA and omits the rest (20). Achieving this however is not always easy (21).

The care environment needs to be tailored specifically to the needs of AYA patients. Inpatient wards with colourful décor and facilities such as relaxation areas, games consoles and music facilities provide patients with an environment they can be happy to attend, something approaching normality, a feeling that their needs have been identified by the hospital, and a forum in which they can build peer relationships with fellow patients. They can also enable services to provide

specifically trained therapists and youth workers in an informal manner, which has been found to be beneficial to AYAs (22).

The rarity of AYA cancers also means that in order to receive the best treatment they should be cared for in specialist centralised centres by health care professionals with expertise in AYA cancers who have regular exposure to managing their cancers (23)(24). The care needs to be provided by an extensive multidisciplinary team that not only encompasses the traditional medical specialists but other healthcare professionals such as clinical psychologists, teachers, social workers and fertility experts. Thus addressing all needs of the AYA patients and not just their cancer. Care in specialist centres can also prevent feelings of isolation from other young people (25). Table A.1 describes the different models of care used across Europe as outlined by Stark *et al* (5).

Table A.1: The models of care for AYA patients currently used across Europe, correct in Summer 2016 (5).

	UK	France	Germany	Italy	Spain	The Netherlands	Denmark
Model of care	Collaboration between pediatric and adult services; Specalisation in AYA care.	National integrated cooperative program, joining pediatric and adult oncology/hematology. National Cancer Plans have an AYA element.	Inpatient treatment of adolescent cancer patients < 18 years takes place within a German Society for Pediatric Oncology and Hematology (GPOH)-certified unit.	Developed within the national pediatric oncology community. Current developing a national program, through collaboration between paediatric and adult oncologists.	Developed by local paediatric oncologists.	Health professionals from regional centres started a national cooperative AYA project in 2013, initiated by medical oncology, focused on those in the 18-35 age range.	No nation model.
Age range	15-24 years (13 to 24 years in several departments)	15-25 years	>18 years	15-29 years	14-30 years	18-35 years	Not defined
Local projects	25 AYA units	8 AYA programs, with 3 AYA units	4 centres with an inter-disciplinary programs	2 TYA units, 1 regional project	1 TYA unit & local initiatives in paediatric centres	2 AYA centres	2 AYA units

Within England centralisation began after the National Institute of Clinical Excellence published guidelines on 'Improving Outcomes Guidance for cancer in children and young people'. These were then supplemented in 2014 with seven statements prioritising areas for service improvement. Under this guidance patients aged 18 years or below at time of diagnosis must start their treatment at a principal centre.

Of course, there are negative aspects to centralised care. Notably the geographical distance that some patients and their families may need to travel in order to access these services, meaning disruption to friendships, education and careers that are so important at this age. AYAs are prone to challenge the views of their elders and for this reason it is beneficial to incorporate their views into developing services which is being done in a number of settings internationally (26). The BRIGHTLIGHT study is completing research involving previous and current patients to address the question "do specialist services for the teenage and young adults with cancer add value?" (27) Other novel approaches to encouraging AYA patients to express their views include through music (28).

Equally as important as where AYAs receive their care is who is providing it. The complex needs of AYA patients requires health care professionals to be educated and skilled not only in the unique biology and treatment requirements of their cancers, but also their psychosocial issues and communication challenges (29) . They need to be able to effectively communicate with AYAs, their families and peers and embrace the challenges that they bring (22). They need to expect and be prepared in advance for the positive and negative approaches to information and care routinely observed in young people, such as challenging authority and fluctuating tensions within families.

An international multicentre study identified a list of competencies required by healthcare professionals working in AYA services. Competences such as identifying the impact of disease on a young people's life, ability to discuss sensitive subjects and ability to use humour appropriately ranked highly. These findings can be used to influence educational curriculum, professional development and inform workforce planning (30). This is important as the skills required are not adequately

covered in the traditional adult or paediatric training programmes (31). The consensus of AYA cancer and Medical Education experts at an international summit meeting hosted by ENCCA and The Teenage Cancer Trust in 2014 included:

- That TYA specific education is needed and should be accredited by Universities, in collaboration with professional societies.
- There should be generic "working with AYA" training programs for all health care professionals who work with young people with serious illness.
- Detailed AYA training should become, in time, compulsory for all doctors leading in AYA cancer care, who should then hold a validated qualification in AYA oncology.

In the UK a collaboration between the Royal Colleges of Paediatrics and Child Health, Nursing, General Practice, and Obstetricians and Gynaecologists has produced an online e-learning module aimed at equipping health professionals with the communication skills required to work with AYAs. Training curricula for AYA are being established in the UK, US, Canada, Australasia and the EU. In Europe the European Network for Teenagers and Young Adults with Cancer (ENTYAC) aims to develop specific practice guidance for AYAs (5) and the European professional societies for medical oncology (ESMO) and Paediatric Oncology (SIOPE) are actively collaborating on professional education in AYA cancer care (32). What is interesting is that although the curricula require a similar knowledge base they differ in the additional skills and attributes needed, which may reflect the different care models used in these countries (29)(33)(34). In an age where we rely heavily on the internet, directing patients and family members to reliable internet resources may be a useful and underused communication adjunct (35).

A.6 Treatment – age appropriate protocols

AYA patients present treatment related challenges not only due to the distinct biology of their cancers as discussed earlier but also the physiological state of their bodies during this stage of life. During the normal process of puberty a number of

physiological and physical changes occur in the body which can influence the absorption, distribution, metabolism and elimination (ADME) of drugs throughout the body. These include hormonal changes, changes in body fat composition and organogenesis of the liver and kidneys (36). The age of onset of these changes varies in each individual patient and is different in males and females (36).

Uncertainty exists regarding what dose intensity of treatment AYA patients should receive. In the mid-2000s a number of international groups compared outcomes of AYA patients with ALL treated with adult versus paediatric protocols (37)(38)(39)(40)(41)(42). Findings demonstrated superior complete response rates, event-free and overall survival for patients treated on paediatric protocols.

Work in osteosarcoma has found that within the same chemotherapy protocols AYA patients are receiving lower doses of chemotherapy, fewer toxicities and worse outcomes. This study suggests that age and sex dependent pharmacological differences play a part (43). There was previously a misconception that AYA patients were unable to tolerate the toxicity of paediatric chemotherapy protocols. Recent studies however have shown this is not the case; using the EURO-EWING 99 protocol, adults experienced less toxicity than children (44). Older patients treated for rhabdomyosarcoma experienced less toxicity than younger patients (45). The degree of myelosuppression seen in patients after chemotherapy has been shown to correlate with outcomes (46)(47). It may therefore be the case that poorer outcomes in AYA patients is related to lower systemic exposure to chemotherapy as reflected in the lower observed toxicity (45).

In comparison to older adult patients AYA patients are often able to tolerate more intense chemotherapy regimes, due to them having fewer comorbidities. Dose dense and dose intense regimes have improved outcomes(48) and every attempt should be made to maintain dose intensity. Barriers to this include the need to avoid irreversible end organ damage which will negatively impact long term quality of life. Compliance with therapy (see later) is also an issue for many. Monitoring for cumulative side effects is an essential component of care during active treatment. The place of care may also influence this as non-specialist centres may be inexperienced and unwilling to give the high dose intense treatments required.

As with cancer patients of all ages supportive management of treatment associated toxicities should be an integral part of cancer care to enable patients to complete treatment (49). The ADME of supportive ancillary medications such as antiemetic and analgesic also needs consideration. Physiological differences may also make AYAs more susceptible to some side effects. For example poorer emesis controlled coupled with more aggressive regimes may result in increased susceptibility to anticipatory nausea and vomiting (50). The use of steroids may be limited by acne, which some patients may find an unacceptable side effect. Experimental use of alcohol, illicit drugs and tobacco along with compliance issues to treatment can also influence drug distribution. Oral contraceptive use should also be considered (36)

A.7 Treatment adherence

Adherence to appointments and treatment, particularly oral medications, can be problematic in AYA patients and lead to worsening of side effects, poorer outcomes (51) and delayed diagnosis of metastasis or local recurrence resulting in the need for additional treatment (52). It must be noted that non-adherence, as with many aspects of AYA care, is likely to be multifactorial and not completely understood (53)(54). Faced with requiring often intensive cancer treatment AYA patients may feel pressured into making decisions that they may not be mature enough to yet (55). In breast cancer patients younger age has been shown to be a predictor of poor adherence to adjuvant endocrine therapy (56).

In order to improve adherence an understanding of the reasons for non-adherence is imperative. Family relationships, treatment setting and treatment intensity are all likely to play apart. Distress is a prevalent association of poor concordance (53). A non-judgemental approach should be used by health care professionals in order to address issues and renegotiate ongoing care plans together. Clinicians should 'pick their battles' reserving them for the most important issues only. By doing this the AYA patient may feel they are able to maintain a level of control over their care rather than being dictated to (57). Recognition of the "sex and drugs and rock 'n' roll" lifestyle (58) of this age group is essential and providing a degree of flexibility in treatment plans enables AYA patients to maintain some normality in their lives,

without hindering their outcomes (55). Family cohesion should be encouraged (59) whilst enabling the patient to maintain some autonomy. The use of a video game intervention has been shown to improve adherence in 13-29 year olds (60), indicating that age-appropriate means of engagement and education have important roles.

A.8 Clinical Trial Recruitment

Clinical trials are often seen as the gold standard of care, leading to enhanced treatment for both those in trials and those receiving care at the same institution (61). Poor inclusion rates in cancer clinical trials have historically been associated with the lag in survival improvements in AYA (62). Participation rates for AYAs ranges from 5-34% compared to over 90% in children (62)(63)(64). The European paediatric Soft tissue sarcoma Study Group (EpSSG) compared the proportion of AYA patients (15-19 year olds) with the proportion of children (0-14 year olds) treated in EpSSG clinical trials based upon incidence and population rates. They noted the observed to expected ratio to be 0.30 for AYAs compared to 0.64 for children, though this varied between subtypes (65). In an attempt to rectify these poor accrual rates there has been a push to improve involvement of AYAs in clinical trials focusing on 5 key areas; appropriateness, availability, accessibility, awareness, and acceptability to patients (66).

The appropriateness of trials refers to the age inclusion criterion, which is often arbitrary and reflective of the clinical practices of trial designers as opposed to having scientific basis (66). This means that AYA patients are often excluded from paediatric trials for being too old or from adult ones for not being old enough (67). Recent shifts have shown adjustments of age criteria to enable AYA participation, for example, the lower age for adult trials being lowered to 16 years in all cancer trials and the upper age limit of paediatric trials increasing to 21-25 years for brain tumours and sarcomas(66). Age range should reflect the group of patients where the biology of the cancer makes the study question relevant. As age ranges become wider there may be confusion over which trials AYA patients should be entered into meaning better collaboration between adult and paediatric oncologists is required (68).

Availability of trials may be limited due to organisational and service boundaries such as having the relevant personnel at a treatment centre to open a trial and the age of patients that services are funded to treat. In addition, the availability of new agents is often limited in this patient population due to a lack of preclinical research and poor funding from drug companies. The rarity of cancers in AYA patients often requires international collaboration to obtain sufficient trial numbers which adds to the financial burden. Trials such as the EUROMOS-1 trial or Euro-Ewings trial series show it possible to overcome the barriers faced.

Trial regulations which have the purpose of protecting minors, particularly in Phase 1 and 2 clinical trials can actually hinder access to potentially beneficial treatments. The ACCELERATE platform is a multi-stake-holder platform founded by the Cancer Drug Development Forum, SIOPE and Innovative Therapies for Children with Cancer (ITCC) European network which aims to accelerate innovation for children and adolescents with cancer (69). Strategies for doing this include reducing trial entry to 12 years of age for phase 2 trials and allowing adolescents to participate in Phase 1 trials where there is scientific rationale and potential therapeutic benefit such as the presence of a drug target.

Patient acceptability of the trial is paramount and thought needs to be given to this particularly if it involves additional hospital visits or investigations. Involvement of AYA patients and their families in trial design may improve this barrier (70).

Cancer clinicians outside of tertiary centres and with limited experience in the rare cancers seen in AYA patients may be unaware of relevant clinical trials, cautious of treating patients with the dose intensity required or simply may not have access to them. There therefore needs to be an increased awareness of the importance of referring AYA patients into specialist centres.

A.9 Path to cancer diagnosis

AYA patients often report a prolonged path to diagnosis which may impact on their potential for cure. A Danish retrospective cohort study looked at the primary care use of AYAs during the two years preceding a cancer diagnosis and found an increase in primary care use 16 months prior to cancer diagnosis which increased exponentially 8 months before diagnosis (71). The timing of the increase was dependant on tumour type: 17 months for CNS tumours, 12 months for sarcomas, 9 months for lymphomas, 5 to 6 months for germ cell tumours, bone tumours and leukaemias and 3 months for malignant melanomas. An increase in the number of blood tests performed was also seen from 11 months (71). A British study found that cancer patients aged 16-25 years were twice as likely as older patients to have three or more GP consultations before referral for diagnostic tests (72). It is therefore not the case that AYAs are not reporting their signs and symptoms but either that what they are reporting is vague and non-specific, or that clinicians are not acting promptly upon specific symptoms because they consider the probability of serious disease to be low. AYA cancers are rare and in a patient presenting four or more times the absolute risk of a patient having cancer is still only 1.8 per 10,000 (73). Zhou and colleagues recently found that in the UK fast-track cancer referrals were less likely to be made for cancers that present with non-specific symptoms and for low cancer incidence demographic groups (74). AYAs are also thought to be less likely to pursue medical attention once they have been reassured about their symptoms compared to adults or the parents of unwell children(75), this may mean AYA require a distinct safety-netting procedure to adults (76). In the UK, guidelines on managing patients attending multiple times with the same problem have been produced and fast track diagnostic pathways put in place in an attempt to combat long pathways to diagnoses (77) which can impact on survival (78). Cancer awareness programmes aimed at AYA patients are also important to encourage reporting of early symptoms (79).

A.10 Palliative care and end of life care

Palliative care skills should be recruited to enhance supportive care and are equally as important for patients being treated with curative intent as those being treated with palliative intent. Introducing palliative care services at the beginning of

treatment will enable patients and their families to build relationships with the team, reducing the feeling of abandonment some patients feel when they finish active treatment.

Palliative care should be provided by healthcare professionals who have expertise in the complex needs of AYA patients and become part of a patient's comprehensive care. It is crucial that care teams don't assume that patients are unwilling to discuss end of life issues because of their age (80). Lyon *et al*. found that having end of life discussions with patients and their families lead to greater congruity between what the adolescent wanted and what the families thought they would want (81). A retrospective study found that half of end of life discussions were initiated in the last 30 days of life allowing minimal time for end of life preparation (82). In this study more than half of the patients died in hospital despite findings that patients prefer to die at home. Half of these patients died on ICU which may reflect that the tipping point from being fit with a good quality of life and able to tolerate active treatment to being very unwell in the last few days of life often rapidly occurs in young patients, making planning while health is still good very important. Exploring individual preferences for the discussion of end of life care may be crucial to improving patient experiences. An exploratory study of 50 patients found adolescents willing to discuss end of life decision making using a personal survey (83).

A.11 Cancer survivorship and late effects

An increase in survival rates from AYA cancers brings a greater population of survivors living with the long-term effects of their cancer. AYA patients experience their own pattern of late effects influenced by their physiology, the cancers they develop and the treatment they receive (84). These undoubtedly have an impact on the quality of life of survivors and financial costs for health services (85). PanCare, a multidisciplinary pan-European network made up of healthcare professionals, survivors and family member, aims to reduce the frequency, severity and impact of late side-effects of children and adolescents with cancer.

A.11.1 Second Primary Cancers

AYA survivors have a significant risk of developing second primary malignancies compared to both the general population (86) and older patients with cancer (87). As well as individual factors such as genetics, co-morbidities and lifestyle an individuals risk of a second malignancy is affected by a number of things including; age at diagnosis, site of original cancer and treatment received (87). Testicular cancer survivors treated with alkylating agents and topoisomerase II inhibitors have been found to be at an increased risk of developing acute myeloid leukaemia (88)(89). These patients are also at a significantly increased risk of developing contralateral testicular cancer, malignant mesothelioma, and cancers of the lung and gastrointestinal tract (90). Radiotherapy exposure has been shown to result in malignancies of the skin and carcinomas of the thyroid, bone, breast and brain (91).

A.11.2 Cardiovascular

Cardiovascular complications are the commonest non-malignant cause of death in cancer survivors (92). Anthracyclines increase an individuals risk of left ventricular dysfunction, cardiomyopathy and dysrhythmias. Cisplatin based chemotherapy regimes have been shown to cause long-term cardiovascular complications in testicular cancer survivors (93)(94). Radiotherapy can also result in cardiomyopathy, pericardial fibrosis and pericarditis, heart valve abnormalities, conduction disorders and coronary, carotid and subclavian artery disease (91).

A.11.3 Other

Pulmonary toxicity can arise from alkylating agents and radiotherapy (95). Patients treated with Bleomycin need to be educated of the possible risk of toxicity from oxygen therapy and the appropriate warnings placed on their medical records. Ifosfamide, methotrexate, platinum agents and radiotherapy can all lead to impairment of renal function and the urinary tract(96). Endocrine complications include abnormalities of thyroid function and pituitary dysfunction and alterations in glucose metabolism (97). Long term neurological complications from cisplatin based chemotherapy include hearing impairments and Raynaud's phenomena (94).

A.11.4 Late psychosocial effects

Socioeconomic late effects of AYA cancers can have a huge impact on a survivors quality of life and should not be overlooked (98). The adolescent and young adult period of life covers the time when individuals are finishing school, embarking on careers or higher education and developing emotional and sexual relationships. It is the time when young people are starting to leave the family home and develop financial independence. A cancer diagnosis during this time can therefore delay or prevent these processes of achieving autonomy.

Cancer survivors are less likely to be married, be living independently, have attained post-secondary school education and be working full time than their siblings (99). Financial difficulties are also reported (98). Anxiety, stress and depression are prevalent in AYA cancer survivors (100).

Neurocognitive delay, both developmental and functional is a lasting complication in patients treated for AYA cancers (99) and can influence an individuals performance at work or in education. AYA patients have reported that cancer has a negative impact on both their career and education plans (101). Some however reconstruct this disruption in a positive light and use it as an opportunity to refocus on their future and individual goals (101). Experienced teams may be able to promote this approach.

Perception of body image can change as a result of cancer lowering self-esteem in a population where appearance is often important. Surgical scars, hair loss, loss of body parts can cause AYAs to feel less attractive and hinder their ability to form relationships with peers and start sexual relationships (102)(98). The risk of infertility and cancer recurrence can also make AYAs more cautious about entering meaningful relationships.

A.11.5 Fertility

Both cancer and its treatment can reduce a patients fertility (91)(103). As survival rates improve more and more patients are having to deal with this consequence in later life. The risk to a patient depends on the treatment they receive. Chemotherapy regimes containing Alkylating agents are harmful to the ovaries and testes. Pelvic radiotherapy can cause oligospermia or azoospermia and ovarian and uterine dysfunction (91). High dose cranial radiotherapy can reduce fertility by impairing hypothalamic pituitary function. Fertile Hope have developed a risk calculator based on clinical experience and published research to aid with the decision-making process (104).

AYA patients may never have considered having children and therefore discussions about fertility preservation could be unexpected and “embarrassing”, inhibiting discussion by professionals who are not regularly practiced in conducting them. Despite this it remains a crucial topic to address and one which may become a source of resentment later on if incompletely or self-consciously discussed. Studies have shown a willingness amongst patients and their parents to discuss fertility options as long as it does not delay treatment (105). A study of male cancer patients found sperm cryopreservation to have a positive emotional impact during treatment (106), possibly as it implies a normal future.

Clinicians should provide AYA patients with comprehensive and current information about fertility preservation at the time of diagnosis to enable them to make the required decisions. This is not an easy task, particularly where female patients are concerned, and requires healthcare professionals keeping up to date with an ever-changing field. There is therefore undoubtedly a need for clinical practice guidelines, education of healthcare professionals and inclusion of fertility experts in the care team of AYA patients.

It should be noted that AYA patients should be educated on the importance of practising safe sex despite potentially reduced fertility in order to prevent sexually transmitted diseases and unplanned pregnancies (103)(91).

A.11.6 Long term follow up and education

It is important that AYA survivors are aware of the potential complications that they may face in later life as a result of their treatment and that they are supported in modifying simple lifestyle factors such as diet, exercise and smoking cessation in order to reduce their risk. A review by Carretier *et al*. identified some prevention strategies (107) and the role of social media should not be overlooked (108).

Ongoing clinical review in AYA cancer survivors is necessary to identify recurrence, late effects and provide reassurance (109). It is therefore crucial that AYA clinicians implement the appropriate surveillance strategy and promote awareness of the risk of late effects amongst community healthcare providers. To support this the Children's Oncology Group (COG) have produced expert consensus guidelines for the long term follow up of younger AYA survivors (91). PanCare are also adding an evidence base and newly completed UK cohort studies of late effects specific to AYA have great promise (110). Risk stratification of AYA cancer survivors according to their risk of developing late effects enables patients to be followed up appropriately for example those at lower risk in the community versus those at higher risk by their specialist centre. New schemes are in place that enable patients to be followed up remotely by specialist teams without the need for hospital visits (111). This not only promotes self-care, it reduces the burden on outpatient services and reduces the disruption on a patient's life, helping them to return to some normality.

A.12 Conclusion

The identification of AYA patients as a group with a unique set of requirements has led to a burst of associated research. Trama *et al*. have demonstrated that this is working to reduce the survival gap but that further progress is still required. Undoubtedly many questions remain unanswered and needs remain apparent. The James Lind Alliance in the UK have recently published a list of ten research priorities which they devised after consultation with patients, family members and health care professionals (112). The aim is to encourage and inspire work which will lead to improvements in outcomes and experiences of AYA patients and their families.

Collaborations and networks between patients, charities (e.g. Teenage Cancer Trust, Canteen and Teen Cancer America), professionals (e.g. SIOPE and ESMO) and organisations (e.g. Teenagers and Young Adults with Cancer and the Italian Society for Adolescents with Oncohematological Deisease (SIAMO)) are bringing together expert knowledge and experience from across the globe facilitating progress in even the rarer cancers. The hope is that AYA oncology will continue to be an advancing field over the coming years.

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Appendix B.

B.1. The use of multiple imputation

As described in section 4.4.4, where data for either height or weight were missing they would be assumed to be missing at random and managed using multiple imputation methodology, the theory of which is described in 3.5.4. After data cleaning, as described in Appendix G, no patients were found to have missing data for weight alone and so MI was used only for height. The code for which is described below:

```
mi set wide

mi register imputed HEIGHT_AT_START_OF_REGIMEN1

mi register regular AGE1 SEX1 QUINTILE_20151 DIAGNOSISYEAR1

mi impute pmm HEIGHT_AT_START_OF_REGIMEN1 c.AGE1 i.SEX1, add
(20) knn (5) replace noupdate
```

The distributions of the imputed and observed vales were compared to check that the imputed values were in keeping with the observed. The stata command `mi xeq` was used to summarise the observed, imputed and completed data, checking for any inconsistences. Midiagplots were used to visually represent the distributions of the observed, imputed and completed data to ensure the distributions were similar.

```
mi xeq 1/ 2: tab HEIGHT_AT_START_OF_REGIMEN1 if _mi==0

mi xeq 1/ 2: tab HEIGHT_AT_START_OF_REGIMEN1 if _mi==1

tab HEIGHT_AT_START_OF_REGIMEN1
```

Sensitivity analyses was performed by comparing the results from complete case analyses to the results from the multiple imputation models to check there were no great differences in the directionality of effects (Table B.5.).

B.2. Proportionality assumptions and model testing

B.2.1 Univariable cox models

```
stcox RDI_ETOP_final_

estat phtest, d

stphplot, by (RDI_ETOP_final_)

sts graph if failcode==1, by (RDI_ETOP_final_) failure

sts graph if failcode==2, by (RDI_ETOP_final_) failure

stcoxkm, by (RDI_ETOP_final_)
```

B2.2 Testing and visualisation of the proportional subhazards assumption using Schoenfield residuals estat phtest

```
stcox RDI_ETOP_final_ AGE1 comorb_adj1 ETH_cat1 QUINTILE_20151
SEX1 region_cat

stphtest, d

stphtest, plot (RDI_ETOP_final_)
```

Table B.1: Description of the clinical trials regimes.

Clinical trial	Inclusion criteria	Exclusion criteria	Regime	Dosing	Year of trial	Number in trial	Median follow up (years)
30873 EORTC	Metastatic testicular non-seminoma with any of; lymph node metastases 5-10 cm, lung metastases n>4 or size > 3 cm, HCG 5000-50 000 IU 1-' or AFP > 1000 IU 1-'.	Patients with extragonadal primary tumours or metastatic sites other than lymph nodes and lung (liver, bone, brain. Pure seminoma (unless HCG levels > 200 IU 1-' or elevated AFP levels), prior radiotherapy or chemotherapy, WBC <2000 ,ltl', platelet count <100 000 ul-' or creatinine clearance < 40 ml min-'.	4 cycles of BEP vs 4 cycles VIP	BEP; cisplatin 20mg/m^2 IV on day 1-5 every 21 days; etoposide 120mg/m^2 iv on day 1, 3, 5 every 3 weeks and bleomycin 30mg IV on day 1 weekly for 12 weeks. VIP; etoposide and cisplatin doing as per BEP, ifosfamide 1.2g/m2 on days 1-5 every 3 weeks.	1987 to 1990	84	7.7
30983 EORTC	Intermediate prognosis metastatic GCC according to International Germ Cell Cancer Consensus.	Patients who had previously received chemotherapy, creatinine clearance less than 40 mL/min, or < 16 or >50 years of age.	4 cycles of T-BEP vs BEP	BEP; cisplatin 20mg/m^2 IV on day 1-5 every 21 days; etoposide 100mg/m^2 iv on day 1- 5 every 3 weeks and bleomycin 30mg IV on day 1 weekly for 12 weeks. T-BEP; BEP as above plus paclitaxel 175 mg/m^2 3-hour infusion prior to day 1.	1998 to 2009	322	5.3

30974 EORTC	Adult male patients aged 15–50 years with previously untreated metastatic poor prognosis non-seminoma according to IGCCCG classification of either testicular or extragonadal origin.	None listed.	1 cycle standard dose + 3 cycles high dose VIP vs 4 cycles standard BEP.	BEP; cisplatin 20mg/m^2 IV on day 1-5 every 21 days; etoposide 100mg/m2 iv on day 1- 5 every 3 weeks and bleomycin 30mg IV on day 1 weekly for 12 weeks. VIP; one cycle cisplatin 20mg/m^2 IV on day 1-5 every 21 days, etoposide 75mg/m^2 iv on day 1- 5, ifosfamide 1.2g/m^2 on days 1-5 every 3 weeks. 3 cycles cisplatin 20mg/m^2 IV on day 1-5 every 21 days, etoposide 300mg/m^2 iv on day 1- 5, ifosfamide 2.4g/m^2 on days 1-5 every 3 weeks.	1999 to 2007	120	4.4
30895 EORTC	Histologically proven NSGCTs In exceptional circumstances, a diagnosis made by tumour markers alone was acceptable.	Prior radiotherapy or chemotherapy; creatinine clearance < 40 mL/min, aged >65 years; significant cardiovascular disease.	3 cycles of BOP + 3 cycles of VIP vs 4 cycles of BEP and 2 cycles EP.	BOP/VIP-B ; 3 cycles of BOP (bleomycin 30mg, vincristine 1.4mg/m^2 and cisplatin 100mg/m^2) at 10 day intervals. After 2 weeks this was followed by 3 cycles of VIP (etoposide 100mg/m^2 on days 1, 3 and 5 and cisplatin 20mg/m^2 on days 1 and 5) at 3 weekly intervals. Bleomycin 30mg was given on day 28 between BOP and VIP and also on days 8 and 15 of each cycle of VIP. BEP/EP; 4 cycles of BEP (etoposide 100mg/m^2 days 1 to 5, cisplatin 20mg/m^2 days 1 to 5, 3 doses of bleomycin 30mg/m^2 were given weekly with each course). This was followed by 2 cycles of EP at the same dose.	1990 to 1994	371	3.1

Table B.2: The percentage of dose modifications made in the clinical trials and National Cancer Registration and Analysis Service datasets.

Modification		Clinical trials Yes (%)	No (%)	Missing (%)	NCRAS Yes (%)	No (%)	Missing (%)
Dose reduction*							
	30873	67.5	32.5	0	3.1	76.7	23.3
	30983	-	-	-			
	30974	-	-	-			
	30895	41.3	54.7	1			
Treatment stopped early**							
	30873	-	-	-	10.4	74.7	14.9
	30983	-	-	-			
	30974	-	-	-			
	30895	19.3	77.7	3			
Time delay							
	30873	20	80	0	6.4	54.6	39
	30983	6.8	92.0	1.2			
	30974	17.8	81.0	1.2			
	30895	13.1	41	45.9			

*Provided in 30895 and 30873.

** Only provided in 30895.

Table B.3: Comparison of 5-year survival in the NCRAS cohort, clinical trials cohort and study by Shaike et al[1].

	NCRAS (817)		Clinical trials (547)*		Shaikh et al. (503)**	
Age	n	5-year survival	N	5-year survival	n	5-year survival
<18	33	97 (80-100)	31	84 (61-94)	109	72 (62-79)
>18	784	95 (93-96)	516	81 (78-85)	394	88 (84-91)

* Excludes patients aged >30 years.

** Excludes those aged <11 years.

[1]. Shaikh F, Stark D, Fonseca A, Dang H, Xia C, Krailo M, Pashankar F, Rodriguez-Galindo C, Olson TA, Nicholson JC, Murray MJ, Amatruda JF, Billmire D, Stoneham S, Frazier AL. Outcomes of adolescent males with extracranial metastatic germ cell tumors: A report from the Malignant Germ Cell Tumor International Consortium. *Cancer*. 2021;127(2):193-202. doi:10.1002/cncr.33273

Table B.4: Sensitivity analysis for Hazard ratios (HRs) and 95% confidence intervals (CIs) from Cox regression models presenting the association between RDI received and risk of death in germ cell tumour patients within patients in (A) the clinical trials cohort and (B) the National Cancer Registration and Analysis Service (NCRAS) cohort.
(A)

	Including patients aged 30 years and over							Excluding patients aged 30 years and over						
	Adjusted*			Unadjusted				Adjusted*			Unadjusted			
	HR	95% CI	P value	HR	95% CI	P value		HR	95% CI	P value	HR	95% CI	P value	
Bleomycin (n=652)	0.21	0.08-0.54	0.00	0.13	0.05-0.31	0.00	Bleomycin (n=437)	0.30	0.08-0.95	0.04	0.16	0.05-0.57	0.00	
Cisplatin (n=739)	0.09	0.02-0.44	0.00	0.06	0.01-0.31	0.00	Cisplatin (n=496)	0.03	0.00-0.18	0.00	0.02	0.00-0.10	0.00	
Etoposide (n=730)	0.18	0.06-0.55	0.00	0.17	0.05-0.59	0.00	Etoposide (n=489)	0.09	0.25-0.30	0.00	0.06	0.20-0.25	0.00	

* Adjusted for age and IGCCCG classification.

(B)

	Initial cohort							Excluding stage 1 tumours							Excluding female patients					
	Adjusted**			Unadjusted				Adjusted**			Unadjusted				Adjusted**			Unadjusted		
	HR	95% CI	P value	HR	95% CI	P value		HR	95% CI	P value	HR	95% CI	P value		HR	95% CI	P value	HR	95% CI	P value
Bleomycin (n=813)	0.35	0.09-1.38	0.13	0.35	0.09-1.37	0.13	Bleomycin (n=697)	0.28	0.07-1.16	0.08	0.29	0.07-1.18	0.08	Bleomycin (n=769)	0.26	0.07-1.04	0.06	0.27	0.07 - 1.04	0.06
Cisplatin (n=842)	0.80	0.39-1.64	0.54	0.74	0.36-1.53	0.42	Cisplatin (n=718)	0.91	0.47-1.73	0.77	0.91	0.48-1.71	0.76	Cisplatin (n=794)	0.87	0.44-1.72	0.69	0.86	0.44 - 1.69	0.67
Etoposide (n=846)	0.68	0.25-1.90	0.46	0.62	0.23 – 1.70	0.35	Etoposide (n=722)	1.01	0.41-2.48	0.98	1.02	0.44-2.39	0.96	Etoposide (n=798)	0.88	0.33-2.34	0.80	0.88	0.34 - 2.26	0.79

** Adjusted for age, dose adjusted for co-morbidity, ethnicity, deprivation quintile, sex and region treatment received in.

Table B.5: Sensitivity analyses comparing the hazard ratios (HRs) and 95% confidence intervals (CIs) from Cox regression models using both the imputed models and complete case models within the National Cancer Registration and Analysis Service cohort.

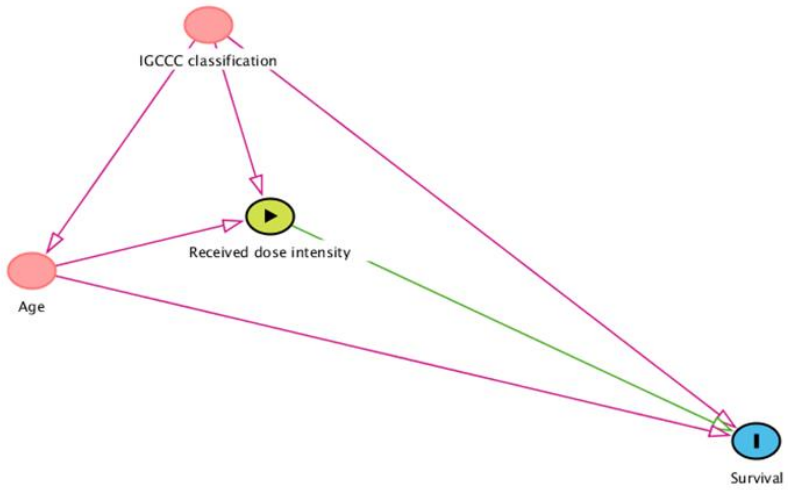
Multiple imputation models							**Complete Case models**						
Chemotherapy drug	**Adjusted****			**Unadjusted**			**Chemotherapy drug**	**Adjusted****			**Unadjusted**		
	HR	**95% CI**	**P value**	**HR**	**95% CI**	**P value**		**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Bleomycin (n=769)	0.26	0.07-1.04	0.06	0.27	0.07-1.04	0.06	Bleomycin (n=627)	0.14	0.03-0.77	0.02	0.35	0.09-1.37	0.13
Cisplatin (n=794)	0.87	0.44-1.72	0.69	0.86	0.44-1.69	0.67	Cisplatin (n=639)	0.99	0.45-2.30	0.04	0.74	0.36-1.53	0.42
Etoposide (n=798)	0.88	0.33-2.34	0.80	0.88	0.34-2.26	0.79	Etoposide (n=642)	0.84	0.26-2.74	0.78	0.62	0.23-1.70	0.35

Table B.6: Comparison of patient characteristics who participated in the individual clinical trials.

Trial	Mean age (years)	Age range	Percentage of IGCCC intermediate Risk (%)	Percentage of IGCCC poor Risk (%)	Percentage of deaths on trial (%)
30873	26.4	16.5 to 39	100	0	11
30983	27	16 to 39	100	0	10
30974	27.2	16 to 39	32	100	35
30895	27	15 to 40	32	58	27

Figure B.1: Directed Acyclic Graphs demonstrating the minimal sufficient adjustment set for A) the clinical trials dataset B) NCRAS dataset.

A)



B)

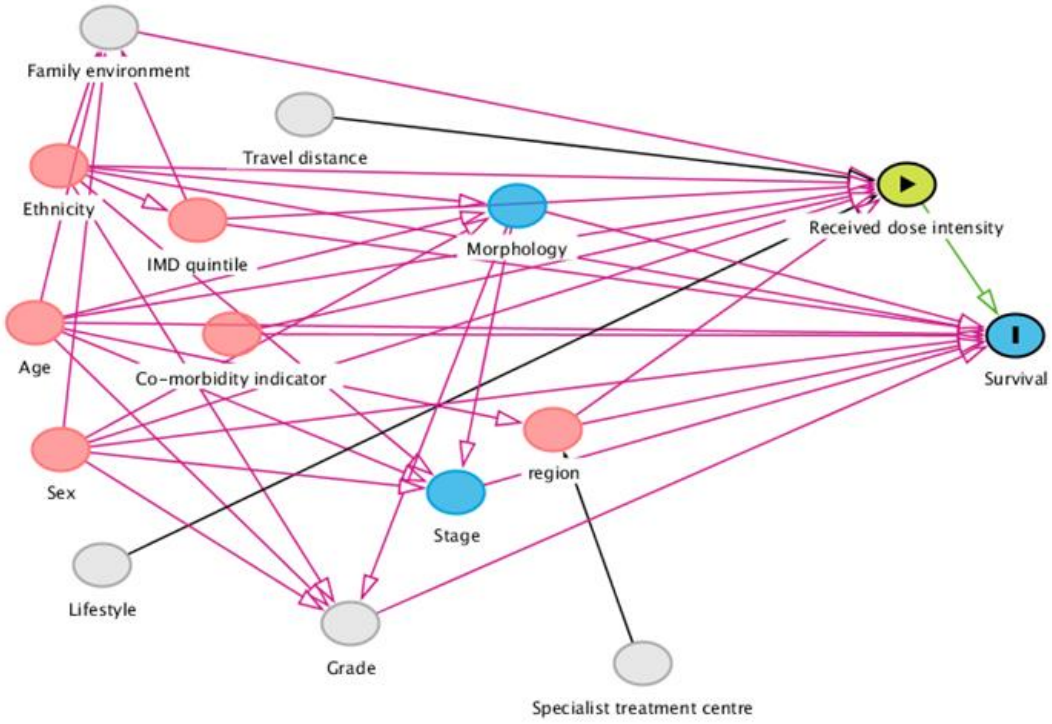
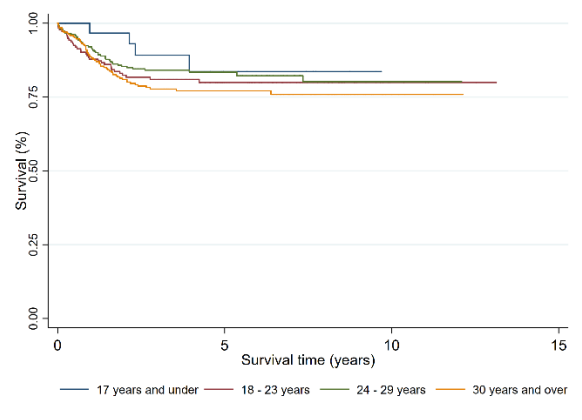
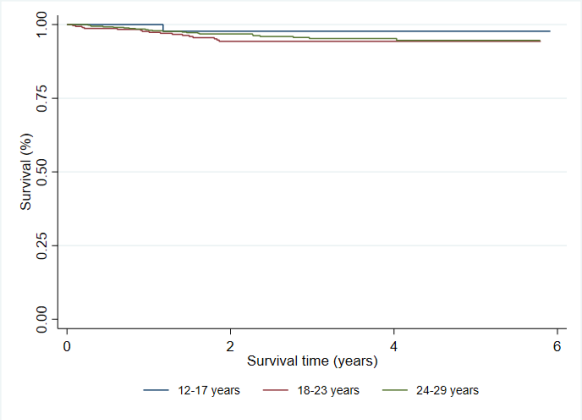

Family environment
Travel distance
Ethnicity
IMD quintile
Morphology
Received dose intensity
Age
Co-morbidity indicator
Survival
Sex
region
Stage
Lifestyle
Grade
Specialist treatment centre

Figure B.2: Kaplan-Meier survival estimates of patients treated within a) the clinical trials and b) NCRAS cohorts. Survival estimates presented separately for i) age category ii) IGCCC risk classification.

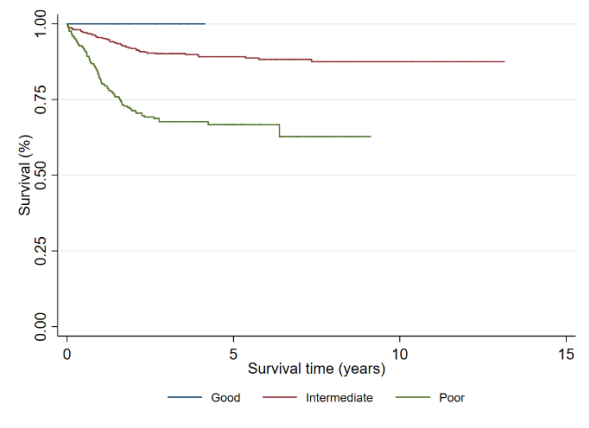
a (i)



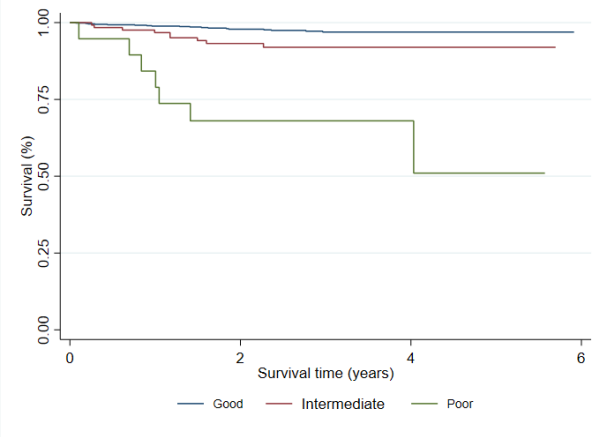
b (i)



a (ii)



b (ii)



Appendix C.

Table C.1: Frequency of organ specific toxicities resulting in TIMT for bone cancers combined, Ewing and osteosarcoma.

Toxicity	Combined n=184	Ewing n=73	Osteosarcoma n=111
Bone marrow	130 (71)	63 (86)	67 (60)
Cardiac	18 (10)	7 (10)	11 (10)
Renal	20 (11)	2 (3)	18 (16)
Neuro	5 (3)	2 (3)	3 (3)
Hepatic	8 (4)	2 (3)	6 (5)
Oral (mucositis)	14 (8)	2 (3)	12 (11)
Sepsis	4 (2)	0 (0)	4 (4)
Anaphylaxis	1 (0.5)	0 (0)	1 (1)
Toxicity unspecified	72 (39)	20 (27)	52 (47)

Table C.2: Frequency of organ specific toxicities resulting in TIMT broken down by sex for bone cancers combined, Ewing and osteosarcoma*.

	Combined		Ewing		Osteosarcoma	
	Males n=110	Females n=74	Males n=45	Females n=28	Males n=65	Females n=46
Bone marrow	74 (67)	56 (76)	37 (82)	26 (93)	37 (57)	30 (65)
Cardiac	11 (10)	7 (9)	3 (7)	4 (14)	8 (12)	3 (7)
Renal	10 (9)	10 (14)	1 (2)	1 (4)	9 (14)	9 (20)
Hepatic	5 (5)	3 (4)	1 (2)	1 (4)	4 (6)	2 (4)
Oral (mucositis)	10 (9)	4 (5)	2 (4)	0	8 (12)	4 (9)
Toxicity unspecified	46 (42)	26 (35)	15 (33)	5 (18)	31 (48)	21 (46)

* for the most common toxicities only.

Table C.3: Frequency of organ specific toxicities resulting in TIMT broken down by age for bone cancers combined, Ewing and osteosarcoma*.

	Combined			**Ewing**			**Osteosarcoma**		
	<12 years	**13-17 years**	**18-29 years**	**<12 years**	**13-17 years**	**18-29 years**	**<12 years**	**13-17 years**	**18-29 years**
	n=41	n=87	n=56	n=19	n=30	n=24	n=22	n=57	n=32
Bone marrow	33 (80)	61 (70)	36 (64)	18 (95)	29 (97)	16 (67)	15 (68)	32 (56)	20 (63)
Cardiac	2 (5)	13 (15)	3 (5)	0	6 (20)	1 (4)	2 (9)	7 (12)	2 (6)
Renal	4 (10)	9 (10)	7 (13)	0	2 (7)	0	4 (18)	7 (12)	7 (22)
Hepatic	0	4 (5)	4 (7)	0	1 (3)	1 (4)	0	3 (5)	3 (9)
Oral (mucositis)	2 (5)	6 (7)	6 (11)	0	0	2 (8)	2 (9)	6 (11)	4 (13)
Toxicity unspecified	13 (32)	28 (32)	31 (55)	2 (11)	3 (10)	15 (63)	11 (50)	25 (44)	16 (50)

* for the most common toxicities only.

Figure C.1: Directed Acyclic Graph demonstrating the minimal sufficient adjustment set required to investigate the causal effect of toxicity induced modifications of treatment (TIMT) on survival.

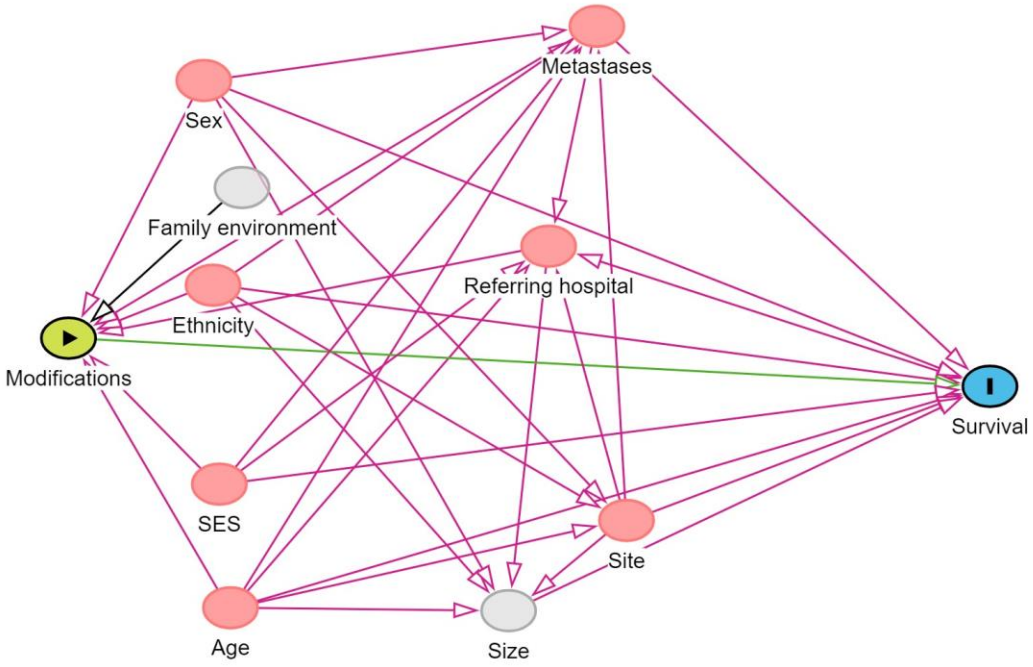
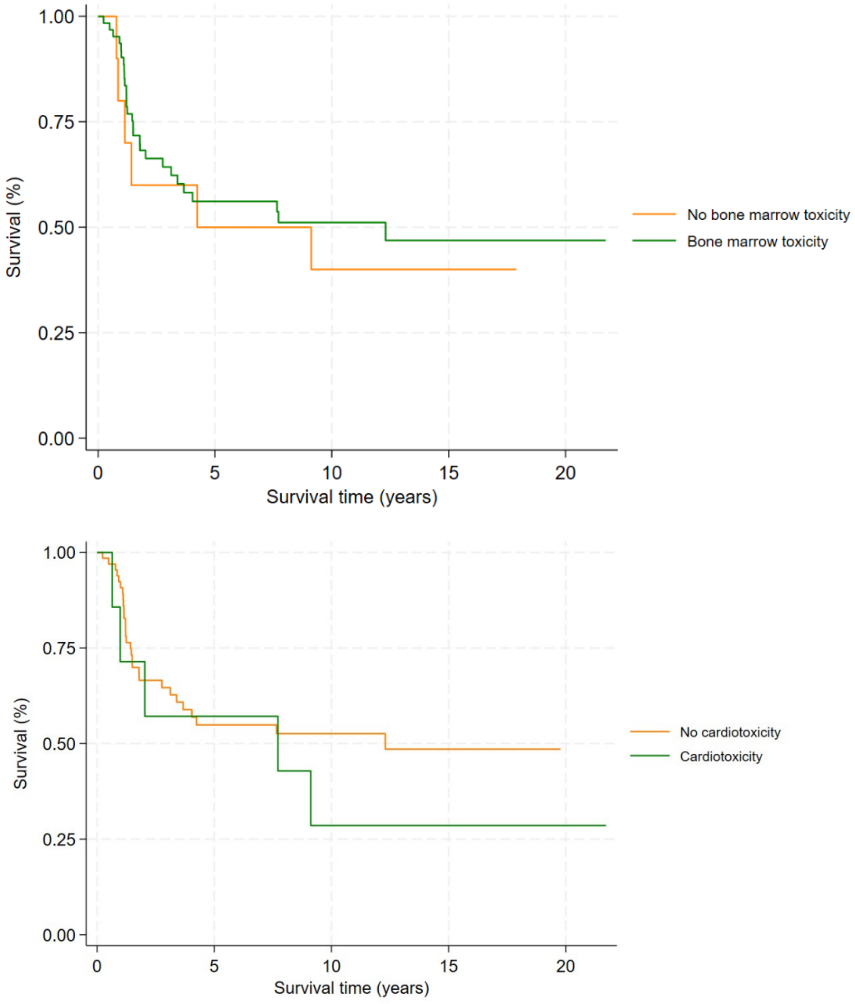
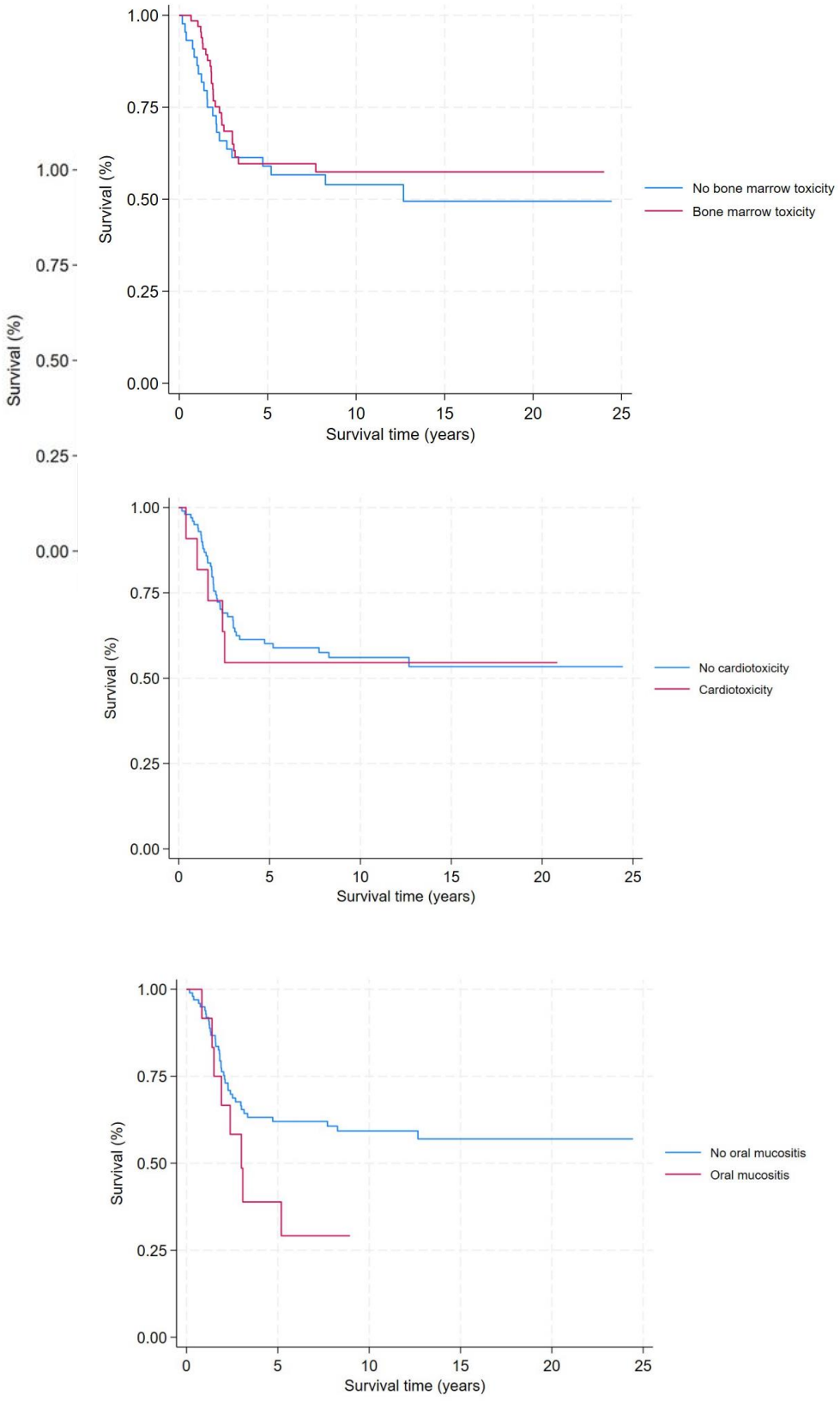


Figure C.2: Kaplan-Meier survival estimates comparing patients who did and did not have a TIMT. Presented for common toxicities in a) Ewing and b) osteosarcoma.

a)



b)


1.00
0.75
0.50
0.25
0.00
Survival (%)
0
5
10
15
20
25
Survival time (years)
No bone marrow toxicity
Bone marrow toxicity
No cardiotoxicity
Cardiotoxicity
No oral mucositis
Oral mucositis

Appendix D.

Table D.1: Workshop 1 schedule.

Overarching workshop aim: To understand what young people/carers understand about cancer data, how it is collected, what it is used for and how data can improve outcomes through research. Also, to identify areas where young people/carers need more information and identify any concerns.

Design of workshop Key: B= In break-out room W= Whole workshop				
Focus group workshop design • We are not merely collecting participants' views, but moving through a process of learning, applying the learning to real-life examples and encouraging debate and reflection to uncover participant-led priorities for future work. • The information we give needs to be unbiased, we should present from all angles and remain neutral in discussions. • We need to ensure the well-being and support of participants is paramount. We will have mechanisms for distress, offline support and contact details for the workshop leaders.				
Time	Segment	Activities	Mins	Speaker
	Pre-Registration– sent the week before and prompt the day before.	Consent form for audio and photos, instructions on how log in and to change zoom name (Zoom guide). Procedures for support given including contact numbers for any difficulties on the day. Remuneration forms sent in advance with details of how to claim and guidance for time to payment.	n/a	
3:55pm	Zoom Main room opened for welcomes.			
4pm	Introductions and ice breaker (W)	Introduce the process and aims to the whole workshop. Group rules and courtesies. Each participant 2 minute introduction.	25	AP/LF
4:30pm	Session 1 – What data is	Presentation.	15	CC

	collected about me? (W)			
5pm	Questions and discussion	Participants are encouraged to ask questions and jot down questions for later on if run out of time or use chat function.	10	NH
5:10pm	Case studies (B)	Group 1 to consider case study 1- Lucy and fill in template (facilitator + professional to go to group)	10	AP/KPJ/CC
		Group 2 to consider case study 2 -Aiden and fill in template (facilitator + professional to go to group) N.B Any other workshop leaders to remain in main room to check for any participants that have issues or questions.	10	NH/RF/LF EC/AG
5:40	Group discussion about tasks (W)	Each group to nominate a speaker to feedback a summary of discussions. Facilitator to prompt discussion.	10	AP
5:50pm	BREAK	All speakers to go to breakout room to discuss how it is going and any modifications needed	10	
6pm	Session 2 – Why researchers need data? (W)	Group to consider why researchers need data. If they were a researcher what data would they want to have access to and why?	5	AP
6:05pm	Stages of research	Presentation of how the YSRCCYP has used patient data and how it is used at various stages of the research cycle. What do the group think? Facilitator to prompt discussions.	10	NH/RF
6:15pm	Barriers and next steps	Summary of workshop. Participants to write down 3 things they have learnt from today, 3 ways to collect data, 3 possible problems that researchers might have when trying to use patient data. Facilitator to and encourage open discussion and discuss potential topics for workshop 2.	15	AP
6:25pm	Thank you and close. Any participants wishing to continue to workshop 2 to send email.		5	AP/CC

Table D.2: Workshop 2 schedule.

Overarching workshop aim: To build upon the last workshop and discuss issues that participants thought would benefit from a deeper understanding. Also, to start to think about outcomes and input from young people, how can they be involved in making a change or increasing awareness. To identify areas where young people/parents need more information and identify any concerns in relation to health data for children and young people with cancer.

Design of workshop Key: B= In break-out room W= Whole workshop				
Focus group workshop design • We are not merely collecting participants' views, but moving through a process of learning, applying the learning to real-life examples and encouraging debate and reflection to uncover participant-led priorities for future work. • The information we give needs to be unbiased, we should present from all angles and remain neutral in discussions • We need to ensure the well-being and support of participants is paramount. We will have mechanisms for distress, offline support and contact details for the workshop leaders				
Time	Segment	Activities	Mins	Speaker
	Pre-Registration– sent the week before and prompt the day before.	Ensure previous consent still viable Procedures for support given including contact numbers for any difficulties on the day Remuneration forms sent in advance with details of how to claim and guidance for time to payment Press clippings and BENCHISTA transparency statement sent for pre-reading	n/a	
3:55pm	Zoom Main room opened for welcomes.			
4:00pm	Introductions and ice breaker (W)	Introduce the process and aims to the whole workshop. Reminder of group rules and courtesies.	10	AP
4:10pm	Questions from last session	Facilitator to give brief summary of what was covered	10	CC

4:20pm	Session 1 – What does cancer health data actually look like?	Presentation of different types of data, when they are collected and by whom. Where are the gaps?	20	CC
4:40pm	Data sharing and data linkage	Brief explanation of the similarities and differences, how would the group explain it in their own words?	10	CC
4:50pm	Project discussion 1 – International data sharing - BENCHISTA		30	AP/KPJ/AL
5:20pm	BREAK	All speakers to go to breakout room to discuss how it is going and any modifications needed.	10	
5.30pm	Project discussion 2 – YSRCCYP – Social outcomes data		30	NH/RF/LF
6:00pm	Trust and communication	Press clippings discussion, what matters to CYP in particular?	25	CC/AP
6.25pm	Next steps	Summary of workshop, run through of ways in which participants can get involved in further projects.	5	CC/EC
6:30pm	Thank you and close. Any participants wishing to volunteer to send email. Briefly outline potential further workshops.		-	CC/EC

Table D.3: The case studies discussed in workshop 1.

Participants were divided between two breakout rooms. For both cases participants were asked to discuss; what type of data will be collected, who will see it, who will the data be shared with and who needs to consent to sharing the data.
Case A – Lucy
A 9-year-old girl who has been diagnosed with Leukaemia. Her Mum and Stepdad have given consent for Lucy to receive treatment. They have also consented for her to take part in a clinical trial. They are happy for Lucy's information to be shared with the hospital and the clinical trial team.
Case B – Aiden
Aiden has been diagnosed with osteosarcoma aged 17 years. He has consented to receive treatment with his parents present. He has also consented to be part of a clinical trial and to have tissue from his tumour stored in the tissue bank.

Table D.4: GRIPP2 form checklist relating to the workshops.

Section and topic	**Item**	**Reported on page No**
Section 1: Abstract of paper		
1a: Aim	Report the aim of the study	3
1b: Methods	Describe the methods used by which patients and the public were involved	3
1c: Results	Report the impacts and outcomes of PPI in the study	4
1d: Conclusions	Summarise the main conclusions of the study	4
1e: Keywords	Include PPI, "patient and public involvement," or alternative terms as keywords	4

Section and topic	Item	Reported on page No
Section 2: Background to paper		
2a: Definition	Report the definition of PPI used in the study and how it links to comparable studies	6
2b: Theoretical underpinnings	Report the theoretical rationale and any theoretical influences relating to PPI in the study	n/a
2c: Concepts and theory development	Report any conceptual or theoretical models, or influences, used in the study	n/a
Section 3: Aims of paper		
3: Aim	Report the aim of the study	6
Section 4: Methods of paper		
4a: Design	Provide a clear description of methods by which patients and the public were involved	6-8
4b: People involved	Provide a description of patients, carers, and the public involved with the PPI activity in the study	Page 9 and Table 6.1
4c: Stages of involvement	Report on how PPI is used at different stages of the study	6-8
4d: Level or nature of involvement	Report the level or nature of PPI used at various stages of the study	6-8
Section 5: Capture or measurement of PPI impact		
5a: Qualitative evidence of impact	If applicable, report the methods used to qualitatively explore the impact of PPI in the study	n/a
5b: Quantitative evidence of impact	If applicable, report the methods used to quantitatively measure or assess the impact of PPI	n/a

Section and topic	Item	Reported on page No
5c: Robustness of measure	If applicable, report the rigour of the method used to capture or measure the impact of PPI	n/a
Section 6: Economic assessment		
6: Economic assessment	If applicable, report the method used for an economic assessment of PPI	n/a
Section 7: Study results		
7a: Outcomes of PPI	Report the results of PPI in the study, including both positive and negative outcomes	9-16
7b: Impacts of PPI	Report the positive and negative impacts that PPI has had on the research, the individuals involved (including patients and researchers), and wider impacts	Table 6.2
7c: Context of PPI	Report the influence of any contextual factors that enabled or hindered the process or impact of PPI	17-20
7d: Process of PPI	Report the influence of any process factors, that enabled or hindered the impact of PPI	17-20
7ei: Theory development	Report any conceptual or theoretical development in PPI that have emerged	n/a
7eii: Theory development	Report evaluation of theoretical models, if any	n/a
7f: Measurement	If applicable, report all aspects of instrument development and testing (eg, validity, reliability, feasibility, acceptability, responsiveness, interpretability, appropriateness, precision)	n/a
7 g: Economic assessment	Report any information on the costs or benefit of PPI	n/a
Section 8: Discussion and conclusions		
8a: Outcomes	Comment on how PPI influenced the study overall.	Table 6.2 and

Section and topic	Item	Reported on page No
	Describe positive and negative effects	pages 17-20.
8b: Impacts	Comment on the different impacts of PPI identified in this study and how they contribute to new knowledge	Table 6.2 and pages 17-20.
8c: Definition	Comment on the definition of PPI used (reported in the Background section) and whether or not you would suggest any changes	n/a
8d: Theoretical underpinnings	Comment on any way your study adds to the theoretical development of PPI	n/a
8e: Context	Comment on how context factors influenced PPI in the study	17-20
8f: Process	Comment on how process factors influenced PPI in the study	17-20
8 g: Measurement and capture of PPI impact	If applicable, comment on how well PPI impact was evaluated or measured in the study	n/a
8 h: Economic assessment	If applicable, discuss any aspects of the economic cost or benefit of PPI, particularly any suggestions for future economic modelling.	n/a
8i: Reflections/critical perspective	Comment critically on the study, reflecting on the things that went well and those that did not, so that others can learn from this study	17-20

Table D.5: The initial themes generated from the PPIE workshops following familiarisation and coding.

	Theme		
	Awareness	**Value**	**Data sharing**
Participant			
YP1	*"Being so young, when I was diagnosed, my parents made most of those decisions for me about data and so I didn't really comprehend that anything was going to be shared… as an adult now, I'd like to feel like I had control of the data or at least continued the consent to use it."* *"I'm in two minds about it. On the one hand, I feel if I just received a random letter in the post saying here's how your data has been used in the past … years since your diagnosis, I'd feel obliged to read it, but knowing that, that could very easily trigger my brain. Almost blissful ignorance is better, like I gave you my data that's yours now. I don't particularly want to think about that time I had the biopsy or that time that I had that treatment. Whereas with this (workshop), I was invited to do this, I'm mentally prepared for it. That's totally cool.*		*"I was just thinking that, if you have got something like an anomaly … the more data you have, there might be more anomalies that then spark ideas for new research. Those sort of pathways are kind of shut off without sharing."*

	But if that information was then sprung on me, I don't think I'd be ready for that."		
YP2	*"How the media portrays it … has negative impacts and it does put you off data sharing. There are multiple positive impacts that I feel aren't shared as loudly and it's just the way it's presented to the public. I think it's important to try and show the benefits that can be achieved."*		*"I think it's very important, not just for rare diagnoses, but also for diagnoses that are quite common in a certain particular group but other people get them too. My diagnosis, it's very common in elderly. I got it when I was very, very young."* *"It definitely sounds like our data is being used appropriately."*
YP3	*"Same for me. You just don't really think about it and it's so in depth as well."*	*"I would 100% give my permission to share all my data with regards to that."*	
YP4		*"I'm someone who struggled with education and employment… I think it's really important. I think it's something that's not really looked into enough. So yeah, I'm all for it".*	*"(Data opt outs can cause problems because)… it wouldn't give a full picture of the group. There might be people that haven't consented that will have different data to the people that have so it doesn't give 100% picture of the group*."
YP5	*"I certainly wasn't ever told about what my data was going to be used for. I suppose before surgeries, and all that sort of stuff you always got told what was going to happen but certainly not what the results were going to be used for."*		
YP6	*"I didn't really have any idea of all the data collected. Especially when*		*"You're more than happy to share extended family history and any types*

	I was going through treatment ... I just didn't have any part in that area … I just got my Mum to sort everything. So it's quite eye opening."		*of information that you feel will be useful at that point … because that's what you need to do in order to try and get better and to start the treatment".*
YP7	*"When I was first diagnosed, I think if you'd sat me down and said all your data is going to be used for X Y, Z, I probably wouldn't have cared less. My whole attitude towards the entire thing was, let's just get the treatment. Let's get it done. But certainly now and certainly after I've had all my surgeries, all the chemo and all that sort of stuff, it would be interesting to go back and say, oh, yeah, your data was used for this, this this. So I think maybe at the end of the treatment."*	*"It's really important, I think, often, the social outcomes side can be really neglected, with people obviously focused on health. But that (social outcomes) can have a massive impact on people's lives in other ways."* *"I think it is more sensitive than some of the health data just because I think for some people, it seems more personal than scientific stuff that feels out of your control."*	
YP8			
YP9			*"If someone else finds themself in the same situation as you, it can help massively with research and helping outcomes and treatment for children and young people. We've all in a way got a responsibility to do our bit."*
YP10			
C1	*"Sometimes it's not obvious data gets produced from something. My child had a tissue sample taken… there would have been digital data produced and that's quite difficult to*		

	imagine … that's not something I'd visualised before." C-1		
C2	*"For me, part of the issue is, as a society, our understanding of data and research is pretty poor. I think part of the problem is that when we talk about data and research, a lot of us start thinking about how we get adverts for things because we've clicked on something. I do wonder whether, case studies of positive uses of data and research need to be a little bit more embedded in school curriculum, so that we can develop skills as a society to differentiate."*	"*To pick up on the point about gathering data after treatment finishes. I've always been really grateful about knowing about the long term side effects that my child might have. People used to say, once you finish their treatment within six months they'll feel a lot better, they'll get their energy back, be able to play sport just like a normal child. And that hasn't happened. Because people have allowed their data to be used, because of the research that's happened, we've been able to see that actually, they might have long term side effects and their mobility might continue to be affected. We might not have known that if people hadn't done the research into long term side effects."*	
C3			
C4	*"There's an assumption that we can't have those conversations … with young people"*		
C5			
C6		*"How the information is presented, that is key here. If it's explained to you clearly and that it's in the best interest of the public, and yourself … there won't be barriers."*	

Table D.6: The revision of key themes. Following the generation of these three themes sub themes were then devised and quotes colour coded accordingly.

	Theme		
	Barriers to trust	**Ways to improve confidence**	**Research priorities**
Participant			
YP1		*"I think it's quite important to highlight that the data is very well organised and very well protected".*	*"I think it's really important that especially information on late effects is available. When I was diagnosed I was 13, fertility was just not mentioned to me. That was something that I had to go out and seek for myself. So if it weren't for that information and that data being out there…, I would never have known that I could go and ask somebody about my fertility and … seek help on that aspect."*
		"Being so young, when I was diagnosed, my parents made most of those decisions for me about data and so I didn't really comprehend that anything was going to be shared… as an adult now, I'd like to feel like I had control of the data or at least continued the consent to use it."	*"I was just thinking that, if you have got something like an anomaly … the more data you have, there might be more anomalies that then spark ideas for new research. Those sort of pathways are kind of shut off without sharing."*

		"I'm in two minds about it. On the one hand, I feel if I just received a random letter in the post saying here's how your data has been used in the past … years since your diagnosis, I'd feel obliged to read it, but knowing that, that could very easily trigger my brain. Almost blissful ignorance is better, like I gave you my data that's yours now. I don't particularly want to think about that time I had the biopsy or that time that I had that treatment. Whereas with this (workshop), I was invited to do this, I'm mentally prepared for it. That's totally cool. But if that information was then sprung on me, I don't think I'd be ready for that."	
YP2	*"How the media portrays it (data use)… has negative impacts and it does put you off data sharing."*	*"There are multiple positive impacts that I feel aren't shared as loudly and it's just the way it's presented to the public. I think it's important to try and show the benefits that can be achieved."*	*"I think it's very important, not just for rare diagnoses, but also for diagnoses that are quite common in a certain particular group but other people get them too. My diagnosis, it's very common in elderly. I got it when I was very, very young."*
YP3	*"Same for me. You just don't really think about it and it's so in depth as well."*		
YP4			*"I'm someone who struggled with education and employment… I think it's really important. I think it's something that's not really looked into enough. So yeah, I'm all for it".*

			“I think it is a more personal area as you don't really have a choice on your cancer, like what your diagnosis is, but you have a choice about how you act with it afterwards. I wouldn't mind giving my data, I feel like other people would feel more judged based on the data they're providing.”
YP5	*“I certainly wasn't ever told about what my data was going to be used for. I suppose before surgeries, and all that sort of stuff you always got told what was going to happen but certainly not what the results were going to be used for.”*		
YP6	*“I didn’t really have any idea of all the data collected. Especially when I was going through treatment ... I just didn’t have any part in that area … I just got my Mum to sort everything. So it’s quite eye opening.”*		
YP7		“*You just have to get it out there somehow like, get it on the internet and things. I feel like people are worried about having really identifiable information about themselves, distributed to loads of different companies. To kind of reassure people that really most of this data is not identifiable …no one can connect it to you… it would actually be hugely*	*“It's really important, I think, often, the social outcomes side can be really neglected, with people obviously focused on health. But that (social outcomes) can have a massive impact on people's lives in other ways.”* *“I think it is more sensitive than some of the health data just because I think for some people, it seems more personal than scientific stuff that feels*

		reassuring."	*out of your control."*
		"When I was first diagnosed, I think if you'd sat me down and said all your data is going to be used for X Y, Z, I probably wouldn't have cared less. My whole attitude towards the entire thing was, let's just get the treatment. Let's get it done. But certainly now and certainly after I've had all my surgeries, all the chemo and all that sort of stuff, it would be interesting to go back and say, oh, yeah, your data was used for this, this this. So I think maybe at the end of the treatment."	
YP8			
YP9			*"If someone else finds themself in the same situation as you, it can help massively with research and helping outcomes and treatment for children and young people. We've all in a way got a responsibility to do our bit."*
YP10			
C1	*"Sometimes it's not obvious data gets produced from something. My child had a tissue sample taken… there would have been digital data produced and that's quite difficult to imagine … that's not something I'd visualised before."*		
C2	"*I think part of the problem is that when we talk about data and*	*"I do wonder whether, case studies of positive uses of data and research*	"*To pick up on the point about gathering data after treatment*

	research, a lot of us start thinking about how we get adverts for things because we've clicked on something."	*need to be a little bit more embedded in school curriculum, so that we can develop skills as a society to differentiate."*	*finishes. I've always been really grateful about knowing about the long-term side effects that my child might have. People used to say, once you finish their treatment within six months they'll feel a lot better, they'll get their energy back, be able to play sport just like a normal child. And that hasn't happened. Because people have allowed their data to be used, because of the research that's happened, we've been able to see that actually, they might have long term side effects and their mobility might continue to be affected. We might not have known that if people hadn't done the research into long term side effects."*
C3			
C4		*"There's an assumption that we can't have those conversations (about data use)… with young people."*	
C5			
C6		*"How the information is presented, that is key here. If it's explained to you clearly and that it's in the best interest of the public, and yourself … there won't be barriers."*	

Subtheme key:

Theme	1. Existing barriers to trust in healthcare data use for research	2. Ways to improve public and patient confidence	3. Research priorities for data use
Subtheme	Lack of awareness	More information about data use in research	Late effects
	Sources of mistrust	Ability to take responsibility for own data	Social and educational outcomes
			Rare tumours and outcomes

Appendix E.

Delivered relative dose intensity in bone tumours. An analysis using linked SACT and COSD data.

E.1 Introduction

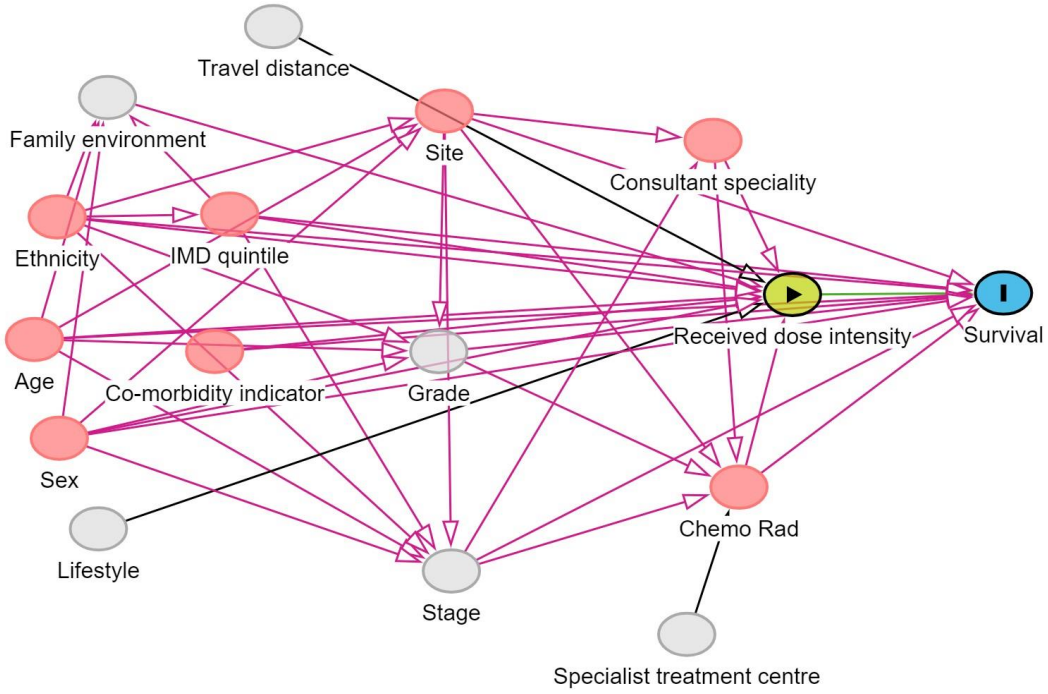
In Chapter 2 of this thesis the literature supporting the survival benefit of maintaining DI in Ewing and osteosarcoma is described. This evidence is derived from clinical trials, the analysis presented in this Appendix however focuses on investigating the impact of the delivered RDI in routine NHS care for these tumour types.

This work has not been written up for publication but was presented as a poster at the Advances in Ewing sarcoma Research symposium, Leeds, UK in October 2022. For this I was awarded the prize for best poster.

E.2 Methods

The same methods were used as in the GCT analysis (206) but with some tumour-specific differences in risk factors extracted including tumour site and whether or not a patient received radiotherapy. Daggitty software was used to create a unique DAG for this analysis in bone tumours (Figure E.1). Data from the Cancer Outcomes and Services dataset (COSD) (157) and the Systemic Anticancer Therapy dataset (SACT)(158), both held by the National Cancer Registration and Analysis Service (NCRAS) were linked to create a dataset of patients diagnosed in England with Ewing or osteosarcoma when aged 12 to 29 years. COSD holds patient details of all cancers diagnosed and resident in England, whilst the SACT dataset comprises chemotherapy prescribing data from all treating NHS hospital trusts in England.

Figure E.1: Directed Acyclic Graph demonstrating the minimal sufficient adjustment set required to investigate the causal effect of RDI on survival in bone tumours.



Inclusion criteria were:

- Patients registered with Ewing or osteosarcoma (ICD-O-2 morphology codes 9180/3 and 9260/3, site codes C40-C41) in the NCRAS dataset and diagnosed aged 12-29 years between 1st April 2014 and 31st December 2018. This period reflected the most up to date SACT data available at the time of data extraction.
- Only patients who had received first line treatment recorded in SACT were included, defined as individuals who received chemotherapy within 60 days of diagnosis.

- Osteosarcoma patients who had received the methotrexate, doxorubicin and cisplatin (MAP) chemotherapy regimen to enable comparison with the EURAMOS 1 trial (209).
- Ewing sarcoma patients who had received vincristine, ifosfamide, doxorubicin and etoposide (VIDE) induction chemotherapy followed by consolidation chemotherapy of either vincristine, dactinomycin and ifosfamide (VAI) or vincristine, dactinomycin and cyclophosphamide (VAC) or the vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide (VDC/IE) chemotherapy regime to enable comparison with the Euro-Ewings 2012 (EE2012) trial (200).

Exclusion criteria included:

- Any registration record missing both height and weight at the start of treatment.
- Patients where administration dose of drug, number of days to administration of drug or drug name were missing.
- Those who had received less than one cycle of treatment.

E.2.1 Patient and treatment related variables

The linked NCRAS dataset was explored and data for patient sex, age at diagnosis (years), stage, ethnicity based on categories from the 2001 Census (120), deprivation, year of diagnosis, region where the patient was living when the tumour was diagnosed and treating speciality were extracted. Stage was derived from TNM imaging, TNM pathology in COSD and stage at the start of treatment in SACT, to maximise completeness. Tumour site was extracted using ICD-O-2 topography code. No data was available for extraction relating to the size of the tumour. Treating specialty codes were provided in accordance with the NHS data dictionary (159) and labelled as either adult or paediatric. Population weighted quintiles of the English Index of Multiple Deprivation (IMD) 2015 (160) were provided by NCRAS as the measure of socio-economic deprivation. Vital status at the time of censoring, the number of days from diagnosis to vital status and year of death were extracted to enable survival analysis. Toxicity was not addressed in this analysis.

E.2.2 RDI calculation

RDI calculation was carried out using the same methods as described in the GCT paper in Chapter 4 but with the time between induction and consolidation chemotherapy removed from the calculation. This “surgical gap” was calculated for each individual patient in order to prevent prolonged surgical recovery affecting the calculations. In the osteosarcoma patients this was the time between cycle 2 and cycle 3 of treatment. In the Ewing patients it was the time between cycles 6 and 7 for those receiving treatment as per arm A of EE2012 (VIDE/ VAI or VIDE/VAC) and for those receiving treatment as per arm B it was the gap following cycle 9 of alternating VDC/IE and the next administered chemotherapy. Doses were capped according to the EE2012 protocol for dactinomycin and vincristine.

E.2.3 Statistical analysis

Survival analyses were performed as described in the GCT paper.

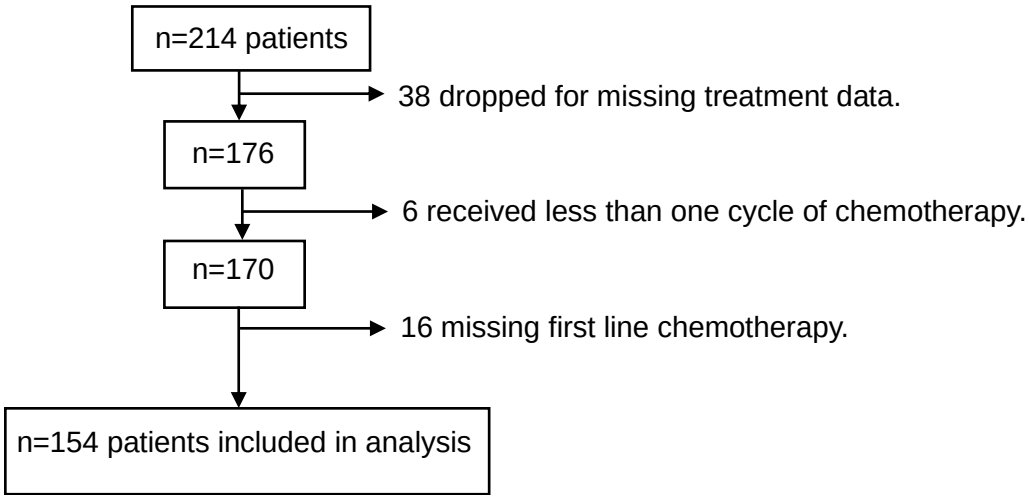
E.3 Results

E.3.1 Patient characteristics

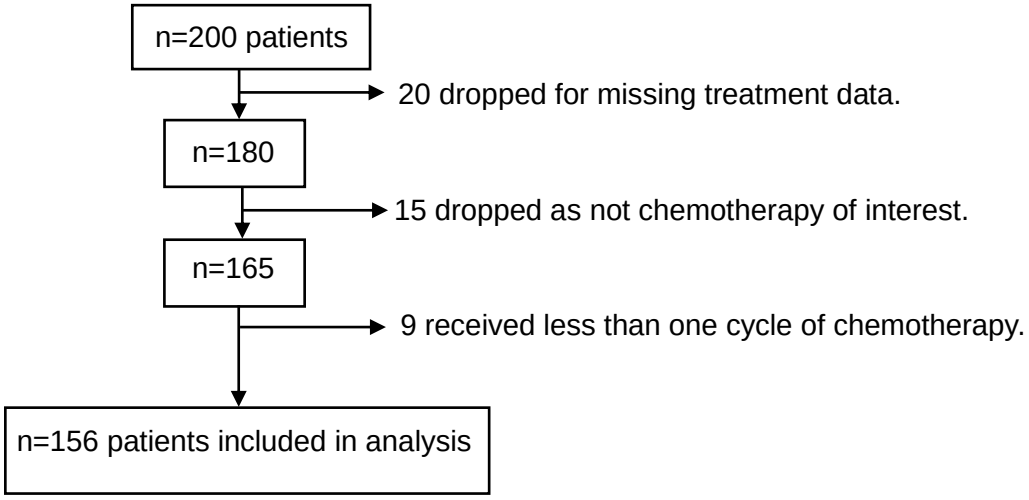
A total of 154 patients with a diagnosis of Ewing sarcoma and 156 with an osteosarcoma met the inclusion criteria and were included in the analyses. The consort diagrams can be seen in Figure E.2. Only three patients received VIDE/BuMel or VDC/IE/BuMel and were therefore dropped from the analysis.

Figure E.2: Consort diagrams showing the flow of patients in a) the Ewing cohort and b) the osteosarcoma cohort.

a)



b)



There was a higher proportion of males in each cohort 62% in Ewing and 58% in osteosarcoma. Median age at diagnosis was higher in the Ewing cohort 19 years (IQR, 15-22) than in osteosarcoma 17 years (IQR, 14-21). White was the most common ethnicity recorded in both tumour types (Ewing 83% and osteosarcoma

73%) as was being in the most deprived quintile (Ewing 25% and osteosarcoma 29%). The majority of patients were treated in an adult specialty (Ewing 73%, osteosarcoma 74%). As was found in the GCT study there was a high proportion of missing data for stage (Ewing 54% and osteosarcoma 37%) and this was also true for grade (Ewing 85% and osteosarcoma 87%). A higher percentage of patients in the Ewing dataset were recorded as being in a clinical trial (64%) compared to those in the osteosarcoma dataset (18%). The same was true for receiving radiotherapy (63% vs 19%). These findings are in keeping with the comparative clinical trial recruitment time period and protocols.

The pelvis was the most common tumour site in Ewing (31%) while in osteosarcoma patients tumours of the lower limb were more common (74%). Only a small proportion of patients were recorded as having their treatment adjusted due to co-morbidities (Ewings 12% and osteosarcoma 8%). Patient characteristics are summarised in Table E.1.

Table E.1: Patient demographic characteristics in the Ewing and osteosarcoma cohorts.

		Ewing n (%)	**Osteosarcoma** n (%)
Total number patients		154	156
Total number of deaths		51 (33)	42 (27)
Sex	Female	59 (38)	66 (42)
	Male	95 (62)	90 (58)
Age at diagnosis (years)	12-17	58 (38)	87 (56)
	18-23	70 (46)	43 (28)
	24-29	26 (17)	26 (17)
Ethnicity	White/ White Irish	128 (83)	114 (73)
	Asian	18 (12)	17 (11)
	Other/ not stated	8 (5)	14 (9)
Deprivation quintile	1 (least deprived)	30 (20)	11 (7)

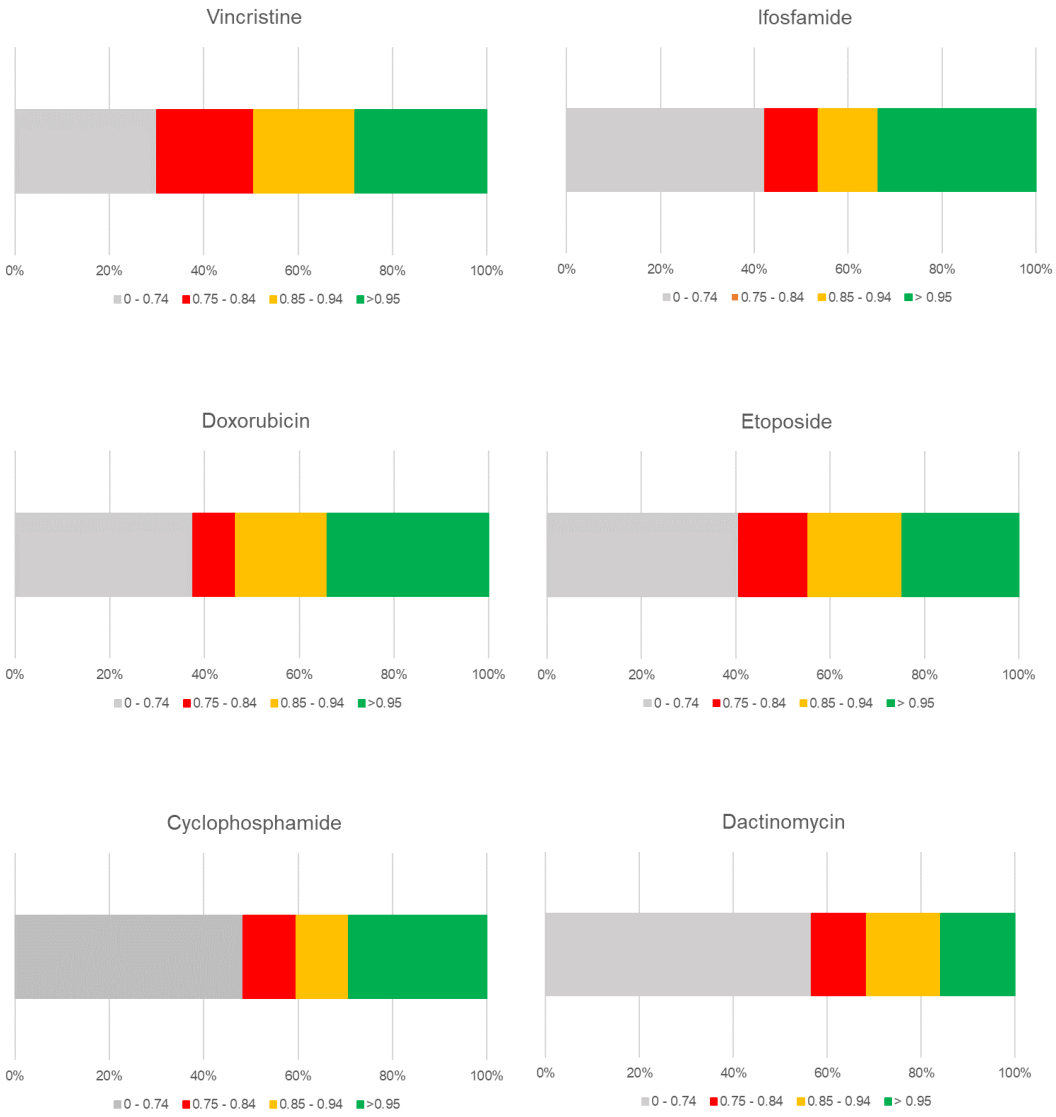
	2	29 (19)	25 (16)
	3	25 (16)	30 (19)
	4	32 (21)	31 (20)
	5 (most deprived)	38 (25)	25 (16)
Diagnosis year	2014	15 (10)	45 (29)
	2015	26 (17)	25 (16)
	2016	35 (23)	33 (21)
	2017	36 (23)	25 (16)
	2018	42 (27)	41 (26)
Treating speciality	Adult	112 (73)	115 (74)
	Paediatric	40 (26)	36 (23)
	Missing	2 (1)	5 (3)
Comorbidity adjustment	Yes	19 (12)	12 (8)
	No	101 (66)	99 (64)
	Missing	34 (22)	45 (29)
Concurrent radiotherapy	Yes	97 (63)	30 (19)
	No	57 (37)	126 (81)
Clinical trial	Yes	99 (64)	28 (18)
	No	47 (31)	114 (73)
	Missing	8 (5)	14 (9)
Stage	1	19 (12)	12 (8)
	2	20 (13)	71 (46)
	3	6 (4)	4 (3)
	4	26 (17)	11 (7)
	Missing	83 (54)	58 (37)
Grade	1		1 (1)
	2		2 (1)
	3	15 (10)	18 (12)
	4	8 (5)	-
	Missing	131 (85)	135 (87)
Site	Upper limb	23 (15)	17 (11)
	Lower limb	42 (27)	116 (74)
	Axial	28 (18)	21 (14)
	Pelvic	47 (31)	-
	Other	14 (9)	2 (1)
Region of England	North	45 (29)	37 (24)
	Midlands	45 (29)	42 (27)
	South	64 (42)	77 (49)

E.3.2 Achieved RDI

The median achieved RDI for each drug ranged between 0.64 and 0.85 in the Ewing cohort and 0.71 and 0.82 in the osteosarcoma cohort (Table E.2). An RDI in the category 0-0.74 was the most commonly achieved RDI for all drugs in both Ewing (doxorubicin 38%, ifosfamide 42%, etoposide 41%, cyclophosphamide 48%, vincristine 45% and dactinomycin 57%) and osteosarcoma (methotrexate 36%, doxorubicin 50% and cisplatin 61%) (Figure E.3). Considering RDIs above 0.75, the most commonly achieved RDI category was greater than 0.95 across all drugs in the Ewings patients apart from dactinomycin (doxorubicin 34%, ifosfamide 34%, etoposide 25%, cyclophosphamide 29%, vincristine 42% and dactinomycin 16%). In osteosarcoma only 10% of patients received a cisplatin RDI greater than 0.95 with the category 0.75 to 0.84 (21%) being the most common, the same was seen for doxorubicin with 26% receiving an RDI of 0.75 to 0.84 and only 12% achieving an RDI greater than 0.95. 31% achieved an RDI greater than 0.95 for methotrexate.

Figure E.3: Bar charts demonstrating the proportion of patients achieving each category of relative dose intensity in a) Ewing and b) osteosarcoma.

a)



b)

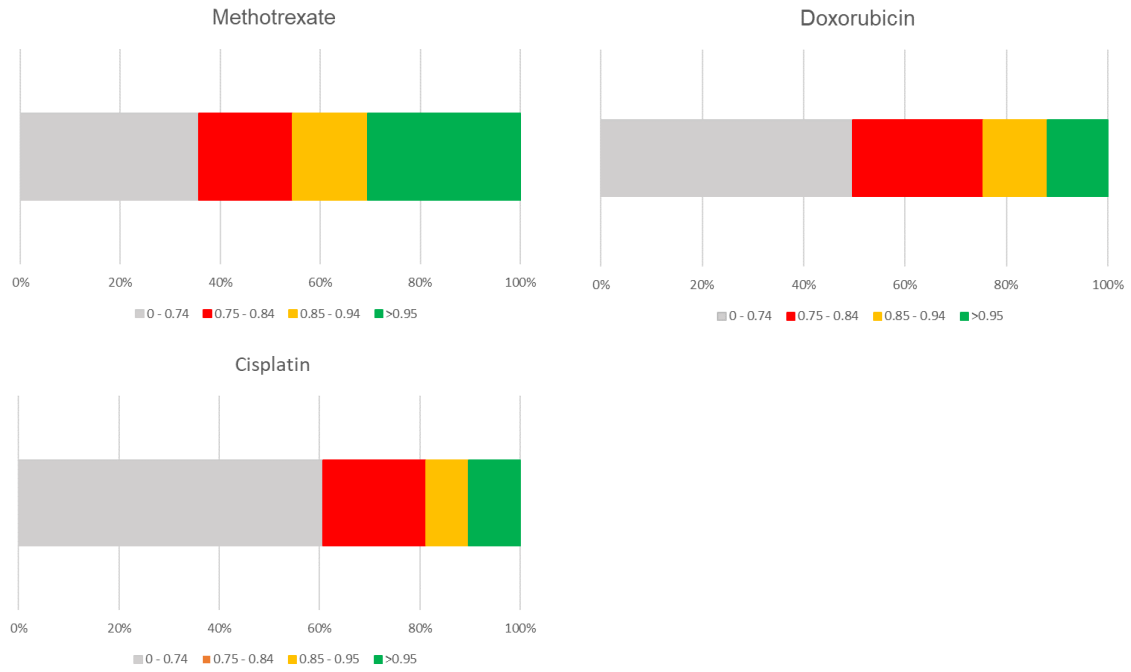

Methotrexate
0%
20%
40%
60%
80%
100%
0 - 0.74
0.75 - 0.84
0.85 - 0.94
>0.95
Doxorubicin
0%
20%
40%
60%
80%
100%
0 - 0.74
0.75 - 0.84
0.85 - 0.94
>0.95
Cisplatin
0%
20%
40%
60%
80%
100%
0 - 0.74
0.75 - 0.84
0.85 - 0.95
>0.95

Table E.2: Median achieved RDI for each drug administered in Ewing and osteosarcoma.

	Ewing			Osteosarcoma	
	Median RDI achieved	**IQR (25%-75%)**		**Median RDI achieved**	**IQR (25%, 75%)**
Dactinomycin	0.64	0.45, 0.90	Methotrexate	0.82	0.68, 0.98
Cyclophosphamide	0.74	0.59, 0.97	Doxorubicin	0.75	0.65, 0.84
Ifosfamide	0.74	0.51, 0.94	Cisplatin	0.71	0.61, 0.82
Etoposide	0.79	0.57, 0.92			
Vincristine	0.73	0.63, 0.88			
Doxorubicin	0.85	0.65, 0.97			

E.3.3 Survival analysis

Overall survival rates for both tumour types were the same at 1-year but lower for Ewing at 2 and 5-years (Ewing; 1-year 94%, 2-years 77%, 5-years 48%, osteosarcoma; 1-year 94%, 2-years 83%, 5-years 67%). Males had lower survival rates than females in both tumour sites and at all time points (Ewings; 1-year males 92% vs females 97%, 5-years males 44% vs females 54%, osteosarcoma; 1-year males 92% vs females 95%, 5-years males 61% vs females 77%). There was no clear pattern relating to survival by age categories seen in these patient cohorts (Table E.3).

Table E.3: Kaplan-Meier one, two and five-year survival estimates presented forewing and osteosarcoma, both overall and by clinical and demographic variables.

		Ewing			Osteosarcoma		
		1 year	**2 years**	**5 years**	**1 year**	**2 years**	**5 years**
Overall		94 (88-96)	77 (69-83)	48 (34-60)	94 (88-97)	83 (76-88)	67 (57-76)
Patient characteristic							
Age category	12-17 years	97 (87-99)	79 (64-88)	34 (8-62)	92 (84-96)	82 (72-89)	69 (57-79)
	18-23 years	94 (85-98)	77 (65-86)	57 (41-70)	95 (83-99)	86 (71-93)	65 (42-81)
	24-29 years	85 (64-94)	70 (46-84)	-	96 (76-99)	80 (58-91)	66 (39-83)
Sex	Male	92 (84-96)	78 (67-85)	44 (27-61)	92 (84-96)	80 (70-87)	61 (48-72)
	Female	97	75	54	95	86	77

		(87-99)	(61-85)	(35-70)	(87-99)	(75-93)	(61-87)
Ethnicity	White	95 (89-97)	78 (69-85)	43 (26-58)	93 (86-96)	83 (74-89)	71 (59-80)
	Asian	83 (57-94)	58 (31-78)	46 (19-70)	94 (65-99)	88 (61-97)	60 (18-86)
	Black	-	-	-	93 (59-99)	76 (42-92)	-
	Other	100	100	100	100	80 (41-95)	-
Deprivation fifth	1	93 (76-98)	80 (59-91)	60 (29-81)	96 (75-99)	87 (64-96)	58 (29-79)
	2	100	88 (67-96)	-	90 (72-97)	76 (56-88)	59 (37-75)
	3	92 (72-98)	75 (53-88)	50 (23-72)	94 (77-98)	90 (72-97)	90 (72-97)

	4	97 (80-100)	68 (47-82)	53 (31-70)	92 (72-98)	79 (56-91)	66 (39-83)
	5	87 (71-94)	74 (56-86)	46 (24-66)	96 (83-99)	82 (67-91)	67 (47-81)
Stage at presentation	1	95 (68-99)	88 (59-97)	-	100	92 (54-99)	83 (46-95)
	2	100	90 (66-97)	-	93 (84-97)	84 (73-91)	68 (52-80)
	3	83 (27-97)	83 (27-97)	-	75 (13-96)	75 (13-96)	75 (13-96)
	4	81 (60-92)	57 (35-73)	24 (8-44)	91 (51-99)	71 (34-90)	34 (6-65)
	Missing	96 (89-99)	77 (65-85)	50 (30-66)	95 (85-98)	82 (70-90)	72 (56-83)
Primary site	Upper limb	96 (73-	85 (60-	46 (18-	100	82 (53-	61 (28-

	99)	95)	70)		94)	83)
Lower limb	98 (84-100)	73 (56-85)	57 (35-74)	94 (88-97)	84 (76-90)	71 (59-80)
Axial	96 (77-99)	89 (69-96)	-	90 (67-98)	81 (56-92)	63 (37-81)
Pelvis	96 (84-99)	78 (62-88)	56 (33-74)	-	-	-
Other	64 (34-83)	46 (18-70)	-	50 (6-91)	50 (6-91)	50 (6-91)

Multivariable regression showed that in the Ewing patients increasing RDI had little effect on risk of death for dactinomycin (HR: 1.05, 95% CI 0.96-1.15) and vincristine (HR: 0.99, 95% CI 0.88-1.11). For doxorubicin however there was an association with a higher risk of death with increasing RDI (HR: 1.51, 95% CI 0.48-4.71) and this association was greater for cyclophosphamide (HR: 3.16, 95% CI 0.92-10.9), ifosfamide (HR: 3.31, 95% CI 1.06-10.4) and etoposide (HR: 4.86, 95% CI 1.46-16.2) (Table E.4). In osteosarcoma a protective association was seen between increased RDI and survival for doxorubicin (HR: 0.39, 95% CI 0.07-2.16), no effect for cisplatin (HR: 0.95, 95% CI 0.21-4.34) and an increased risk of death for methotrexate (HR: 1.78, 95% CI 1.2-2.64) (Table E.5).

Table E.4: The hazard ratios for each individual drug for overall survival in Ewing sarcoma where RDI is considered a continuous variable (patients n = 154, deaths n= 51).

	Adjusted*			***Unadjusted***		
Chemotherapy drug	**Hazard ratio**	**95% confidence interval**	**P value**	**Hazard ratio**	**95% confidence interval**	**P value**
Dactinomycin (n=77)	1.05	0.96 to 1.15	0.30	1.05	0.96 to 1.14	0.26
Cyclophosphamide (n=89)	3.16	0.92 to 10.9	0.07	1.28	0.82 to 2.01	0.28
Ifosfamide (n=149)	3.31	1.06 to 10.4	0.04	3.49	1.39 to 8.78	0.01
Etoposide (n=150)	4.86	1.46 to 16.20	0.01	2.97	1.09 to 8.11	0.03
Vincristine (n=150)	0.99	0.88 to 1.11	0.84	0.98	0.90 to 1.07	0.70
Doxorubicin (n=144)	1.51	0.48 to 4.71	0.48	1.89	0.70 to 5.07	0.21

* adjusted for age at diagnosis, concurrent radiotherapy, comorbidity adjustment, treating speciality, ethnicity, deprivation quintile and sex.

Table E.5: The hazard ratios for each individual drug for overall survival in osteosarcoma where RDI is considered a continuous variable (patients n = 156, deaths n = 42).

Chemotherapy drug	*Adjusted**			*Unadjusted*		
	Hazard ratio	**95% confidence interval**	**P value**	**Hazard ratio**	**95% confidence interval**	**P value**
Cisplatin (n=153)	0.95	0.21 to 4.34	0.94	0.95	0.21 to 4.26	0.95
Doxorubicin (n=149)	0.39	0.07 to 2.16	0.28	0.37	0.07 to 1.95	0.24
Methotrexate (n=152)	1.78	1.2 to 2.64	0.00	1.77	1.21 to 2.61	0.00

* adjusted for age at diagnosis, concurrent radiotherapy, comorbidity adjustment, treating speciality, ethnicity, deprivation quintile and sex.

Cause of death was explored to see if treatment toxicity was contributing to the high hazard ratios seen for some of the drugs. A total of 51 deaths occurred in the Ewings cohort and a cause of death ICD 10 code was provided for 50 patients. Only one cause of death of sepsis within 18 days of treatment could have been related to toxicity. No causes of death were related to toxicity in the osteosarcoma cohort.

E.3.4 Further analysis

Due the results suggesting an association between higher RDI and a greater risk of death for some of the drugs further analysis was carried out in attempt to gain a greater understanding of what was happening.

The dosing of some of the agents in the EE2012 protocol varies both across treatment arms and also within the same arm according to cycle number. For example, in treatment arm A the dose of ifosfamide changes from 9g/m^2/cycle in

VIDE induction to 6g/m^2/cycle in the consolidation cycles. Etoposide is administered at 450 mg/m^2/cycle in arm A and 500 mg/m^2/cycle in the consolidation cycles of arm B. The dose of cyclophosphamide is 1500mg/m^2/cycle in arm A and 1200mg/m^2/cycle in arm B. Although RDI was calculated according to these different regimes (and variations within them), analysis ideally would be carried out according to each arm to investigate the causal effects of the different doses. Unfortunately, due to limited patient numbers it was not possible to carry out multivariable analysis for each arm of the study. The results of unadjusted analysis were therefore considered and are show in Table E.6.

Table E.6: The hazard ratios of each individual drug on overall survival in Ewing sarcoma where RDI is considered a continuous variable. Results presented according to individual treatment arm and for all patients combined. Unadjusted models only.

Chemotherapy drug	***Arms combined***			***Arm A (VIDE)***			***Arm B (VDC/IE)***		
	Hazard ratio	**95% confidence Interval**	**P value**	**Hazard ratio**	**95% confidence Interval**	**P value**	**Hazard ratio**	**95% confidence Interval**	**P value**
Dactinomycin (n=77)	1.05	0.96 to 1.14	0.26	1.05	0.96 to 1.14	0.26	*	*	*
Cyclophosphamide (n=89)	1.28	0.82 to 2.01	0.28	1.02	0.37 to 2.83	0.97	3.27	1.11 to 9.61	0.03
Ifosfamide (n=149)	3.49	1.39 to 8.78	0.01	4.03	1.26 to 12.86	0.02	2.92	0.51 to 16.6	0.23
Etoposide (n=150)	2.97	1.09 to 8.11	0.03	3.21	0.85 to 12.18	0.09	3.58	0.61 to 20.9	0.16
Vincristine (n=150)	0.98	0.90 to 1.07	0.70	0.98	0.85 to 1.11	0.72	6.90	1.23 to 38.8	0.03
Doxorubicin (n=144)	1.89	0.70 to 5.07	0.21	1.43	0.21 to 9.90	0.72	1.99	0.60 to 6.61	0.26

These findings need to be interpreted with caution due to the small numbers in each arm (arm A n=91, arm B n=60) as evidenced by the wide confidence intervals. There is suggestion of a greater negative effect of higher cyclophosphamide and vincristine RDIs in arm B while the negative association with ifosfamide is greater in arm A.

Ideally analysis would be limited to patients who completed the full course of chemotherapy to enable direct comparisons to be made. This is not reflective however of real world treatment or indeed in clinical trials, as demonstrated in Table E.7 below where treatment completion rates in this NCRAS cohort are compared to those in EE2012.

Table E.7: Number of patients completing induction and consolidation chemotherapy in the NCRAS dataset compared to EE2012.

	NCRAS				Euro Ewing 2012			
	n	**Number of patients completing induction n (%)**	**Number of patients completing full course n (%)**	**Died n (%)**	**n**	**Number of patients completing induction n (%)**	**Number of patients completing full course n (%)**	**Died n (%)**
Arm A	91	85 (93)	7 (21.9)	35 (38.5)	318	304 (95)	184 (58)	95 (58)
Arm B	60	50 (83)	29 (48.3)	16 (26.7)	316	291 (91)	240 (75)	68 (42)

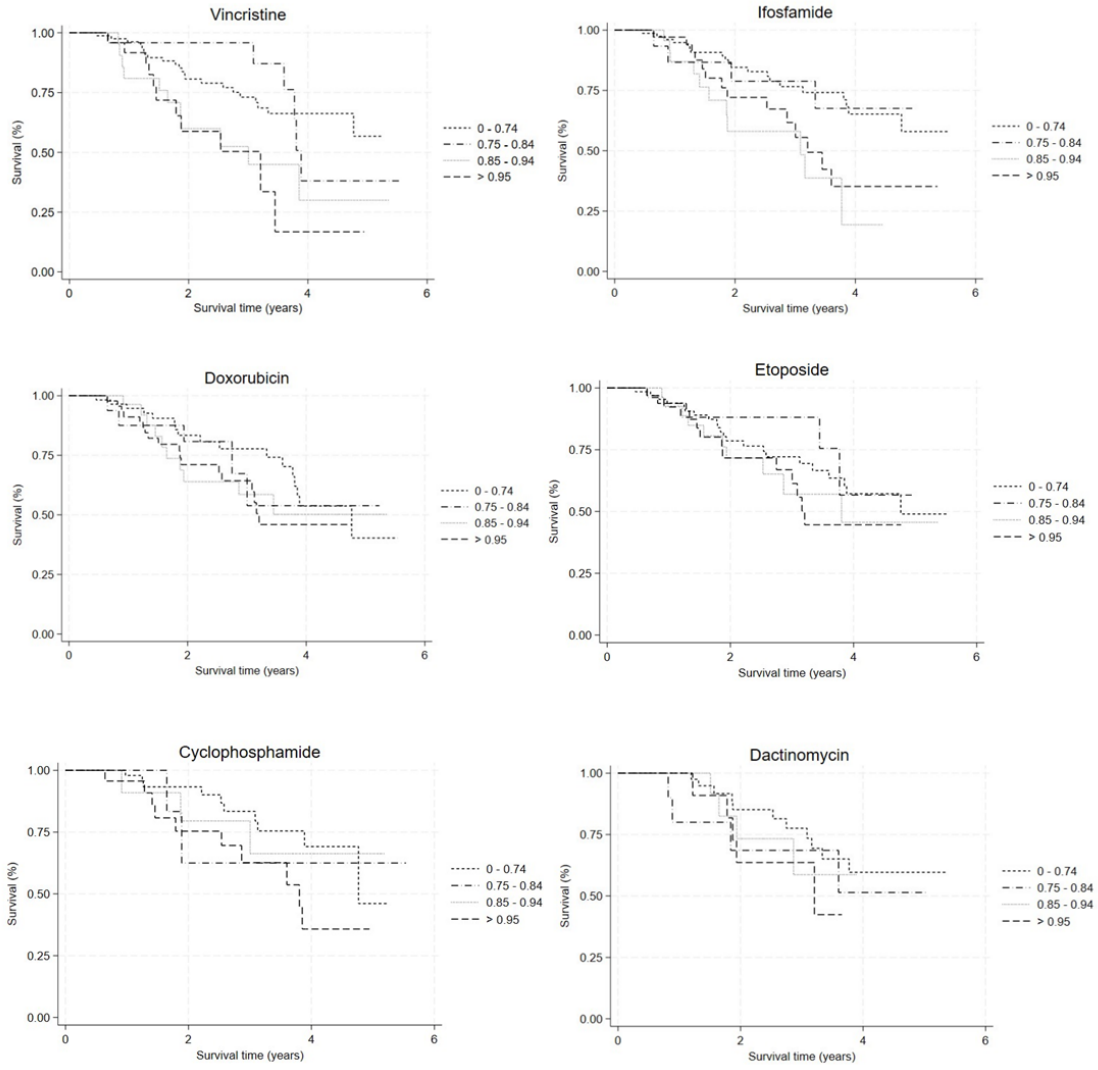
E.3.5 Survival outcomes according to RDI category

Interpretation of the Kaplan-Meir curves (Figure E.4) for both bone tumour types are limited by the small number of patients and short follow up duration.

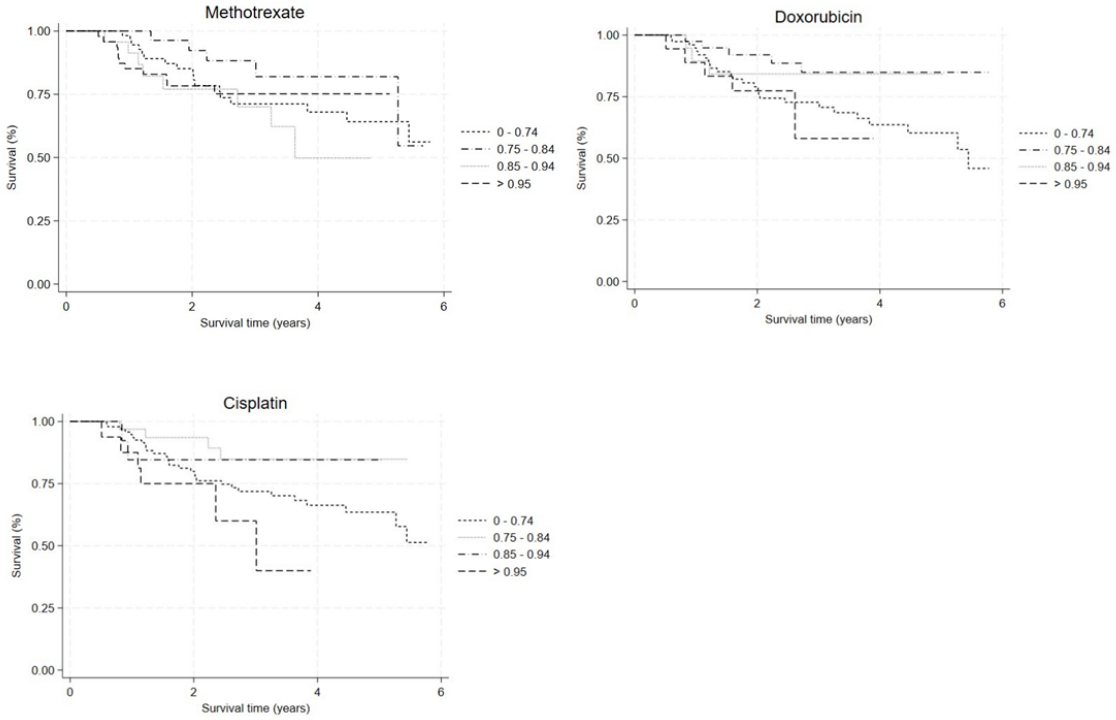
In patients with Ewing, those who received an RDI in the lowest two categories (0–0.74 and 0.75-0.84) had better outcomes for doxorubicin, etoposide, vincristine and ifosfamide. Worst survival outcomes were seen for those receiving an RDI of greater than 0.95 in doxorubicin and etoposide and vincristine. No clear pattern was seen for cyclophosphamide and dactinomycin. In osteosarcoma, if survival at 4 years is compared it can be seen that for cisplatin and doxorubicin superior survival is seen in the RDI categories 0.75 to 0.84 and 0.85 to 0.94. In methotrexate patients who received an RDI in the 0.75 to 0.84 had superior survival at 4 years.

Figure E.4: Kaplan-Meier survival estimates for each chemotherapy drug presented by achieved relative dose intensity in a) Ewing and b) osteosarcoma.

a)



b)



E.4 Discussion

The overall interpretation of this analysis is complex, particularly in relation to the chemotherapy received in Ewing where multiple different drugs are used at varying doses across the regime.

In Ewing the findings of the increased HR for the relationship between increasing RDI and risk of death for doxorubicin, etoposide, ifosfamide and cyclophosphamide are suggestive that whilst maintaining dose intensity is important, so too is adherence to dose reductions according to toxicity. This may reflect the toxicity associated with the regimes investigated as evidenced by at least 90% of patients experiencing a grade 3 to 5 adverse event in EE2012(200) and only between 58% and 75% completing the full course of chemotherapy. In the EURAMOS-1 trial (198) 19 patients had their treatment discontinued due to toxicity and between 58 and 62%, depending on treatment arm, had a dose reduction or dose delay in

treatment in line with the trial protocol. The findings of Figure E.3 are in keeping with a number of dose modifications being made in these trials. This is especially true in Ewing where the majority of patients received RDIs in the lower categories. Comparing the Kaplan-Meier curves in Figure E.4 it can be seen that patients who received the higher RDI categories for cisplatin and doxorubicin in osteosarcoma had superior survival rates. For methotrexate and many of the drugs used in Ewing those receiving the lower RDI categories had the superior survival. The hazard ratios for cisplatin and doxorubicin in osteosarcoma indicate a survival advantage from higher RDIs in these agents, more so for doxorubicin compared to cisplatin. These findings together suggest that the optimal amount of chemotherapy in AYA differs according to drug and tumour type. With higher DIs being more beneficial in osteosarcoma. It should also be considered whether such high intensities of all the drugs are required.

There was a lower percentage of patients completing chemotherapy in the NCRAS Ewing patients compared to those treated within EE2012 (Table E.7) and it needs to be considered whether this is due to missing data or whether this is reflective of not all patients in the NCRAS cohort being treatment on trial (64%, Table E.1). The EE2012 protocol initially excluded patients with extrapulmonary metastases it could therefore be that the patients in the NCRAS cohort had worse disease than those in the trials. A lower number of deaths was observed in the NCRAS cohort compared to EE2012 (Table E.7) is likely to be in part due to the limited follow up available. Regarding clinical trial participation, 64% of the patients with Ewing were recorded as being in a clinical trial compared to only 18% of patients with osteosarcoma. This reflects the time periods of recruitment for EE2012 and EURAMOS-1, the former recruiting over the time period that this SACT data was collected, the latter having ended recruitment. It should therefore be considered whether this may have influenced the prescribing practices of clinicians and therefore the RDIs received in the two different tumour types.

The results of EE2012 found a greater effect on EFS for patients aged under 14 compared to those over 14 years (arm A HR 0.57 (0.36-0.92) vs HR 0.78 (0.58-1.06), arm B HR 0.40 (0.22-0.73) vs 0.74 (0.51-1.08)). Response to treatment received, as discussed in Chapter 7 of this thesis, may play a part in this difference. I attempted to compare the survival rates at 1 and 5 years in the NCRAS for under

14s and over 14s and found no difference at these time points. This is limited by the age range under investigation in this cohort being 12-29 years (14 years and under n=28, 15 to 29 years n=126).

The reason for these increased HR remains unclear and require further investigation. The findings of current ongoing PK studies may help to address the unanswered questions. Repeating this analysis using treatment data from the clinical trials, as carried out in the GCT paper, may also be beneficial.

Appendix F

The impact of sociodemographic factors on received RDI.

F.1 Introduction

One of the current benefits of RWD over that obtained from clinical trials is the ability to analyse associations between sociodemographic factors and outcomes. Identifying any existing inequalities can lead to measures being implemented to help improve outcomes for certain subsets of patients.

The impact of socio-economic and ethnic inequalities on survival has been described in AYA internationally (1,2) where patients from the more deprived areas have been shown to have worse survival than those from more affluent areas and patients of black ethnicity to have worse outcomes than other ethnic groups. In England and Wales whilst socio-economic differences have been described in adults (3,4), little work has been done in AYA. The impact of both ethnicity and socioeconomic deprivation in children with cancer has been described by the team at the YSRCCYP(5), work to which I contributed outside of this thesis. In doing this work we concluded that in some areas it is not possible to model the true direct causal effects of ethnicity or socio-economic distribution due to inherent structural confounding. For example, in Yorkshire patients of south Asian ethnicity are more likely to live in the more deprived areas. Whilst an in-depth investigation into associations between sociodemographic factors, outcomes and treatment received is at important area for investigation, it is outside the scope of this thesis. Survival at 1, 2 and 5 years according to age, sex, ethnicity and deprivation quintiles on survival outcomes have been described in Chapters 4, 5 and Appendix E. The impact of sex and age on TIMT has been described in detail for osteosarcoma and Ewing in Chapter 5.

In this Appendix, descriptive statistics are used to summarise whether any associations exist between sociodemographic factors and the RDI of treatment received.

F.2 Methods

The sociodemographic factors investigated were determined by the data items available in the NCRAS dataset as described in Table 1 (Chapter 3) and comprised of: sex, age, ethnicity, socioeconomic status and the region of England that the chemotherapy was received in. This analysis used the linked datasets as described in Chapter 4 and Appendix E. Population weighted quintiles of the English Index of Multiple Deprivation (IMD) 2015 (6) were provided by NCRAS as the measure of socio-economic deprivation. Ethnicity was based on categories from the 2001 Census (7). Region of treatment was provided as County in which treatment was received and then divided into the north, midlands and south of England.

Median RDI was selected as the value for osteosarcoma and Ewing above which a patient was deemed to have received adequate RDI. This value was chosen for the cut off due to the wide variation in achieved RDI that was found in Appendix E. For GCT a RDI of 0.95 was chosen due to the high median RDIs achieved in this cohort.

Descriptive statistics were produced using Stata 18 (8) to describe the proportion of patients in each category of the sociodemographic variables who achieved an adequate RDI. The results were explored for any existing trends.

F.3 Results

F.3.1 Age

GCT

For bleomycin, etoposide and cisplatin patients in the age category 12-17 years were the least likely to achieve an RDI of 0.95 or above and those aged 18-23 years most likely (bleomycin: 12-17 years 62%, 18-23 years 76%, 24-29 years 70%;

etoposide: 12-17 years 62%, 18-23 years 69%, 24-29 years 65%; cisplatin: 12-17 years 67%, 18-23 years 74%, 24-29 years 68%) (Table F.1).

Osteosarcoma

The age group in which the lowest proportion of patients received the median RDI or above was 18-23 year olds for methotrexate and doxorubicin (methotrexate: 12-17 years 60%, 18-23 years 40%, 24-29 years 50%; doxorubicin: 12-17 years 56%, 18-23 years 42%, 24-29 years 54%). In cisplatin it was 24-29 year olds (cisplatin: 12-17 years 49%, 18-23 years 53%, 24-29 years 46%) (Table F.2).

Ewing

A lower proportion of patients aged 12-17 years received a median RDI or above compared to those in the older age groups for doxorubicin (12-17 years 38%, 18-23 years 61%, 24-29 years 65%), cyclophosphamide (12-17 years 64%, 18-23 years 71%, 24-29 years 88%) and etoposide (12-17 years 40%, 18-23 years 51%, 24-29 years 77%). In vincristine (12-17 years 50%, 18-23 years 47%, 24-29 years 73%) and ifosfamide (12-17 years 50%, 18-23 years 47%, 24-29 years 69%) the lowest percentage of patients was found in those aged 18-23 years. For dactinomycin there was little difference across the age ranges but with more patients aged 12-17 years receiving the higher RDIs than the older age categories (12-17 years 78%, 18-23 years 73%, 24-29 years 73%) (Table F.3).

F.3.2 Sex

GCT

More males compared to females achieved higher RDIs across all agents (bleomycin: males 72% females 69%, etoposide: males167% females 56%, cisplatin: males 71% females 54%) (Table F.3).

Osteosarcoma

Females were more likely than males to achieve the median RDI or above across all drugs (methotrexate: males 48% females 59%, doxorubicin: males 48% females 58%, cisplatin: males 48% females 53%) (Table F.2).

Ewing

With regards to sex a higher proportion of males compared to females received the median RDI or above for all drugs apart from dactinomycin for which there was no difference (ifosfamide: males 55% females 47%, doxorubicin: males 54% females 53%, cyclophosphamide: males 75% females 66%, vincristine: males 63% females 36%, etoposide: males 59% females 39%, dactinomycin: males 75% females 75%) (Table F.3).

F.3.3 Ethnicity

GCT

Patients of white and other ethnicity had the highest proportion of patients achieving the higher RDIs compared to those of black and Asian ethnicity, with lowest proportions occurring in patients of black ethnicity. The results however need to be interpreted with caution due to the low number of patients of ethnicities other than white in the cohort (white n=85%). Bleomycin (white 72%, Asian 67% black 50% and other 75%), cisplatin (white 70%, Asian 64%, black 50% and other 75%), etoposide (white 66%, Asian 64%, black 3% and other 71%) (Table F.1).

Osteosarcoma

Individuals of black and other ethnicity had a higher proportion of patients receiving the higher RDIs for methotrexate (white 52%, Asian 41% black 71% and other 55%). There was little difference across the ethnic groups for doxorubicin with those in the other category being least likely to achieve a high RDI (white 54%, Asian 53% black 43% and other 36%) and cisplatin (white 51%, Asian 47% black 50% and other 45%) (Table F.2).

Ewing

Patients of other ethnicity were least likely to receive a median RDI or above for ifosfamide (white 59%, Asian 72%, other 50%) whilst it was white patients in doxorubicin (white 55%, Asian 67%, other 63%), and cyclophosphamide (white 73%, Asian 83%, other 75%). There was little difference across the categories for vincristine (white 74%, Asian 72%, other 75%) and etoposide (white 55%, Asian 50%, other 50%) with a lower percentage of Asian patients receiving the higher RDIs in dactinomycin (white 75%, Asian 72%, other 88%) (Table F.3).

F.3.4 Deprivation quintile

GCT

More patients in the least deprived quintiles received an RDI of 0.95 or above for bleomycin and cisplatin. Whilst for etoposide there were more patients in the most deprived quintile receiving the higher RDIs. The differences overall between patients in each quintile across the three drugs were small (bleomycin: quintile 1 75%, quintile 2 74%, quintile 3 71%, quintile 4 68%, quintile 5 72%; cisplatin: quintile 1 75%, quintile 2 63%, quintile 3 68%, quintile 4 70%, quintile 5 74%; etoposide: quintile 1 66%, quintile 2 62%, quintile 3 62%, quintile 4 68%, quintile 5 72%) (Table F.1).

Osteosarcoma

Patients in the most deprived quintile were the least likely to receive a median RDI or above for methotrexate compared to patients in other quintiles (quintile 1: 56%, quintile 2: 60%, quintile 3: 52%, quintile 4: 56%, quintile 5: 44%). This was also seen in cisplatin although there was little difference seen across the quintiles for this drug (quintile 1: 48%, quintile 2: 50%, quintile 3: 48%, quintile 4: 60%, quintile 5: 47%). For doxorubicin the opposite was seen with patients in the least deprived quintile being the least likely to achieve a median RDI or above (quintile 1: 40%, quintile 2: 63%, quintile 3: 42%, quintile 4: 48%, quintile 5: 60%) (Table F.2).

Ewing

More patients in the two most deprived quintiles received a median RDI or above for ifosfamide (quintile 1: 40%, quintile 2: 55%, quintile 3: 56%, quintile 4: 63%, quintile

5: 63%) and doxorubicin (quintile 1: 43%, quintile 2: 48%, quintile 3: 52%, quintile 4: 72%, quintile 5: 63%). For these two drugs the lowest proportion of patients achieving the higher RDIs were in the least deprived quintiles. There was no clear pattern of deprivation effect for cyclophosphamide (quintile 1: 73%, quintile 2: 62%, quintile 3: 84%, quintile 4: 66%, quintile 5: 79%). For etoposide (quintile 1: 60%, quintile 2: 55%, quintile 3: 56%, quintile 4: 56%, quintile 5: 47%), vincristine (quintile 1: 70%, quintile 2: 76%, quintile 3: 84%, quintile 4: 81%, quintile 5: 63%) and dactinomycin (quintile 1: 70%, quintile 2: 83%, quintile 3: 88%, quintile 4: 72%, quintile 5: 68%) the lowest proportion of patients were in the most deprived quintile (Table F.3).

F.3.5 Region

GCT

Patients who received their chemotherapy in the south of England had the lowest proportion of patients receiving high RDIs compared to patients treated in the north of England or the Midlands for bleomycin (north: 78%, midlands: 72%, south: 68%), etoposide (north: 76%, midlands: 69%, south: 58%) and cisplatin (north: 69%, midlands: 80%, south: 65%) (Table F.1).

Osteosarcoma

When looking at the region in which treatment was delivered those who received treatment in the south were more likely of have achieved an adequate RDI for methotrexate (north: 51%, midlands: 50%, south: 55%). Those in the north were more likely to receive the median RDI or above for doxorubicin (north: 59%, midlands: 50%, south: 49%) and cisplatin (north: 62%, midlands: 60%, south: 39%) with the lowest proportions being present in the south (Table F.2).

Ewing

There was no clear effect across region. A greater percentage of patients treated in the midlands receiving higher RDIs for ifosfamide (north: 56%, midlands: 69%, south: 58%), cyclophosphamide (north: 76%, midlands: 80%, south: 70%) and etoposide (north: 49%, midlands: 69%, south: 48%), in the north for doxorubicin

(north: 76%, midlands: 56%, south: 44%) and the south for vincristine (north: 56%, midlands: 67%, south: 78%) and dactinomycin (north: 62%, midlands: 71%, south: 88%) (Table F.3).

F.3.6 Common features

Common features across the different tumour types for the drugs etoposide, doxorubicin and cisplatin were considered, each of which were used in two of the tumour types investigated. The lowest proportions of patients receiving an adequate RDI were treated in the south of England for all 3 drugs across all tumour types. A common association was also seen for etoposide with patients in the age category 12 to 17 years and female patients having the lowest percentages achieving adequate RDI compared to males and the older age categories.

Table F.1: The proportion of patients achieving an RDI of less than 0.95 or greater than 0.95 according to sociodemographic characteristics in patients with a germ cell tumour receiving bleomycin, cisplatin and etoposide chemotherapy.

		Bleomycin		Cisplatin		Etoposide	
Patient characteristic		Less than 0.95	0.95 and above	Less than 0.95	0.95 and above	Less than 0.95	0.95 and above
Age	12-17 years	17 (38)	28 (62)	15 (33)	30 (67)	17 (38)	28 (62)
	18-23 years	73 (24)	229 (76)	79 (26)	223 (74)	94 (31)	208 (69)
	24-29 years	154 (30)	364 (70)	164 (32)	354 (68)	181 (35)	337 (65)
Sex	Male	229 (28)	588 (72)	236 (29)	581 (71)	271 (33)	546 (67)
	Female	15 (31)	33 (69)	22 (46)	26 (54)	21 (44)	27 (56)
Ethnicity	White	205 (28)	525 (72)	216 (30)	514 (70)	247 (34)	483 (66)
	Asian	20 (33)	41 (67)	22 (36)	39 (64)	22 (36)	39 (64)
	Black	3 (50)	3 (50)	3 (50)	3 (50)	4 (67)	2 (33)
	Other	16 (25)	47 (75)	16 (25)	47 (75)	18 (29)	45 (71)
Deprivation quintile	1	38 (25)	113 (75)	38 (25)	113 (75)	52 (34)	99 (66)
	2	36 (26)	102 (74)	51 (37)	87 (63)	53 (39)	85 (62)
	3	51 (29)	125 (71)	56 (32)	120 (68)	67 (38)	109 (62)
	4	60 (32)	128 (68)	57 (30)	131 (70)	60 (32)	128 (68)
	5	59 (28)	153 (72)	56 (26)	156 (74)	60 (28)	152 (72)
Region of England	North	55 (22)	192 (78)	76 (31)	171 (69)	59 (24)	188 (76)
	Midlands	66 (28)	173 (72)	48 (20)	191 (80)	73 (31)	166 (69)
	South	123 (32)	256 (68)	134 (35)	245 (65)	160 (42)	219 (58)

Table F.2: The proportion of patients achieving a median RDI according to sociodemographic characteristics in patients with osteosarcoma receiving methotrexate, doxorubicin and cisplatin chemotherapy.

		Methotrexate		Doxorubicin		Cisplatin	
Patient characteristic		Less than 0.82	0.82 and above	Less than 0.75	0.75 and above	Less than 0.71	0.71 and above
Age	12-17 years	35 (40)	52 (60)	38 (44)	49 (56)	44 (51)	43 (49)
	18-23 years	26 (60)	17 (40)	25 (58)	18 (42)	20 (47)	23 (53)
	24-29 years	13 (50)	13 (50)	12 (46)	14 (54)	14 (54)	12 (46)
Sex	Male	47 (52)	43 (48)	47 (52)	43 (48)	47 (52)	43 (48)
	Female	27 (41)	39 (59)	28 (42)	38 (58)	31 (47)	35 (53)
Ethnicity	White	55 (48)	59 (52)	52 (46)	62 (54)	56 (49)	58 (51)
	Asian	10 (59)	7 (41)	8 (47)	9 (53)	9 (53)	8 (47)
	Black	4 (29)	10 (71)	8 (57)	6 (43)	7 (50)	7 (50)
	Other	5 (45)	6 (55)	7 (64)	4 (36)	6 (55)	5 (45)
Deprivation quintile	1	11 (44)	14 (56)	15 (60)	10 (40)	13 (52)	12 (48)
	2	12 (40)	18 (60)	11 (37)	19 (63)	15 (50)	15 (50)
	3	15 (48)	16 (52)	18 (58)	13 (42)	16 (52)	15 (48)
	4	11 (44)	14 (56)	13 (52)	12 (48)	10 (40)	15 (60)
	5	25 (56)	20 (44)	18 (40)	27 (60)	24 (53)	21 (47)
Region of England	North	18 (49)	19 (51)	15 (41)	22 (59)	14 (38)	23 (62)
	Midlands	21 (50)	21 (50)	21 (50)	21 (50)	17 (40)	25 (60)
	South	35 (45)	42 (55)	39 (51)	38 (49)	47 (61)	30 (39)

Table F.3: The proportion of patients achieving a median RDI according to sociodemographic characteristics in patients with Ewing sarcoma receiving vincristine, ifosfamide, doxorubicin, etoposide, cyclophosphamide and dactinomycin chemotherapy as part of the VIDE/VAC, VIDE/VAI and VDC/IE regimes.

		Ifosfamide		**Doxorubicin**		**Cyclophosphamide**		**Vincristine**		**Etoposide**		**Dactinomycin**	
Patient characteristic		Less than 0.74	0.74 and above	Less than 0.85	0.85 and above	Less than 0.74	0.74 and above	Less than 0.73	0.73 and above	Less than 0.79	0.79 and above	Less than 0.64	0.64 and above
Age	12-17 years	29 (50)	29 (50)	36 (62)	22 (38)	21 (36)	37 (64)	29 (50)	29 (50)	35 (60)	23 (40)	13 (22)	25 (78)
	18-23 years	37 (53)	33 (47)	27 (39)	43 (61)	20 (29)	50 (71)	37 (53)	33 (47)	34 (49)	36 (51)	19 (27)	51 (73)
	24-29 years	8 (31)	18 (69)	9 (35)	17 (65)	3 (12)	23 (88)	7 (27)	19 (73)	6 (23)	20 (77)	7 (27)	19 (73)
Sex	Male	43 (45)	52 (55)	44 (46)	51 (54)	24 (25)	71 (75)	35 (37)	60 (63)	39 (41)	56 (59)	24 (25)	71 (75)
	Female	31 (53)	28 (47)	28 (47)	31 (53)	20 (34)	39 (66)	38 (64)	21 (36)	36 (61)	23 (39)	15 (25)	44 (75)
Ethnicity	White	52 (41)	76 (59)	58 (45)	70 (55)	34 (27)	94 (73)	33 (26)	95 (74)	57 (45)	71 (55)	32 (25)	96 (75)
	Asian	5 (28)	13 (72)	6 (33)	12 (67)	3 (17)	15 (83)	5 (28)	13 (72)	9 (50)	9 (50)	5 (28)	13 (72)
	Other	4 (50)	4 (50)	3 (38)	5 (63)	2 (25)	6 (75)	2 (25)	6 (75)	4 (50)	4 (50)	1 (13)	7 (88)
Deprivation quintile	1	17 (57)	12 (40)	17 (57)	13 (43)	5 (17)	22 (73)	9 (30)	21 (70)	12 (40)	18 (60)	9 (30)	21 (70)
	2	10 (34)	16 (55)	15 (52)	14 (48)	11 (38)	18 (62)	7 (24)	22 (76)	13 (45)	16 (55)	5 (17)	24 (83)
	3	8 (32)	14 (56)	12 (48)	13 (52)	4 (16)	21 (84)	4 (16)	21 (84)	11 (44)	14 (56)	3 (12)	22 (88)
	4	12 (38)	20 (63)	9 (28)	23 (72)	11 (34)	21 (66)	6 (19)	26 (81)	14 (44)	18 (56)	9 (28)	23 (72)
	5	14 (37)	24 (63)	14 (37)	24 (63)	8 (21)	30 (79)	14 (37)	24 (63)	20 (53)	18 (47)	12 (32)	26 (68)
Region of England	North	20 (44)	25 (56)	11 (24)	34 (76)	11 (24)	34 (76)	11 (24)	34 (56)	23 (51)	22 (49)	17 (38)	28 (62)
	Midlands	14 (31)	31 (69)	20 (44)	25 (56)	9 (20)	36 (80)	15 (33)	30 (67)	14 (31)	31 (69)	13 (29)	32 (71)

South	27 (42)	37 (58)	36 (56)	28 (44)	19 (30)	45 (70)	14 (22)	50 (78)	33 (52)	31 (48)	8 (13)	56 (88)

F.4 Discussion

These results suggest that variations exist in the RDI of chemotherapy achieved by individuals across different sociodemographic categories and for different drugs. This is important for cancers where dose matters for outcomes, to guide further research and enable extra support to be put in place for patients to enable them to receive adequate chemotherapy.

As previously described by the YSRCCYP research team the investigation of sociodemographic factors is complex (5). When considering their impact on treatment received this is likely to be the result of a combination of biological factors (effecting the PK and PD of chemotherapy agents) and social factors, both of which have their own challenges when trying to overcome them.

When looking at ethnicity the small patient numbers in AYA limit subgroup analyses possible. Potential ethnic variations in drug metabolism have been described (9,10) including for many of the drugs investigated in this thesis. Cyclophosphamide for example is a prodrug which requires activation by cytochrome P450 (CYP) enzymes. Polymorphisms have been found to exist in some of these enzymes across ethnic and racial groups and as a result it has been hypothesised that these polymorphisms contribute to variations in treatment outcomes seen (11). Ethnicity related differences have also been found for molecular mechanisms involved in the PK and PD of ifosfamide, cisplatin and bleomycin (10). Biological variations in cancers across different ethnic groups, and accompanying variation in severity as seen in breast (12) and colorectal (13), may also play a role in differences seen.

When investigating associations with deprivation a number of other factors also need to be considered. Research has shown that individuals from more deprived areas commonly present with cancers at more advanced stages of illnesses (14) including cancer (15,16). These may in part be due to access to health services hindered for example by language barriers and perceived attitudes towards healthcare providers (17). Variation in treatment adherence should also be taken into account. AYA have been found to be the age category least likely to adhere to treatment (18) which can have a negative effect on outcomes (19). Of less

relevance in the UK due to the state funded health system is the inequalities that arise due to the need for health insurance.

Differences according to the region in which treatment was received in could be due to a number of factors. Distance a patient lives from the treatment centre will impact all patients, with those living further away having a greater financial burden associated with attending appointments (20). Whilst charity support is available to help with this it will have a greater impact on those from more deprived backgrounds. The associated loss of earnings of parents and caregivers having to stop work to support young people also needs to be considered(21). The effect of whether or not treatment is received in a specialist treatment centre has previously been discussed in Chapters 2 and 4, with the inability to investigate this due to data minimisation is a limitation of the NCRAS dataset used described in Chapter 4.

AYA are known to be poorly recruited to clinical trials compared to younger children and older adults (22–24). Within the low proportion of AYA participating further disparities exist. Patients of lower socioeconomic status are less likely to take part in a clinical trial (25). AYA of Black ethnicity have been shown to be less likely to enrol on a clinical trial compared to White counterparts (25,26).

This work highlights the need for associations between deprivation and ethnicity and the treatment received by patients to be investigated in more detail. This would require data on these variables being routinely collected in clinical trials and would enable detailed subgroup analyses of clinical trial outcomes to be carried out. The findings would inform areas for future research and guide the implementation of changes to service provision.

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Appendix G.

In this appendix further detail is provided for the analysis carried out in Chapter 4. In section G.1 detailed description is given on how the SACT and COSD data were cleaned.

G.1 Data cleaning

G.1.1 Variables for Relative Dose Intensity calculation

Height and weight

Height and weight in the SACT data are essential to the calculation of relative dose intensity, because body surface area in m^2 is required for calculation of the standard dose. This is the dose that the patient should have received according to treatment guidelines. The calculation of RDI is described in Chapter 4.

If a patient had both height and weight missing then they were dropped from analysis as demonstrated in the consort diagram (Figure 4.1).

Two weight options are available in SACT for each individual. Weight at the start of the regime and weight at the start of the cycle. Weight at the start of the regime was found to be more complete (97.8% as opposed to 95.4%) and was therefore used in this analysis. Where the start of the regime value was missing but start of the cycle weight present this value for weight was used. This method resulted in 100% completeness for weight. Given the time duration of which chemotherapy is given in these patients I was satisfied this was an adequate method to use and a simple review of the differences between the two weight found the fluctuations to be minimal.

Height was found to be missing in 3.98% of cases, multiple imputation (MI) methods we used to deal with this missing height data as described in section 3.5.4. Further details of the MI carried out is demonstrated in Appendix B.

Drug group

This variable describes the administered drug. Drug group was dropped if listed as NOT CHEMO, DEXAMETHASONE, STEROID, MESNA, HYDROCORTISONE, ZOLENDRONIC ACID or MISSING. This was due to my analysis only being interested in chemotherapy agents. Where the DRUG_GROUP was “MULTIPLE” the drugs were reviewed and changed to the relevant chemotherapy agent if possible. For example if the dose was that of cisplatin and was given within a BEP regime.

Analysis Group

This variable provides details of the chemotherapy regime administered. Analysis groups listed as NOT MATCHED and TRIAL were reviewed to see if they fit into a known treatment regime of interest. All regimes were reviewed and altered or grouped where required. For example Bleomycin on occasions was given an analysis group of BLEOMYCIN but on review of the treatment was given within the BEP (bleomycin, etoposide and cisplatin) regime along with EP (etoposide and cisplatin).

Actual dose per administration

This variable relates to the dose in mg or other applicable unit for each administration in a SACT cycle, for example, 400 milligrams, 200 units, 1.5 grams. If the actual dose per administration was missing then the patient was dropped as no analysis of the RDI can be performed. The patient was also dropped if the dose given was not plausible and likely a random entry for example 0.9 entered. Doses were also reviewed to standardise the prescribed units. For example, the dose of Bleomycin was commonly entered as 30 and required multiplying by 1000 to provide the dose in units.

G.1.2 Confounding variables

Age and Sex

These variables required no cleaning and were 100% complete.

Ethnicity

For analysis this variable was categorised into the categories white, mixed, Asian, black and other.

White British, White Irish and any other White background were categorised into White.

White and Black Caribbean, White and Black African, White and Asian and any other mixed background were classified into the Mixed category.

The Asian category comprised of patients of Indian, Pakistani, Bangladeshi, Chinese and any other Asian background.

Patients with Caribbean, African and any other Black background were placed in the Black ethnic category.

The other category contained patients classified as any other ethnic group.

Stage and grade

Stage is missing for 50% of patients and grade for 94.0% of patients. Due to high percentage of missing data these variables cannot be included in the analysis and will be considered an unobserved variable in the DAG.

Primary diagnosis

100% complete. Where two different ICD codes were listed for one patient the most detailed one was used. If a site of metastatic disease e.g. mediastinum and the site of origin e.g. testis was given then the site of origin (testis) was used.

Diagnosis year

100% complete and no data cleaning required.

Consultant speciality code

Where two different consultant codes were present the code input during chemotherapy of interest (as detailed in the section 4.4 was used. Where both Medical Oncology and Clinical Oncology were both coded the speciality prescribed more was used. Where two different specialities were given the most appropriate was selected e.g. paediatrics when the listed specialities were paediatrics versus gynaecology.

Co-morbidity adjustment indicator

This is an indicator of whether or not a patient's overall physical state (other diseases and conditions) was a significant factor in deciding on regimen, or in varying the dose or treatment interval. This variable is based on the Charlson co-morbidity index which considers co-morbidities such as myocardial infarction, strokes, liver disease, chronic obstructive pulmonary disease etc. These illnesses are highly unlikely to be relevant when considering prescribing AYAs chemotherapy. However no alternative co-morbidity score was available.

Clinical trial indicator

If this changed throughout the treatment regime the patient was coded yes or no according to what was stated at the start of treatment.

Deprivation

Measure of deprivation at small area level made up from the income domain in 2015, quintiles are calculated from populations. No cleaning of this variable was required.

Postcode and treating hospital

Due to data minimisation only the outward postcode is provided in the national dataset. Similarly a pseudo-code is provided for the treating hospital. This means that distance to the treatment centre cannot be calculated and it cannot be determined whether treatment was received in a tertiary hospital. These variables therefore were not used in this analysis but were included as unobserved variables.

Cancer network

Cancer network (CNT) was provided as an indicator of region in the country that treatment was provided in. This was only 43.72% complete at the start but I was able to use PCT name to derive the missing cancer networks to give 100% completion.

Each CNET was labelled and categorised initially into one of nine regions.

1. North east – North of England.
2. North west – Greater Manchester and Cheshire, Lancashire and South Cumbria, Merseyside and Cheshire.
3. Yorkshire and Humber – Humber and Yorkshire Coast, Yorkshire.
4. East midlands – Trent, Arden, East Midlands, Greater Midlands, North Trent.
5. West midlands - Three Counties, Pan Birmingham,
6. East – Anglia, Essex.
7. London – Mount Vernon, North East London, North London, West London.
8. South east – Central South Coast, SE London, Surrey, West Sussex and Hampshire, Sussex and Thames Valley.
9. South west – Avon, Somerset and Wiltshire, Dorset, Kent and Medway, Peninsula, SW London, Wessex, Central South Coast.

1,2 and 3 were then combined to represent the North. 4, 5 and 6 the Midlands. 7, 8 and 9 the South.